The Clinical Utility of the Four Mountains Test in the Early Diagnosis of Alzheimer's Disease: A Measure of Allocentric Memory Ability

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OVERVIEW

This thesis examines early diagnosis of dementia by understanding the impact Mild Cognitive Impairment has on quality of life (QoL) and the clinical utility of a newly developed instrument in aiding early diagnosis of AD by differentiating it from other forms of dementia. This thesis formed part of a wider PHD project that is still being completed.

Part 1 is a literature review investigating the impact being diagnosed with Mild Cognitive Impairment (MCI) has on Quality of Life (QoL) in comparison to cognitively healthy controls and people with dementia. A total of 15 studies were examined. Overall, the evidence was inconsistent and methodological quality of the included research papers was weak. The review highlighted the need for further good quality research investigating the impact of MCI on QoL.

Part 2 is an empirical paper that reports the findings of a study examining the clinical utility of the Four Mountains Test (4MT), a measurement of hippocampal dependent allocentric memory processing, in aiding early and differential diagnosis of AD. A total of 35 participants with differing types of early dementia from a memory service completed the 4MT alongside neuropsychological measures of memory, language, visuospatial, fluency, attention, executive function and premordid functioning. No significant results were found. Study implications and limitations are discussed with ideas for future research.

Part 3 is a critical appraisal that provides reflections on the process of conducting the thesis. It discusses relevance of non-significant findings and potential of computer based tests such as the 4MT as well as the dilemmas encountered, methodological limitations and wider clinical implications of carrying out research with people with dementia.

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PART 1: SYSTEMATIC REVIEW

The Impact of Mild Cognitive Impairment on Quality of Life: A Systematic Review

ABSTRACT

Background: The intermediate state between normal ageing and dementia, Mild Cognitive Impairment (MCI), has recently become a primary target of aging research. This has led to an interest in the quality of life (QoL) of people diagnosed with MCI.

Aim: This review aimed to understand the impact having MCI has on QoL and factors that influence the extent to which QOL is affected.

Method: A systematic literature search was conducted. Of 878 studies identified, 15 studies published between 1999 and 2014 met the inclusion criteria. Quality was rated using pre-specified criteria**.** Studies were divided into the following categories based on QoL components covered: perceived QoL, psychological well-being and social relationships.

Results: The evidence was highly inconsistent and of poor to adequate quality. Most studies found no evidence of differences in perceived QoL for MCI relative to dementia or normal cognition groups. However, there was evidence of a reduction in psychological well-being and social relationships in an MCI population. Conflicting evidence was found regarding the concordance of MCI informant and patient ratings of QoL. Depression was found to be a strong, consistent predictor of MCI impact on QoL across studies.

Discussion*:* Inconsistent evidence and methodological weaknesses limit the conclusions drawn from the review about the impact of MCI on QoL. Longitudinal studies are needed before conclusive interpretations can be made. Implications of these findings for clinical practice are discussed alongside the limitations of the evidence base and future research directions.

INTRODUCTION

Mild Cognitive Impairment

Over the last decade much interest has developed in the intermediate state between healthy cognition and dementia, originating from a desire to identify individuals at risk of developing Alzheimer's Dementia (AD). The term Mild Cognitive Impairment (MCI) is most frequently used to refer to a transitional zone between normal cognitive function and early AD (Petersen et al, 2001; Winbald et al; 2004; Albert et al, 2011). There has been an increase in the UK prevalence of people with MCI, affecting between 5 and 20 per cent of the population aged 65 or over (Ray & Davidson, 2014). However, with increased awareness of dementia and availability of memory services it has been stated that the rates of referral for assessment and, hence, diagnosis of MCI will increase in the UK in the coming years (Dean & Wilcock, 2012).

Conversion to dementia

There is research that has demonstrated a link between MCI and increased risk of progressing to probable AD (Lopez et al, 2003; Busse et al, 2006; Plassman et al, 2008; Manly et al, 2008). However, other studies examining the conversion rates of MCI to AD show that not all individuals with MCI go on to develop AD (Bruscoli & Lovestone, 2004; Koepsell & Monsell, 2012; Plassman et al, 2008; Mitchell & Shiri-Feshki, 2009). For example, in a population based sample of older adults 32% of individuals with MCI were diagnosed with AD five years later, 15% were diagnosed with other forms of dementia such as vascular dementia and some individuals recovered with time (Tuokko et al, 2005). Fisk and Rockwood (2007) found that 20-30% of individuals with MCI showed no cognitive impairment at follow up five years later. These results have led some researchers to suggest that MCI represents a heterogeneous disorder with various potential outcomes (Petersen et

al, 2014).

Defining MCI

There is significant heterogeneity in the criteria used to define MCI with subtle differences in the conceptualisations, which may contribute to differing estimates of prevalence, incidence and conversion rates (Kumar et al, 2005; Bischkopf et al, 2002; Ritchie et al, 2001). Petersen et al (1999) first described MCI to identify individuals at risk of developing AD. The criteria emphasised the presence of a memory complaint in the absence of cognitive impairment, dementia and no deficits in activities of daily (ADLs). The criteria for MCI have since evolved following the formation of an international expert working group (Winbald et al, 2004; Petersen, 2003; 2004) that refined the criteria to reflect the heterogeneous clinical presentation of MCI. This resulted in the inclusion of other types of cognitive impairment beyond memory and minimal impairment to basic ADLs as well as preserved ADLs. The cognitive impairment is to be defined by either self and/or informant report in addition to evidence from objective measures of cognitive functioning.

The most recent classification (Albert et al, 2011) also identifies three MCI subtypes: (1) MCI with a memory impairment (MCI amnestic); (2) MCI with impairment in a single non-memory domain (non-amnestic MCI); (3) MCI with impairment in multiple cognitive domains e.g. language, executive function and visuospatial skills (multiple domain MCI). However, amnestic and non-amnestic MCI are most commonly used within the clinical and research field. The different subtypes likely reflect different aetiologies, including degenerative, vascular, psychiatric or trauma-related causes. For example, the amnestic MCI is thought to primarily constitute a prodromal phase of AD (Morris, 2006), whereas individuals with non-amnestic MCI may have higher likelihood of progression to other forms of dementia, such as vascular or fronto-temporal dementia.

Quality of Life in dementia

Quality of Life (QoL) has increasingly become an important construct within healthcare in understanding the impact of diseases and associated treatments particularly for chronic disorders (Muldoon et al, 1998). In the UK it is estimated that over 750,000 people have dementia and that this number is expected to double in the next thirty years (Department of Health, 2009). In line with this, there has been an increased interest in the QoL of older people with dementia or other forms of cognitive impairment (Whitehouse, 1999). Maximising and maintaining the well-being of both people with cognitive impairment and their carers has become a primary aim for dementia treatment in the absence of biological treatments for the underlying disease processes (Logsdon, McCurry & Teri, 2007). QoL has therefore been identified as an important domain for dementia assessment and treatment outcome (Lawton, 1994). The cognitive, behavioural, and functional symptoms seen in dementia can significantly impact patients' general well-being or QoL. Multiple studies using various rating scales to measure QoL have demonstrated decreased QoL in participantss with dementia compared to those without cognitive impairment (Thorgrimsen et al, 2003; Ready et al, 2004; Ettema et al, 2005; Vogel, Mortensen et al, 2006; Missotten et al, 2008; Hurt et al., 2008; Conde-Sala et al 2009; Rosas-Carrasco et al, 2010; Lapid et al; 2011)

Definitions of QoL in dementia

QoL is a complex multi-dimensional construct and therefore defining QoL in dementia is challenging due to the variety of relevant life domains affected dependent on the different stages of the disease or type of dementia. A variety of definitions have been proposed which vary significantly in the breadth of domains incorporated and there is still to date no single consensus definition of QoL available. There has been significant disagreement about how broad QoL should be as a construct. Broader definitions have been considered problematic blurring the line between what constitutes the symptoms and signs of dementia (i.e. memory

loss, functional impairment) and QoL. Narrower definitions of QoL tend to be considered more accessible allowing a more straightforward exploration of the relationship between QoL and dementia (Ready et al, 2004). Despite this lack of general consensus, there have been some areas of agreement of components that are critical to consider and supported by research. These universally recognised components of QoL include mood, preserved positive affect (i.e. pleasure, interest and contentment), absence of negative affect (e.g. anger, anxiety, and depression) and interpersonal relationships (Albert et al, 1996; Brod et al, 1999; Weiner et al, 2000; Burgener and Twigg, 2002; Logsdon et al, 2002; Ready et al, 2004).

Measurement of QoL in dementia

Measuring QoL in people with cognitive impairment presents a challenge due to its subjective nature and subsequent reliance on self-perceptions (Frank et al, 2011). As a person's dementia progresses cognitive and memory impairments lead to a reduction of insight into their deficits. Self-ratings of QoL may not therefore accurately reflect their abilities and recent experiences. In light of this, many scales involve a caregiver's perspective to allow clarification about events that the person may have forgotten. Additionally, this provides an opportunity for an examination of the differences and similarities between patient and caregiver perceptions of QoL. A number of QoL measurement tools have been developed over the years that involve a range of assessment methods (i.e. self ratings, informant ratings, direct observation; Lodgson et al, 2002). A comprehensive evaluation of QoL should consist of both self-administered and objective proxy assessment. Direct assessment of QoL of patients with dementia may be reliable in the earlier stages of illness (Brod et al, 1999). The assessment method selected is often dependent on the stage of dementia the measure is attempting to target. Research has demonstrated that people with a Mini Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) score of 10 or greater can usually participate in an interview about their

QoL to some degree that are as reliable as carer reports (Logsdon et al, 2000; Brod et al, 1999; Selai et al, 2000). In light of this, when measuring QoL in milder dementia or MCI it is particularly important to use measures that incorporate input from the person.

QoL in MCI

Research has demonstrated that the cognitive, behavioural and functional symptoms associated with dementia can significantly impact general well-being and QoL (Teng et al, 2012). Given that the symptoms consistent with early dementia are also often present in MCI, reductions in QoL might also be expected in this population. However, no specific tools have been designed to assess QoL in MCI. Given the crossover of MCI symptoms with early AD many studies have used measures designed to assess QoL in a dementia population e.g. QoL-AD (Tatsumi et al, 2011). A number of studies have investigated the impact having MCI has on QoL compared to healthy cognition and/or dementia. A better understanding of the impact of MCI on QoL may allow for more refined support from health services to maximize and maintain well-being. However, to date there has been no review of studies that have explored the impact of QoL in an MCI population and any potential determinants.

Current Literature Review

There has been no review to date that has specifically investigated the impact on QoL for people with MCI and how this compares to older people with no cognitive impairment or dementia. Dean and Wilcock (2012) conducted a review that focused on the experiences of living with MCI and found that MCI patients and carers encountered a range of cognitive, neuropsychiatric and practical issues. However, this review did not specifically review studies using QoL as the main outcome and solely from a quantitative perspective. Other previous reviews have specifically focused on understanding the prevalence of neuropsychiatric symptoms in an MCI population finding higher levels of mood disturbances (e.g. depression, anxiety) (Apostolova & Cummings, 2008; Yates et al, 2013;

Seeher, Low & Reppermund, 2013). Previous reviews have not directly investigated how QoL and the specific components that contribute to QoL are affected in MCI as well as any associated factors that may predict the degree of impact on QoL in MCI. In of light of this, the perceived aim of this review was to summarise quantitative evidence exploring the QoL of people with MCI from the patient perspective.

Literature review questions

The review addressed the following research questions:

1. Do differences in ratings of perceived QoL exist between individuals with MCI and those with no cognitive impairment or dementia?
2. How are specific aspects of QoL (i.e. psychological well-being and social relationships) affected by MCI and how do these differ from those with no cognitive impairment or dementia?
3. Do differences exist between self and informant ratings of QoL in MCI?
4. Are there any factors that predict the impact of MCI on QoL?

METHOD

Search Strategy

A 3-step search strategy was utilised in this review. An initial limited search of Psychinfo was undertaken followed by analysis of the text words contained in the title and abstract, and of the subject headings used to describe an article. A second search using all identified keywords and subject heading relevant to the specific databases was then undertaken across all included databases in January 2015. The following electronic databases were searched for studies: Psychinfo, Web of Science, Medline, CINAHL and EMBASE databases. Keywords were entered to request studies involving people diagnosed with MCI (Mild Cognitive Impairment, MCI) and the perspective (patient, client, elderly, older adult, geriatric). Keywords were also used to identify studies evaluating the impact on QoL (quality of life, QoL, well-being, satisfaction, life). In order to focus the review on recent evidence in the field, only studies published between 1999 to present were included in the review. This date was selected because there was an emergence of research in the dementia field after Petersen (1999) published his diagnostic criteria defining MCI as a clinical entity. Furthermore, when running the search there were only 4 papers published before 1999 that were unrelated to QoL in an MCI population. Titles, abstracts and excerpts were reviewed according to the inclusion and exclusion criteria (see below). The reference lists of articles meeting the inclusion criteria were also reviewed to identify additional publications. Studies were required to meet the following criteria to be included in the review:

Inclusion Criteria

- Included studies investigating QoL as a primary outcome
- Included studies investigating specific components of QoL: psychological well-being (i.e. depression, positive affect, negative affect) or social relationships
- Included studies evaluating patients perspectives alongside carer/informant perspectives

- Included studies that employed quantitative measures and data analysis
- Included journals published between 1999 to present (as stated above) in English and in peer- reviewed journals

Exclusion Criteria

- Excluded studies looking exclusively at a dementia population
- Excluded neuropsychological studies of MCI concerning cognitive features and abilities
- Excluded biologically based studies of MCI concerning brain pathology, physiology or genetics
- Excluded studies concerned with psychosocial or drug interventions
- Excluded studies that included only carer perspectives
- Excluded studies that had taken place within care homes and acute geriatric services
- Excluded studies addressing QoL measure design and validation
- Excluded studies in languages other than English
- Excluded studies employing qualitative measures and data analysis methods
- Excluded editorials, reviews, commentaries, letters or other articles that contained no original data
- Excluded studies published before 1999
- Excluded dissertation or conference papers
- Excluded single case study design

Data extraction

Information was extracted from eligible studies on country of study, design, population age, sample size, participant source, diagnostic criteria, components and measurement of QoL, confounders adjusted for and main findings. The author extracted data independently.

Quality Assessment

The quality of the studies were rated using the adapted Newcastle Ottawa Scale (NOS) for cross-sectional studies (Wells et al, 2000) (see Appendix 1). It was developed to assess the quality of design and content of non-randomised studies for systematic literature review results in an efficient way. A quality score is calculated based on three major components: (1) selection of the groups of study, (2) comparability, (3) assessment of the outcome or exposure. A 'star system' is used to judge the three broad categories on a scale from 0 (poorest quality) to 9 (highest quality). In this review, the studies were classified into groups based on cut off scores which have been used in previous research that used the NOS to rate methodological quality (Backhaus et al, 2014). The categories included poor (less than 3 stars), adequate (4–7 stars), or high (8–9 stars) quality (see Table 3 for quality scores).

Classification of QoL studies in specific areas

It was necessary to classify studies in accordance with the different components of QoL to usefully compare the studies included in the review. Studies assessing perceived QoL within an MCI population comprised the first category. Additionally, studies were divided into two further categories that related to the specific components that contribute to perceived QoL in line with research; psychological well-being (i.e. mood, positive and negative affect) and social relationships (Albert et al, 1996; Brod et al, 1999; Weiner et al, 2000; Burgener & Twigg, 2002; Logsdon et al, 2002; Ready et al, 2004). The review did also consider in less depth other components of QoL that were assessed in specific QoL measures (e.g. QoL-AD) such as physical health, self-efficacy.

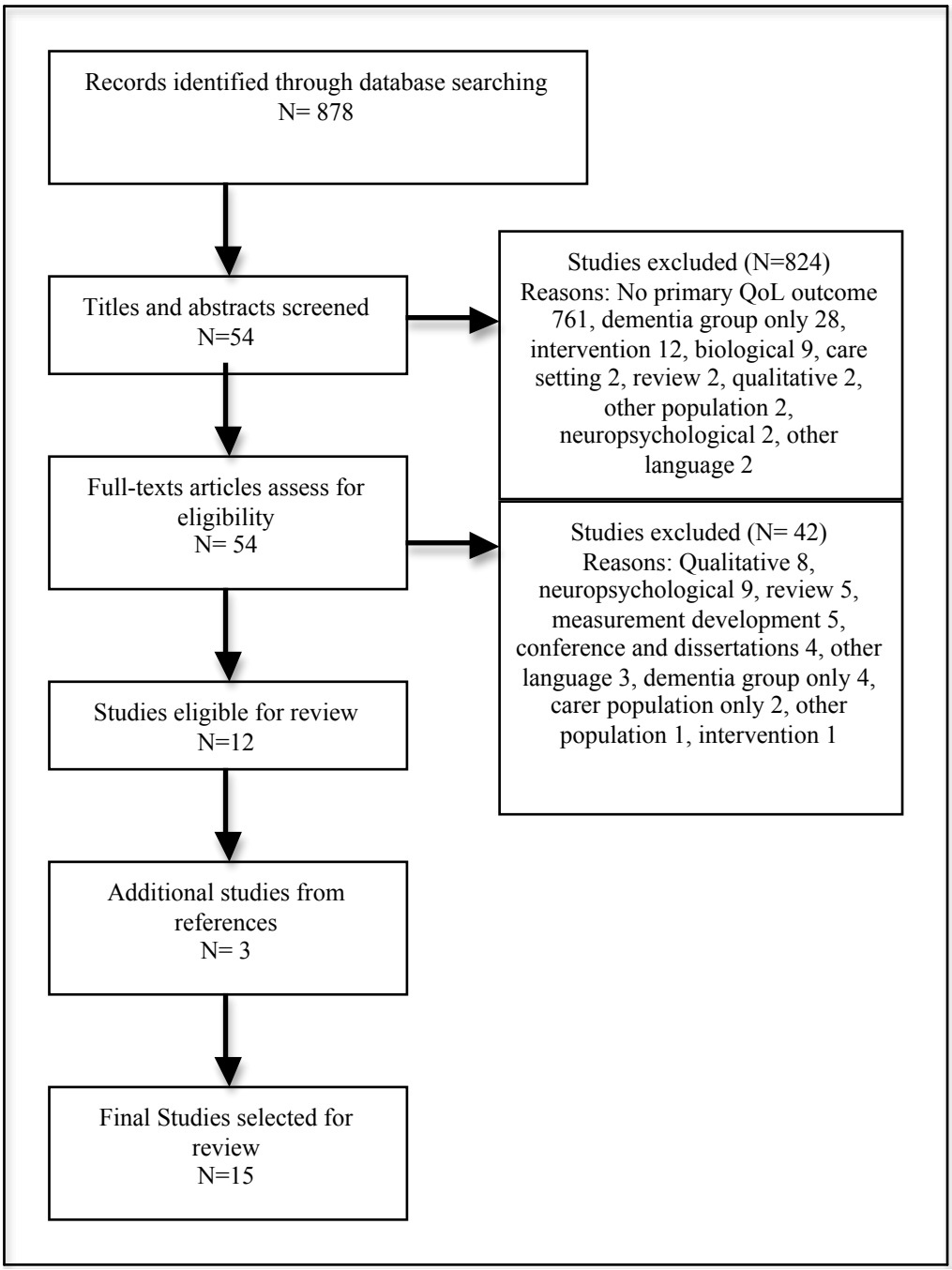
Potential predictors of QoL components were also identified and catergorised into 3 categories based on Pearson's correlation co-efficient strength (Taylor, 1990). Correlations were therefore classified accordingly: weak (+/- 0.2 to 0.29), moderate (+/- 0.3 and 0.39), strong (above +/- 0.4). Correlations below 0.2 were classified as no relationship and therefore were not considered possible predictors.

RESULTS

Overview of results

A total of 878 articles were identified from the database search. The final review included 15 studies; the database search yielded 12 studies with a further 3 studies identified from reference lists. The remaining studies were excluded because they were unrelated to the QoL topic being reviewed (761) or investigated QoL exclusively within a dementia population (31) as well as other clinical populations (4). In addition, studies were excluded if they included exclusively carer's perspective (2) or were conducted in acute care settings (2). Neuropsychological (19), biological (9) and treatment (13) studies concerned with MCI and/or QoL were also excluded from the review. Furthermore, studies concerned with QoL measure development and validation were also excluded even if involving an MCI population (5). The remaining studies were either not published in English (5), were dissertation or conference papers (4) or did not include original data i.e. review articles, book chapters or case studies (5). No studies were excluded due to study design (see figure 1 for overview of review process). The studies were conducted across a variety of different countries within Europe, USA and South East Asia (see table 3).

Figure 1: ***Flow chart of review process***



Study design and quality

Fifteen cross-sectional studies were included in the review. According to the NOS criteria, 9 studies were rated as adequate quality and 6 studies were rated as poor quality (see Table 3). Cross-sectional studies are susceptible to bias due to comparison of different population groups at a single point in time without manipulation of variables. It is therefore

essential to reduce error by including comparison groups, controlling for potential confounding variables and having a large representative sample (Miller, 1998). Thirteen studies utilised a comparison group design including a control group and/or a dementia group and only one included solely an MCI group (Garand et al, 2007). The studies recruited participants from a range of clinical (i.e. memory services, health units) and/or community settings (see table 3). Control for confounding variables across the studies was mixed with only 3 studies matching control groups on age, gender and education years (Teng et al, 2007; Clement et al, 2009; Shin et al, 2012). All studies conducted statistical comparisons between demographics variables, however, only 2 out of 4 studies statistically adjusted for variable differences when found (Fujiwara et al, 2013; Momtaz, Hamid & Ibrahim, 2013). None of the studies specifically accounted for the sample size by describing an appropriate power analysis and only 5 studies provided descriptions of non-responders (Fujiwara et al, 2013; Momtaz, Hamid & Ibrahim, 2013; St John & Montgomery, 2010; Shin et al, 2012; Muangpaisan, Intalapaporn & Assantachai, 2008).

Outcome measures

The studies included in this review used several different instruments for QoL assessment (see table 1). The majority of studies employed self-report measures specifically designed to obtain patient ratings of perceived QoL. Five studies used measures that incorporated caregiver ratings of QoL (Teng et al, 2012; Barrios et al, 2013; Muangpaisan et al, 2008; Maki et al, 2014; Ready et al, 2004; Lapid et al, 2011). None of the scales were specifically designed for use with people with MCI but had all been used previously with dementia populations. All of the specific QoL measures provided sub ratings of individual QoL domains (see Table 1).

Five studies employed validated self-report measures that assessed the individual components of QoL i.e. social relationships or psychological well-being (Muangpaisan,

Intalapaporn and Assantachai, 2008; Clement et al, 2009; Wettstein et al, 2014; Shin et al, 2012; St John and Montgomery, 2010; Garand et al, 2007). Only one study used direct self-report of sexual functioning instead of a validated scale (Momtaz, Hamid & Ibrahim, 2013). However, the majority of measures used where not specifically designed for use with older people with cognitive impairment.

A variety of standardized measures and neuropsychological tests were also used in all the studies to control for confounding variables such as depression, ADLs and cognitive function (see table 3).

MCI classification

There was variation in the methods used to categorise MCI and as a result the criteria used to define it. Ten studies employed a range of diagnostic criteria to define MCI that included the criterion of presence of an objective impairment, subjective complaint and preserved or slight impairment to ADLs (see table 2). Four of the studies used solely neuropsychological cut-off scores to define MCI using a range of cognitive assessment tools and cut off thresholds (see table 2). Only one study did not describe how the MCI group was characterised (Lapid et al, 2011). Four studies made distinctions between MCI subtypes i.e. amnestic MCI vs. non-amnestic MCI either focusing on making group comparisons (Garand et al, 2007; Fujiwara et al, 2013) or focusing on amnestic MCI (Barrios et al, 2013; Clement et al, 2009; Muangpaisan, Intalaporn & Assantachai, 2008) (see table 2). One study compared the modified single domain amnestic to the multiple domains (Clement et al, 2009). Making a distinction between MCI subtypes may be valuable and offer prognostic information, as there is preliminary evidence that amnestic MCI patients may more commonly convert to AD (De Carli et al, 2003).

Table 1: ***Description of specific QoL measures and sub-components***

QoL Measure	Study	Components

QoL-AD	Teng et al, 2012 Barrios et al, 2013	Perceived QoL Behavioural competence Psychological status Interpersonal environment Physical functioning
SDL	Maki et al, 2014	Physical function, Home life, Social life Work life Personal development/Fulfilment Recreation Material well-being
D-QoL	Ready et al, 2004	Perceived QoL Positive affect Negative affect Feelings of belonging Self esteem Sense of aesthetics
ADRQL	Missotten et al, 2008	Social Interaction Awareness of Self Feelings and Mood Enjoyment of Activities Response to Surroundings
WHOQOL-BREF	Muangpaisan et al, 2008	Physical health Psychological health Social relationships Environmental relationships
LASA	Lapid et al, 2011	Physical well-being Emotional state Faith Religious involvement Intellectual state Social interactions Pain frequency Pain intensity Coping ability

QOL-AD- Quality of Life in Alzheimer's Disease Scale, SDL- Satisfaction with Daily Life Scale, WHOQOL-BREF- WHO Quality of Life-BREF, DQOL- Dementia Quality of Life Scale, ADRQL- Alzheimer's Disease Related Quality of Life, LASA- Linear Analog Scale Assessment

There was also variation in depth of assessment methods used to measure MCI diagnostic criteria. Six studies incorporated extensive clinical assessments, neurological and neuropsychological assessments (Wettstein et al, 2014; Teng et al, 2012; Clement et al, 2009; Barrios et al, 2013; Garand et al, 2007; Clement et al, 2009), with one study conducting brain imaging (Barrios et al, 2013). Only 7 studies described exclusion criteria, which included factors such as depression, substance misuse and other neurological disorder

that may have independently impacted QoL (see Table 2).

Table 2: ***Descriptions of tools and criteria used in the studies to categorise MCI***

	Tests	MCI criteria				MCI subtypes			Excluded groups
Study		Objective complaint*	Subjective complaint	ADL*	Definition of MCI	MCI	AMCI	naMCI	
Teng et al, 2012	CERAD; IADL	✓	✓	✓	Original Petersen criteria	+			Other neurologic disorders, alcohol or substance abuse, institutionalised
Barrios et al, 2013	WMS; IADL	✓	✓	✓	European Consortium on AD		+		Alcohol/substance abuse, other neurological/psychiatric/medical disorders, major depressive episode (>10 on GDS), and education less than 4 years
Maki et al 2014	MMSE	✓	✓	×	International working group criteria	+			Not described
Missotten et al, 2008	MMSE; CAMCOG; IADL	✓	×	✓	Original Petersen criteria	+			Not described
Ready et al, 2004	MMSE; CERAD; IADL	✓	✓	✓	Modified Petersen criteria	+			Other neurologic disorders in past 2 yrs, alcohol or substance abuse, institutionalised
St John & Montgomery, 2010	3MS; OARS	✓	×	✓	3MS < 78	+			Not described

Wettstein et al, 2014	CERAD CAMCOG-R	✓	✓	✓	International working group criteria	+	Diagnosis of dementia, severe psychiatric disorders, sensory deficits affecting mobility, sever somatic illness, use of prescription drugs affecting cognition
Muangpaisan, Intalaporn & Assantachai, 2008	TMSE IADL	✓	✓	✓	Modified Petersen criteria	+	TMSE < 24, major depression, other psychiatric disorders diagnosed with DSM-IV, taking psychotropic drugs that affect cognition

* *Cognitive impairment generally implies performance >1.5 SD below AEAS on standard cognitive tests* * *ADLs either intact or slight impairment*

CERAD- Consortium to Establish A Registry of Alzheimer's Disease, IADL- Instrumental Activities of Daily Living Scale, WMS- Wechsler Memory scale, MMSE- Mini Mental State Examination, CAMCOG-R- Cambridge Examination for Mental Disorders of the Elderly, 3MS- The Modified Mini-Mental State Test, OARS- Older Americans Resources and Services, TMSE- Thai Mini Mental State Examination, HHIES-The Hearing Handicap Inventory for Elderly-Screening, ROILs- Record of Independent Living, DRS- Disability Rating Scale, MOCA- The Montreal Cognitive Assessment, MDRS- Mattis Dementia Rating Scale, SMAF- The Functional Autonomy Measurement System, MOCA-J- The Montreal Cognitive Assessment: Japanese Version.

Impact on QoL

Perceived QoL

The review identified 7 studies that directly measured the impact MCI has on perceived QoL compared to cognitively healthy controls with 3 studies also incorporating a dementia comparison group (see Table 3). The synthesis of the studies yielded mixed findings relating to the differences between perceived QoL within MCI compared to cognitively healthy controls. Two studies found a decrease in MCI self ratings of perceived QoL compared to cognitively healthy controls (Teng et al, 2012; Barrios et al, 2013). However, both studies were rated as poor in quality with selected clinical based samples, unjustified sample sizes and limited control for confounding variables. Conversely, five studies found no significant differences between MCI self ratings of perceived QoL and cognitively healthy control ratings (Muangpaisan et al, 2008; Maki et al, 2014; Ready et al, 2004; Missotten et al, 2008; Lapid et al, 2011). The quality of this evidence ranged from poor (Ready et al, 2004; Missotten et al, 2008; Lapid et al, 2011) to adequate (Muangpaisan et al, 2008; Maki et al, 2014). The poorer rated studies included highly unrepresentative clinical samples (i.e. frail participants in institutions; Missotten et al, 2008), limited control for other confounding factors as well as unjustified and insufficient sample sizes reducing generalisability and increasing bias.

Three of these studies also included a dementia comparison group. Two studies found no differences between self-rated perceived QoL for MCI and dementia groups (Ready et al, 2004; Lapid et al, 2011). One study found that MCI participants gave significantly higher rating of perceived QoL compared to the dementia group (Missotten et al, 2008). However, these studies had variability within the selected samples including exclusively participants above 90 years (Lapid et al, 2011), advanced dementia (Missotten et al, 2008) and mild dementia (Ready et al, 2004). This may have contributed to the differences in findings. None

of the studies analysed differences in perceived QoL ratings between the different MCI subtypes i.e. amnestic vs. non-amnestic MCI.

Psychological Well-being

Eight studies explored psychological well-being within an MCI population (see Table 3). These studies looked at a variety of mood related symptoms including depression, positive and negative affect, and anxiety. Four studies employed specific QoL measures with sub-components assessing aspects of psychological well-being whereas 4 studies used measures that assessed specific aspects of psychological well-being exclusively such as a mood scale. The study findings have been categorised and evaluated based on the areas of psychological well-being assessed. There were a number of studies that assessed multiple aspects of psychological well-being and have therefore been discussed separately in each section.

Depression

Three studies examined depression using specific QoL measures with an associated component. Two of the studies found a decrease in MCI self ratings for mood compared to cognitively healthy controls using to QoL-AD scale (Teng et al, 2012; Barrios et al, 2013). One study found no significant difference between MCI participants and cognitively healthy controls on the feelings/mood component of the ADRQL (Missotten et al, 2008). However, all 3 of these studies were rated as poor in quality due to unrepresentative and unjustified sample sizes as well as limited control for confounding variables.

Using independent measures of depression, Shin et al (2012) found adequate quality evidence that depression levels did not significantly differ between the MCI participants and cognitively healthy controls that were matched on age, gender, education and IADLs. Strengths of this study included use of a validated measure of depression designed for a geriatric population (GDS) as well as a large, community based sample and controlling for a

large variety of socio-demographic factors. Muangpaisan, Intalapaporn and Assantachai (2008) also found adequate evidence that MCI participants did not differ significantly in depression subscale scores using a neuropsychiatric symptom scale. However, the study only controlled for a limited number of confounding factors (i.e. age) and had uneven sample sizes across the two groups thus reducing the validity of finding.

Table 3: ***Descriptions of studies exploring QoL in MCI***

Study	Study quality	N	Sample	Informant ratings?	Age and education controlled	QoL Scale	Analysis	Results- QoL Components
Teng et al 2012	3	**MCI** *Memory service* 108 **Aged/education matched Controls** *Community* 97 USA	**Age (yrs)** MCI 72 Control 70.1 **Gender (%males)** MCI 43.5 Control 53.6 **Education Level (yrs)** MCI 15.9 Control 16.5	✓+	✓	****** QoL-AD Administration not described.	T-tests Effect sizes Correlations	✓ Perceived QoL ✓ Mood ✓ Memory
Barrios et al 2013	3	**MCI** *Memory service* 50 **Healthy controls** *Medical Outpatient center* 50 Portugal	**Age (yrs)** MCI 70.8 Control 66.3 **Gender (%males)** MCI 56 Control 50 **Education Level (yrs)** MCI 10.7 Control 9	✓×	×	****** QoL-AD Administration by interviewer	T-tests ANOVAs	✓ Perceived QoL ✓ Social Environment ✓ Mood

**Validated measure*
**Previously used in MCI*
Poor quality *Adequate quality*

+ Concordance in MCI self & informant & QoL ratings
× No concordance in MCI self & informant QoL ratings

✓ Significant differences in MCI & control ratings ($p<0.05$)
× No significant differences in MCI & control ratings ($p<0.05$)
✓ Significant differences in MCI & dementia ratings ($p<0.05$)
× No significant differences in MCI & dementia ratings ($p<0.05$)

Maki et al 2014	6	**MCI** *Community* 37 **Healthy controls** *Community* 120 Japan	**Age (yrs)** MCI 73.1 Control 71.9 **Gender (%males)*** MCI 46 Control 25 **Education Level (yrs)** MCI 11.5 Control 11.9	×	✓ & depression, memory complaints, self-efficacy, social environment	** SDL Administration by interviewer.	T-tests Correlations Regression	× Perceived QoL
Missotten et al, 2008	3	**MCI** *Home or residential care* 36 **Frail elderly** *Home or residential care* 72 **Dementia** *Home or residential care* 357 Belgium	**Age (yrs)** MCI 83.72 Control 79.15 Dementia 84.19 **Gender (%males)*** MCI 25 Control 30.56 Dementia 15.13 **Education Level (yrs)** MCI N/A Control N/A Dementia N/A	✓	×	** ADRQL Administer by interviewer.	T-test ANOVA Post hoc tests	×✓ Perceived QoL ✓ Social interaction ✓ Mood ✓ Enjoyment of activities ✓ Awareness of Self ✓ Response to activities

**Validated measure*
**Previously used in MCI*
Poor quality
Adequate quality
+ Concordance in MCI self & informant & QoL ratings
× No concordance in MCI self & informant QoL ratings
✓ Significant differences in MCI & control ratings ($p<0.05$)
× No significant differences in MCI & control ratings ($p<0.05$)
✓ Significant differences in MCI & dementia ratings ($p<0.05$)
× No significant differences in MCI & dementia ratings ($p<0.05$)

Ready et al, 2004	3	**MCI** *Memory Service* 30 **Elderly Controls** *Community* 23 **AD** *Memory Service* 26 USA	**Age (yrs)** MCI 77.4 Control 74.7 Dementia 78.2 **Gender (%males)** MCI Not described Control Not described Dementia Not described **Education Level (yrs)** MCI 13.2 Control 14.5 Dementia 12.4	✓+	×	** DQOL Administration by interviewer (neuropsychologists)		×× Perceived QoL ✓ Self esteem
Muangpaisan et al 2008	5	**MCI** *Community* 85 **Healthy Controls** *Community* 37 Thailand	**Age (yrs)** MCI 66.7 Control 63.9 **Gender (%males)** MCI 29.4 Control 29.7 **Education Level (yrs)** MCI 6.5 Control 7.3	×	✓	** WHOQOL-BREF Administration not described.	T-test Fisher exact ANOVA Correlations	× Perceived QoL ✓ Psychological

**Validated measure*
**Previously used in MCI*
Poor quality *Adequate quality*

+ Concordance in MCI self & informant & QoL ratings
× No concordance in MCI self & informant QoL ratings

✓ Significant differences in MCI & control ratings (p<0.05)
× No significant differences in MCI & control ratings (p<0.05)
✓ Significant differences in MCI & dementia ratings (p<0.05)
× No significant differences in MCI & dementia ratings (p<0.05)

Lapid et al, 2011	3	**MCI** *Community* 13 **Healthy Controls** *Community* 56 **Dementia** *Community* 41 **DEMSP** *Community* 34 USA	**Age** MCI 93.9 Control 93.3 Dementia 94.2 DEMSP 94.1 **Gender (%males)** MCI 88 Control 51 Dementia 63 DEMSP 73 **Education Level (yrs)** MCI 12.8 Control 13.73 Dementia 12.3 DEMSP 12.4	✓+	×	** LASA Self-completed	Fisher exact Correlations	×× Perceived QoL ✓✓ Physical well-being ✓✓ Intellectual Well-being ✓✓ Pain frequency ✓✓ coping with stress ability
Shin et al, 2012	5	**MCI** *Community Health Unit* 81 **Controls** *Community Health Unit* 81 Korea	**Age** MCI 71.2 Control 71.2 **Gender** MCI N/A Control N/A **Education Level** MCI 7.9 Control 7.8	N/A	✓ Matched controls & IADLs	** GDS	T-tests Regression	✓ Depression

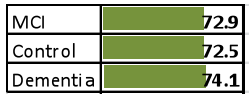
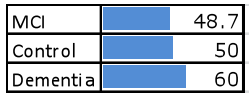
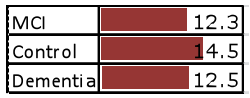
**Validated measure* + *Concordance in MCI self & informant & QoL ratings* ✓ *Significant differences in MCI & control ratings ($p<0.05$)*

**Previously used in MCI* × *No concordance in MCI self & informant QoL ratings* × *No significant differences in MCI & control ratings ($p<0.05$)*

✓ *Significant differences in MCI & dementia ratings ($p<0.05$)*

× *No significant differences in MCI & dementia ratings ($p<0.05$)*

Poor quality *Adequate quality*

Clement et al, 2009	**4**	**MCI** *Memory service* 30 **Controls** *Community* 27 France	**Descriptive statistics not described.**	**N/A**	✓ Matched controls & social functioning, physical health	****** PSI PGC-S	ANOVAs ANCOVAs MANCOVAs Correlations	✓ Depression ✓ Morale ✓ Anxiety ✓ Hostility
Wettstein et al, 2014	**3**	**MCI** *Memory clinic* 76 **Controls** *Community* 146 **AD** *Memory clinic* 35 Germany and Israel	**Age**  **Gender**  **Education Level** 	**N/A**	✓ **(education only)** & country	****** GDS ****** PANAS	ANCOVA MANCOVA Effect sizes	✓✓ Positive affect ✓ Negative affect

**Validated measure*
**Previously used in MCI*
Poor quality
Adequate quality

+ Concordance in MCI self & informant & QoL ratings
✘ No concordance in MCI self & informant QoL ratings

✓ Significant differences in MCI & control ratings (p<0.05)
✘ No significant differences in MCI & control ratings (p<0.05)
✓ Significant differences in MCI & dementia ratings (p<0.05)
✘ No significant differences in MCI & dementia ratings (p<0.05)

Fujiwara et al, 2013	**6**	**MCI** *Community* 315 **Controls** *Community* 496 Japan	**Age** MCI 71.8 Control 76.9 **Gender** MCI 64.2 Control 30 **Education Level** MCI 10.6 Control 12.6	**N/A**	✓ & gender	Self rated	Chi-square Fisher Exact Regression	✓ Depression
Muangpaisan, Intalapaporn and Assantachai, 2008	**5**	**MCI** *Community health unit* 77 **Controls** *Community health unit* 30 Thailand	**Age** MCI 66.3 Control 63.7 **Gender** MCI 35 Control 25 **Education Level** MCI 6.1 Control 6.7	**N/A**	×	****** NPI	T-tests Fisher exacts Chi Square Regression	✓ Anxiety ✓ Apathy ✓ Dsyphoria

*****Validated measure*
*****Previously used in MCI*
Poor quality
Adequate quality

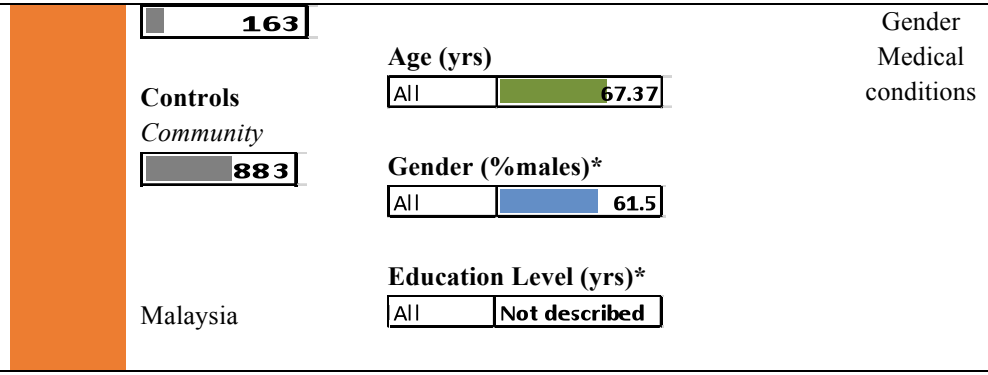
+ Concordance in MCI self & informant & QoL ratings
× No concordance in MCI self & informant QoL ratings

✓ Significant differences in MCI & control ratings ($p<0.05$)
× No significant differences in MCI & control ratings ($p<0.05$)
✓ Significant differences in MCI & dementia ratings ($p<0.05$)
× No significant differences in MCI & dementia ratings ($p<0.05$)

St John &	**5**	**MCI**	**Age (yrs)**	×	✓	*	T-test	✓ Social LS

Montgomery, 2010		*Community* 94 **Healthy controls** *Community* 1468 **Dementia** *Community* 58 Canada	MCI 80.3 Control 75.4 Dementia 82.9 **Gender (%males)*** MCI 57.4 Control 40 Dementia 39.7 **Education Level (yrs)*** MCI 6.1 Control 9.8 Dementia 6.8		& depression gender functional impairment	TDS Administered by interviewer.	ANOVA	
Garand et al, 2007	**4**	**MCI** *Research centre* 27 **USA**	**Age (yrs)** MCI 70.7 **Gender (%males)*** MCI 14.8 **Education Level (yrs)*** MCI 21	×	✓ & caregiver distress	* DAS	Correlations Regression	Marital Quality (see table 3)
Momtaz et al, 2013	**6**	**MCI** *Community*	**Descriptive statistics not described for each group.**	×	✓ &	Self report	Regressions	✓ Sexual activity

**Validated measure*
**Previously used in MCI*
Poor quality
Adequate quality
+ Concordance in MCI self & informant & QoL ratings
× No concordance in MCI self & informant QoL ratings
✓ Significant differences in MCI & control ratings (p<0.05)
× No significant differences in MCI & control ratings (p<0.05)
✓ Significant differences in MCI & dementia ratings (p<0.05)
× No significant differences in MCI & dementia ratings (p<0.05)



*Validated measure
*Previously used in MCI

+ Concordance in MCI self & informant & QoL ratings
✘ No concordance in MCI self & informant QoL ratings

✓ Significant differences in MCI & control ratings ($p<0.05$)
✘ No significant differences in MCI & control ratings ($p<0.05$)
✓ Significant differences in MCI & dementia ratings ($p<0.05$)
✘ No significant differences in MCI & dementia ratings ($p<0.05$)

Poor quality Adequate quality

DAS- dynamic adjustment scale; TDS- Terrible Delightful Scale, NPI- Neuropsychiatric Inventory, PANAS- Positive and Negative Affect Scale, GDS- Geriatric Depression, PSI- Psychiatric Symptom Index, PGC-MS- revised Philadelphia Geriatric Center Morale Scale, LASA- Linear Analog Scale Assessment, WHOQOL-BREF- WHO Quality of Life-BREF, DQOL- Dementia Quality of Life Scale, ADRQL- Alzheimer's Disease Related Quality of LIfe , SDL- Satisfaction with Daily Life Scale, QOL-AD- Quality of Life in Alzheimer's Disease Scale

Another study found an increase in depressive symptoms for MCI participants compared to cognitively healthy controls but with small effect sizes (Wettistein et al, 2014). There were no differences in depression levels between MCI and AD participants. However, the quality of the findings were rated as poor due to selection and comparability issues. This study also included a longitudinal analysis finding that depression declined over time in MCI participants and cognitively healthy controls but increased in AD participants. However, these finding must be interpreted with significant caution due to very small sample sizes. Conversely, another study found more adequate evidence that MCI participants had significantly higher levels of depression compared to cognitively healthy controls (Clement et al, 2009). However, it is important to note that this study was conducted in a clinical setting making it less representative and conducted a high number of statistical comparisons that may have introduced error.

Positive and negative affect

Two studies looked specifically at positive and negative affect, with one study using a general QoL measure with an associated sub-component (Ready et al, 2004) and the other using a specific affect scale (Wettstein et al, 2014). The studies found conflicting evidence, however, both were rated poor in quality due to lack of control for confounding variables, clinical samples and significant differences in demographics across the groups. Ready et al (2004) found no significant differences between MCI participants and cognitively healthy control ratings of positive and negative affect using DQOL. Wettstein et al (2014) found that MCI participants reported less positive affect than cognitively healthy controls but these group differences were of small effect sizes. Furthermore, Wettstein and colleagues included a dementia comparison group but found no differences across the two groups in affect. A longitudinal analysis found that positive affect increased for all groups over time but that negative affect increased in the MCI group only. However, these longitudinal findings must be interpreted with significant caution due to a small sample size. Two further studies explored specific negative and positive affect symptoms, and found adequate evidence for higher anxiety, dsyphoria, hostility and irritability (Muangpaisan,

Intalapaporn & Assantachai, 2008; Clement et al, 2009) and lower morale (Clement, 2009) in MCI participants compared with elderly controls.

Four studies also looked at enjoyment of life, a specific aspect of positive affect, using a variety of measures (Barrios et al, 2004; St John & Montgomery, 2010; Missotten et al, 2008; Ready et al; 2004) (see Table 3). Barrios et al (2013) found decreases in MCI reports on the ability to enjoy themselves component of the QoL-AD scale. Two further studies found no significant differences between MCI participants and controls on the life enjoyment components of ADRQL (Missotten et al, 2008) and D-QOL; Ready et al, 2004). St John and Montgomery (2010) found that MCI participants rated significantly lower satisfaction with life than controls. The quality of this study was adequate but had significant weakness due to measure selection and discrepancies in demographics and sizes of the group samples. Two studies also included a comparison with a dementia group with both finding no significant differences in life enjoyment between MCI and people with dementia (St John & Montgomery, 2010) and AD (Ready et al, 2004).

Social relationships

Seven studies investigated different aspects of social functioning and how they are affected in MCI participants compared to cognitively healthy controls and/or dementia participants (see Table 3). Most of the studies used a range of validated self-report measures, which either measured QoL with a social component or measured a specific aspect of social relationships. St John and Montgomery (2010) found poor quality evidence that social satisfaction was lower in MCI participants than cognitively healthy controls but with no significant differences between MCI and AD participants. However, this study did not control for significant demographic discrepancies between the groups and used a measure not validated with an older adult population. Barrios et al (2013) also found that MCI participants reported a decrease in the quality of social relationships using the QoL-AD but was considered poor evidence due to issues with sample selection and comparability of the data.

Two further studies also using the QoL-AD found no significant differences between MCI participants and cognitively healthy controls on the social relationship domain (Teng et al, 2012; Muangpaisan et al, 2008). Two other studies also found no significant differences on the social interaction component of ADRQL (Missotten et al, 2008) and social life component of SDL (Maki et al, 2014).

The quality of these studies ranged from poor (Teng et al, 2012; Missotten et al, 2008) to adequate (Muangpaisan et al, 2008; Maki et al, 2014). The higher quality studies used a more representative sample from the community compared to clinical services used in the other two studies and therefore can be perceived as more generalisable.

Two studies looked specifically at aspects of social relationships that are impacted by MCI; marital quality (Garrand et al, 2007) and sexual activity (Momtaz, Hamid & Ibrahim, 2013). Garrand et al (2007) found that lower marital satisfaction was significantly related to MCI-related behaviours such as repeated questioning, remembering recent events, less communication and anger. However, the lack of a comparison group and an unrepresentative sample of educated, Caucasian women from a clinical population meant the study only provided adequate evidence. Momtaz, Hamid & Ibrahim (2013) found that people with MCI were less likely to have sex than cognitive healthy controls. However, these finding are poor in quality due to lack of confound control and weak outcome measurement i.e. self-report.

Other QoL components

Seven studies using specifically designed QoL measurements also assessed other components related to QoL (see Table 3). Only four studies found significant differences between MCI participants, cognitively healthy controls and/or dementia on particular components. In comparison to cognitively normal controls two studies found reduced memory in MCI participants (Teng et al, 2012; Barrios et al; 2013). Another study found MCI participants endorsed better physical and intellectual well-being, pain frequency and ability to cope with stress

in comparison to cognitively healthy controls and dementia participants (Lapid et al, 2011). Furthermore, significant differences were found between MCI and dementia participants on other components of QoL including response to activities, awareness of self (Missotten et al, 2008) and self-esteem (Ready et al, 2004). However, it is worth emphasising that all of these studies were rated as poor in quality with weaknesses that impact both the validity and reliability of the findings. No significant differences were found on components relating to physical health and functioning, the behavioural component, home and work life, recreation, material well-being, personal fulfilment or environmental relationships.

Informant vs. self QoL ratings

Five studies used measures that also incorporated informant perspectives of perceived QoL (Ready et al, 2004; Teng et al, 2012; Barrios et al, 2013; Lapid et al, 2011) but one study did not analyse informant data (Missotten et al, 2008). All 4 studies explored concordance between self and informant ratings of perceived QoL within each group (i.e. MCI, dementia, control). Two studies found significant agreement between MCI informants and self ratings of perceived QoL (Ready et al, 2004; Lapid et al, 2011). One study found a positive correlation between perceived QoL ratings but this did not reach statistical significance and no differences were found between the mean perceived QoL scores (Teng et al, 2012). Furthermore, there were no differences found between amnestic MCI and non-amnestic MCI informant ratings of perceived QoL (Teng et al, 2012). A third study found that MCI participants rated perceived QoL significantly more favourably than informants (Barrios et al, 2013). On analysing informant and self ratings on individual QoL components one study found that MCI participants were more favourable than their informants on ratings of family, ability to do house chores, self as a whole & life as a whole.

Three studies also compared MCI informant ratings against the informant comparison groups i.e. control or dementia. Two studies found that MCI informants reported significantly lower perceived QoL compared to cognitively healthy control informants (Teng et al, 2012; Barrios et al, 2013). More specifically, one study also found significant impairment on informant ratings

for specific QoL sub-components informants such as mood, ability to enjoy activities, life as a whole and memory (Teng et al, 2012). Conversely, one study found no differences between the MCI and cognitively healthy control informant ratings of perceived QoL or individual QoL components (Ready et al, 2004). However, the authors found that AD informants reported significantly lower perceived QoL and self esteem than MCI informants. Only one study explored potential predictors of informant ratings of perceived QoL and found that reduced QoL was associated with decreased functional abilities, higher levels of depression and greater neuropsychiatric symptoms (Teng et al, 2012). However, it is important to note that all 4 studies had significant weaknesses in their design that affects the quality of these findings and reduces the inferences that can be drawn.

Predictors of QoL

A number of the studies investigated factors that determine the impact of MCI on perceived QoL and specific QoL components. Five studies explored a variety of factors that influence perceived QoL and could be considered potential predictors (see Table 4; Teng et al, 2012; Maki et al, 2013; Muangpaisan et al, 2008; Barrios et al, 2013; Lapid et al, 2011). Four studies found higher levels of depression were associated with reductions in QoL for MCI participants using the GDS and these correlations were categorised as strong (Teng et al, 2012; Maki et al, 2013; Muangpaisan et al, 2008; Barrios et al, 2013). Furthermore, using regression analysis two studies found depression to be a significant negative predictor of perceived QoL after controlling for other demographic and cognitive factors (Maki et al, 2013; Barrios et al, 2012). Additionally, Maki et al (2014) found that greater memory complaints, reduced self-efficacy and poorer social environment were also strongly associated with a decrease in perceived QoL for MCI participants. Furthermore, QoL was found to be predicted positively by self-efficacy after controlling for depression and social environment in a regression analysis. They also found that more impaired ADLs and increased age was associated with lower perceived QoL for MCI participants, however, these correlations were much weaker. Surprisingly, only one study

demonstrated a strong association between cognitive function and perceived QoL (Lapid et al, 2011).

Three studies explored possible predictors of psychological well-being (Muangpaisan et al, 2008; Clement et al, 2009) Muangpaisan et al (2008) found a strong negative correlation between depression scores on the GDS and NPI depression subscale i.e. higher level of depression was associated with decrease in QoL for MCI participants. Clement et al (2009) found that psychological health decreased with increased cognitive impairment after controlling for age and was classified as a moderate correlation. In relation to positive affect, St John and Montgomery (2010) found that lower cognition resulted in lower life satisfaction for each group and remained consistent after controlling for age, education, depression and functional impairment in a linear regression model. Across all the groups higher life satisfaction was most strongly predicted by less depressive symptoms and less impaired functional status. Higher education and higher income security were also predictive of higher life satisfaction but to a lesser extent.

Two studies also explored predictors of quality of social relationships (St John & Montgomery, 2010; Garand et al, 2007). Using a linear regression model, St John and Montgomery (2010) found that higher social satisfaction was predicted by gender, higher education, more income security, fewer depressive symptoms, less disability and less impaired cognition. Specifically exploring quality of marital relations, Garand et al (2007) found that higher marital quality was strongly associated with a number of MCI related behaviours (i.e. anger, dependency, memory impairment). However, after controlling for age and caregiver stress using a linear regression limited communication remained the only significant predictor of marital satisfaction, cohesion and affective expression whereas repetitive questioning predicted marital satisfaction onl

Table 4: ***Correlations between potential predictors of QoL and the different QoL components***

Perceived QoL												
Study	Study Quality	Depression	Memory Complaint	IADL	Age	Social environment	Self efficacy	Cognitive function	Education	Income	Gender	MCI specific behaviour
Teng et al, 2012	3	↓		X	X			X	X			
Maki et al, 2014	6	↓ **	↓ **	↑	↓	↑	↑ **	X				
Muangpaisan et al, 2008	5	↓				X		X				
Lapid et al, 2011	3	X						↓				
Psychological wellbeing												
Study	Study Quality	Depression	Memory Complaint	IADL	Age	Social environment	Self efficacy	Cognitive function	Education	Income	Gender	MCI specific behaviour
Clement et al, 2009	4							↓ *				
Muangpaisan et al, 2008	5	↓						X				
Social relationships												
Study	Study Quality	Depression	Memory Complaint	IADL	Age	Social environment	Self efficacy	Cognitive function	Education	Income	Gender	MCI specific behaviour
St John and Montogomery, 2010	5	↓		↓				↑	↑	↑	↑	
Garand et al, 2007	4											↑
Life enjoyment												
Study	Study Quality	Depression	Memory Complaint	IADL	Age	Social environment	Self efficacy	Cognitive function	Education	Income	Gender	MCI specific behaviour
St John and Montogomery, 2010	5			↓	X			↑	↑			

* *Controlled for SE* * *Controlled for depression* **Controlled for memory complaint* *X = no significant correlation mean*

↓ *= Strong negative correlation* ↓ *= Moderate negative correlation* ↓ *= Weak negative correlation* *poor*

↑ *= Strong positive correlation* ↑ *= Moderate positive correlation* ↑ *= Weak positive correlation* *adequate*

DISCUSSION

Summary of findings

This review evaluated studies exploring QoL within an MCI population that took place across different countries and employed a range of specifically designed QoL measures. All of the studies are cross-sectional in design and recruited samples from many settings i.e. clinical memory services to community dwellers. A range of diagnostic criteria has also been used to define MCI. The main findings from the review have been summarised below.

Impact on perceived QoL

The evidence regarding the impact of MCI on patients' self-perceived QoL is inconclusive due to a lack of good quality studies. The majority of the evidence indicated that people with MCI do not view their QoL as affected compared to those without cognitive impairment or dementia (Muangpaisan et al, 2008; Maki et al, 2014; Ready et al, 2004; Missotten et al, 2008; Lapid et al, 2011). Only poor quality evidence demonstrated a reduction in perceived QoL for people with MCI compared to those who are cognitively healthy or those with dementia (Teng et al, 2012; Barrios et al, 2013). These findings were somewhat surprising given findings obtained in other reviews that MCI presents a number of emotional and practical challenges (Dean & Wilcock, 2012). However, heterogeneity across the sample populations (i.e. from community dwellers to frail institionalised elderly) along with unjustified sample sizes make comparisons across the studies difficult thus limiting conclusions drawn and may have contributed to the conflicting findings.

Impact on psychological well-being

Attempts to define the core components that comprise QoL are in agreement that conceptually psychological well-being plays an essential role (Lawton et al, 1991). The studies explored a variety of aspects of psychological well-being i.e. depression, positive affect and negative affect

but in general yielded inconsistent and poor quality findings. There was adequate evidence that depression was higher in MCI participants compared with cognitively healthy controls (Teng et al, 2012; Barrios et al, 2013; Wettistein et al, 2014; Clement et al, 2009). However, the studies included clinical samples where baseline of depression or distress relating to cognitive symptoms maybe higher illustrated in the need to seek out support services. Evidence from community-based studies indicated no difference in depression and was deemed adequate in quality (Shin et al, 2012; Muangpaisan, Intalapaporn & Assantachai, 2008). There was also somewhat adequate evidence for higher levels of anxiety, dsyphoria, hostility irritability and lower morale in MCI population (Clement et al, 2009; Muangpaisan, Intalapaporn & Assantachai, 2008). Evidence exploring differences between MCI and dementia patients in aspects of psychological well-being was limited and poor in quality thus not making it possible to draw conclusions.

Impact on social relationships

Another important component of QoL indicated by previous studies is the quality of social relationships (Lawton, 1991). The review again yielded conflicting findings across studies regarding the impact MCI has on social relationships. Most evidence demonstrated a decrease in social satisfaction (St John & Montgomery, 2010) and relationships (Muangpaisan et al, 2008; Teng et al, 2012; Missotten et al, 2008) compared to cognitively healthy controls. However, this evidence was poor with limited control for confounding variables and use of clinically unrepresentative samples. More consistent evidence indicated that MCI might present an issue within spousal relationships with reduction in marital quality related to MCI specific behaviours (Garand et al, 2007) and a reduction in sexual activity (Momtaz, Hamid & Ibrahim, 2013). Evidence comparing MCI and dementia was limited and poor in quality thus no firm conclusion can be drawn.

Impact on other QoL components

The review provided evidence for other areas of QoL that appeared to be impacted by MCI

including memory (Teng et al, 2012; Barrios et al, 2013), self-esteem (Ready et al, 2008), awareness and responsive to environment (Missotten et al, 2008), physical and intellectual well-being, experiences of pain and ability to cope with stress (Lapid et al, 2011) compared to people with healthy cognition and/or different types of dementia. No studies were identified that specifically investigated these components with independent methods and this evidence was deemed poor in quality with poor validity and reliability thus firm conclusions could not be drawn.

Informant ratings

There was poor and inconsistent evidence regarding the concordance with MCI participants and their informants QoL report making it not possible to draw conclusions (Teng et al, 2012; Barrios et al, 2013). The evidence comparing MCI and cognitively healthy informants was more consistent with the majority of studies demonstrating less favourable reports of perceived QoL, mood, life enjoyment and memory for MCI informants (Teng et al, 2012; Barrios et al, 2013). However, poor methodological issues (see below) greatly reduced the validity and reliability of these findings and firm conclusions could not be drawn. There was limited evidence comparing with dementia informants with only one study indicating better perceived QoL and self-esteem for MCI informants (Ready et al, 2004).

Predictors of QoL

There was consistent evidence indicating depression as a significantly strong predictor of reduced perceived QoL, psychological well-being and social relationships in MCI (Barrios et al, 2013; Teng et al, 2012; Maki et al, 2013; Muangpaisan et al, 2008; St John & Montgomery, 2010; Clement et al, 2009; Garand et al, 2007). Memory complaints, self-efficacy, social environment and cognitive functioning also strongly predicted MCI impact on perceived QoL (Maki et al, 2013; Lapid et al, 2011). There was good evidence of level of cognitive impairment as a predictor of psychological well-being and social relationships (Muangpaisan et al, 2008; Clement et al, 2009; St John & Montgomery, 2010). Meanwhile, there was weaker evidence for

gender, age, education, income security, disability and MCI specific behaviours as predictors of the impact MCI has on different components of QoLs but most commonly marital relationships (Garand et al, 2007).

Methodological and conceptual l issues

A number of methodological issues across the studies limit the conclusions that can be made from this review. Firstly, the cross-sectional nature of all studies does not permit causal inferences to be drawn from any of the findings. Longitudinal studies are required before firm conclusions can be drawn from the evidence regarding MCI and QoL. Secondly, comparability was an issue for many of the studies due to lack of controls for confounding variables (i.e. physical health) and a minimal number of studies using exclusion criteria. This is essential in cross sectional studies to reduce overestimates or underestimates of the true effect of a disease on an outcome. For example, a number of the studies excluded people with psychiatric disorder that may have influenced the impact on psychological well-being. Thirdly, the participants were recruited from a mixture of clinical services or community dwellers, which poses a challenge when comparing the findings, and introduces selection bias. Furthermore, the findings from the clinical samples cannot be generalized to the general population of cognitively impaired adults. Fourthly, all of the studies failed to describe a power analysis in the methods and therefore it is unknown whether the samples are powered correctly. Cross sectional studies require a high sample size to be adequately powered and therefore it can be assumed that some of these studies may be underpowered increasing the risk of a Type 2 error (Dos Santos Silva, 1999). Other frequent problems that occurred in the reviewed studies included significant discrepancies in the sample sizes across the groups, limited description of non-responders and ascertainment of exposure to risk that may have introduced further error and bias in the findings. These methodological issues across the studies may account for many of the inconsistent and conflicting findings found in this review.

There were also a number of conceptual issues that posed a problem at this review and may

have further contributed to the inconsistent results. Firstly, the studies took place across a number of different countries that have varying cultural practices in care for the elderly. For example, Asian cultures have a tendency for family focused care where western cultures tend focus on independence and indivdidualised care (Bengston et al, 2000). This may influence the extent to which QoL is impacted by MCI thus reducing the comparably of the studies findings and applicability to the UK.

Secondly, the majority of the measures used in the studies involved participants rating their own QoL enabling the possibility of capturing aspects of dementia only available to patients and therefore improve the measurement of therapeutic intervention effects (Frank et al, 2011). However, researchers have raised concerns about using patient report measures in cognitive impairment due to impairments and loss of insight interfering with accurate completion reducing the reliability and validity of study findings (Frank et al, 2011). They therefore emphase a need to incorporate informant and clinician report (Vogel et al, 2004; Farias et al, 2005). In this review, a number of studies used measures that also incorporated an informant perspective to gain a more reliable estimate of QoL and reduce bias within the findings. Additionally, these studies analysed agreement within these further increasing reliability. However, there are concerns also with the accuracy of informant reports, especially family caregivers, due to biases introduced by caregiver depression and lack of awareness of some symptoms (Arguelles et al, 2001). It would have therefore be helpful to include objective measures of QoL, however, none of studies in this review did this. Furthermore, none of the measures had been specifically designed for use with an MCI population and therefore may reduced the generalisability of the findings.

A third conceptual issue was the range of diagnostic criteria used to categorise MCI across the studies (see Table 2) that undoubtedly impacts the extent to which an MCI cohort is cognitively impaired. For example, studies using MOCA cut off scores of less than 26 will have a less cognitively impaired sample than studies using scores less than 23. This may affect the impact

MCI has on QoL inline with evidence that differences in criteria used to define MCI results in differing estimates of prevalence, incidence and conversion rates (Bischkop et al, 2002; Ritchie et al, 2001; Kumar et al, 2005). Additionally, the majority of studies failed to separate the MCI groups into the specific subtypes despite research demonstrating different possible outcomes associated with amnestic MCI and non-amnestic MCI (Petersen et al, 2014).

Furthermore, a fourth related conceptual issue adding to the heterogeneity across the samples is the varying stringency of exclusion criteria used across the studies. There were some studies that excluded participants based on a variety of factors that might have reduced cognitive functioning (e.g. psychotropic drugs) whilst other studies did not describe exclusion at all. This may have further impacted the amount to which the cohorts were cognitively impaired. It is plausible to assume that the varying exclusion criteria and lack of attention given to MCI subtypes will have resulted in more heterogeneity across the MCI groups that may have contributed to the inconsistent and conflicting findings.

Implications for future research and clinical practice

This review has found somewhat inconsistent evidence for the impact a diagnosis of MCI has on QoL. With a national priority for early diagnosis and treatment of dementia (Prince et al, 2011) the rates of referral for assessment and, hence, diagnosis of MCI is expected to increase in the UK in the coming years (Dean & Wilcock, 2012). The findings from this review, however inconsistent, have demonstrated some reduction across a variety of aspects of QoL that warrant further exploration. Further longitudinal research is needed on a large community scale that is adequately powered to yield high quality evidence concerning QoL in MCI. Previous reviews have demonstrated the negative impact a diagnosis of MCI has on emotional and practical lives of the person and those who care for them (Dean and Wilcock, 2012). A clearer understanding of how a diagnosis of MCI impacts QoL directly will enable the development of appropriate psychosocial interventions to best support the needs of this population, in line with the UK dementia strategy (Logsdon, McCurry & Teri, 2007). Furthermore, in order to fully understand

the impact on QoL, future research will need to combine qualitative work alongside use of objective and subjective measures, and find innovative ways of combining quantitative and qualitative findings (Lewin, Glenton, & Oxman, 2009).

A plausible explanation for some of the inconsistencies currently found within the literature is the shortage of specific outcome measures designed to assess QoL in an MCI population. The measures used in the majority of studies were designed to measure QoL or aspects of this within an older adult or dementia population and therefore may not be applicable to MCI were the cognitive and behavioural symptoms differ. There has been some research attempting to validate QoL measures within an MCI population (Tatsumi et al, 2011) but with an increasing emphasis on symptoms, correlates, and impact of MCI research should focus on the development of new MCI specific QoL measures. This would enable more in depth understanding of the impact and thus aid the development of clinical interventions to maximize this accordingly. However, before measures can be developed a more coherent definition of QoL in MCI is needed to aid future research. Past research has also highlighted the importance of incorporating the informant when assessing QoL in this population due to potentially limited insight arising from cognitive impairment (Whitehouse, 1999; Frank et al, 2011). In the current review only a limited amount of studies incorporated informant ratings of QoL from a close relative, mainly spousal partner, and the evidence regarding concordance in rating was conflicting (Ready et al, 2004; Teng et al, 2012; Barrios et al, 2013; Missotten et al, 2008; Lapid et al, 2011). It would therefore be beneficial to investigate this further using an objective measure of QoL as well as subjective ratings using newly designed measures to incorporate this perspective.

There was consistent evidence in the review regarding the negative impact MCI diagnosis has on social relationships and more specifically spousal relations. Authors developing interventions to maximise QoL for people with MCI should consult the literature on spousal relationships and MCI from both perspectives to understand how best to develop services to support these

relationships. Furthermore, there was also consistent evidence provided in this review regarding the predictive impact of level of depression on reducing QoL in MCI. This is in line with a significant amount of research that demonstrates QoL is intrinsically associated with low mood (Jugwirth et al, 2004; Pearman & Storandt, 2004; Wang et al, 2004). These findings demonstrate the need to integrate depression scales into assessment procedures to ascertain those at higher risk of QoL reduction following an MCI diagnosis. This would then enable interventions to reduce depression to be targeted early and potentially maximize QoL for these people and their support networks. However, these cross-sectional correlates may differ from predictors of QoL and therefore the data needs to be replicated within a longitudinal design before being interpreted with confidence (Ready et al, 2004). Meanwhile, researchers choosing to continue to investigate QoL within MCI need to firstly consider the issues of MCI diagnostic criteria and the wide variety currently used within the research field.

Conclusion

The current evidence exploring how QoL is affected within an MCI population lacks good quality studies and has yielded conflicting findings. No firm conclusions can be drawn due to a number of methodological and conceptual limitations. The inconsistencies in findings most probably reflect the heterogeneous group that MCI comprises and diversity in diagnostic criteria used. Furthermore, there are seldom measures specifically designed to assess QoL within MCI, which is important given the differences between MCI and dementia functions. There is a need for further longitudinal evidence to understand the impact a diagnosis of MCI has on QoL and thus design interventions to best support the MCI population and maximise their QoL where needed.

REFERENCES

Albert, M. S. (1996). Cognitive and neurobiologic markers of early Alzheimer disease. *Proceedings of the National Academy of Sciences*, 93(24), 13547–13551.

Albert, M. S., DeKosky, S. T., Dickson, D., et al. (2011). The diagnosis of mild cognitive impairment due to Alzheimer's disease: recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. *Alzheimers Dementia*, 7, 270–9.

Apostolova, L. G., & Cummings, J. L. (2008). Neuropsychiatric manifestations in mild cognitive impairment: a systematic review of the literature. *Dementia and Geriatric Cognitive Disorders*, 25(2), 115–126.

Arguelles, S., Loewenstein, D. A., Eisdorfer, C., & Arguelles, T. (2001). Caregivers' judgments of the functional abilities of the Alzheimer's disease patient: impact of caregivers' depression and perceived burden. *Journal of Geriatric Psychiatry and Neurology*, 14, 91–98.

Backhaus, R., Verbeek. H., van Rossum, E., Capezuti, E., & Hamers, J. P. (2014). Nurse staffing impact on quality of care in nursing homes: a systematic review of longitudinal studies. *Journal of the American Medical Directors Association*, 15(6), 383-393.

Bárrios, H., Narciso, S., Guerreiro, M., Maroco, J., Logsdon, R., & de Mendonça, A. (2013). Quality of life in patients with mild cognitive impairment. *Aging & Mental Health*, 17, 3, 287-292.

Bengston, V. L., Kim, K. D., Myers, G., & Eun, K. S. (2000). *Aging in the East and West: Families, States and the Elderly*, New York: Springer.

Bischkopf, J., Busse, A., Angermeyer, M. C. (2002). Mild cognitive impairment--a review of prevalence, incidence and outcome according to current approaches. *Acta Psychiatrica Scandinavica*, 106(6), 403-414.

Brod, M., Stewart, A. L., Sands, L., & Walton, P. (1999). Conceptualization and measurement of quality of life in dementia: the dementia quality of life instrument (DQoL). *Gerontologist,* 39, 25–35.

Bruscoli, M., & Lovestone, S. (2004). Is MCI really just early dementia? A systematic review of conversion studies. *International Psychogeriatrics*, 16(2), 129–140.

Burgener, S., & Twigg, P. (2002). Relationships among caregiver factors and quality of life in care recipients with irreversible dementia. *Alzheimer Disease and Associated Disorders*, 16, 88–102.

Busse, A., Hensel, A., Gühne, U., Anger-meyer, M. C., Riedel-Heller, S. G. (2006). Mild cognitive impairment: long-term course of four clinical subtypes. *Neurology*, 67, 2176-85.

Clément, F., Belleville, S., Bélanger, S., & Chassé, V. (2009). Personality and psychological health in persons with mild cognitive impairment. *Canadian Journal on Aging,* 28(2), 147-156.

Collie A, Maruff P, Currie J. (2002). Behavioral characterization of mild cognitive impairment. *Journal of Clinical Experimental Neuropsychology*, 24(6), 720-33.

Conde-Sala, J. L., Garre-Olmo, J., Vilalta-Franch, J., Llinàs-Reglà, J., Turró-Garriga, O., LozanoGallego, M., & López-Pousa, S. (2012). Predictors of cognitive decline in Alzheimer's

disease and mild cognitive impairment using the CAMCOG: A five-year follow-up. *International Psychogeriatric*s, 24, 948–958.

Davis, H. S., & Rockwood, K. (2004). Conceptualization of mild cognitive impairment: A review. *International Journal of Geriatric Psychiatry*, 19(4), 313–319.

Dean, K., & Wilcock, G. (2012). Living with mild cognitive impairment: the patient's and carer's experience. *International Psychogeriatrics*, 17, 1-11.

Department of Health. (2009). *Living Well with Dementia: A National Strategy*. London: HMSO.

Dos Santos Silva, I. (1999). *Cancer Epidemiology: Principles and Methods*. International Agency for Research on Cancer: France.

Ettema, T., Droes, R., de Lange, J., Mellenbergh, G. & Ribbe, Met. (2005). A review of quality of life instruments used in dementia. *Quality of Life Research*, 14, 675–686.

Farias, S. T., Mungas, D., & Jagust, W. (2005). Degree of discrepancy between self and other-reported everyday functioning by cognitive status: dementia, mild cognitive impairment, and healthy elders. *International Journal of Geriatric Psychiatry*, 20**,** 827-834.

Fisk, J. D., Merry, H. R., & Rockwood, K. (2003). Variations in case definition affect prevalence but not outcomes of mild cognitive impairment. *Neurology*, 61, 1179–84.

Folstein, M. F., Folstein, S. E., McHugh, P. R. (1975). Mini-Mental State: A practical method for grading the state of patients for the clinician. *Journal of Psychiatric Research,* 12, 189-198.

Frank, L., Lenderking, L. R., Howard, K., & Cantillon, M. (2011). Patient self-report for evaluating mild cognitive impairment and prodromal Alzheimer's disease. *Alzheimer's Research & Therapy*, 3, 35.

Fujiwara, Y., Suzuki, H., Kawai, H., Hirano, H, Yoshida, H., Kojima, M., Ihara, K., & Obuchi, S. (2013). Physical and sociopsychological characteristics of older community residents with mild cognitive impairment as assessed by the Japanese version of the montreal cognitive assessment. *Journal of Geriatric Psychiatry and Neurology*, 26(4), 209-220.

Garand, L., Dew, M. A., Urda, B., Lingler, J. H., DeKosky, & S. T., Reynolds. (2007). Marital quality in the context of mild cognitive impairment. *Western Journal of Nursing Research*, 29(8), 976-992.

Hurt, C., Bhattacharyya, S., Burns, A., Camus, V., Liperoti, R., Marriott, A., & Byrne, E.J. (2008). Patient and caregiver perspectives of quality of life in dementia. An investigation of the relationship to behavioural and psychological symptoms in dementia. *Dementia and Geriatric Cognitive Disorders*, 26, 138–146.

Jungwirth, S., Fischer, P., Weissgram, S., Kirchmeyr, W., et al. (2004). Subjective memory complaints and objective memory impairment in the Vienna-Transdanube aging community. *Journal of the American Geriatrics Society*, 52(2), 263-8.

Knapp, M., Prince, M., Albanese, E., et al. (2007). *Dementia UK: The Full Report*. Alzheimer's Society: London.

Koepsell, T. D., Monsell. S. E. (2012). Reversion from mild cognitive impairment to normal or near-normal cognition. *Neurology,* 79(15), 1591-1598.

Kumar, R., Dear, K. B., Christensen, H., Ilschner, S., Jorm, A. F., Meslin C., et al. (2005). Prevalence of mild cognitive impairment in 60- to 64-year-old community-dwelling individuals: the personality and total health through life 60+ study. *Dementia and Geriatric Cognitive Disorder,* 19, 67–74.

Lapid, M. I., Rummans, T. A., Boeve, B. F., et al. (2003). What is the quality of life in the oldest old? *International Psychogeriatric*, 23, 1003–1010.

Lawton, M. P. (1991). 'A Multidimensional View of Quality of Life in Frail Elders', In Birren, J.E., Lubben, J., Rowe J., Deutchman, D.(eds)., *The Concept and Measurement of Quality of Life*. New York, Academic Press.

Lawton, M. P. (1994). Quality of life in Alzheimer disease. *Alzheimer Disease and Associated Disorders*, 8(suppl 3), 138–150.

Lewin, S., Glenton, C., & Oxman, A. D. (2009). Use of qualitative methods alongside randomised controlled trials of complex healthcare interventions: Methodological study. *BMJ*, 339, b3496.

Logsdon, R. G., Gibbons, L. E., McCurry, S. M., & Teri, L. (2000). Quality of life in Alzheimer's disease: Patient and caregiver reports. In S. M. Albert, & R. G. Logsdon (Eds.), *Assessing quality of life in Alzheimer's disease* (pp. 17–30). New York: Springer Publishing Company.

Logsdon, R. G., Gibbons, L. E., McCurry, S. M., & Teri, L. (2002). Assessing quality of life in older adults with cognitive impairment. *Psychosomatic Medicine*, 64, 510–519.

Logsdon, R. G., McCurry, S. M., & Teri, L. (2007). Evidence-based psychological treatments for disruptive behaviors in individuals with dementia. *PsychologicalAging*, 22(1), 28-36.

Lopez, O. L., Jagust, W. J., DeKosky, S. T. et al. (2003). Prevalence and classification of mild cognitive impairment in the Cardiovascular Health Study Cognition Study: part 1. Archives of Neurology, 60:1385-9.

Manly, J. J., Tang, M. X., Schupf, N., Stern, Y., Vonsattel, J. P., Mayeux, R. (2008). Frequency and course of mild cognitive impairment in a multiethnic community. *Annals of Neurology,* 63:494-506.

Maki, Y., Yamaguchi, T., Yamagami, T., Murai, T., Hachisuka, K., Miyamae, F., & Yamaguchi, H. (2014). The impact of subjective memory complaints on quality of life in community-dwelling older adults. *Psychogeriatrics*, 14(3):175-81

Miller, F. G., Rosenstein, D. L. & DeRenzo, E. G. (1998) Professional integrity in clinical research. *JAMA*, 280,1449–1454.

Missotten, P., Squelard, G., Ylieff, M., et al. (2008). Quality of life in older Belgian people: comparison between people with dementia, mild cognitive impairment, and controls. *International Journal of Geriatric Psychiatry,* 23, 103–1109.

Mitchell, A. J., Shiri-Feshki, M. (2009). Rate of progression of mild cognitive impairment to dementia. Acta Psychiatrica Scandinavica, 119(4), 252-265.

Momtaz, Y. A., Hamid, T. A., & Ibrahim, R. (2013). The impact of mild cognitive impairment on sexual activity. *American Journal of Alzheimer's Disease and Other Dementias*, 28 (8), 759 762.

Morris, J. C. (2006). Mild cognitive impairment is early-stage Alzheimer disease. Archives of *Neurology*, 63, 15–16.

Morris, J. C., Storandt, M., Miller, J. P., McKeel, D. W., Price, J. L., Rubin, E. H., & Berg, L. (2001). Mild cognitive impairment represents early-state Alzheimer disease. *Archives of Neurology*, 58, 397-405.

Muangpaisan. W., Assantachai, P., Intalapaporn, S., et al. (2008). Quality of life of the community-based patients with mild cognitive impairment. *Geriatric & Gerontology International,* 8, 80–85.

Muangpaisan, W., Intalapaporn, S., & Assantachai, P. (2008). Neuropsychiatric symptoms in the community-based patients with mild cognitive impairment and the influence of demographic factors. *International Journal of Geriatric Psychiatry*, 23 (7), 699–703.

Muldoon, M. F., Barger, S. D., Flory, J. D. & Manuck, S. B. (1998). What are quality of life measurements measuring? *British Medical Journal*, 316, 542-545.

Pearman, A., & Storandt, M. (2004). Predictors of subjective memory in older adults. *Journal of Gerontology & Psychological Sciences*, 59B, 4-P6

Petersen, R. C. (2003). *Conceptual overview*. In: Petersen RC, editor. Mild Cognitive Impairment: Aging to Alzheimer's Disease. London: Oxford University Press. p. 1-14.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine,* 256, 183-194.

Petersen, R. C., Smith, G. E., Waring, S. C., Ivnik, R. J., Tangalos, E. G., & Kokmen, E. (1999). Mild cognitive impairment: clinical characterization and outcome. *Archives of Neurology,* 56, 303–8.

Petersen, R. C., Stevens, J. C., Ganguli., M., Tangalos, E. G., Cummings, J. L., & DeKosky, S. T. (2001). Practice parameter: Early detection of dementia: Mild cognitive impairment (an evidence- based review). Report of the Quality Standards Subcommittee of the American Academy of Neurology. *Neurology,* 56, 1133-1142.

Petersen, R. C., Caracciolo, B., Brayne, C., Gauthier, S., Jelic, V., Fratiglioni, L. (2014). Mild cognitive impairment: a concept in evolution. *Journal of International Medicine,* 275:214–228; 2014.

Plassman, B. L., Langa, K. M., Fisher, G. G. et al. (2008). Prevalence of cognitive impairment without dementia in the United States. *Annals of International Medicine*, 148, 427-34.

Ready, R. E., Ott, B. R., & Grace, J. (2004). Patient versus informant perspectives of Quality of Life in Mild Cognitive Impairment and Alzheimer's disease. *International Journal of Geriatric Psychiatry*, 19:256–265.

Ray, S. and Davidson, S. (2014) *Dementia and cognitive decline. A review of the evidence*. Age UK: London. Available from: www.ageuk.org.uk/Documents/ENGB/Forprofessionals/Research/Cognitive_decline_and_dementia_evidence_review_Age_UK.pdf?dtrk= true (accessed 29 September 2015).

Ritchie, K., Artero, S. & Touchon, J. (2001) Classification criteria for mild cognitive impairment. A population-based validation study. *Neurology*, 56, 37-42.

Rosas-Carrasco, O., del Torres-Arreola, L. P., de Guerra-Silla, M. G., et al. (2010). Validation of the Quality of Life in Alzheimer's Disease (QOL-AD) scale in Mexican patients with Alzheimer, vascular and mixed-type dementia. *Review of Neurology*, 51:72–80.

Seeher, K., Low, L.-F., Reppermund, & S., Brodaty (2013). Predictors and outcomes for caregivers of people with mild cognitive impairment: A systematic literature review. *Alzheimer's & Dementia*, 9(3), 346-355.

Selai, C. E., Trimble, M. R., Rossor, M. N., *et al* (2001). Assessing quality of life in dementia: preliminary psychometric testing of the quality of life assessment schedule. *Neuropsychological Rehabilitation*, 11, 219– 243.

Shin, K. R., Kang, Y., Kim, M., Jung, D., & Kim, M. (2012). Comparative Study between depression in Korean elderly with mild cognitive impairment and normal cognitive function. *Nursing & Health Sciences*, 14(1), 81–86.

St John, P. D., & Montgomery, P.R. (2010). Cognitive impairment and life satisfaction in older adults. *International Journal of Geriatric Psychiatry,* 25(8), 814–821.

Tatsumi, H., Yamamoto, M., Nakaaki, S., Hadano, K., & Narumoto, J. (2011). Utility of the Quality of Life-Alzheimer's Disease Scale for mild cognitive impairment. *Psychiatry and Clinical Neurosciences,* 65, 533.

Taylor, R. (1990). Interpretation of Correlation Coefficient: A basic Review. *JDMS*, 1, 35-39.

Teng, E., Tassniyom, K., & Lu, P. H. (2012). Reduced quality-of-life ratings in mild cognitive

impairment: Analyses of subject and informant responses. *American Journal of Geriatric Psychiatry*, 20(12), 1016-1025.

Thorgrimsen, L., Selwood, A., Spector, A., Royan, L., de Madariaga Lopez, M., Woods, R. T., & Orrell, M. (2003). Whose quality of life is it anyway? The validity and reliability of the quality of life – Alzheimer's Disease (QoL–AD) scale. *Alzheimer Disease and Associated Disorders*, 17, 201– 208.

Tuokko, H., Morris, C., & Ebert, P. (2005). Mild cognitive impairment and everyday functioning in older adults. *Neurocase*, 11(1), 40–47.

Vogel, A., Stokholm, J., Gade, A., Andersen, B. B., Hejl, A. M., & Waldemar, G. (2004). Awareness of deficits in mild cognitive impairment and Alzheimer's disease: do MCI patients have impaired insight? *Dementia and Geriatric Cognitive Disorders,* 17,181–187.

Vogel, A., Mortensen, E. L., Hasslebalch, S. G., Andersen, B. B. & Waldemar, G. (2006). Patient versus informant reported quality of life in the earliest phases of Alzheimer's disease. *International Journal of Geriatric Psychiatry,* 21(12), 1132-1138.

Wang, L., van Belle, G., Crane, P., Kukull, W. A., Bowen, J. D., McCormick, W. C., & Larson, L. B. (2004). Subjective memory deterioration and future dementia in people aged 65 and older. *Journal of the American Geriatrics Society*, 52, 2045–2051.

Weiner, M. F., Martin-Cook, K., Svetlik, D. A., Saine, K., Foster, B., & Fontaine, C. S. (2000). The Quality of Life in late-stage Dementia (QUALID) scale. *Journal of American Medical Directors' Association*, 1, 114-116.

Wells, G. A., Shea, B., O'Connell, D., Peterson, J., Welch, V., Losos, M. (2000). The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomized studies in meta-analyses. Available at: **http://www.ohri.ca/programs/clinical_epidemiology/oxford**.

Wettstein, M., Seidl, U., Wahl, H. W., Shoval, N., & Heinik, J. (2014). Behavioral competence and Emotional well-being of older adults with mild cognitive impairment: Comparison with cognitively healthy controls and individuals with early-stage dementia. *The Journal of Gerontopsychology and Geriatric Psychiatry*, 27(2), 55-65.

Whitehouse, P. (1999). Quality of life in Alzheimer's disease: future directions, *Journal of Mental Health and Aging*, 5, 1, 107-111.

Winbald, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni L, Wahlund L-O., Nordber, A., Bäckman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., De Leon, M., DeCarli, C., T. Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., Van Duijn, C., Visser, P., & Petersen, R. C. (2004). Mild cognitive impairment: beyond controversies, towards a consensus: report to the International Working Groups on mild cognitive impairment. *Journal of Internal Medicine*, 256, 3, 240–6.

Yates, J. A., Clare, L., & Woods T, R. (2013). Mild cognitive impairment and mood: a systematic review. *Reviews in Clinical Gerontology*, *23*(4), 317- 356.

PART 2: EMPIRICAL PAPER

The Clinical Utility of the Four Mountains Test in the Early Diagnosis of Alzheimer's Disease: A Measure of Allocentric Memory Ability

ABSTRACT

Background: The Four Mountains Test (4MT) has been shown to capture impairment in hippocampus-dependent allocentric memory in early Alzheimer's Disease (AD) thus demonstrating potential as a helpful diagnostic aid.

Aims: The study aimed to explore the clinical utility of the 4MT as an early diagnostic aid by understanding how 4MT performance relates to dementia type in a memory service.

Design: A cross-sectional study was conducted within a memory service. Neuropsychological tests alongside the 4MT were administered in a face-to-face research appointment. A total of 35 participants with a range of mild dementias were recruited including AD, vascular dementia, mixed dementia, and MCI.

Measures: Measures of allocentric memory processing (Four Mountain Test; 4MT), estimated premorbid functioning (Test of Premorbid Functioning; TOPF), executive functioning (Trail Making Test; TMT) cognitive functioning (Addenbrooke's Cognitive Examination-III; ACE-III), depression and anxiety (Hospital Anxiety and Depression Scale; HADs) were administered.

Results: No statistically significant results were found in 4MT performance for AD participants versus other dementia types, and no specific factors influencing or predicting dementia diagnosis type. Visuospatial abilities and executive functions significantly correlated with 4MT scores in the other dementia type groups but no correlations were found in the AD group. All dementia groups differed significantly from healthy control data taken from a previous study (Bird et al, 2010).

Conclusions: The utility of the 4MT maybe compromised within a clinical setting and most particularly with the influence of participants with vascular dementia. The findings are discussed with reference to limitations, clinical implications and recommendations for future research.

INTRODUCTION

Dementia

The prevalence of dementia worldwide is estimated at 35.6 million with this set to double by 2030 and triple by 2050 (World Alzheimer Report, 2012). It has an enormous impact on health and social care services (Department of Health, 2009) and improving care for dementia has become a national priority (Department of Health, 2012). Dementia is an umbrella term used to describe a set of symptoms such as loss of memory, mood changes, and communication difficulties caused by certain neurodegenerative conditions usually associated with ageing. There are many different dementia types and some are more common than others.

Alzheimer's Disease

Alzheimer's Disease (AD) is a neurodegenerative disorder and the most common cause of dementia. It initially affects mediotemporal structures, particularly the hippocampus, but over time more brain regions are damaged and symptoms worsen. The most common early symptom is episodic memory impairment but as the disease progresses other cognitive domains are affected (e.g. executive functioning, language, visuospatial functioning). A certain diagnosis of AD is reliant on an autopsy therefore all AD diagnoses are considered probable until confirmed otherwise (Agamanolis, 2014).

Vascular Dementia

Vascular Dementia (VD) is the second most common type of dementia, occurring because of diseased blood vessels reducing blood supply to the brain. This usually begins suddenly after a cerebrovascular disease (e.g. stroke). VD commonly progresses in a 'stepped way' where symptoms remain constant for a time and then may rapidly deteriorate (Jagust, 2001; Micieli, 2006; Román et al, 1993; Sachdev et, 1999). Difficulties in executive functioning, speed of processing, reduced concentration and sudden confusion are often the earliest symptoms. However, there is overlap in symptoms with AD dependent on the location of the brain injury

i.e. memory, visuospatial and language difficulties. The risk factors are those that contribute to cardiovascular diseases some of which can be controlled via lifestyle and others that can not due to age and genes.

Mixed dementia

At least 10 per cent of people with dementia are diagnosed with a mixed dementia meaning the abnormal protein deposits associated with AD coexist with blood vessel problems linked to VD. The symptoms may vary dependent on the brain region affected and similar to those of either AD or VD. Research from autopsies suggests the condition is significantly more common than realised but the prevalence of this diagnosis is still not known (Bowler, 2002).

Other Dementias

Fronto-temporal lobe Dementia (FTLD) is associated with frontal lobe cell damage, being characterised by changes in personality and behavior, and difficulty with language. Other forms of dementia include Lewy bodies (DLB) and Huntington's disease, which rarely present to memory services.

Mild Cognitive Impairment

Mild cognitive impairment (MCI) is classified as the intermediate state between healthy cognition and dementia. It is defined by the presence of a memory or cognitive complaint in the absence of dementia and minimal or no deficits in daily living (Winbald et al, 2004; Petersen, 2003; 2004). Some research suggests MCI increases the risk of developing AD with conversion estimates varying from about 7-16% per annum (Ganguli et al, 2004; Petersen et al, 2005). However, many people with MCI remain stable or eventually improve. There are two main MCI subtypes; amnestic MCI (aMCI) that is associated with memory impairments and non-amnestic MCI (naMCI) that is associated with other cognitive impairment. Research has also shown that people with aMCI have a greater progression to dementia that those with naMCI, however, most MCI cases remain stable (Ganguli et al, 2011).

Early Diagnosis of AD

Being the most common dementia, AD has become a particular public health concern with a need to improve diagnosis and management. There have been a number of significant developments made in pharmacological and psychosocial interventions that are most effective when initiated early in the disease (Mittelman et al, 1996; Gaugler et al, 2005; Molinuevo et al, 2009; Rountree et al, 2009). The neurodegenerative processes of AD often precede clinical onset making it difficult to detect AD in the earliest stages when memory deficits are less overt and symptoms are often more vague (e.g. disturbance of daily functioning) (Morris, 2005). This makes it difficult to differentiate between early AD and normal aging or other forms of dementia thus having implications for prognosis and management. Furthermore, differentiating AD from other dementia types is particularly difficult due to considerable overlap in both pathology and behavioral symptoms (Boyle, 2001; Rosenstein, 1998). There is a growing need for clinical instruments that target early deficits of AD so accurate differentiation between other forms of dementia and healthy ageing can be made (Prince et al, 2011).

AD and Topographical Disorientation

One of the earliest clinical manifestations of AD is topographical disorientation (TD) that reflects a deficit in spatial memory i.e. the ability to encode, store and retrieve spatial information. Successful topographical orientation has been proposed to depend on the continuous construction of abstract representation known as a "cognitive map" (Gallistel, 1990; O'Keefe & Nadel, 1978; Tolman, 1948). Many studies have investigated TD in AD with a view to identify early cognitive markers (Gazova et al., 2012; Iachini et al., 2009; Lithfous et al., 2013; Vlcek & Laczó, 2014).

Spatial Memory

Research with animals and humans distinguish between two types of basic spatial representation that form the basic structure of spatial memory and allow for spatial navigation (Klatzky, 1998). The first is egocentric representation where locations are represented by an individual's

orientation (self-centered) and are dependent mainly on the parietal cortices and caudate nucleus brain regions (O'Keefe & Nadel, 1978; Maguire, 1998; Packard, 2002; White & McDonald, 2002, Weniger et al, 2009). The second is allocentric representation where locations are unrelated to the individual's orientation (world-centred) and centred on objects and/or environmental characteristics. Allocentric encoding provides enduring and flexible mental representations that are stored in long-term memory, and thus related to the development of cognitive maps (O'Keefe & Nadel, 1978; Tolman, 1948).

Hippocampus and Allocentric Representations

The hippocampus is believed to play a significant role in allocentric representation and memory (Maguire, 1998; Packard, 2002; White & McDonald, 2002, Weniger et al, 2009; O'Keefe & Dostrovsky, 1971). Animal studies in the 1970's first demonstrated a link between the mammalian hippocampus and allocentric processing on finding 'place cells' in the hippocampus of rodents (O'Keefe, 1976). It was found that the firing of these cells encoded the specific location of the rodent independent of the heading direction and in relation to environmental boundaries (Muller, 1996; O'Keefe & Burgess, 1996; Cressant et al, 1997). More recently, human studies have likewise associated hippocampal processing with spatial memory for locations irrespective of viewpoint and orientation environment (Abraham et al, 1999; Holdstock et al, 2000; King et al, 2002; Ekstrom et al, 2003) and in relation to environmental boundaries (Doeller et al, 2008).

AD and Allocentric Representation

The initial stages of AD are associated with pathology in the hippocampus that has been shown to predate the onset of symptoms in patients with AD (Alafuzoff et al, 2008; Braak et al, 2006; Braak & Braak, 1991, 1996; Dickson, 1997; Morris et al, 1996; Thal et al, 2002; Schott et al, 2003). Many studies have provided evidence of impairment in allocentric hippocampal dependent memory rather than egocentric parietal representation in patients with early AD degeneration (Maguire & Cipolotti, 1998; Chan et al, 2001; Galton et al, 2001; Kalova et al,

2005; Burgess, 2006). Research suggests therefore that the hippocampal degeneration associated with AD therefore diminishes the ability to construct and maintain a long-term allocentric representation of the surrounding environments. Studies have indicated that impairment in allocentric representations could be a helpful cognitive marker and tests that target this maybe reliable tools in facilitating early AD diagnosis.

Four Mountains Test

Four Mountains Test (4MT) is a memory test developed by Hartley et al (2007) to investigate topographical processing in humans. It was specifically designed to capture hippocampal dependent allocentric memory abilities. The test uses computer-generated landscapes containing four mountains where the topography of the landscape (i.e. the geometry of the surface) and its non- spatial visual features can be independently varied. It assesses a person's ability to recognize places from their layout even when the viewpoint changes (see Method section for detail). Hartley et al (2007) found that patients with damage to the hippocampus had particular difficulty with the test demonstrating the hippocampal role in allocentric memory processing.

Bird and colleagues (2010) adminstered the 4MT to a mild dementia population to investigate the core cognitive processes underpinning TD in AD patients comparing performance with presentations of MCI, FTLD, subjective memory impairment (SMI) and age matched controls. They found that short-term retention of topographical information was impaired in patients with AD and an MCI but not in patients with FTLD or SMI. This further demonstrated an inability to form and retain allocentric representations of large-scale environments in AD due to hippocampal atrophy. The authors argued that the 4MT could be a helpful tool to aid earlier diagnosis of AD. However, no study to date has included patients with VD and thus their performance on the 4MT is unknown.

Current Study

Research demonstrates that a core deficit in early AD is the ability to form and retain allocentric

representations of large-scale environments due to hippocampal atrophy (Laczó et al, 2009; Bird et al, 2010; Vlcek, 2011; Gazova et al, 2012). Thus, adding allocentric memory tests to neuropsychological batteries could facilitate differentiation of AD from other types of dementia and healthy aging thus facilitating early diagnosis. The 4MT has been demonstrated to specifically target the hippocampus and the allocentric topographical processing associated with this area of the brain (Hartley et al, 2007; Bird et al, 2010). Furthermore, patients with AD and aMCI had impaired performance on the 4MT compared to other memory disorders. However, this was conducted in an experimental setting and excluded other major forms of dementia (e.g. vascular dementia). Therefore little is known about the relationship the 4MT has with other dementia types and within a clinical setting, where presentations may overlap in symptoms and differentiation is complex. The test's relationship with dementia type within a clinical setting needs to be established to better understand it's potential utility as a screening tool to differentiate early AD from other forms of dementia and healthy aging thus supporting diagnosis and treatment.

To accurately understand 4MT clinical utility certain cognitive abilities need to be controlled for using neuropsychological tests to provide an indication of whether any may have confounded 4MT performance. Visual-spatial and scanning abilities are essential for engagement with 4MT due to the visual nature of the test. Comprehending (language) and remembering (memory) task instructions alongside expressing answers (fluency) and needing to inhibit, plan and problem solve (executive functioning. inhibition) are also important skills necessary for engagement. Premorbid functioning ability is known to influence rate of cognitive decline and thus potential confound on 4MT performance (Sharp, & Gatz, 2011). Depression and anxiety are also known to negatively impact memory thus potentially interfering with 4MT performance (Burt, Zembar & Niederehe, 1995). The neuropsychological tests used to measure these abilities are described in the Methods section.

Aim

The aim of this study was to investigate the application of the 4MT in a clinical setting to understand how performance relates to dementia type at the earlier stages of the disease. This is the next step in understanding the potential utility of the 4MT as a tool to differentiate between AD, in the early stages and normal ageing as well as forms of dementia. Given the 4MT has only so far been applied in small-scale experimental research it is also important to consider the feasibility of using this test within a clinical context with people with mild dementia. Therefore, the current study will consider the initial feasibility of using the 4MT in a memory service as a way to further understand the clinical utility.

Hypotheses

1. Participants with AD will have significantly lower 4MT scores than participants diagnosed with other forms of dementia including VD and mixed dementia or MCI.
2. Participants with AD will have a greater reduction 4MT scores compared with normative data from healthy volunteers than participants with other forms of dementia.
3. There will be a positive correlation between 4MT scores and memory scores compared with other cognitive functions for participants with different dementias.
4. An exploratory hypothesis was included to understand whether 4MT scores or any of the measured variables were predictors of a diagnosis of AD or other forms of dementia.
5. The 4MT will be feasible to use within a clinical setting with patients with mild dementia.

METHOD

Design

A cross-sectional observational design was used to explore how performance on the 4MT is related to type of dementia diagnosis and performance in other cognitive domains. All participants completed the neuropsychological battery of tests and 4MT.

Setting

The study took place across two NHS Memory Services and their associated Dementia Advisor services provided by the Age Concern Charity. These services were located in West London. The majority of the research appointments were conducted at the participant's home (32), however, a smaller number were conducted at the memory service (3). The study was conducted as part of wider dementia study exploring the accessibility of Cognitive Behavioural Therapy (CBT) for people with dementia. The wider study aims to understand the ability of people with dementia to perform the core cognitive abilities required to benefit from CBT treatment. Participants in this study therefore completed measures assessing cognitive mediation, thought/feeling/behaviour differentiation, emotion recognition and association of emotion with event alongside the subset of measures used in this study (see appendix 2).

Participants

Inclusion/exclusion criteria

All participants who had been referred to memory services or were involved with the dementia advisor services were initially considered eligible for the study. Participants invited to participate had met the following inclusion criteria:

- Fluent in English language and did not require use of an interpreter
- Aged 50 years or over
- Scored above 70 on the Addenbrooke's Cognitive Examination- III at the initial assessment

(ACE-III)

- No current significant mood or anxiety disorders, psychotic symptoms, substance misuse problems or a premorbid learning disability
- No sensory difficulties that would interfere with completion of neuropsychological measures i.e. problems with sight
- Deemed to have capacity to consent to take part in the study

Thus the sample included patients with a range of memory difficulties and subsequent dementia diagnoses. Scores below 70 on ACE-III tend to be indicative a more moderate to severe dementia and more global deficits on functioning can be expected regardless of dementia type. The study aimed to explore early diagnosis and differential cognitive profiles are unlikely to fall into this category thus these participants would be unlikely to fall into this category. Furthermore, floor effects on 4MT would be expected. Participants with ACE-III scores above 70 were also considered likely to have retained capacity to consent to research. Further to this, the researcher re-assessed capacity to consent in accordance with the Mental Capacity Act (2005) at the research appointment.

Diagnostic assessment

Diagnosis of dementia was given in accordance with ICD 10 criteria following a clinical interview and assessment of cognitive ability using ACE-III. A clinician from the memory service conducted the diagnostic assessment. In most cases this was substantiated via an MRI and in certain cases when a presentation was more complex then participants were referred for further neuropsychological testing. Results from all assessments were discussed in a multi-disciplinary team and a diagnosis was decided. Following this, patients were assigned an allocated clinician who disclosed the diagnosis.

Ethics

Ethical approval for this study was granted after review by the City Road and Hampstead

National Research Ethics Service Committee (see Appendix 3 for ethical approval letter). The study was also registered with local research and development departments associated with the memory services.

Sample Size

A power analysis was conducted to estimate the required sample size for this study and reduce the possibility of the findings being underpowered. The power analysis was predicated on using logistic regression analysis to explore the main aim of the study, which was to understand the whether 4MT performance can predict dementia diagnosis type. Furthermore, logistic regression is a less powerful form of analysis and therefore establishing the sample size using this statistic would result in a larger sample size that would ensure that all other statistical analysis used in this study were adequately powered (i.e. Independent Samples and One Sample t-tests, Pearson's Correlation Coefficients)." The effect size for the difference on these performances was identified as medium (d= 0.58) based on research using the 4MT in a similar sample (Bird et al, 2010). Chinn's (2000) equation was to used to provide an approximate odds ratio (the d value is multiplied by 1.81 and then this result is anti-logged). Using the d = 0.58, an odd's ratio of 2.86 was calculated using this equation. The sample size was calculated (using GPower3) with this odds ratio of 2.86, and with alpha setting at 0.05 and power at 0.80. This produced a sample size estimate of 44 (N=44) with a power of 0.81 for this study.

Measures

Neuropsychological measures were administered to characterise the sample and examine relationships between 4MT and other abilities. The researcher was trained and experienced in administering neuropsychological tests. Demographic information was also collected both during the testing and retrospectively using the NHS electronic patient database. The orders of the tests in the battery were randomized using Qualtrics, an online survey system designed for administering research protocols. This enabled the researchers to control for the potential impact of fatigue and carry-on effects on performance.

Test of Premorbid Functioning *(TOPF)* (Welscher, 2011) was administered to estimate premorbid cognitive functioning prior to the onset of the dementia. The TOPF is based on a reading paradigm that requires pronunciation of 70 atypical words (e.g. paradigm) that have irregular grapheme-to-phoneme translation. This test was administered using a face-to-face interface and in accordance to the standardized instructions. Overall TOPF reliability is high, with good internal consistency (Chronbach's alpha = 0.95). Test-retest reliability of the TOPF is also good (corrected correlations between r=.89 and r=.95; Wechsler, 2011). The TOPF also correlates to Wechsler Adult Intelligence Scale- Fourth Edition (WAIS-IV) Full Scale IQ scores (R=.72, p<0.001; R^2=0.52, P<0.001). Premorbid IQ can be calculated from the raw score, adjusted for sex and years of education or other demographic variables. It can be used to predict therefore sub-scale scores on the WAIS-IV and Wechsler Memory Scale (WMS). Research demonstrates the TOPF as a valid method for assessing change between premorbid and current cognitive functioning with a clinical dementia sample (Duff, Chelune and Dennett, 2011).

The Addenbrooke's Cognitive Examination-III *(ACE-III*; Mioshi et al, 2006) is the updated version of the ACE-R (Mioshi et al, 2006) designed to assess five cognitive domains attention/orientation, memory, verbal fluency, language and visuo-spatial abilities. The test was administered following the instructions detailed in the manual. Each cognitive domain involves the completion of a series of pen to paper tasks (see Appendix 4). The total score is 100; higher scores reflect better ability. The ACE-III is minimally adapted from ACE-R, which has been extensively validated within a dementia population (Hsieh et al, 2013). Cognitive domains in the ACE-III correlated significantly with corresponding standardized neuropsychological tests (Hsieh et al, 2013). It also compared favourably with the ACE-R (r= 0.99, p < 0.01), with similar levels of sensitivity and specificity (Hsieh et al, 2013). The ACE-III was designed to be sensitive to early stages of dementia and demonstrates high sensitivity and specificity at cut-offs previously recommended: with cut offs of 88 (sensitivity = 1.0; specificity = 0.96) and 82 (sensitivity = 0.93; specificity = 1.0). Internal reliability of the ACE-III, measured by

Cronbach's α coefficient, was 0.88.

Trail Making Test (TMT) (Reitan, 1958; 1992) is a visual attention and task-switching test. It consists of two parts involving connecting a set of twenty-five consecutive symbols (A: numbers and B: numbers and letters) as fast as possible while maintaining accuracy. It measures complex visual scanning (Shum, McFarland & Bain, 1990), speed of processing (Lezak, 1995), cognitive flexibility and executive functioning (Gaudino, Geisles & Squires, 1995). This test was administered face to face and in accordance to the standardized instructions. Test-retest reliability is reported at r=0.80 (Spreen & Strauss, 1991) and validity r= 0.59 (Delis, Kaplan & Kramer, 2001). It has been used extensively in work with dementia (Strauss, Spreen & Sherman, 2006) and is sensitive to the detection of cognitive impairment including AD (Tombaugh, 2004). Longitudinal studies have found that as subjects become older, the time required to finish the TMT, in particular part B, increases significantly and that this time is significantly longer in older patients with dementia (Rasmusson, et al, 1998). Higher test times suggest poorer performance, whilst lower times reflect better. The raw score of times in seconds and number of errors made were converted used for analysis using the Ashendorf and colleagues norms adjusted for age and years of education (Ashendorf et al, 2008).

The Hospital Anxiety and Depression Scale *(HADS)* is a 14 item questionnaire that produces two 7-item subscales assessing depression and anxiety over the preceding two weeks. It is a self-assessment rated on a four-point likert scale, with a maximum score of 21 on each subscale (higher scores correspond to higher symptom severity; Johnston et al, 2000; Herrero et al, 2003). Importantly, it deliberately leaves out physical indicators of psychological distress such as dizziness, headaches, insomnia, and fatigue, to prevent interference with somatic disorders making it suited for the detection of depression in older adults (Herrmann, 1997; Bjelland et al, 2002; Wang et al, 2006). Symptoms of severe psychopathology are also omitted to avoid the "floor effect" frequently encountered in non-psychiatric patients (Herrmann, 1997; Bjelland et al, 2002). The scale has a high internal consistency with a Cronbach's α coefficient of 0.7–0.9

(Herrmann, 1997; Aben et al, 2002; Bjelland et al, 2002; Herrero et al, 2003; Lowe et al, 2004; Bambauer et al, 2005; Thomas et al, 2005). Two-week test–retest reliability is also high ($r > 0.80$), demonstrating a satisfactory stability of the scale (Herrmann, 1997). It has been used successfully in research settings with dementia (Samaras, 2013). In this study, the HADS was administered as a semi-structured interview rather than an independent questionnaire in accordance with other dementia studies (Samaras et al, 2013).

The 4MT is a memory test designed to measure hippocampal dependent topographical memory processing in humans. The 4MT is an experimental test that has only previously been used in a series of laboratory based research studies and thus the psychometric properties are yet to be formally established. However, in terms of the validity of the measure research has demonstrated that the 4MT is sensitive to hippocampal volume, which specifically influences performance on the allocentric memory subtest (Hartley and colleagues, 2007; Bird et al, 2010; Kuven et al, *In Press).* This provides evidence that the 4MT captures the hippocampal dependent allocentric ability it was designed to measure.

The original test developed by Hartley and colleagues (2007) was comprised of 4 subtests independently assessing perception and short-term retention of differing information contained in computerised landscape pictures administered in an A4 booklet (see Hartley et al, 2007 for details). Hartley and colleagues later redesigned the test into a computerised version that solely administered the topographical memory subtest of the 4MT. The test therefore comprised of a series of 30 computer-generated landscapes of 4 mountains in the central foreground (see figure 1). Stimuli were constructed by varying the topographical (i.e., surface geometry) and non-spatial (e.g., lighting, cloud cover) features of the landscape and the viewpoint from which landscapes were observed. Participants were presented with a "sample" image on a computer screen for 10 seconds and then a blank screen for approximately 2 seconds. On the next computer slide 4 alternative landscape scenes were presented that were arranged randomly in a 2 by 2 grid. To prevent participants being misled by local matches with small-scale features

each of the four stimuli were rendered from a different camera position. Furthermore, the 3 alternative responses were also rendered from different prevailing conditions from the sample image as well as each other. Participants had 20 seconds to select the correct test image. The task was to identify the target image were all topographical information is preserved but the viewpoint has been changed. Answers were recorded independently by the participant using the provided grid sheet (see Appendix 4). The test was administered on a laptop but the researcher controlled the laptop and the timings of the images at all times to reduce need for participants to interact with the computer interface and minimize potential confounds.

Procedure

All patients referred to the memory clinic for an assessment during the recruitment phase of the study were considered to take part. Patients who had previously joined a trust wide NHS research register, who granted consent to be contacted about research being conducted, were contacted following dementia diagnosis disclosure. In addition clinician's follow up caseloads were frequently reviewed to identify potential participants who may have not signed the research register. These potential participants were contacted prior by the involved clinician to gain permission to be contacted about research. Identified participants were then screened against the inclusion criteria outlined above by the researcher. This information was obtained by accessing patient's files on an electronic patient database. Participants were then contacted by the researcher via telephone to outline the main aims and procedures of the project. A research appointment was also arranged, which took place in either the participant's home or the memory clinic dependent on their preference. Information sheets were also posted to participants prior to the visit (see Appendix 6). The study information sheet was reviewed again jointly at the visit to ensure participants understood the study aims and requirements. Written consent was then gained from each participant whom had capacity and demographic information collected (see Appendix 7). The neuropsychological tests were administered (see measure section). An electronic data system was used for in vivo entry of the raw data. The research sessions lasted approximately 2 hours and all participants were debriefed at the end of the testing. The

researcher remained blind to the type of dementia the participant had until data was collected when dementia diagnosis was matched to the data. This study formed part of a wider project and therefore further questionnaires were also administered during these appointment but were not relevant to the aims of this study.

Data Analysis

Data was entered and analysed using the Statistical Package for the Social Sciences version 17.0. Initial descriptive exploration of the data was conducted to investigate distribution and representativeness. Independent Samples T-Tests were conducted to investigate differences in 4MT scores for AD versus other forms of dementia. One Sample T-Tests were also computed using control data from Bird et al (2010) study to compare how dementia 4MT scores differed to cognitively healthy controls. A series of Pearson's Correlation Coefficients were also conducted to explore relationships between scores on the 4MT, scores on the background neuropsychological tests and different dementia diagnosis. A logistic regression was finally conducted to explore further if any measured variables predicted dementia diagnosis.

RESULTS

Eighty-Eight participants were initially identified as prospective participants (66 memory service; 22 Age Concern). Twenty-six potential participants were excluded at the initial screening phase for not meeting the inclusion criteria i.e. ACE below 70 (14), current mental health difficulties (4), no diagnosis of dementia (6), physical health difficulties (1) and required an interpreter (1). Thirty-six participants who met the inclusion criteria did not take part in the study for reasons including not wanting to take part (23), unable to make contact (9), had been admitted to hospital or care home (3), or had significant visual impairment (1). Subsequently, consent was obtained from 35 participants (19 memory service; 16 Age Concern). Meanwhile, 3 participants terminated the 4MT during administration reporting that they found it too challenging and these cases were excluded from the main analysis of the 4MT being deemed to represent floor effects. Data was therefore analysed for 32 participants in relation to the hypothesis, meaning the study was slightly underpowered; the results below should therefore be treated with caution. Prior to the research appointment all participants had a scored above 70 on the ACE-III at initial memory service assessment, in line with the inclusion criteria. However, when the ACE-III was re-administered to participants at the research appointment it was discovered that five participants scored below 70 on the ACE-III. An exploratory analysis was performed with these participants included and then excluded from the data. The exclusion of these participants did not change the results and so a decision was made to include these cases in the analysis.

Participant Characteristics

The demographic information and baseline neuropsychological scores for the sample (N= 32) are presented in Table 1. There were no significant differences between any of the dementia groups in terms of age, gender and years of education when compared separately (see Table 2).

Table 1: ***Demographic and clinical characteristics of participants (N=32)***

	N	%	Mean	SD	Range
Age (years)	-	-	78.57	6.76	58-91
Years of Education	-	-	13.88	3.93	7-25
ACE score	-	-	74.77	13.44	38-96
Dementia Diagnosis					
AD	14	43.8	-	-	-
Vascular Dementia	8	25.0	-	-	-
Mixed Vascular and AD	5	12.5	-	-	-
MCI	4	15.6	-	-	-
Other	1	3.1	-	-	-
Gender					
Female	15	53.1	-	-	-
Male	17	46.9	-	-	-
Ethnicity					
White British	17	53.1	-	-	-
Irish	1	3.1	-	-	-
White Other	8	25.0	-	-	-
Black Caribbean	2	6.3	-	-	-
Indian	2	6.3	-	-	-
Bangladeshi	2	6.3	-	-	-
Baseline scores					
Anxiety	-	-	6.84	3.57	0-14
Depression	-	-	6.06	3.62	1-13
Estimated Premorbid functioning	-	-	48.44	16.86	10-70
Memory	-	-	15.93	4.99	15.93
4MT	-	-	10.88	3.42	3-18
Visuospatial	-	-	13	2.05	10-16

Mean scores with standard deviations and the range. Neuropsychological data based on raw scores for ACE, TOPF and HADS.

Neuropsychological Assessment

Independent sample t-tests indicated no significant differences in the cognitive or psychological domains between AD and other dementia types groups for the sample (N= 32). There were no significant differences also on cognitive and psychological measures between AD and VD groups (N=22). Furthermore, on checking the distribution of scores on measures the zero scores were not outliers, but rather were consistent with the variance of the sample - hence they were maintained in the analysis even though technically these scores were slightly below chance performance. The full breakdowns of test scores are detailed below in Table 2. Pearson's Correlation Coefficients were also employed to investigate relationships between measured variables when split by AD or other dementia type and VD (see appendix 7).

Table 2: ***Mean and standard deviation scores of test scores for each type of dementia (N=32)***

	Dementia Diagnosis				
	AD (N=14)	**VD (N=8)**	**MCI (N=4)**	**Mixed AD & VD (N=5)**	**Other Dementia Type[a] (N=18)**
Age (Years)	77.42 (6.24) 63-87	78 (8.73) 58-86	77.25 (6.29) 70-83	82.8 (5.93) 77-91	79.37 (7.03) 58-91
Education (Years)	14.79 (4.23) 10-25	14 (4.44) 7-19	12.75 (3.5) 9-17	12.8 (2.95) 10-17	13 (3.62) 7-19
4MT	10.43 (3.82) 3-18	11 (3.74) 7-17	13 (1.83) 11-15	10.8 (3.03) 7-15	11.16 (3.08) 7-17
ACE-III Total	75.69 (10.22) 64-96	75.63 (13.03) 54-90	83.33 (9.07) 75-93	73.20 (16.04) 45-85	74.61 (15.45) 38-93
ACE-III Memory	14.77 (4.87) 8-26	17.63 (5.45) 10-25	17.67 (7.37) 12-26	16.20 (3.42) 11-20	16.94 (4.91) 10-26
ACE-III Attention	16 (2.31) 11-18	16.38 (1.59) 14-18	15.67 (.58) 15-16	15.40 (2.07) 12-17	15.72 (2.14) 10-18
ACE-III Language	22.23 (3.0) 17-26	21.75 (3.01) 17-24	25 (1.0) 24-26	19.80 (7.46) 7-26	21.39 (5.10) 7-26
ACE-III Visuo-spatial	13.46 (1.66) 10-16	12.25 (2.12) 10-16	14 (3.46) 10-16	13 (1.87) 11-15	12.61 (2.23) 10-16
ACE-III Fluency	9.23 (2.13) 6-13	7.63 (3.25) 1-11	11 (1.0) 10-12	8.80 (3.70) 4-13	8.33 (3.43) 1-13
Trails Making A (Seconds)	54.01 (25.1) 26-98	69.88 (42.19) 33-160	39 (10.55) 26-49	48.40 (15.24) 30-63	55.79 (30.74) 26-160
Trails Making B (Seconds)	129.75 (81.89) 64-279	187.33 (76.79) 105-257	105 (24.88) 49-78	73.50 (40.3) 45-102	128 (68.39) 45-257
TOPF	50.7 (14.22) 24-70	48 (19.12) 23-69	54.75 (11.59) 38-63	46.20 (21.67) 10-65	46.58 (18.61) 10-69
Anxiety	6.64 (2.90) 2-13	8.25 (3.77) 3-14	6 (6.24) 1-13	4.80 (3.11) 0-8	7 (4.0) 0-14
Depression	5.93 (3.73) 2-13	7 (3.5) 2-11	3.33 (.58) 3-4	6.20 (4.82) 1-13	6.17 (3.54) 1-13

Mean scores with standard deviations and the range. Neuropsychological data based on raw scores for ACE, Trails Making Test, TOPF, HADS.

[a]*Other dementia category not included in breakdown as only 1 participant but is included in the wider other dementia type sample*

Current sample vs. Bird study sample

Demographic and neuropsychological characteristics of the participants in the current study and Bird et al (2010) are shown in Table 3. The Bird control group consisted of spouses/partners of the participating patients and other age-matched adults recruited through a volunteer database. The Bird control participants had younger mean ages than the AD and other the dementia type participants in the current study. The AD participants in the current study and the Bird control participants were comprised of a similar ratio of male and females, with more males compared to females. The other dementia group had more equal numbers of males and females. In terms of premorbid functioning, the Bird control had a higher mean predicted IQ scores (within the high average range) than the AD and other dementia type participants in the current study (within the average range).

Dementia groups in the both studies were comprised of participants in the earlier stages of the disease. Reliable comparisons of disease severity of the Bird AD group to the AD and other dementia type group in the current study were not possible as different neuropsychological measures were used to measure overall cognitive functioning. All of the Bird AD participants were experiencing mild dementia (MMSE = 26.1, SD = 2.8) and had been provided with a formal diagnosis of probable AD. The majority of AD (ACE-III = 75.69, SD = 10.22) and other dementia participants (ACE-III = 74.61, SD= 15.45) in the current study were also experiencing mild dementia and all had been provided with a formal diagnosis of dementia. The Bird AD participants had higher mean predicted IQ scores (within the high average range) than the AD and other dementia type participants in the current study (within the average range). There were no significant differences in the AD participant's 4MT scores in the current study (M=10.46, SD=3.971) and those in the Bird study AD (M=12.2, SD= 5.34) ($t(13)= -1.736$, $p= .106$). Bird et al (2010) did not include a VD group so comparison cannot be made in this analysis. Please

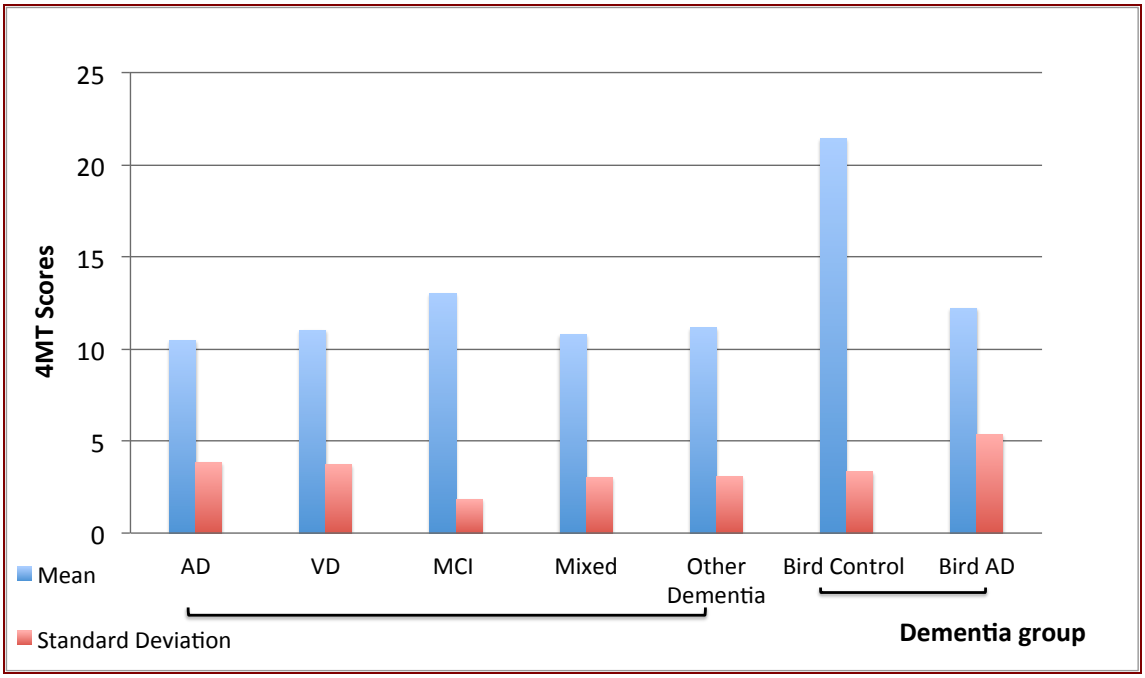
see Figure 1 for comparisons of 4MT scores between all groups in the current study and the Bird control and AD groups.

TABLE 3: ***Demographic and neuropsychological data from the current study and Bird study***

Group	N	Sex (F:M)	Age	Estimated Premorbid Functioning	4MT scores
AD (Bird Study)	7	2:5	65.3 (11.0) 57–79	114.3 (8.7) 90–128[a]	12.2 (5.34) 4-20
AD (Current Study)	14	5:8	77.15 (6.4) 63-87	105.2 (11.8)	10.46 (3.97) 3-18
Controls (Bird Study)	25	9:16	65.3 (7.6) 51–79	112.7 (12.2) 85–130[a]	21.4 (3.34) 16-30
Other dementia (Current Study)	18	10:9	79.37 (7.03) 58-91	101.7 (15.1)	11.16 (3.08) 7-17

Mean and Standard deviations. Estimated premorbid functioning scores are shown as predicted full-scale IQ scores (standardized (z) scores) based on published normative data; n.t., not tested
[a]Based on National Adult Reading Test (2nd Ed; Nelson, 1991)
[b]Based on TOPF

Figure 1: ***4MT performance for dementia groups in the current study and Bird study***



Hypothesis 1: AD participants will have significantly lower 4MT scores than those with other forms of dementia

Independent sample t-tests were conducted to compare 4MT scores for participants with AD and other dementia types. There was no significant difference in 4MT scores of AD participants (M= 10.43, SD= 3.82) and all other types of dementia (M= 11.16, SD= 3.08) (t(30)= -.559, *p*= .532; d = -.1992; 95% CId= -.5027 - +.8669).Furthermore, no significant differences were also found in 4MT scores of AD participants (M= 10.43, SD= 3.82) and VD participants (M= 11, SD= 3.74) (t(*20*)= -.340, *p*= .665; d = -.1507; 95% CId= -.7211 – +1.0188). A comparison of 4MT scores of AD participants (M= 10.43, SD= 3.82) and other dementia types excluding those with mixed diagnosis (M= 11.29, SD= 3.20) was also conducted but no significant difference was found (t(25)= -.556, *p*= .685; d = -.2142; 95% CId= -.5454 - +.9692).

Hypothesis 2: AD participants will have a greater reduction in 4MT scores compared with normative data from healthy controls than participants with other forms of dementia

Although control data were not collected in this study, tentative comparisons were made using one sample t-tests between dementia groups and cognitively healthy participants' data from the Bird et al (2010) study. However, these should be interpreted with caution in light of the differences in the characteristics between the Bird control group and the two main dementia groups of the current study (i.e. AD and other dementia type group). Overall, the 4MT score for the dementia sample collected in this study (M= 10.88, SD= 3.42) differed significantly from the control data from the Bird Study (M=21.4, SD= 3.34) (t (31)= -17.387, p < .001). There were significant differences were found between control data (M=21.4, SD= 3.34) and the AD group (M=10.46, SD=3.971) (t (12) = -9.932, p < .001). Furthermore, significant differences were also found in 4MT scores between control data (M=21.4, SD=3.34) and the other dementia group (M=11.16, SD= 3.078) (t (18) = -14.505; p= .000).

NOT identical sample but work limitations of minimal resource.

Hypothesis 3: Positive correlation between 4MT scores and memory scores compared with

other cognitive functions for participants with different dementias

Pearson's Correlation Coefficient were conducted to explore the relationships between 4MT scores and other cognitive functions for AD versus other types of dementia. The cognitive functions included memory, visuospatial, language, fluency, attention, executive functioning and estimated premorbid functioning. There were no significant correlations found between 4MT scores and memory scores (ACE-III) for either AD ($r(10)= -.035$, p= .915) or other dementia type groups ($r(16)= .016$, p= .951). Furthermore, in the AD group there were no correlations found between 4MT scores and any other cognitive functions (see table 3). However, in the other dementia type group, 4MT scores had a moderate positive correlation with TMT B scores ($r(16)= .541$, p= .017) and negative correlation with visuospatial scores ($r(16)= -.477$, p= .045). However, it should be noted that these findings would not survive correction for Type I error across this set of correlations. Neither depression nor anxiety correlated with 4MT scores across the dementia groups.

Table 4: ***Pearson's Correlations between measured variables and 4MT scores split by dementia (N= 32)***

	AD 4MT		**Other dementia 4MT**	
	r	*p value*	*r*	*p value*
ACE total	-.195	.544	.312	.208
Memory	-.035	.915	.016	.951
Attention	.344	.274	.285	.251
Language	-.299	.344	.353	.151
Visuospatial	-.516	.086	.477*	.045
Fluency	.022	.946	.249	.319
EPF	.101	.743	.319	.183
TMT A	-.238	.456	.325	.174
TMT B	.286	.368	.541*	.017
Depression	.008	.980	-.397	.103
Anxiety	.009	.976	-.088	.728

* *Correlation is significant at the 0.05 level (2-tailed).*

** *Correlation is significant at the 0.01 level (2-tailed).*

Hypothesis 4: whether 4MT scores or any of the measured variables were predictors of diagnosis of AD or other forms of dementia.

An exploratory logistic regression was conducted to investigate whether any of the measured variables contributed to a diagnosis of AD versus other forms of dementia. Measured variables inputted into the regression model were selected based on correlational and clinical significance, and included TMT B scores, visuospatial, memory, fluency, 4MT scores, estimated premorbid functioning. In step 1, the selected variables were entered into the regression model as predictors of dementia diagnosis (i.e. AD or other dementia). The overall model did not classify a significant proportion of the individuals ($x2(6)= 6.81$, $p= .339$) and none of the variables were significant predictors of the outcome, AD or other dementia diagnosis. A stepwise logistic regression was also attempted to incorporate all the measured variables in an exploratory investigation, however, it was not possible to fit a model better than the constant term.

Feasibility

A total of 35 participants were recruited to the current study, however, three participants terminated the 4MT task during administration. Two of these participants had a diagnosis of early AD whereas one participant had a diagnosis of VD. The participant with VD had an ACE-III score below 70 and low average premorbid functioning. This may have impacted the ability to successfully complete the 4MT. The two participants with AD performed well on all background cognitive tests suggesting that difficulties with 4MT engagement might be due to topographical memory impairment. None of the three participants had depression or anxiety scores within the clinical ranges. Two of the three participants terminated the testing half way through the administration. Both participants gave the reason that they were finding the test too difficult and stressful. The other participant stopped the 4MT during the practice phase, giving the reason that the test they found the test trivial and did not feel the need to continue.

Based on the 32 participants who completed the test participant scores on 4MT were normally distributed with a mean score of 10.87 (SD= 10.87, range= 3–15). The 4MT scores in this study where significantly lower than the Bird control data with a mean score of 21.4 (SD= 3.34, range =16-30). Only one participant obtained a 4MT score below chance level (<25%) demonstrating that participants with mild dementia can effectively complete the 4MT to provide a useful measure of topographical memory. Formal feedback about the experience of completing the 4MT was not collected in this study but the researcher noted qualitative feedback given by participants on completion of the task. The majority of participants reported finding the test difficult and had performed poorly. Although the subjective experience of difficulty did not appear to result in actual poor performance on the 4MT. A number of participants also complained about the length of the 4MT, which took approximately 30 minutes to complete.

DISCUSSION

Summary of results

The current study aimed to investigate the application of the 4MT in a clinical setting to understand how performance varies according to dementia type at the earlier stages of the disease. Contrary to the hypothesis, 4MT performance was not found to be significantly impaired in AD participants compared to other types of dementia including VD. As hypothesised, AD participants had significantly poorer performance on the 4MT than the control group from the Bird et al (2010) study. This significantly poorer 4MT performance was also indicated in comparison of the other dementia type group to the Bird control group. However, the control participants were younger with higher estimated premorbid functioning compared to the dementia participants in the current study. These findings therefore should be interpreted tentatively (see *Limitations* for further discussion). Statistical analysis of MCI participants could not be conducted due to a small sample size.

Opposing another hypothesis, memory performance in AD participants did not correlate with 4MT performance nor were there any significant relationships found between these two variables for any type of dementia. Furthermore, there were no significant relationships between 4MT and other cognitive functions for AD participants. However, the 4MT performance of participants with other forms of dementia had significant relationships with executive functioning and visuospatial abilities. Depression and anxiety did not appear to have an impact on 4MT performance in any of the dementia groups. Unsurprisingly, on exploration of potential predictors of diagnosis of AD versus other forms of dementia there did not appear to be any significant predictors of the outcome. Consistent with non-significant finding, CI is broad and indicates study is underpowered.

Comparison with previous research

Previous research has demonstrated impairment in allocentric memory in early AD and suggested that tests tapping these hippocampal dependent abilities could aid early diagnosis (Maguire and Cipolotti, 1998; Chan et al., 2001; Galton et al., 2001; Kalova et al, 2005). The results of this study do not correspond with previous research conducted that impaired 4MT scores differentiated AD from other dementias in the context of hippocampal damage (Hartley et al, 2007; Bird et al, 2010; Kuven et al, *In Press*). Bird and colleagues (2010) found that short-term retention of topographical information was impaired in patients with AD but not in patients with FTLD or subjective memory impairment. These results also concurred with a recent study that found that 4MT topographical short-term memory subtest was impaired in MCI and AD patients compared to cognitively healthy controls in both UK and Italy populations and correlated with hippocampal volume (Kuven et al, *In Press*).

Previous studies support the future application of the 4MT in the diagnosis of early AD and to differentiate between other forms of dementia or healthy aging. However, a number of alternative studies have, to the contrary, demonstrated that the specific impairment underlying TD in early AD is the translation between the parietal egocentric and hippocampal allocentric representations (Cooper et al, 2001; Maguire, 2001; Vann et al, 2009). Research has suggested that this specific impairment is not measured in equivalent allocentric spatial tasks (Morganti et al, 2013). These results may coincide with this alternative explanation and account for the non-significant results i.e. the 4MT is not sufficiently sensitive to the allo- to ego-centric translation impairment. However, further research is needed to clarify this tentative comparison.

There are also differences in the recruitment and diagnostic processes of the clinical groups between the Bird et al. study and the current study that may contribute to the unexpected findings. Both studies recruited patients experiencing mild dementia and the lack of significant differences in 4MT performance across the two AD samples suggests that participants were at similar stages of the disease. However, unlike the current study, the Bird AD sample was

recruited from a research centre and more extensive diagnostic assessments were conducted (i.e. interview, neuropsychological assessment and imaging). Different diagnostic criteria was also used to define the AD group, which offers a more in depth cognitive analysis (i.e. NINCDS-ADRDA for Bird Study). Furthermore, more stringent exclusion criteria were applied to the clinical groups including a history of learning disability, and/or below baseline attention ability. Thus, comparatively the Bird AD group may comprises a more homogenous and defined group of mild AD participants with less co-morbid difficulties, whereas the current AD sample maybe more heterogeneous in presentation and severity. Thus, caution should be taken when making comparisons between the two studies and may contributed to the conflicting findings. The current study was conducted within an affluent area of London, which may have created bias and contribute to the findings. However, there is no description of the social factors of the Bird et al sample and therefore comparisons cannot be made in terms of the impact affluence may have had 4MT and cognitive test performance.

Interpretation of findings

In this study, VD formed the second largest dementia group in line with national statistics and it is possible that the inclusion of this group may account for the conflicting findings. Previous studies using 4MT did not include participants with VD, the second most common form of dementia to present to memory services (Bird et al, 2010; Kuven et al, *In Press*). The pathology of VD is often heterogeneous and hippocampal atrophy can often be present (Pol et al, 2011). It is plausible that the 4MT is therefore not sensitive enough to differentiate between AD and VD given the overlap in atrophy and may account for the findings. The lack of significant differences in memory performance between AD and other forms of dementia including VD supports this interpretation as it could suggest potential hippocampal atrophy in both groups. Furthermore, there were a number of participants with diagnosis of mixed AD and VD suggesting they may have atrophy to hippocampal regions that may have further reduced the other dementia type group 4MT performance. However, on exclusion of participants with mixed VD and AD from the other dementia type group the non-significant differences in 4MT

remained across the two groups. Thus, supporting the idea of potential pathology and symptom cross-over between the AD and VD groups.

The results may also reflect a wider issue in translating laboratory design tests into clinical settings and that the 4MT may have poor ecological validity. Often in clinical practise, dementia presentations can be complex and diverse thus making it hard to make a clear and definite diagnosis. However, being referred to a memory clinic suggests that the patient or a significant other is aware of the cognitive symptoms as they are having an impact on daily functioning. Thus, samples recruited from memory clinics may include patients with more moderate dementias and less patients within the very earliest of stages of the disease for which the 4MT has demonstrated utility. It should be considered when interpreting these findings therefore that perhaps the results do not suggest a significant flaw within the 4MT but rather a clinical dilemma of stage of dementia and the ability to usefully engage with 4MT.

The non-significant differences in 4MT performances between AD and other dementia types as well as the lack of correlations with specific cognitive functions are interesting findings. A major contributing factor to this may be that the study is underpowered due to a smaller sample size than expected, the implications of which are discussed in detail below (see limitation section). However, a number of other findings may provide plausible explanations of the unexpected results. The significant relationship between visuospatial and 4MT performance in the other dementia group is surprising. It can tentatively be inferred that poor abilities in the visual domain were influencing poor 4MT performance thus possibly contributing to the similarities in 4MT with AD participants. However, in the regression analysis visuospatial was not indicated to be a determinant of dementia group and therefore this interpretation remains tentative requiring further exploration. There were no significant differences in neuropsychological characteristics between the AD group and other dementia type group or the VD group. This suggests that participants were similar in areas of neuropsychological functioning reducing any confounding influence on 4MT performance that could have

contributed to the lack of significant differences across the groups. Interestingly, when participants scoring zero on 4MT (N=32), which can be deemed well below chance thus representing a floor effect, were excluded from the neuropsychological score comparisons these non-significant differences remained further supporting this assumption.

Limitations

There are also a number of methodological limitations in this study that may have contributed to the non-significant findings. The most significant is the sample size of this study, which is smaller than the estimation for sufficient power suggested in the preliminary power analysis. However, it is important to note that the estimated sample size was predicated on a medium effect size. Therefore, the lack of a findings with 32 participants speaks against a large effect but the study was sufficiently powered for d=1 on a t-test if N=32. It can therefore be assumed that the study was underpowered to find a medium to large effect size. This may have increased the chance of type II errors occurring thus reducing the validity and reliability of the findings. It should be noted that a significant effort was made to reach the desired sample size but was hindered by limited resources (e.g. sole researcher), strict time constraints (e.g. DClinPsy deadlines) and significant staff changes to the recruitment sites.

The cross sectional design of this study is also a limitation and it is not possible to draw firm conclusions from these findings especially regarding causal relationships. Therefore, it remains unclear whether the 4MT is a reliable tool that can aid the diagnosis of early AD and whether any other cognitive factors influence this relationship. Future studies in this area are encouraged to utilise longitudinal designs. Another issue with cross-sectional design is the influence of confounding variables. A number of confounds were measured in this study using self-report and neuropsychological tests that may have contributed to performance on 4MT (e.g. age, education level, visuo-spatial abilities). Elderly participants are particularly vulnerable to fatigue and therefore keeping the testing battery short was a priority and the measures included were carefully considered to meet the study aims. More in depth measures of cognitive abilities

using the WAIS-IV or WMS may have provided more valid indicators of cognitive abilities and memory functioning (i.e. delayed vs immediate memory). Furthermore, additional measures could have been included to capture further confounding variables such as hearing and visual abilities, which would enabled them to be statistically controlled for in the regression model. However this may have markedly increased the time required to complete the testing battery, which would not have been deemed ethical given the vulnerabilities of a dementia population.

The post diagnosis recruitment may have also contributed to the non-significant findings as this introduced a time delay between initial assessments and being contacted about the research, in some cases up to 4 months. Thus, participants may have advanced in their dementia from when the referral was made. This was also reflected in ACE-III scores where a small but significant number of participants were scoring below 70 at the research appointment after scoring above this at initial screening. However, assessment for dementia can be an uncertain time for patients creating distress and anxiety (Lecouturier et al, 2008). For this reason the National Ethics Committee felt it was unethical to conduct the study prior to the participants being disclosed a diagnosis of dementia. Furthermore, despite the time delay, when exploring the data of participants with low ACE-III scores they appeared to perform relatively well on 4MT despite cognitive impairment suggesting minimal impact to the findings.

There were also limitations with conducting the majority of the research in a participant's home environment. The lack of consistent and distraction free environment may have interfered with performance on neuropsychological testing and thus reduced the internal validity of the findings. However, restricting testing to the memory service would reduced the representativeness of the sample as it would have meant excluding the more frail participants who would have struggled to travel for an appointment. Ideally, being able to fund all participants to come to the memory service in pre-arranged transport would have enabled a more consistent research environment that may have increased validity and reliability, however, this was beyond the resources of this study.

It is well evidenced that low mood and anxiety can interfere with performance on cognitive tests (Beaudreau & O'Hara, 2009) and memory (Burt et al, 1995; Eysenck and Calvo, 1992). Although there was no significant relationship between anxiety and depression on 4MT performance, individual analysis of the scores suggests that some participants were within clinical range. Furthermore, disclosure of a dementia diagnosis has been associated with negative emotional reactions including low mood and anxiety in some people (De Lepeleire, Buntinx & Aertgeerts, 2004). Although efforts were made to exclude participants with mental health difficulties at initial screening there is a possibility that such psychological difficulties impacted performance on 4MT and the other cognitive tests. Tighter exclusion of participants with these symptoms may have increased the validity of the current findings i.e. incorporating depression and anxiety screening questionnaires prior to testing. However, given the overall non-significance of clinical symptoms in the sample, indicated by the HADs questionnaire, these effects may have been minimal.

The current study aimed to understand the clinical utility of the 4MT and therefore was concerned with performance across the clinical groups. Therefore it was not deemed necessary to collect a control comparison group in light of resource being limited and time restrained. The clinical 4MT data was compared to the Bird et al (2010) control data in the absence of the control group in the current study. However, there were differences in demographic and neuropsychological characteristics of the Bird control group when compared to the AD and other dementia type group in the current study that reduced the reliability of the comparisons and therefore limit the inferences that can be drawn from the significant findings. Ageing is known to cause an increasing decline in cognitive abilities including memory (Peters, 2006). The Bird control group was comprised of younger participants than the clinical groups in the current study and therefore a less impaired cognitive baseline that may have enhanced performance on the 4MT and other neuropsychological tests. Furthermore, the Bird control group also had superior estimated premorbid functioning, which is considered a protective

factor against cognitive decline (Peters, 2006) and may have further enhanced performance on the measures. These differences affect the reliability of the comparisons and therefore the significant differences found between controls data and the clinical groups should be interpreted with caution. It would be helpful to replicate this study using a control group matched to the clinical groups in terms of demographic variables.

Clinical implication

The results of the study provide conflicting evidence to previous research that suggested the usefulness of the 4MT as a potential tool to facilitate early AD diagnosis. This study demonstrates that the 4MT appears to encounter difficulties differentiating between the two most common forms of dementia; AD and VD. This therefore raises the question whether the 4MT is as applicable as previously suggested to a clinical setting where these presentations are common as well as often more complex and less clearly defined. In of light of the current findings, to fully understand the 4MTs potential as a clinical tool to aid early diagnosis of AD further research is needed and helpful ideas for this are discussed below. Researchers have raised a need for a more ecological assessment of spatial abilities that reflect real life situations as it was felt that most traditional tests are insensitive to topographical disorientation (Nadolne & Stringer, 2001). The 4MT is a tool that simulates a more ecological situation, however, it is clear that further studies applying this test to clinical settings is needed prior to drawing conclusions regarding clinical utility.

These findings also raise the wider issue in translating laboratory design tests into clinical settings. The 4MT was developed in a controlled test environments where it was possible to conduct vigorous diagnostic assessment, make more definitive and clear diagnosis and utilise homogeneous samples. However, these laboratory settings are not reflective of clinical settings where presentations are complex and diverse, resource is limited and administration takes place in less than perfect environments (i.e. patient's home). The findings of this study highlight the need for researchers to consider the ecological validity issues posed when developing tests, such

as 4MT, in laboratory settings. The design of the 4MT attempted to overcome issues of ecological validity by using stimuli that reflect real world settings (i.e. mountain landscapes). However, future early diagnostic tests would benefit from being developed within clinical settings where environments more closely resemble those found in these settings (i.e. heterogeneous samples, brief completion time). This would increase ecological validity, enhance clinical utility and provide tools that can operate more effectively in clinical practice.

As discussed previously, past studies using the 4MT did not include a VD group, unlike the current study. A number of previous studies have reported evidence of significant hippocampal atrophy in vascular dementia (Laakso et al, 1996; Barber et al, 2000; Hanyu et al, 2000; Fein et al, 2000; Du et al, 2002; Gainotti et al, 2004; Burton et al, 2009). This has led to a new subtype of VD being proposed known as subcortical VD (Erkinjuntti et al, 2000), which is presumed to be the most common type of vascular dementia (van de Pol, 2011). The non-significant differences on 4MT performance between the AD and VD groups provides further evidence for hippocampal atrophy in VD. The findings therefore support the need for more well-defined and homogeneous subtypes of VD, such as subcortical VD, in order to enable more predictable clinical presentation, outcome and treatment responses (Erkinjuntti et al, 2000). This raises significant questions for the effectiveness of tests of allocentric memory impairment in early dementia diagnosis that merit further investigation.

There is a growing interest in the early diagnosis of dementia in order to enable patients and their families access timely information and advice, useful medical and psychosocial interventions, and allow planning about future care (Prince et al, 2011; Department of Health, 2012). This study supports and adds to this evidence base, but there are ethical dilemmas posed with the advancement of early diagnostic tools when the available treatments only delay symptoms for a relatively short period of time. It is important to acknowledge the potential dilemmas associated with early dementia screening. Early diagnosis of dementia has been associated with anxiety, depression and even suicide in patients (Draper et al, 2010). Other

potential negative implications include difficulties with sustaining employment and purchasing insurance, as well as a reduced sense of autonomy, self-image and overall quality of life (Lliffe, Manthorpe & Eden, 2003; Mattison, Brax & Zetterberg, 2010). Early diagnosis may also impact negatively on carers and family members, in terms of feelings of shame, stigma and isolation, and in changing the relationship with the patient (Mattison, Brax & Zetterberg, 2010). Furthermore, some of these emotional and practical challenges have also been found to occur within an MCI population, a diagnosis that is rising as a result of the emphasis on assessing people earlier for dementia (Dean & Wilcock, 2012). It is important therefore that the early diagnostic research is balanced with research investigating the associated potential risks and adverse consequences to guarantee ethical and thoughtful practice.

Future Research

To overcome the issues with power discussed above and allow for more conclusive findings it would be helpful to replicate this study with a higher sample size. However, alongside this it would also be beneficial to include a larger VD and MCI group as well as participants who did not received a diagnosis as an additional comparison group. Furthermore, administering the 4MT prior to diagnosis of dementia and as early in the disease as possible would enabled further understanding of its clinical use in aiding early diagnosis of AD. For example, replication of the study within a primary care setting when a patient first reports memory symptoms to the GP would enable access to participants at early stages of dementia. However, it is likely that the same ethical dilemmas would arise and careful consideration is needed. Furthermore, to make more firm conclusions about causal relationships it would be helpful to incorporate a longitudinal aspect with administration of 4MT through the course of dementia progression. This would enable understanding of how performance changes as the disease progresses across the different dementias.

Another helpful future direction for this research project would be to match MRI scans to data collected of those participants whom had one conducted at the initial assessment. This would

enable a deeper understanding of the non-significant differences in 4MT scores and the relationship to hippocampal atrophy. Furthermore, this would hopefully provide more understanding of the clinical utility of the 4MT to differentiate between AD and VD with regards to overlap in brain pathology. Furthermore, including a test that is able to control and manipulate the egocentric point of view would allow for the evaluation of whether AD spatial deficits are linked to difficulties with storing an allocentric map or the translation between the different spatial representations.

REFERENCES

Aben, I., Verhey, F., Lousberg, R., Lodder, J., & Honig, A. (2002). Validity of the Beck Depression Inventory, Hospital Anxiety and Depression Scale, SCL-90 and Hamilton Depression Rating Scale as screening instruments for depression in stroke patients. *Psychosomatics*, 43, 386–393.

Abrahams, S., Morris, R. G., Polkey, C. E., Jarosz, J. M., Cox, T. C., Graves, M., & Pickering, A. (1999). Hippocampal involvement in spatial and working memory: a structural MRI analysis of patients with unilateral mesial temporal lobe sclerosis. *Brain & Cognition*, 41, 39–65.

Agamanolis, D. P. (2014, June). *Alzhiemer's Disease*. Retrieved from http://neuropathology-web.org/agamanolis.html

Alafuzoff, I., Arzberger, T., Al-Sarraj, S., Bodi, I., Bogdanovic, N., Braak, H., Bugiani, O., Del-Tredici, K., Ferrer, I., Gelpi, E., Giaccone, G., Graeber, M. B., Ince, P., Kamphorst, W., King, A., Korkolopoulou, P., Kovács, G. G., Larionov, S., Meyronet, D., Camelia Monoranu, C., Parchi, P., Patsouris, E., Roggendorf, W., Seilhean, D., Tagliavini, F., Stadelmann, C., Streichenberger, N., Thal, D. R., Wharton, S. B., & Kretzschmar, H. Staging of neurofibrillary

pathology in Alzheimer's disease: A study of the BrainNet Europe Consortium. *Brain Pathology*, 18, 484–96.

Ashendorf, L., Jefferson, A. L., O'Connor, M. K., Chaisson, C., Green, R. C., & Stern, R. A. (2008). Trail Making Test errors in normal aging, mild cognitive impairment, and dementia. *Archives of Clinical Neuropsychology*, 23, 129–37.

Baddeley, A. D., Emslie, H., & Nimmo-Smith, I. (1994). *The Doors and People Test*. Bury St. Edmunds, Suffolk: The Thames Valley Test Company.

Bambauer, K. Z., Locke, S. E., Aupont, O., Mullan, M. G., & McLaughlin, T. J. (2005). Using the Hospital Anxiety and Depression Scale to screen for depression in cardiac patients. *General Hospital Psychiatry*. 2005, 27, 275–84.

Barber, R., Ballard, C., McKeith, I. G., Gholkar, A., O'Brien, J. T. (2000). MRI volumetric study of dementia with Lewy bodies: a comparison with AD and vascular dementia. *Neurology*, 54, 1304–1309.

Beaudreau, S, A., & O'Hara, R. (2009).The Association of Anxiety and Depressive Symptoms with Cognitive Performance in Community-Dwelling Older Adults. *Psychological Aging,* 24(2), 507–512.

Bird, C. M., Chan, D., Hartley, T., Pijnenburg, Y. A., Rossor, M. N., & Burgess, N. (2010) Topographical short-term memory differentiates Alzheimer's disease from frontotemporal lobar degeneration. *Hippocampus,* 20(10), 1154 – 1169.

Bjelland, I., Dahl, A. A., Haug, T. T., & Neckelmann, D. (2002). The validity of the Hospital Anxiety and Depression Scale: an update literature review. *Journal of Psychosomatic Research*, 52, 69–77.

Bowler, J. V. (2002). The concept of vascular cognitive impairment. *Journal of Neurological Sciences, 202-203, 11-15.*

Boyle, P. A. (2001). Decision-making strategies used by neuropsychologists in the differential diagnosis of dementia. *Dissertation Abstracts International: Section B: The Sciences and Engineering*, 61(7-B), 3832.

Braak, H., & Braak, E. (1991). Neuropathological staging of Alzheimer-related changes. *Acta Neuropathologica,* 82, 239–259.

Braak, H., & Braak, E. (1996). Development of Alzheimer-related neurofibrillary changes in the neocortex inversely recapitulates cortical myelogenesis. *Acta Neuropathologica*, 92, 197 –201.

Burgess, N., Trinkler, I., King, J., Kennedy, A., & Cipolotti, L. (2006). Impaired allocentric spatial memory underlying topographical disorientation. *Reviews in the Neurosciences*, 17(1-2), 239.

Burt, D. B., Zembar, M.J., & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychological Bulletin*, 117, 285–305.

Burt, D. B., Zembar, M. J. & Niederehe, G. (1995). Depression and memory impairment: a meta-analysis of the association, its pattern, and specificity. *Psychology Bulletin*, 117(2):285-305.

Burton, E. J., Barber, R., Mukaetova-Ladinska, E. B., Robson, J., Perry, R. H., Jaros, E., Kalaria, R. N., O'Brien, J. T. (2009). Medial temporal lobe atrophy on MRI differentiates Alzheimer's disease from dementia with Lewy bodies and vascular cognitive impairment: a prospective study with pathological verification of diagnosis. Brain, 46, 195–203.

Chan, D., Fox, N. C., Scahill, R. I., Cahill, R. I., Crum, W. R., Whitwell, J. L., Leschziner, G., Rossor, A. M., Stevens, J. M., Cipolotti, L., & and Rossor, M. N. (2001). Patterns of temporal lobe atrophy in semantic dementia and Alzheimer's disease. *Annals of Neurology,* 49, 433-442.

Chinn, S. (2000). Statistics in Medicine. A simple method for converting an odds ratio to effect size for use in meta-analysis. *Statistical. Medicine*, 19, 3127–3131.

Cooper, B. G., Manka, T. F., & Mizumori, S. J. (2001). Finding your way in the dark: The retrosplenial cortex contributes to spatial memory and navigation without visual cues. *Behavioural Neuroscience*, 115, 1012–1028.

Cressant, A., Muller, R. U., & Poucet, B. (1997). Failure of centrally placed objects to control the firing fields of hippocampal place cells. *Journal of Neuroscience*, 17, 2531–2542.

De Lepeileire, J., Heyman, J., & Buntinx, F. (1998). The early diagnosis of dementia: triggers, early signs and luxating events. *Family Practice*, 15(5), 431–436.

De Lepeleire, J., Buntinx, F., & Aertgeerts, B. (2004). Disclosing the diagnosis of dementia: the performance of Flemish general practitioners. *International Psychogeriatr*ic, **16**(4)**,** 421-428.

Delis, D. C., Kaplan, E., & Kramer, J. (2001). *Delis Kaplan Executive Function System*. San Antonio TX: Psychological Corporation.

Department of Health (2009). *National Dementia Strategy.* Available from http://www.dh.gov.uk/en/SocialCare/NationalDementiaStrategy/index.htm.

Lakey, L. (2012). *Dementia 2012: A National Challenge.* Available from: http://www.alzheimers.org.uk/site/scripts/documents_info.php?documentID=341.

Dickson D. W. (1997). The pathogenesis of senile plaques. *Journal of Neuropathology & Experimental Neurology*, 56, 321–339.

Doeller C. F., King J. A., & Burgess N. (2008). Parallel striatal and hippocampal systems for landmarks and boundaries in spatial memory. *Proceedings of the National Academy of Sciences*, USA, 105, 5915–5920.

Du A. T., Schuff, N., Laakso, M. P., Zhu, X. P., Jagust, W. J., Yaffe, K., Kramer, J. H., Miller, B. L., Reed, B. R., Norman, D., Chui, H. C., Weiner, M. W. (2002). Effects of subcortical ischemic vascular dementia and AD on entorhinal cortex and hippocampus. *Neurology,* 58, 1635–1641.

Duff, K., Chelune, G.J., & Dennett, K. (2011). Predicting estimates of premorbid memory functioning: Validation in a dementia sample. *Archives of Clinical Neuropsychology*, 26, 701-705.

Ekstrom, A. D., Kahana, M. J., Caplan, J. B., Fields, T. A., Isham, E. A., Newman, E. L., & Fried, I. (2003). Cellular networks underlying human spatial navigation. *Nature*, 425, 184–188.

Erkinjuntti, T., Inzitari, D., Pantoni, L., Wallin, A., Scheltens, P., Rockwood, K., Roman, G. C., Chui, H., Desmond, D. W. (2000). Research criteria for subcortical vascular dementia in clinical trials. *Journal of Neural Transmission*, 59, 23–30.

Eysenck, M. W., & Calvo, M. G. (1992). Anxiety and performance: the processing efficiency theory. *Cognition and Emotion*, 6, 409–434.

Fein, G., di Sclafani, V., Tanabe, J., Cardenas, V., Weiner, M. W., Jagust, W. J., Reed, B. R., Norman, D., Schuff, N., Kusdra, L., Greenfield, T., Chui, H. (2000). Hippocampal and cortical atrophy predict dementia in subcortical ischemic vascular disease. *Neurology*, 55, 1626–1635.

Gainotti, G., Acciarri, A., Bizzarro, A., Marra, C., Masullo, C., Misciagna, S., Tartaglione, T., Valenza, A., Colosimo, C. (2004). The role of brain infarcts and hippocampal atrophy in subcortical ischaemic vascular dementia. Neurological Sciences, 25, 192–197.

Gallistel C. R. (1990). *The Organization of Learning*. Cambridge, MA: MIT Press.

Galton, C. J., Patterson, K., Graham, K. S., Williams, G., Antoun, N., Sahakian, B. J., & Hodges, J. R. (2001). Differing patterns of temporal lobe atrophy in Alzheimer's disease and semantic dementia: Diagnostic and theoretical implications. *Neurology*, 57, 216-225.

Ganguli, M., Dodge, H. H., Shen, C., & DeKosky, S. T. (2004). Mild cognitive impairment, amnestic type: An epidemiologic study. *Neurology*, 63, 115-121.

Ganguli, M., Snitz, B. E., Saxton, J. A., Chang, C. C., Lee, C. W., Vander, Bilt. J., Hughes, T. F., Loewenstein, D. A., Unverzagt, F. W., & Petersen, R. C. Outcomes of mild cognitive impairment depend on definition: a population study. *Archives of Neurology,* 68, 761–767.

Gaudino, E. A., Geisler, M. W., & Squires, N. K. (1995). Construct validity in the Trail Making Test: What makes Part B harder? *Journal of Clinical Expermental Neuropsychology*, 17 (4), 529-535.

Gaugler, J. E., Kane, R. L., Kane, R. A., & Newcomer, R. (2005). Early community-based service utilization and its effects on institutionalization in dementia caregiving. *Gerontologist,* 45(2), 177-185.

Gazova, I., Vlcek, K., Laczó, J., Nedelska, Z., Hyncicova, E., Mokrisova, I., Sheardova, K., & Hort, J. (2012). Spatial navigation—a unique window into physiological and pathological aging. *Frontiers in Aging Neuroscience,* 4, 16.

Hanyu, H., Asano, T., Iwamoto, T., Takasaki, M., Shindo, H., Abe, K. (2000). Magnetization transfer measurements of the hippocampus in patients with Alzheimer's disease, vascular dementia, and other types of dementia. *AJNR American Journal of Neuroradiology,* 21, 1235–1242.

Hartley, T., Bird, C. M., & Chan, D. (2007). The hippocampus is required for short-term topographical memory in humans. *Hippocampus*, 17, 34–48.

Herrero, M. J., Blanch, J., Peri, J. M., De Pablo, J., Pintor, A., & Bulbena, A. (2003). A validation study of the Hospital Anxiety and Depression Scale (HADS) in the Spanish population. *General Hospital Psychiatry*, 25, 277-283.

Herrmann, C. (1997). International experiences with the Hospital Anxiety and Depression Scale: A review of validation data and clinical results. *Journal of Psychosomatic Research*, 42, 17–41.

Holdstock, J. S., Mayes, A. R., Cezayirli, E., Isaac, C. L., Aggleton, J. P., & Roberts, N. (2000). A comparison of egocentric and allocentric spatial memory in a patient with selective hippocampal damage. *Neuropsychologia*, 38, 410 – 425.

Hsieh S., Schubert S., Hoon C., Mioshi E. & Hodges J. R. (2013). Validation of the Addenbrooke's Cognitive Examination III in Frontotemporal Dementia and Alzheimer's Disease. *Dementia and Geriatric Cognitive Disorders*, 36, 242–250.

Inagaki, H., Meguro, K., Shimada, M., Ishizaki, J., Okuzumi, H., & Yamadori, A. (2002). Discrepancy between mental rotation and perspective-taking abilities in normal aging assessed by Piaget's Three-mountain task. *Journal of Clinical and Experimental Neuropsychology,* 24, 18–25.

Jak, A. J., Bondi, M. W., Delano-Wood, L., Wierenga, C., Corey-Bloom, J., Salmon, D. P., & Delis, D. C. (2009). Quantification of five neuropsychological approaches to defining mild cognitive impairment. *American Journal of Geriatric Psychiatry*, 17, 368–375.

Jagust, W. (2001). Untangling vascular dementia. *Lancet*, 358(9299), 2097–2098.

Johnson, G., Burvill, P. W., Anderson, C. S., Jamrozik, K., Chakera, T. M., & Stewart-Wynne, E. G. (1995). Screening instruments for depression and anxiety following stroke: experience in the Perth community stroke study. *Acta Psychiatrica Scandinavica,* 91, 252-257.

Kalová, E., Vlcek, K., Jarolímová, E., & Bures, J. (2005). Allothetic orientation and sequential ordering of places is impaired in early stages of Alzheimer's disease: corresponding results in real space tests and computer tests. *Behavioural Brain Research*, 159, 175–186.

King J, A., Burgess, N., Hartley, T., Vargha-Khadem, F., & O'Keefe, J. (2002). The human hippocampus and viewpoint dependence in spatial memory. *Hippocampus*, 12, 811–820.

Klatzky, R. L. (1998). *"Allocentric and egocentric spatial representations: definitions, distinctions, and interconnections," in Spatial Cognition*. An Interdisciplinary Approach to Representing and Processing Spatial Knowledge, eds C. Freksa and C. Habel (Heidelberg: Springer), 1–17.

Kuven, K. M., Minati, L., Contarino, V. E., Prioni, S., Wood, R., Cooper, R., D'Incerti, L., Tagliavini, & F., Chan, D. (In Press). Diagnostic differentiation of mild cognitive impairment due to Alzheimer's disease using a hippocampus-dependent test of spatial memory. *Hippocampus,* manuscript accepted for publication.

Laczó, J., Vlclek, K., Vyhnálek, M., Vajnerová, O., Ort, M., Holmerová, I., Tolar, M., Andeˇl, R., Bojar, M., & Hort, J. (2009). Spatial navigation testing discriminates two types of amnestic mild cognitive imairment. *Behavioural Brain Research*, 202, 252–259.

Laakso, M. P., Partanen, K., Riekkinen, P., Lehtovirta, M., Helkala, E. L., Hallikainen, M., Hanninen, T., Vainio, P., Soininen, H. (1996). Hippocampal volumes in Alzheimer's disease, Parkinson's disease with and without dementia, and in vascular dementia: an MRI study. *Neurology*, 46, 678–681.

Lecouturier, J., Bamford, C., Hughes, J.C., Francis, J.J., Foy, R., Johnston, M. & Eccles, M.P. (2008). Appropriate disclosure of a diagnosis of dementia: Identifying the key behaviours of 'best practice'. *BMC Health Services Research*, 8, 95.

Lezak, M.D. (1995). *Neuropsychological assessment.* (3rd ed.). Oxford: Oxford University Press.

Lithfous, S., Dufour, A., & Despres, O. (2013). Spatial navigation in normal aging and the prodromal stage of Alzheimer's disease: insights from imaging and behavioral studies. *Ageing Research Review*, 12, 201–213.

Lowe, B., Spitzer, R. L., Grafe, K., Kroenke, K., Quenter, A., Zipfel, S., Buchholz, C., Witte, & S., Herzog, W. (2004). Comparative validity of three screening questionnaires for DSM-IV depressive disorders and physicians' diagnoses. *Journal of Affective Disorders*, 78, 131 -140.

Maguire, E. A., & Cipolotti, L. (1998). Selective sparing of topographical memory. *Journal of Neurology, Neurosurgery & Psychiatry,* 65, 903-909

Maguire, E. A., Frith, C. D., Burgess, N., Donnett, J. G., & O'Keefe, J. (1998). Knowing where things are parahippocampal involvement in encoding object locations in virtual large-scale space. *Journal of Cognitive Neuroscience*, 10, 61–76.

Maguire, E. A., Burgess, N., Donnett, J. G., Frackowiak, R. S., Frith, C. D., & O'Keefe, J. (1998). Knowing where and getting there: a human navigation network. *Science* 280, 921–924.

McFarlane, J., Welch., & J. Rodgers. (2006). Severity of Alzheimer's disease and effect on premorbid measures of intelligence. *British Journal of Clinical Psychology*, 45(4), 453–463.

Micieli, G. (2006). Vascular dementia. *Neurological sciences: official journal of the Italian Neurological Society and of the Italian Society of Clinical Neurophysiology, 27,* S37–39.

Mioshi, E., Dawson, K., Mitchell, J., Arnold, R., & Hodges J, R. (2006). The Addenbrooke's Cognitive Examination Revised (ACE-R): a brief cognitive test battery for dementia screening. *Internal Journal of Geriatric Psychiatry*, 21, 1078–1085.

Mittelman, M. S., Ferris, S. H., Shulman, E., Steinberg, G., & Levin, B. (1996). A family intervention to delay nursing home placement of patients with Alzheimer disease. A randomized controlled trial. *JAMA*, 276(21), 1725- 1731.

Molinuevo, J. L., Berthier, M. L., & Rami, L. (2011). Donepezil provides greater benefits in mild compared to moderate Alzheimer's disease: implications for early diagnosis and treatment. *Archives of Gerontology Geriatrics*, 52(1), 18-22.

Morganti, F., Stefanini, S., & Riva, G. (2013). From allo- to egocentric spatial ability in early Alzheimer's disease: a study with virtual reality spatial tasks. *Cognitive Neuroscience*, 4, 171-180.

Morris, J. C., Storandt, M., McKeel, D. W. Jr., Rubin, E. H., Price, J. L., Grant, E. A., & Berg, L. (1996). Cerebral amyloid deposition and diffuse plaques in "normal" aging: Evidence for presymptomatic and very mild Alzheimer's disease. *Neurology*, 46, 707–719.

Morris, J. C. (2005). Mild cognitive impairment and preclinical Alzheimer's disease. *Geriatrics*, 9-14.

Muller, R. U. (1996). A quarter of a century of place cells. *Neuron,* 17, 813–822.

Nadolne, M.J., & Stringer, A.Y. (2001). Ecologic validity in neuropsychological assessment: prediction of wayfinding. *Journal of the International Neuropsychological Society*, 7 (06), 675–682.

O'Keefe , J., & Dostrovsky, J. (1971). The hippocampus as a spatial map. Preliminary evidence from unit activity in the freely-moving rat. *Brain Research,* 34, 171–175.

O'Keefe, J. (1976). Place units in the hippocampus of the freely moving rat. *Experimental Neurology,* 51, 78–109.

O'Keefe, J., & Nadel, L. (1978). *The Hippocampus as a Cognitive Map*. Oxford University Press, New York.

O'Keefe J., & Burgess N. (1996). Geometric determinants of the place fields of hippocampal neurons. *Nature*, 381, 425–428.

Packard, M. G., & Knowlton, B. J. (2002). Learning and memory functions of the basal ganglia. *Annual Review of Neuroscience*, 25, 563–593.

Paolo, A., Troster, A., Ryan, J. & Koller, W. (1997). Comparison of NART and Barona Demographic Equation Premorbid IQ Estimates in Alzheimer 's disease. *Journal of Clinical Psychology*, 53(7), 713-722.

Peters, R. (2006). *Ageing and the brain*. Postgraduate Medical Journal, 82(964): 84-88.

Petersen, R. C. (2003). *Conceptual overview*. In: Petersen RC, editor. Mild Cognitive Impairment: Aging to Alzheimer's Disease. London: Oxford University Press. p. 1-14.

Petersen, R. C. (2004). Mild cognitive impairment as a diagnostic entity. *Journal of Internal Medicine,* 256, 183-194.

Petersen, R. C., Doody, R., Kurz, A., Mohs, R. C., Morris, J. C., Rabins, P. V., Ritchie, K., Rossor, M., Thal, L., & Winblad, B. (2001). Current concepts in mild cogni- tive impairment. *Archives of Neurology,* 58, 1985–1992.

van de Pol, L., Gertz, H. J., Scheltens, P., & Wolf, H. (2011). Hippocampal atrophy in subcortical vascular dementia. *Neurodegenerative Disorder*, 8(6), 465-9.

Prince, M., Bryce, R., & Ferri, C. (2011). *World Alzheimer report 2011: the benefits of early diagnosis and intervention*. London (UK): Alzheimer's Disease International (ADI).

Rasmusson, X., Zonderman, A., Kawas, C. & Resnick, S. (1998). Effects of age and dementia on the Trail Making Test. *The Clinical Neuropsychologist,* 2, 169-178.

Reitan, R. M. (1958). Validity of the Trail Making Test as an indicator of organic brain damage. *Perceptual and Motor Skills*, 8, 271–276.

Reitan. R. M. (1992). *Trail making test: Manual for administration and scoring.* Neuropsychology Laboratory, Tucson, AZ.

Roman, G. C., Tatemichi, T. K., Erkinjuntti, T., Cummings, J. L., Masdeu, J. C., Garcia, J. H., Amaducci, L., Orgogozo, J. M., Brun, A., Hofman, A., Moody, D. M., O'Brien, M. D., Yamaguchi, T., Grafman, J., Drayer, B. P., Bennett, D. A., Fisher, M., Ogata, J., Kokmen, E., Bermejo, F., Wolf, P. A., Gorelick, P. B., Bick, K. L., Pajeau, A. K., Bell, M. A., DeCarli, C., Culebras, A., Korczyn, A. D., Bogousslavsky, J., Hartmann, A., & Scheinberg, P. (1993).

Vascular dementia: diagnostic criteria for research studies, Report of the NINDS-AIREN International Workshop. *Neurology*, 43:250–260.

Rosenstein, L. D. (1998). Differential diagnosis of the major progressive dementias and depression in middle and late adulthood: A summary of the literature of the early 1990s. *Neuropsychology Review, 8,* 109–167.

Rountree, S. D., Chan, W., Pavlik, V. N., Darby, E. J., Siddiqui, S., & Doody, R. S. (2009). Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. *Alzheimer's Research and Therapy*, 1(2), 7.

Sachdev, P. S., Brodaty, H., & Looi, J. C. L. (1999). Vascular dementia: Diagnosis, management and possible prevention. *Medical Journal of Australia, 170,* 81–85.

Samaras, N., Herrmann, F. R., Samaras, D., Lang, P. O., Canuto, A., Forster, A., Hilleret, H., & Gold, G. (2013). The Hospital Anxiety and Depression Scale: low sensitivity for depression screening in demented and non-demented hospitalized elderly. *International Psychogeriatrics*, 25(1), 82-87.

Schott, J. M., Fox, N. C., & Frost, C. (2003). Assessing the onset of structural change in familial Alzheimer's disease. *Annals of Neurology*, 53, 181–188.

Sharp, E, S., & Gatz, M. (2011). The Relationship between Education and Dementia An Updated Systematic Review. *Alzheimer Disease Association Disorder*, 25(4): 289-304.

Shum, D.H.K., McFarland, K.A., & Bain, J.D. (1990). Construct validity of eight tests of attention: Comparison of normal and closed head injured samples. *The Clinical Neuropsychologist*, 4, 151-162.

Spreen, O., & Strauss, E. (1991). *A Compendium of Neuropsychological Tests: Administration, Norms, and Commentary*. New York, NY: Oxford University Press.

Strauss, E., Sherman, E. M. S., & Spreen, O. (2006). *A compendium of neuropsychological tests: Administration, norms and commentary* (3rd ed.). New York: Oxford University Press.

Thal, D. R., Rub, U., Orantes, M., & Braak, H. (2002). Phases of A beta-deposition in the human brain and its relevance for the development of AD. *Neurology,* 58, 1791–1800.

Thomas, B. C., Devi, N., Sarita, G. P., Rita, K., Ramdas, K., Hussain, B. M., Rejnish, R., & Pandey, M. (2005). Reliability & validity of the Malayalam hospital anxiety & depression scale (HADS) in cancer patients. *Indian Journal of Medical Research*, 122, 395-399.

Tolman, E. C. (1948). Cognitive Maps in Rats and Men. *The Psychological Review, 55(4),* 189-208.

Tombaugh, T. N. (2004). Trail Making Test A and B: normative data stratified by age and education. *Archives of Clinical Neuropsychology,* 19(2)**,** 203-214.

Vann,S. D., Aggleton, J. P., Maguire, E. A. (2009). What does the retrosplenial cortex do? *Nature Reviews Neuroscience*, 10,792–802.

Laczó, J., Andel, R., Vyhnalek, M., Vlcek, K., Nedelska, Z., Matoska, V., Gazova, I., Mokrisova, I., Sheardova, K., & Hort, J. (2014, April 21). APOE and Spatial Navigation in Amnestic MCI: Results From a Computer-Based Test. Neuropsychology. Advance online publication. http://dx.doi.org/10.1037/neu0000072.

Vlcek, K. (2011). *"Spatial navigation impairment in healthy aging and Alzheimer's disease,"* in The Clinical Spectrum of Alzheimer's Disease. The Charge toward Comprehensive Diagnostic and Therapeutic Strategies, ed. S. De La Monte (Rijeka, Croatia: Intech), 75–100.

Wang, L., Larson, E. B., Bowen, J. D., & van Belle, G. (2006). Performance-based physical function and future dementia in older people. *Archives of International Medicine,* 166, 1115–1120.

Wechsler, D. (2011). *Test of Premorbid Functioning. UK Version (TOPF UK)*. Bloomington, MN: Pearson I.

Weniger, G., Ruhleder, M., Wolf, S., Lange, C., & Irle, E. (2009). Egocentric memory impaired and allocentric memory intact as assessed by virtual reality in subjects with unilateral parietal cortex lesions. *Neuropsychologia*, 47, 59–69.

Weniger, G., Ruhleder, M., Lange, C., Wolf, S., & Irle, E. (2011). Egocentric and allocentric memory as assessed by virtual reality in individuals with amnestic mild cognitive impairment. *Neuropsychologia,* 49, 518–527.

White, N. M., & McDonald, R. J. (2002). Multiple parallel memory systems in the brain of the rat. *Neurobiology Learning Memory*, 77, 125–184.

Winbald, B., Palmer, K., Kivipelto, M., Jelic, V., Fratiglioni L, Wahlund L-O., Nordber, A., Bäckman, L., Albert, M., Almkvist, O., Arai, H., Basun, H., Blennow, K., De Leon, M., DeCarli, C., T. Erkinjuntti, T., Giacobini, E., Graff, C., Hardy, J., Jack, C., Jorm, A., Ritchie, K., Van Duijn, C., Visser, P., & Petersen, R. C. (2004). Mild cognitive impairment: beyond

controversies, towards a consensus: report to the International Working Groups on mild cognitive impairment. *Journal of Internal Medicine*, 256, 3, 240–6.

World Health Organization and Alzheimer's Disease International. (2012). *Dementia: A Public Health Priority*. Geneva: World Health Organization. Retrieved from http://www.who.int/mental_health/publications/dementia_report_2012/en/

PART 3: CRITICAL APPRAISAL

Introduction

This paper provides a reflection on the process of conducting research exploring the clinical utility of a newly developed hippocampal reliant instrument to support the early diagnosis of AD and differentiate it from other forms of dementia within a memory service. The discussion will draw on my initial motivations for the project. I will then discuss the value of non-significant findings in research with reference to the study results. I will also discuss the merits of using computerised tests such as the 4MT to aid dementia diagnosis. Finally, I will reflect on the dilemmas faced when setting up and conducting the study and consider the influence this process has had on my wider clinical practice.

My initial motivation for the project

The World Health Organisation (2012) recognise dementia as a global health challenge and the numbers of people living with dementia is expected to double every 20 years. The UK government have begun to recognise the importance of dementia research to make improvements in diagnosis and management. During my clinical training it became apparent how clinical psychology can significantly contribute to this evidence base. Furthermore, like many others, I have experienced dementia within my own family adding to my interest in dementia research. I therefore took the opportunity to undertake my own research in this exciting and developing area making a contribution to improving the lives of people with dementia and those who care for them.

Equating non significance with insignificance

Generally, in psychological research it is difficult to publish non-significant findings, particularly in high tier journals. Statistical significance is a useful way to screen out manuscripts and deal with the high demand submitted to academic journals. However, this has created bias in the literature towards studies that find statically significant results. For example, research demonstrated how non-significant versions of otherwise identical manuscripts were 3 times more likely to be rejected than the significant versions of the manuscript by consulting

editors for APA journals (Atkinson, Furlong, & Wampold, 1982). This publishing bias has long been problematic as it increases the frequency of Type I errors published thus creating unrepresentative and a potentially misleading evidence base (Pagell et al, 2009). Furthermore, the reliance on statistical significance to define study value leads to overall quality and contribution being neglected.

The process of conducting a study from start to finish, which subsequently resulted in non-significant findings caused me to reflect on this superiority of statistical significance. When I analysed my results for the first time I was initially filled with dejection and disappointment on finding the research hypotheses were not supported by significant results. However, on discussion with my thesis supervisors, I began to realise my non-significant findings potentially provided valuable information about the application of the 4MT in a clinical setting. Although there were clear flaws in the methodology of the study i.e. it was underpowered, the 4MT was potentially not as useful in differentiating between AD and other types, especially VD, in a clinical setting as previously implied from previous research. Thus, the results offered meaning i.e. that in a clinical setting the 4MT appears to have small or no effect in opposition to laboratory based findings (Hartley et al, 2007; Bird et al, 2010) that would benefit from future research.

This research process has therefore taught me that non-significant findings can create potential avenues for future research that may otherwise remain unexplored. Furthermore, it prevents replication of unhelpful research saving valuable time and resources that could be applied to other research ventures. As a result of this experience in my future career I will endeavour to challenge this long held assumption and increase understanding of the potential value of such results so it can be more integrated into the literature. However, I am also aware that not all studies with non-significant results are worth publishing and that a balance needs to be struck to reduce the publishing bias.

Use of a Computerised Test

The 4MT can be presented as a computerised test, as it was in this study. Although to reduce confounding influence of computer illiteracy the researcher interacted with the computer. The 4MT is just one example of how developments in technology have enabled the production of new computerized testing tools. Paper and pencil tests are still widely used and are central to neuropsychological assessment of dementia due to high validity and reliability (Lezak, 2004). However, it has been suggested that computerised tests overcome a number of the challenges presented by pen and paper tests. These include the ability to alternate the administration form (Fichman et al, 2008), conduct automatic scoring (Fredrickson et al, 2010), reduce researcher interaction and involvement (Woo, 2008), provide accurate time control of stimuli presentation and measurement of motor response accuracy (Witt, Alpherts & Helmstaedter, 2013). Computerised tests can also enable the measuring and monitoring of cognition at home thus indicating potential decline in aging people and facilitating early diagnosis of dementia (Canini et al, 2014). Studies, such as this one, are therefore important and valuable as they aid the understanding of the utility of the 4MT, a computerised instrument that could have the potential to aid early diagnosis of and intervention in AD. The results of this study did not provide firm conclusions about the 4MTs clinical utility but demonstrate that further research would be worthwhile to fully understand the role it could play in aiding early AD diagnosis and differentiating it from other forms of dementia.

Dealing with dilemmas

Through the planning, recruitment and analysis phases of the research project I have learnt many important lessons about how to effectively undertake research across NHS clinical services. I have also experienced a number of dilemmas when conducting research within a dementia population and encountered a number of unanticipated obstacles at different stages thus learning the importance of remaining flexible in my approach to resolve them. I will now take this opportunity to discuss some examples of this.

The most significant flaw in the study is the underpowered sample size, which arose due to difficulties encountered with recruitment highlighting the challenges of conducting research in clinical settings. During the planning stages of the study, referral rates and caseloads suggested that enough participants could be recruited to enable the regression analysis. Furthermore, I was integrated into the team with a clinical placement in the services enabling the opportunity to remind clinicians about the study and identifying potential participants. The research register form was included in the assessment packs and clinicians agreed to ask patients to complete this at the time of the initial assessment. I reminded clinicians regularly in team meetings to ask patients to complete the form where appropriate. Although many of the clinicians made an active effort to get these forms completed, it was difficult for others to remember them in the midst of the essential assessment paper work. I learnt quickly that despite good intentions and support from the staff, relying on busy clinicians to recall the form when they have other clinical priorities was going to become an issue for the sample size. In anticipation of this we had permission to invite existing clients from clinician's caseloads but with the involved clinician needing to make contact with the patient first to gain their consent. Again, the reliance on clinicians posed somewhat of an issue but this appeared to be overcome by the strong working relationships I forged during my clinical placement. However, I leant a valuable lesson to integrate a variety of recruitment pathways into a study to provide options should any barriers arise, as it did in this study, and maximise sample size.

Another unforeseen recruitment issue that arose half way through the data collection was that the memory services went through significant management and frontline staff changes. This increased the time taken for patients to be allocated to a clinician for a diagnosis disclosure, reducing the amount of participants ready to contact as participants needed to have a disclosed diagnosis to take part. This meant that the recruitment rate became slower than had been anticipated and resulted in a reduction in the sample size. To add to this, both dementia advisors also left their posts creating a further lull in potential participants. I became more present in the

service and continued to promote the project to the staff team in a hope for more participants. However, unfortunately there was relatively little I could do to overcome this issue other than wait for new members of staff to start at the service. This meant extending the time frame for data collection. However, this was worth doing in order to maximise sample size and minimise the findings being significantly underpowered. Unfortunately, the thesis timeframes needed to be observed and recruitment had to eventually be terminated despite not reaching the desired sample size.

As recruitment for the study was undertaken within NHS clinical services, I gained my first experience of submitting a research proposal for NHS ethical review. People with dementia are considered a vulnerable population and this presented us with complex ethical issues during the planning of this study. Compromises had to be made with the methodological design quality to ensure that the research being conducted was ethical. The most significant of these was the ethical requirement that participants could only be recruited following the disclosure of their diagnosis, which may have limited the findings of this study. However, precautions were taken to maximise validity, such as the researchers being blind to diagnosis and excluding people who were moderately to significantly impaired at time of diagnosis (i.e. ACE-III scores below 70). It was also considered a clinically beneficial study to conduct with potentially valuable findings despite the compromises to study design quality.

Furthermore, there were also issues relating to the validity and reliability of neuropsychological testing in this study. The length of neuropsychological battery had to be limited to minimise tiredness and fatigue to which the elderly are more susceptible. The testing was therefore matched to a normal set of neuropsychological tests used in routine clinical practice. However, this meant reducing the amount of potential confounding variables controlled for thus reducing the methodological quality.

Furthermore, to maximise cognitive performance on neuropsychological testing it is usually conducted in a formal setting with minimal distractions and interference increasing the validity and reliability of the scores. The dementia population tend to experience difficulties independently travelling to the memory service due to the cognitive impairment and physical health difficulties. It was decided to conduct the testing at the participant's home where preferable to minimise burden to the participants and their carer/s. During testing, a number of interruptions and distractions often occurred (i.e. telephone or door ringing), which may have interfered with performance on these tests. However, minimising disruptions to participant's daily routines was considered to outweigh the need for creating a consistent research environment. It also enabled participants to be more comfortable in home surrounding and reduce anxiety and dementia related confusion, which are known to impact neuropsychological performance (Larson et al, 2009). Furthermore, by conducting the research at the memory service many of the more frail participants would have not taken part in the study. This may have introduced bias into the sample as we would have mainly recruited physically healthier and younger participants as well as those potentially with strong motivation to take part.

Memory impairment also added to difficulties when working with people with dementia. There were a number of occasions when participants forgot the appointment. Where possible I would ring the participants in the morning to remind them of the appointment but despite this some participants still did not remember. This was at times frustrating particularly when recruitment numbers were reduced (see below) as it wasted valuable time and cost in travelling to locations around London. This further added to the reduced sample size.

Gaining informed consent from people with dementia is a key issue facing all research in this field. The process implies the person having capacity to understand the significant benefits, risks and alternatives of the proposed assessment to then make and communicate a decision (Uniform Health Care Decisions Act of 1993, 1994). Compromised cognitive ability to make health care decisions is often affected by dementia. Special measures had to be taken to ensure

participants were able to provide informed consent in this study. Information sheets were developed in line with Easy Read Guidance (2010), a Department of Health Strategy for making information more accessible for people with learning disabilities. These were also designed in consultation with people with dementia to ensure that the information was clear and accessible. Capacity to consent was assessed by the involved clinicians but also repeated on the day of testing. Time was spent before the testing to ensure the participants understood the aims and their involvement in the study. This added to the demands of the study and the length of the home visit, however, it was an essential ethical component to the study. The inclusion of assent procedures to gain consent from carers in light of a participant lacking this capacity was considered but not implemented given the interest in the early phases of the dementia where we would assume capacity remains.

Reflecting upon the literature review and the empirical paper the limitations posed by the cross-sectional design of the studies in the literature review were also relevant to the empirical paper. These include correlations not offering causal effects, small sample sizes and possible confounding variables. These limitations clearly have implications on the conclusions made in the empirical paper. When writing the literature review it was notable that longitudinal study designs could reduce the limitations posed and enabled more valid findings. However, whilst undertaking my own research I experienced first-hand some of the challenges of conducting research with regards to recruitment, ethics and analysis described above. Furthermore, to conduct a large scale longitudinal study would have required a significant amount of resources and time that would have been beyond the scope of a doctorate in clinical psychology thesis.

Implications for clinical practice

There is a prevailing negative stereotype of people with dementia and misconceptions about the disease mainly of incapacitation and dependency (Batsch & Mittelman, 2012). It has been suggested that it is stigma that creates the largest barrier to early diagnosis and intervention (Prince, Bryce & Ferri et al, 2011). It prevents people from acknowledging symptoms and

obtaining the help they need to improve cognition and continue to live a good quality of life (Zebrowitz, & Montepare, 2000; Nelson, 2008). Thus, dementia remains significantly under diagnosed within the UK as well as worldwide (Prince, Bryce & Ferri et al, 2011). It has also been demonstrated that many health care professionals are reluctant to give the label of dementia due to this stigma, which further prevents the early evaluation of cognitive function (Koch & Ilffe, 2010; Werner & Giveon, 2008). It has been argued that early diagnosis has the potential to change the way society views and approaches dementia (Prince, Bryce & Ferri et al, 2011). Furthermore, it can empower people with dementia by allowing them to fully participate in the planning of their own lives and make important decisions about their future care.

This study therefore plays an important role in aiding early diagnosis and therefore indirectly challenging stigma. The process of conducting a thesis into the early phases of dementia challenged many of my pre-existing assumptions about this population. On reflection, I am aware that perhaps I was also susceptible to these negative perceptions. I wonder now whether this was creating me to feel apprehensive when making a diagnosis of dementia in my own clinical work. However, meeting with the many participants across my research I saw that many were living content and independent lives. A number of the participants even commented to me about their dislike of word dementia due to the associated stigma, which was not their actual lived experience. This experience taught me about the important need to challenge this stigma to maximise the benefits of early diagnostic research and reduce the barrier it poses to engaging in helpful interventions. This notion is further supported by the literature review were some evidence demonstrated minimal differences in QoL between people with dementia and those with MCI or normal cognition.

As a Trainee Clinical Psychologists we are expected to learn skills as a clinician and a researcher. On interaction with participants a conscious effort had to be made to retain research boundaries e.g. following instructions verbatim for each participant to ensure the research findings were as valid and reliable as possible. This was particularly difficult when participants

raised concerns, such as isolation. A conscious effort needed to be made to prevent a move into clinician mode and exploring concerns further as I would in a clinical meeting. Instead, I would signpost the participant to their relevant clinican. However, having a strong repertoire of clinical skills had benefits such as enabling better participant engagement in research.

Finally, there were many participants who reported to find the research appointments enjoyable and empowering that was linked to a desire to give back to others. I was humbled by the willingness of people to participate in this research with the sole motivation that it might improve the lives of others with dementia but potentially not there own. This demonstrates the value of conducting research with this population, as it does not just appear to have academic gains but potentially clinical gains for the individual.

Conclusions

Conducting research in the field of dementia is challenging. It requires careful thought into how to work with and think sensitively about the person's needs. The emotional impact of working with people who are undergoing the assessment process should also not be minimised. Despite this, the work was extremely rewarding and inspiring. Supporting research that facilitates the early diagnosis of dementia enables access to effective treatments to improve cognitive functioning, emotional well-being and quality of life for people with dementia and those who care for them. There is much that remains unknown about dementia and differential diagnosis in the earliest phases still remains a challenge that needs to be addressed. This thesis, despite its limitations, is therefore considered important in advancing instruments that aid the identification of early AD from other forms of dementia and better understand the underlying changes to the brain and cognition.

REFERENCES

Atkinson, D. R., Furlong, M. J., & Wampold, B. E. (1982). Statistical significance, reviewer evaluations, and the scientific process: Is there a (statistically) significant relationship? *Journal of Counseling Psychology, 29*, 189–194.

Banerjee S., & Wittenberg, R. (2009). Clinical and cost effectiveness of services for early diagnosis and intervention in dementia. *International Journal of Geriatric Psychiatry*, 24(7), 748-754.

Batsch, L. N., & Mittelman, M. S. (2012). International World Alzheimer Report 2012: Overcoming the Stigma of Dementia. Retrieved from https://www.alz.co.uk/research/WorldAlzheimerReport2012.pdf

Canini, M., Battista, P., Della Rosa, P. A., Catricala, E., Salvatore, C., Gilardi, M. C., & Castiglioni, I. (2014). Computerized Neuropsychological Assessment in Aging: Testing Efficacy and Clinical Ecology of Different Interfaces. *Comput Math Methods Med*.

Department of Health. (2010). *Making written information easier to understand for people with learning disabilities Guidance for people who commission or produce Easy Read information.* London: DoH Publications.

English, D. M. & Meisel, A. (1994). *Uniform HealthCare Decisions Act Gives New Guidance*. 21 EST. PLAN. 355.

Fichman, H.C., Nitrini, R., Caramelli, P., & Sameshima, K. (2008). A new brief computerized cognitive screening battery (CompCogs) for early diagnosis of Alzheimer's disease. *Dementia e Neuropsychologia*, 2(1), 13–19.

Fredrickson, J., Maruff, P., & Woodward, M. (2010). Evaluation of the usability of a brief computerized cognitive screening test in older people for epidemiological studies. *Neuroepidemiology*, 34(2), 65–75.

Gaugler, J. E., Kane, R. L., Kane, R. A., & Newcomer, R. (2005). Early community-based service utilization and its effects on institutionalization in dementia caregiving. *Gerontologist,* 45(2), 177-185.

Koch, T., Iliffe, S., & EVIDEM-ED project. (2010). Rapid appraisal of barriers to the diagnosis and management of patients with dementia in primary care: a systematic review. *BMC Family Practice*, 11, 52.

Larson, M.J., Kaufman, D.A., Schmalfuss, I.M., & Perlstein, W.M. (2007). Performance monitoring, error processing, and evaluative control following severe TBI. *Journal of the International Neuropsychological Society*, 13(6), 961-971.

Lezak, M. D.(2004). *Neuropsychological Assessment*. Oxford, UK: Oxford University Press.

Mittelman, M. S., Ferris, S. H., Shulman, E., Steinberg, G., & Levin, B. (1996). A family intervention to delay nursing home placement of patients with Alzheimer disease. A randomized controlled trial. *JAMA*, 276(21), 1725- 1731.

Molinuevo, J. L., Berthier, M. L., & Rami, L. (2011). Donepezil provides greater benefits in mild compared to moderate Alzheimer's disease: implications for early diagnosis and treatment. *Archives of Gerontology and Geriatrics*, 52(1), 18- 22.

National Conference of Commissioners on Uniform State Laws. *Uniform Health Decisions Act 1993*. Accessed May 8, 2014.

Nelson, T. D. (2004). *Ageism: Stereotyping and Prejudice Against Older Persons*. Cambridge, MA: MIT Press.

Pagell, M., Kristal, M., & Blackmon, K. (2009). Special topic forum on nonsignificant and contradictory results. J*ournal of Supply Chain Management, 45,* 70.

Prince, M., Bryce, R., & Ferri, C. (2011). *World Alzheimer report 2011: the benefits of early diagnosis and intervention*. London (UK): Alzheimer's Disease International (ADI).

Rountree, S. D., Chan, W., Pavlik, V. N., Darby, E. J., Siddiqui, S., & Doody, R. S. (2009). Persistent treatment with cholinesterase inhibitors and/or memantine slows clinical progression of Alzheimer disease. *Alzheimer's Research and Therapy*, 1(2), 7.

Werner, P., & Giveon, S. M. (2008). Discriminatory behavior of family physicians toward a person with Alzheimer's disease. *International Psychogeriatrics*, 20, 824–839.

Witt, J. A., Alpherts, W., & Helmstaedter, C. (2013). Computerized neuropsychological testing in epilepsy: overview of available tools. *Seizure,* 22(6), 416–423.

Woo, E. (2008). Computerized neuropsychological assessments. *CNS Spectrums*, 13(10), 14–17.

World Health Organization. (2012). World Health Organization and Alzheimer's Disease International. Dementia: A Public Health Priority. Retrieved from http://www.who.int/mental_health/publications/dementia_report_2012/en/

Zebrowitz, L. A. & Montepare, J. M. (2000). “Too young, too old”: Stigmatizing adolescents and elders. In T. Heatherton, R., Kleck, M., Hebl., & J. Hull (eds.). *The social psychology of stigma*. New York: Guilford Press

APPENDICES

Appendix 1: Newcastle Ottawa Scale

Newcastle-Ottawa Scale adapted for cross-sectional studies

Selection: (Maximum 5 stars)

1) Representativeness of the sample:

a) Truly representative of the average in the target population. * (all subjects or random sampling)

b) Somewhat representative of the average in the target population. * (non-random sampling)

c) Selected group of users.

d) No description of the sampling strategy.

2) Sample size:

a) Justified and satisfactory. *

b) Not justified.

3) Non-respondents:

a) Comparability between respondents and non-respondents characteristics is established, and the response rate is satisfactory. *

b) The response rate is unsatisfactory, or the comparability between respondents and non-respondents is unsatisfactory.

c) No description of the response rate or the characteristics of the responders and the non-responders.

4) Ascertainment of the exposure (risk factor):

a) Validated measurement tool. **

b) Non-validated measurement tool, but the tool is available or described.*

c) No description of the measurement tool.

Comparability: (Maximum 2 stars)

1) The subjects in different outcome groups are comparable, based on the study design or analysis. Confounding factors are controlled.

a) The study controls for the most important factor (select one). *

b) The study control for any additional factor. *

Outcome: (Maximum 3 stars)

1) Assessment of the outcome:

a) Independent blind assessment. **

b) Record linkage. **

c) Self report. *

d) No description.

2) Statistical test:

a) The statistical test used to analyze the data is clearly described and appropriate, and the measurement of the association is presented, including confidence intervals and the probability level (p value). *

b) The statistical test is not appropriate, not described or incomplete.

This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for cohort studies to perform a quality assessment of cross-sectional studies for the systematic review, “Are Healthcare Workers’ Intentions to Vaccinate Related to their Knowledge, Beliefs and Attitudes? A Systematic Review”.

We have not selected one factor that is the most important for comparability, because the variables are not the same in each study. Thus, the principal factor should be identified for each study.

In our scale, we have specifically assigned one star for self-reported outcomes, because our study measures the intention to vaccinate. Two stars are given to the studies that assess the outcome with independent blind observers or with vaccination records, because these methods measure the practice of vaccination, which is the result of true intention.

Appendix 2: Joint Project Submission Declaration

Declaration of overlap between my DClinPsy thesis and my supervisor's PhD

My thesis and my supervisor (Joshua Stott's) PhD thesis (which will be submitted in the future) contain some overlapping data and are part of a collaborative endeavour. In these cases we are required to follow the guidance created by Norah Frederikson, Professor of Educational Psychology at UCL, to cover cases of overlap between professional doctorates and PhDs.

This guidance requires that I make a declaration that my thesis will 'make a distinct contribution to the knowledge of the subject and will afford evidence of originality as shown by the discovery of new facts and/or the exercise of independent critical power.'

I confirm that this is the case and that the questions asked in my thesis and that which will be addressed in my supervisor's PhD are completely separate questions.

Furthermore the guidance requires that I clarify that while the two theses do have some data in common they do not contain completely overlapping datasets. I confirm that this is the case.

Finally it requires that I confirm that I am happy for my thesis to be made confirm that I am happy for this to happen.

The guidance requires that myself and my supervisor sign this declaration to confirm it is true and accurate to the best of our knowledge and we have done so below.

Lucy Gore	Joshua Stott
Trainee Psychologist	Senior Clinical Tutor
19/06/2015	19/06/2015

The full guidance follows on the next page for your reference.

Guidance to Undertaking a PhD while Supervising the Research

of Professional Doctorate Students

1. There are many advantages to undertaking doctoral research as part of a collaborative team and this is encouraged. However in these circumstances it is essential that the contribution of each party and the way in which the thesis meets the following criteria (which apply to all doctoral programmes) is explicitly stated in a declaration and submitted with the thesis.

The thesis will make a distinct contribution to the knowledge of the subject and will afford evidence of originality as shown by the discovery of new facts and/or the exercise of independent critical power.

- In the case of Professional Doctorate students the declaration should be signed by each of the students involved in the project and their supervisor. The same examiner will be appointed for these theses.

- In the case of staff undertaking a PhD, the declaration should be signed by the staff member themselves and their supervisor and the declarations from all Professional Doctoral thesis based on data which overlaps at all with data reported in the PhD thesis should be submitted with the declaration. The examiners of the PhD thesis should be advised that these Professional Doctoral theses are available to them to consult at their request.

2. In planning their thesis work, team members should ensure that no studies are planned which involve completely overlapping data. For example Professional Doctorate student 1 might collect data on variables A, B and C in Year 1, Professional Doctorate student 2 might collect data on variables A, B and D in Year 2 and the staff member might analyse longitudinal data on the variables A and B in a PhD thesis study.

3. For the PhD upgrading the staff member should, in addition to the other documentation required, submit a draft of the declaration they envisage submitting with their thesis so that any questions that need to be resolved can be addressed at this stage and plans with the regard to use of shared data can be formally approved.

Appendix 3: Ethical Approval Letter

NRES Committee London - City Road & Hampstead
Bristol Research Ethics Committee Centre
Level 3, Block B
Whitefriars
Lewins Mead
Bristol
BS1 2NT

Telephone: 0117 342 1385
Facsimile: 0117 342 0445

16 May 2014

Dr Joshua Stott
Senior Clinical Tutor and Joint Admissions Tutor
University College London
Research Department of Clinical, Educational and Health Psychology
University College London
Gower Street London
WC1E 6BT

Dear Dr Stott

Study title:	**Exploring cognitive mediation ability in people with dementia: the factors that influence it and effects of difference in ability**
REC reference:	**14/LO/0554**
IRAS project ID:	**147241**

Thank you for your letter of 07 May 2014, responding to the Committee's request for further information on the above research and submitting revised documentation.

The further information has been considered on behalf of the Committee by the Vice-Chair.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details, unless you expressly withhold permission to do so. Publication will be no earlier than three months from the date of this favourable opinion letter. Should you wish to provide a substitute contact point, require further information, or wish to withhold permission to publish, please contact the REC Assistant Miss Marjolein Groot Bluemink, nrescommittee.london-cityroadandhampstead@nhs.net.

Confirmation of ethical opinion

On behalf of the Committee, I am pleased to confirm a favourable ethical opinion for the above research on the basis described in the application form, protocol and supporting documentation as revised, subject to the conditions specified below.

Ethical review of research sites

NHS sites

The favourable opinion applies to all NHS sites taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non-NHS sites

Conditions of the favourable opinion

The favourable opinion is subject to the following conditions being met prior to the start of the study.

Management permission or approval must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission ("R&D approval") should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements.

Guidance on applying for NHS permission for research is available in the Integrated Research Application System or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of approvals from host organisations

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publically accessible database within 6 weeks of recruitment of the first participant (for medical device studies, within the timeline determined by the current registration and publication trees).

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non clinical trials this is not currently mandatory.

If a sponsor wishes to contest the need for registration they should contact Catherine Blewett (catherineblewett@nhs.net), the HRA does not, however, expect exceptions to be made. Guidance on where to register is provided within IRAS.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Approved documents

The final list of documents reviewed and approved by the Committee is as follows:

Document	*Version*	*Date*
Covering Letter		01 May 2014
Evidence of insurance or indemnity		26 July 2013
GP/Consultant Information Sheets	1	24 April 2014
Other: CV - Joshua Stott		
Other: CV - Lucy Gore		
Other: Scientific Critique of Aim 1		05 February 2014
Other: Scientific Critique of Aim 2		08 October 2013
Participant Consent Form: Clinical Stage 1	3	24 April 2014
Participant Consent Form: Clinical Stage 2	3	24 April 2014
Participant Consent Form: Control Stage 1	3	24 April 2014
Participant Consent Form: Control Stage 2	3	24 April 2014
Participant Information Sheet: Clinical Stage 1	4	24 April 2014
Participant Information Sheet: Clinical Stage 2	4	24 April 2014
Participant Information Sheet: Control Stage 1	4	24 April 2014
Participant Information Sheet: Control Stage 2	4	24 April 2014
Protocol	2	17 February 2014
Questionnaire: Cognitive Mediation Questionnaire		
Questionnaire: Reed and Clements Assessment		
Questionnaire: Thoughts/feelings/behavious differentiation assessment		
Questionnaire: Emotion Recognition Test		
REC application		04 March 2014
Response to Request for Further Information		07 May 2014
Summary/Synopsis	1	17 February 2014

Statement of compliance

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document *"After ethical review – guidance for researchers"* gives detailed

guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The NRES website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

Feedback

You are invited to give your view of the service that you have received from the National Research Ethics Service and the application procedure. If you wish to make your views known please use the feedback form available on the website.

Further information is available at National Research Ethics Service website > After Review

14/LO/0554	**Please quote this number on all correspondence**

We are pleased to welcome researchers and R & D staff at our NRES committee members' training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

pp
Mr Hari Jayaram
Vice Chair

Email:nrescommittee.london-cityroadandhampstead@nhs.net

Enclosures: "After ethical review – guidance for researchers" *[SL-AR2]*

Copy to: *Suzanne Emerton*
Dr Tumi Kaminskas, North Central London Research Consortium

Appendix 4: ACE-III

ADDENBROOKE'S COGNITIVE EXAMINATION – ACE-III
English Version A (2012)

Name: Date of Birth: Hospital No. or Address:	Date of testing: ___/___/___ Tester's name:_____ Age at leaving full-time education:_____ Occupation: _____ Handedness: _____

ATTENTION

➢ Ask: What is the	Day _____	Date _____	Month _____	Year _____	Season _____	**Attention** [Score 0-5] ☐
➢ Ask: Which	No./Floor _____	Street/Hospital _____	Town _____	County _____	Country _____	**Attention** [Score 0-5] ☐

ATTENTION

➢ Tell: "I'm going to give you three words and I'd like you to repeat them after me: lemon, key and ball." After subject repeats, say "Try to remember them because I'm going to ask you later". ➢ Score *only* the first trial (repeat 3 times if necessary). ➢ Register number of trials: _____	**Attention** [Score 0-3] ☐

ATTENTION

➢ Ask the subject: "Could you take 7 away from 100? I'd like you to keep taking 7 away from each new number until I tell you to stop." ➢ If subject makes a mistake, do not stop them. Let the subject carry on and check subsequent answers (e.g., 93, 84, 77, 70, 63 – score 4). ➢ Stop after five subtractions (93, 86, 79, 72, 65): ____ ____ ____ ____ ____	**Attention** [Score 0-5] ☐

MEMORY

➢ Ask: 'Which 3 words did I ask you to repeat and remember?' _____ _____ _____	**Memory** [Score 0-3] ☐

FLUENCY

➢ **Letters**
Say: "I'm going to give you a letter of the alphabet and I'd like you to generate as many words as you can beginning with that letter, but not names of people or places. For example, if I give you the letter "C", you could give me words like "cat, cry, clock" and so on. But, you can't give me words like Catherine or Canada. Do you understand? Are you ready? You have one minute. The letter I want you to use is the letter "P".

Fluency
[Score 0 – 7]
☐

				≥ 18	7
				14-17	6
				11-13	5
				8-10	4
				6-7	3
				4-5	2
				2-3	1
				0-1	0
				total	correct

➢ **Animals**
Say: "Now can you name as many animals as possible. It can begin with any letter."

Fluency
[Score 0 – 7]
☐

				≥ 22	7
				17-21	6
				14-16	5
				11-13	4
				9-10	3
				7-8	2
				5-6	1
				<5	0
				total	correct

MEMORY

➢ Tell: "I'm going to give you a name and address and I'd like you to repeat the name and address after me. So you have a chance to learn, we'll be doing that 3 times. I'll ask you the name and address later."

Score only the third trial.

Memory [Score 0 – 7] ☐

	1st Trial	*2nd Trial*	*3rd Trial*
Harry Barnes 73 Orchard Close Kingsbridge Devon	_____ _____ ___ _____ _____ _____ _____	_____ _____ ___ _____ _____ _____ _____	_____ _____ ___ _____ _____ _____ _____

MEMORY

➢ Name of the current Prime Minister.....
➢ Name of the woman who was Prime Minister .....
➢ Name of the USA president.....
➢ Name of the USA president who was assassinated in the 1960s.....

Memory [Score 0 – 4] ☐

LANGUAGE

➢ Place a pencil and a piece of paper in front of the subject. As a practice trial, ask the subject to "**Pick up the pencil and then the paper.**" If incorrect, score 0 and do not continue further.

➢ If the subject is correct on the practice trial, continue with the following three commands below.
- Ask the subject to "**Place the paper on top of the pencil**"
- Ask the subject to "**Pick up the pencil but not the paper**"
- Ask the subject to "**Pass me the pencil after touching the paper**"

Note: Place the pencil and paper in front of the subject before each command.

Language [Score 0-3] ☐

LANGUAGE

➢ Ask the subject to write two (or more) complete sentences about his/her last holiday/weekend/Christmas. Write in complete sentences and do not use abbreviations. Give 1 point if there are two (or more) complete sentences about the one topic; and give another 1 point if grammar and spelling are correct.

Language [Score 0-2] ☐

LANGUAGE

➢ Ask the subject to repeat: '**caterpillar**'; '**eccentricity**; '**unintelligible**'; '**statistician**'
Score 2 if all are correct; score 1 if 3 are correct; and score 0 if 2 or less are correct.

Language [Score 0-2] ☐

Updated 20/11/2012

LANGUAGE

➢ Ask the subject to repeat: **'All that glitters is not gold'**

Language [Score 0-1] ☐

➢ Ask the subject to repeat: **'A stitch in time saves nine'**

Language [Score 0-1] ☐

LANGUAGE

➢ Ask the subject to name the following pictures:

Language [Score 0-12] ☐












LANGUAGE

➢ Using the pictures above, ask the subject to:

Language [Score 0-4] ☐

- Point to the one which is associated with the monarchy .....
- Point to the one which is a marsupial .....
- Point to the one which is found in the Antarctic .....
- Point to the one which has a nautical connection .....

Updated 20/11/2012

LANGUAGE

➢ Ask the subject to read the following words: (Score 1 only if all correct)

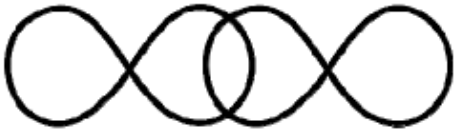
Language
[Score 0-1]

sew
pint
soot
dough
height

VISUOSPATIAL ABILITIES

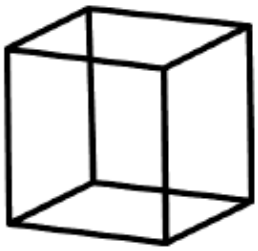
➢ Infinity Diagram: Ask the subject to copy this diagram

Visuospatial
[Score 0-1]



➢ Wire cube: Ask the subject to copy this drawing (for scoring, see instructions guide).

Visuospatial
[Score 0-2]



➢ Clock: Ask the subject to draw a clock face with numbers and the hands at ten past five. (For scoring see instruction guide: circle = 1, numbers = 2, hands = 2 if all correct).

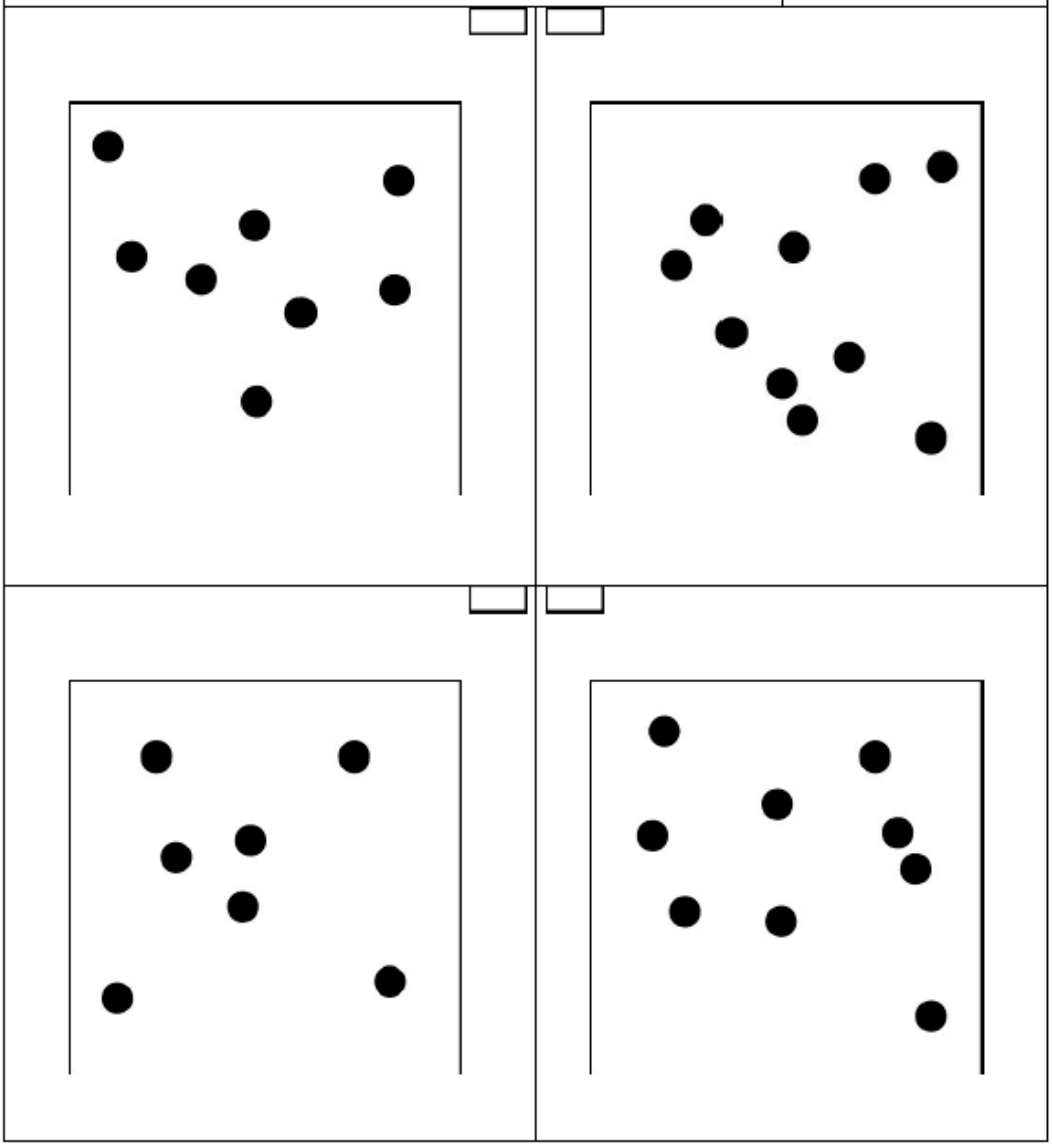
Visuospatial
[Score 0-5]

Updated 20/11/2012

VISUOSPATIAL ABILITIES

➢ Ask the subject to count the dots without pointing to them

Visuospatial
[Score 0-4]

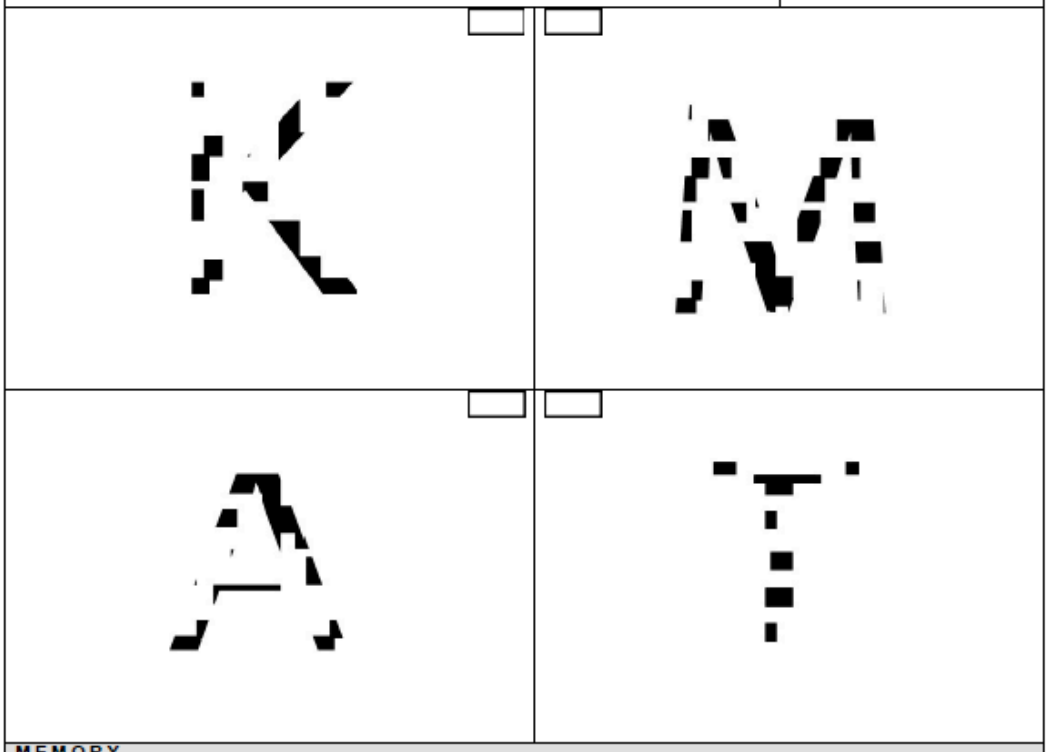


Updated 20/11/2012

VISUOSPATIAL ABILITIES

➢ Ask the subject to identify the letters

Visuospatial [Score 0-4] ☐



MEMORY

➢ Ask "Now tell me what you remember about that name and address we were repeating at the beginning"

Harry Barnes 73 Orchard Close Kingsbridge Devon	…… …… …… ……	**Memory** [Score 0-7] ☐

MEMORY

➢ This test should be done if the subject failed to recall one or more items above. If all items were recalled, skip the test and score 5. If only part was recalled start by ticking items recalled in the shadowed column on the right hand side; and then test not recalled items by telling the subject "ok, I'll give you some hints: was the name X, Y or Z?" and so on. Each recognised item scores one point, which is added to the point gained by recalling.

Memory [Score 0-5] ☐

Jerry Barnes	☐	Harry Barnes	☐	Harry Bradford	☐	recalled	☐
37	☐	73	☐	76	☐	recalled	☐
Orchard Place	☐	Oak Close	☐	Orchard Close	☐	recalled	☐
Oakhampton	☐	Kingsbridge	☐	Dartington	☐	recalled	☐
Devon	☐	Dorset	☐	Somerset	☐	recalled	☐

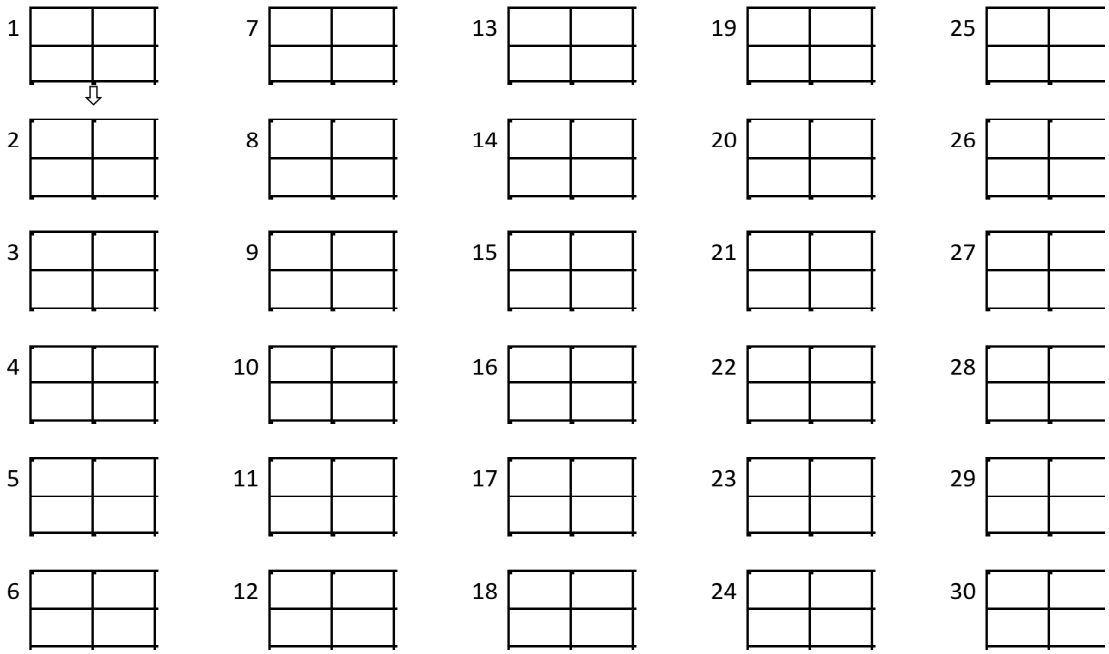
SCORES

TOTAL ACE-III SCORE	/100
Attention	/18
Memory	/26
Fluency	/14
Language	/26
Visuospatial	/16

Updated 20/11/2012

Appendix 5: Four Mountain Grid Sheet

Tick ONE box for EACH ITEM in the test (1-30) to indicate which of the four test images shows the SAME PLACE you saw in the previous picture.



Appendix 6: Participant Information Sheet

RESEARCH DEPARTMENT OF CLINICAL, EDUCATIONAL AND HEALTH PSYCHOLOGY

Stage 1 Participant Information Sheet- Clinical Sample

Can people with memory difficulties and dementia do 'Cognitive behaviour therapy' (CBT)

We would like to invite you to take part in our research study. Before you decide, we would like you to understand why the research is being done and what it would involve for you. One of our team will go through the information sheet with you and answer any questions you have. This will take 10 minutes. Talk to others about the study if you wish. Part 1 will tell you the purpose of this study and what will happen to you if you take part. Part 2 will give you more detailed information about the conduct of the study. Ask us if there is anything that is not clear.

PART 1

What is the purpose of the study?

We are researching early diagnosis and therapy for people with dementia or memory difficulties. There are two main reasons for doing this study:

1. People with dementia/memory difficulties can often feel quite depressed or anxious. Sometimes they are offered a type of counseling called CBT to help them with this. However, elements of CBT can be quite difficult for some people to understand. The aim of this study is to see how easy it is for people with dementia/memory difficulties to understand the different parts of CBT.

2. It is hard to diagnose dementias early. To help us identify people with dementia we use pencil

and paper tests of memory and other abilities. This study will look at whether a newly developed pencil and paper test called 'four mountains' helps us spot early Alzheimer's disease compared to other dementias.

Why have I been invited?

You have been invited because you are over 50 and have problems with your memory or dementia. We are inviting some people who have memory difficulties or dementia and some people who don't to take part in the study so that we can look at differences between them.

Do I have to take part?

It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You can change your mind at any time and withdraw from the study. This will not affect your care.

What will happen if I take part?

You will meet with a researcher for one to one and a half hours. The researcher will meet with you in a place of your choosing, generally our clinic or your home.

Expenses

Participants who travel to the clinic for the research will be reimbursed for the full cost their journey.

What will I have to do?

The research will involve filling in some questionnaires and doing some pencil and paper tasks to look at memory and other abilities.

What are the possible disadvantages and risks of taking part?

We will be giving you some questionnaires and pencil and paper tasks. While we don't think it is likely, this might make you feel worried or distressed. If this were the case you could stop the research at any time. We would also discuss with you what sources of support are available and direct you to them. You may have questions about your current clinical care from the service or your current diagnosis. We cannot offer any clinical advice during the research but we will direct you to someone who can answer any questions.

What are the possible benefits of taking part?

We cannot promise the study will help you but we hope the information we get from this study will help improve the treatment of people with dementia and memory difficulties. Some people have also told us they enjoy the process of doing the questionnaires and pencil and paper tests.

What happens when the research study stops?

After you have taken part the researcher may ask you if you are interested in taking part in the second stage of this study. It will involve another hour of testing either at your home or at the clinic where you will complete questionnaires and a short interview about a recent life event. Information sheets about the second part of the study will be provided at the end of the research session to help you decide whether to take part. You will have time to take this away and think about your decision. A smaller number of people are needed for this second part of this study so when we have enough people for stage 2 we will stop asking people if they want to take part in this.

If you are interested in how you have done on the questionnaires and tasks then we can provide you with individualised feedback. You can contact Dr Joshua Stott on 0207 679 5950 or Lucy Gore on 07801536706 if you want this.

You and all other participants will be invited to a feedback session once the study is completed. At this session, we will present what we have found and answer questions you may have about the research.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed. The detailed information on this is given in Part 2.

Will my taking part in this study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence. The details are included in Part 2.

If the information in Part 1 has interested you and you are considering participation, please read the additional information in Part 2 before making any decision.

PART 2

What if relevant new information becomes available?

If the study is stopped for any reason, we will tell you and arrange your continuing care.

What will happen if I don't want to carry on with the study?

You can withdraw from the study at any time and this will not affect your usual care. We will discuss with you whether you want all of your information withdrawn from the study.

What if there is a problem?

If you wish to complain, or have any concerns about any aspect of the way you have been approached or treated by members of staff you may have experienced due to your participation in the research, National Health Service or UCL complaints mechanisms are available to you (please see harm section below). Please ask your researcher if you would like more information on this.

Harm

In the event that something does go wrong and you are harmed during the research and this is due to someone‘s negligence then you may have grounds for a legal action for compensation against University College London but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you.

If you suspect that the harm is the result of the Sponsor’s (University College London) or the hospital's negligence then you may be able to claim compensation. After discussing with your researcher, please make the claim in writing to Dr Joshua Stott who is the Chief Investigator for the research and is based at UCL. The Chief Investigator will then pass the claim to the Sponsor’s Insurers, via the Sponsor’s office. You may have to bear the costs of the legal action initially, and you should consult a lawyer about this.

If you suspect harm is the result of the National Health Service and wish to make a formal complaint, you can do this by conducting the Patient Advice and Liaison Service who can offer advice on the best service to address your complaint. They can be contacted on pals.cnwl@nhs.net or 020 3214 5773.

Will my taking part in this study be kept confidential?

All information, which is collected, about you during the course of the research will be kept

strictly confidential, and any information about you which leaves the hospital/surgery will have your name and address removed so that you cannot be recognised. We will keep this data stored securely for 5 years and it will only be look at by the research team.

If you decide to take part in the study we will write to your GP to let them know about your involvement in the study. We will explain in the letter what participating in the study will involve and that you have made an informed decision after being made aware of what it will involve and your rights as a participant.

What will happen to the results of the research study?

The results of the research may be published in scientific journals. You will not be identified in any data or report unless you have given your consent

Who is organising and funding the research?

The research is organized and funded by University College London and, Central and North West London NHS Trust.

Who has reviewed the study?

All research in the NHS is looked at by an independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given favourable opinion by the National Research Ethics Committee. This particular research has also been reviewed and approved by academic staff at University College London.

Further information and contact details

If you want further information about the study or have any concerns about it, please do contact Dr Joshua Stott on [redacted] or Lucy Gore on [redacted]

Appendix 6: Participant Consent Form

RESEARCH DEPARTMENT OF CLINICAL, EDUCATIONAL AND HEALTH PSYCHOLOGY

Patient Identification Number for this trial:

CONSENT FORM- Stage 1
Clinical Sample

Title of Project: Can people with dementia access Cognitive Behavioural Therapy (CBT)?

Name of Chief Investigator: Dr Joshua Stott

Name of Student Researcher: Lucy Gore

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated 17/02/2014 (version 2) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from **University College London** or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I agree to my GP being informed of my participation in the study. ☐

5. I agree to take part in the above study. ☐

Name of Participant Date Signature

Name of Person	Date	Signature

taking consent.

Appendix 7: Supplemental Correlation Tables

Supplemental Table 1: Pearsons Correlation for all measured variables split by AD (N=16) versus Other Dementia (N=19)

AD												
	ACE total	Memory	Attention	Language	Fluency	Visuospatial	TOPF	TMT A	TMT B	Anxiety	Depression	4MT
ACE total	1											
Memory	.861**	1										
Attention	.528	.500	1									
Language	.606*	.412	-.194	1								
Fluency	.708**	.572	.236	.450	1							
Visuospatial	.713**	.366	.213	.593*	.487	1						
TOPF	.368	.187	.250	.268	.110	.364	1					
TMT A	.237	.156	-.251	.431	.657*	.324	.313	1				
TMT B	.545	.448	.169	.365	.790**	.539	.409*	.530	1			
Depression	-.162	-.029	-.184	-.220	.076	-.363	-.568*	-.162	-.254	1		
A	-.090	.081	.187	-.271	-.505	-.373	-.189	-.785**	-.687*	.147	1	
4MT	-.195	-.035	.344	-.299	.022	-.516	.101	-.238	.286	.009	.008	1
Other dementia type												
	ACE total	Memory	Attention	Language	Fluency	Visuospatial	TOPF	TMT A	TMT B	Anxiety	Depression	4MT
ACE total	-											
Memory	.807**	-										
Attention	.877**	.698**	-									
Language	.873**	.550*	.734**	-								
Fluency	.799**	.441	.623**	.715**	-							
Visuospatial	.647**	.557*	.446	.403	.449	-						
TOPF	.856**	.691**	.767**	.770**	.677**	.569*	-					
TMT A	.312	.014	.112	.269	.692**	.294	.273	-				
TMT B	.284	.067	.170	.226	.433	.371	.355	.598**	-			
Anxiety	-.455	-.458	-.323	-.427	-.394	-.066	-.516*	-.219	-.099	-		
Depression	-.459	-.138	-.219	-.617**	-.606**	-.223	-.540*	-.679**	-.476*	.458	-	
4MT	.312	.016	.285	.353	.249	.477*	.319	.325	.541*	-.088	-.397	-

** Correlation is significant at the 0.05 level (2-tailed).*

*** Correlation is significant at the 0.01 level (2-tailed.*

Supplemental Table 3: Pearsons Correlation for all measured variables split by AD (N= 15) versus VD (N=9)

AD												
	ACE total	Memory	Attention	Language	Fluency	Visuospatial	TOPF	TMT A	TMT B	Anxiety	Depression	4MT
ACE total	1											
Memory	.854**	1										
Attention	.571*	.529*	1									
Language	.635*	.462	-.091	1								
Fluency	.685**	.574*	.242	.459	1							
Visuospatial	.501	.124	.161	.349	.248	1						
TOPF	.190	.057	.094	.127	.084	.153	1					
TMT A	.174	.012	-.167	.329	.466	.382	.240	1				
TMT B	.472	.392	.127	.272	.727**	.522	.447	.306	1			
Depression	.002	.136	.225	-.187	-.456	-.146	-.288	-.711**	-.503	1		
Anxiety	.010	.048	-.023	-.095	.030	.061	-.611*	-.173	-.079	.356	1	
4MT	.021	.041	.315	-.119	-.03	.110	-.161	-.222	.352	.285	.460	1
VD												
	ACE total	Memory	Attention	Language	Fluency	Visuospatial	TOPF	TMT A	TMT B	Anxiety	Depression	4MT
ACE total	1											
Memory	.890**	1										
Attention	.891**	.818**	1									
Language	.935**	.753*	.835**	1								
Fluency	.805**	.566	.553	.737*	1							
Visuospatial	.784*	.546	.685*	.698*	.680*	1						
TOPF	.885	.767*	.899**	.821**	.716*	.652	1					
TMT A	.377	.051	.025	.376	.734*	.509	.253	1				
TMT B	.384	.250	.411	.302	.295	.525	.444	.633	1			
Anxiety	-.200	-.272	.398	-.215	-.207	.202	.050	-.781*	-.576	1		
Depression	-.435	-.566	-.437	-.296	.373	-.044	-.607	-.300	-.563	.464	1	
4MT	.417	.185	.600	-.439	.237	.619	.372	.338	.648	.281	-.011	1

** Correlation is significant at the 0.05 level (2-tailed).*

*** Correlation is significant at the 0.01 level (2-tailed.*