Detecting Dementia Earlier: The development and analysis of Spatial & Episodic Memory tests for cognitive ageing and Alzheimer's disease.

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Detecting Dementia Earlier: The development and analysis of Spatial & Episodic Memory tests for cognitive ageing and Alzheimer's disease.

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Declaration

The author confirms that the following works presented in this thesis is her own and proper credits have been given to the works of others in which references have been made. None of the presented works has been submitted elsewhere for any other degree or qualification.

Statement of Copyright

Abstract

Reliably detecting Alzheimer's disease (AD) earlier is a global priority, to ensure that therapies can be propitiously targeted to those who most need them. Current diagnostics are not sufficiently accurate, and the best cannot be scaled to large populations. Diagnostic tools which are cost-effective, sensitive to early neurodegeneration, and easy-to-administer are crucial to progress. The hippocampal formation degenerates early on in AD, therefore tests which tap hippocampal function may prove valuable in detecting early-stage AD. The present thesis explored this idea.

Chapter 3 examined *current* AD tests. I meta-analysed which existing neuropsychological tests best predict early AD (i.e. conversion from MCI to AD). Results identified six neuropsychological tests of promise and suggested these may provide diagnostic performance similar to that of 'gold-standard' cerebrospinal fluid (CSF) markers.

Chapter 4 asked whether a recently developed spatial memory task (4MT), and a forced-choice space and sequence memory video task (SSEVT) specifically developed for this project, were sensitive to the age-related decline in cognitive ability thought to be hippocampus-dependent. As hypothesised, the SSEVT and to some extent the 4MT did, and unexpectedly the commonly used ACE-III test did not, show such sensitivity. An advantage of the SSEVT over the 4MT was that education was not significantly associated with SSEVT performance.

Chapter 5 compared the performance of MCI patients to healthy-ageing (HA) controls on the above three tasks (4MT, SSEVT and ACE III), and two self-report questionnaires (one probing spatial ability, one probing social embedding) developed for this project. Promisingly, the 4MT and SSEVT discriminated well between the MCI and HA groups, as predicted (while the ACE-III task did not). The two groups did not differ on the spatial ability questionnaire. The MCI group were less socially embedded than the HA group, offering some support for ideas that social interaction protects against dementia and cognitive decline.

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I would like to sincerely thank my friends and family. My parents for their unwavering emotional, financial, and motivational support and love over the many years of being a student and to Matt, I know that I'm lucky to have such a supportive partner and team-mate in life.

My interest in Dementia research developed during my undergraduate degree, working within the care sector and through familial experience. I would like to thank my Grandparents for always remaining my biggest fans and my motivation. I hope that I have made you proud.

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Chapter 1: Introduction.

1.1: Alzheimer's disease: History, Epidemiology and Pathology

In 1906 Alois Alzheimer published 'a particular disease of the cerebral cortex', in which he described plaques, neurofibrillary tangles and arteriosclerotic changes in the brain of Auguste D, a 51 year old woman with presenile dementia who was experiencing episodic memory loss, profound language deficits, anxiety and paranoid delusions. When she died, her brain was sent to Alzheimer who reported the necropsy. Figure 1.1 presents Alzheimer's drawings of Auguste D's material, specifically the neurofibrillary tangles present at an advanced stage of the disease.

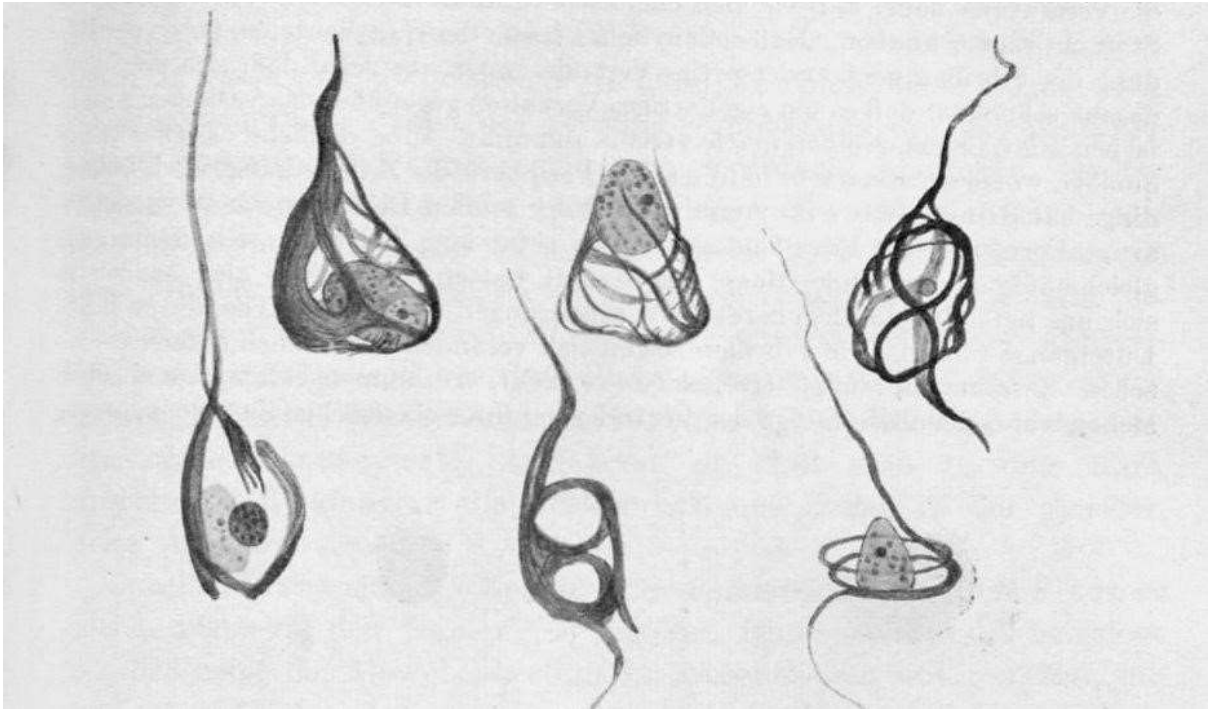


Figure 1. 1. **Drawings of histological preparations of Auguste D's material. The drawing demonstrates neurofibrillary tangles at an advanced stage of the disease.**

Source: Zeitschrift fuer die gesamte Neurologie und Psychiatrie, 1911.

Amongst his patient's many difficulties, were spatial and episodic memory impairments as suggested by the following observations:

A) '*Soon a rapidly increasing loss of memory could be noticed. She could not find her way around in her own apartment*.'

B) '*She was totally disorientated to time and place. Occasionally she stated she could not understand and did not know her way around.*'

C) 'If one pointed to objects, she named most of them correctly, but immediately afterwards she would forget everything. When reading she went from one line to another, reading the letters or reading with a senseless emphasis (Maurer, Volk & Gerbaldo, 1997).'

Alzheimer went on to describe the neuropathology of the disease that would be named after him. For another half a century, the term 'Alzheimer's Disease' was limited to severe forms of presenile dementia until it was determined that neuropathological manifestations of both presenile and senile dementia were virtually identical and were no longer referred to as separate diseases (Amaducci, Rocca & Schoenberg, 1986).

The term 'Dementia' is used to describe a large range of symptoms including a loss of memory, communication difficulties, and mood changes. There are over 200 subtypes of dementia but the most common are vascular dementia, dementia with Lewy bodies, frontotemporal dementia, and Alzheimer's disease (AD), with Alzheimer's disease accounting for two thirds of all dementias (Patterson, 2018). The dementia that this thesis focuses on is sporadic (Late-onset) Alzheimer's disease.

The number of people affected by dementia worldwide is predicted to double between 2020 (42 million) and 2040 (81 million) (Ferri, Prince & Brayne, 2005) with 65% of

those living with dementia being women (Prince et al, 2014). Indeed, 16.3% of women died due to health conditions associated with Alzheimer's disease and other dementias in 2016 in the UK, making it the leading cause of death for women in that year (England and Wales; Mortality Statistics: Research Agency Registrar General Annual Report 2016).

Dementia research, treatment and care are fast becoming both a national and global priority. Without disease-modifying treatment, it has been estimated that 35% of women and 24% of men born in 2015 will develop dementia within their lifetime (Maignen, 2016).

1.1.1: Epidemiology

The distribution of worldwide prevalence data seems to vary according to cultural and socioeconomic differences, but interestingly overall prevalence of dementia seems to be higher in developed rather than developing countries (Rodriguez, Ferri & Acosta, 2008). This has been attributed to the differences in the level of exposure to risk factors such as smoking, obesity, diabetes and hypertension (Rodriguez, Ferri & Acosta, 2008), factors which are explored in more depth in Section 1.3.1. However, this effect is also argued to be attributed, at least in part, to limited access to medical care and shorter life expectancy (Prince et al, 2012).

Indeed, age remains the single biggest risk factor of AD. Whilst the risk of developing 'probable AD' for those aged 60-69 is <1%, the prevalence of the disease roughly doubles every 5 years after the age of 65 (Prince, Albanese & Guerchet, 2014). This equates to around a 20% risk for those aged 85-89 (Prince, 2014).

1.1.2: Macroscopic Pathology of Alzheimer's Disease.

A main consequence of Alzheimer's disease is neuronal death which exhibits macroscopically as atrophy. This results in the widening of sulcal spaces, an increase in size of the ventricles and cortical thinning (Morales et al, 2010), as can be seen in Figure 1.2. The extent and rate at which this atrophy occurs depends on the brain region; the entorhinal cortex and hippocampus are significantly affected early on, whereas the sensory, visual, and motor cortices are relatively unaffected until the advanced stages of the disease (Thompson et al, 2007; Johnson et al, 2012). Thus, it is to be expected that hippocampal dependent functions are disrupted at a particularly early stage.

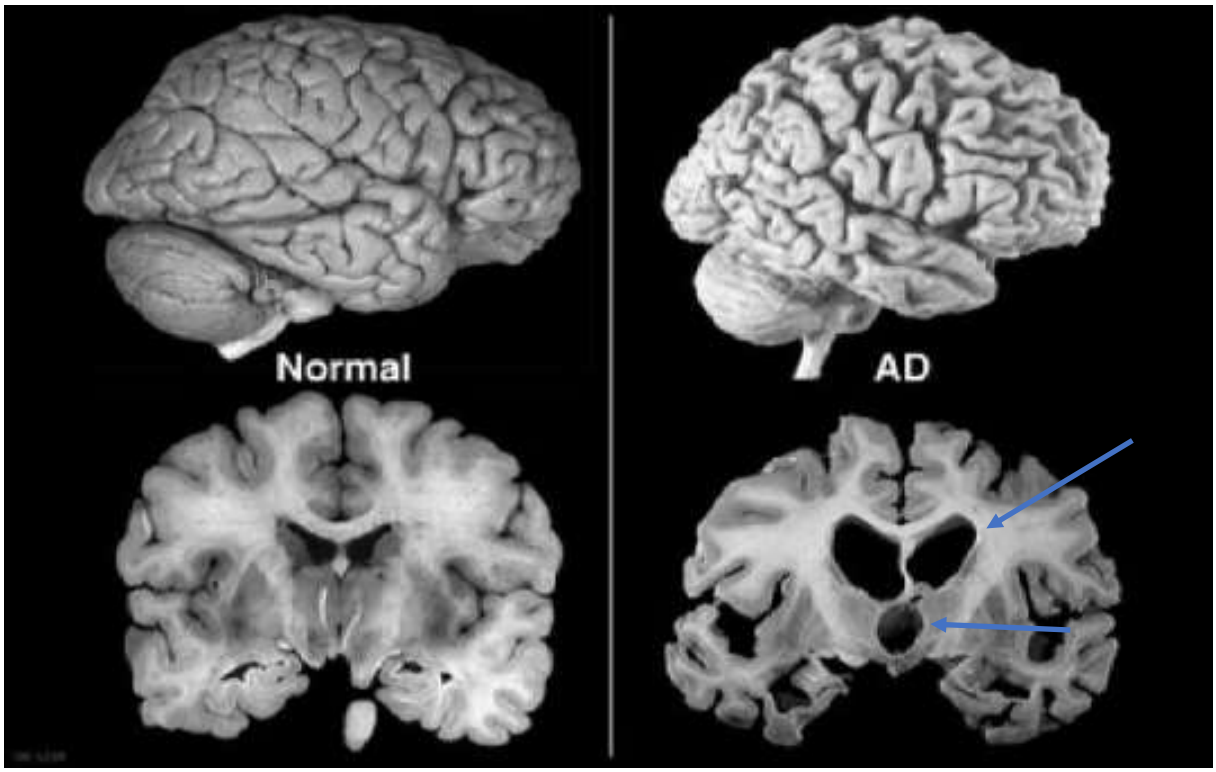


Figure 1. 2. **Brain Atrophy in Advanced Alzheimer's Disease.**
Alzheimer's disease is characterised by atrophy in the cerebral cortex due to the loss of neurons and synapses.
Source: Morales et al, 2010.

1.1.3: Microscopic pathology of Alzheimer's disease.

From Alzheimer's original paper until the present day, the major pathological hallmarks of AD have remained constant; amyloid plaques and neurofibrillary tangles (Figure 1.3).

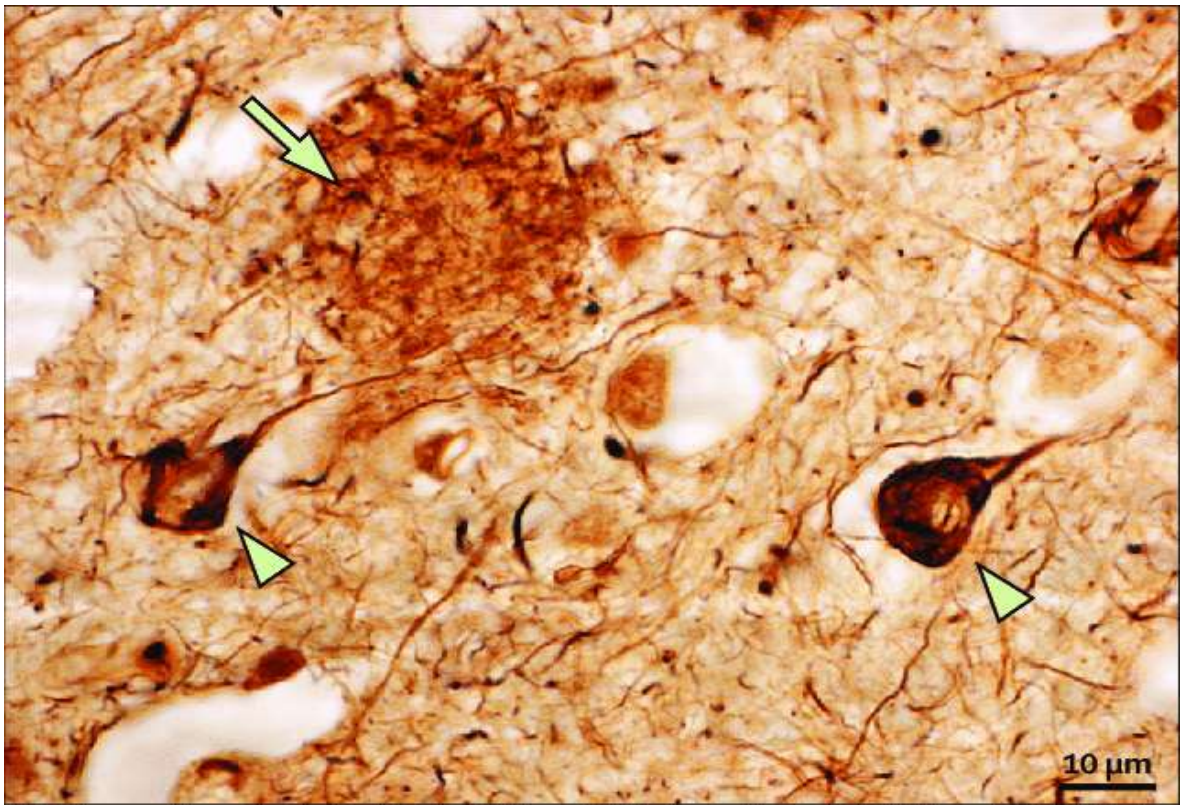


Figure 1. 3: **Image of an AD patient's frontal cortex post-mortem.**

Post-mortem Bielschowsky silver staining of frontal cortex from a patient with Alzheimer's disease, showing the presence of a neuritic amyloid plaque (arrow) consisting of aggregated extracellular amyloid β fibrils, and intraneuronal neurofibrillary tangles (arrowheads).

Source: Winblad et al, 2016.

1.1.3.1: Amyloid Plaques

The beta-amyloid protein that is involved in Alzheimer's disease comes in many different molecular forms that collect between neurons and is created from the breakdown of a larger protein, namely amyloid precursor protein. One particular form, known as beta-amyloid 42, is thought to be especially toxic. In those with Alzheimer's the abnormal levels

of this protein clump together, forming plaques between neurons and severely disrupting cell function (Hardy & Higgens, 1992; Parihar & Hemnani, 2004).

1.1.3.2: Neurofibrillary Tangles

The tau proteins are a group of six highly soluble protein isoforms which are produced by alternative splicing from the MAPT (microtubule-associated protein tau) gene (Goedert et al, 1998). Their role is to stabilise microtubules in axons and are abundant in the neurons of the central nervous system (CNS). Alzheimer's disease is associated with tau proteins that have become hyperphosphorylated insoluble aggregates called neurofibrillary tangles. Hyperphosphorylation leaves tau unable to bind and the microtubules become unstable and begin disintegrating. This unbound tau sticks to other tau molecules which go on to form threads and eventual tangles inside neurons (Alonso et al, 2008). The presence of these tangles severely compromise synaptic communication between neurons. These can be seen in Figure 1.3, which shows clear similarities to the original drawings by Alzheimer in Figure 1.1.

As the disease progresses, many anatomical lesions occur within the brain, along with the appearance of these senile plaques which consist of amyloid beta (Aβ) and neurofibrillary tangles containing phosphorylated tau, leading to synaptic loss and neuronal death (Perl, 2010). There is also the presence of significant oxidative stress and mitochondrial abnormalities. The pathological changes that occur in AD are illustrated in figure 1.4.

The behavioural symptoms of Alzheimer's Disease become more apparent and correlate with the accumulations of these plaques and neurofibrillary tangles, serving as an

observable consequence of the damage to synapses that mediate cognition and memory (Marshall et al, 2006; Wesson et al, 2010; Bloom, 2014). The observable effects of AD are outlined in the section below (1.2) and in Table 1.1.

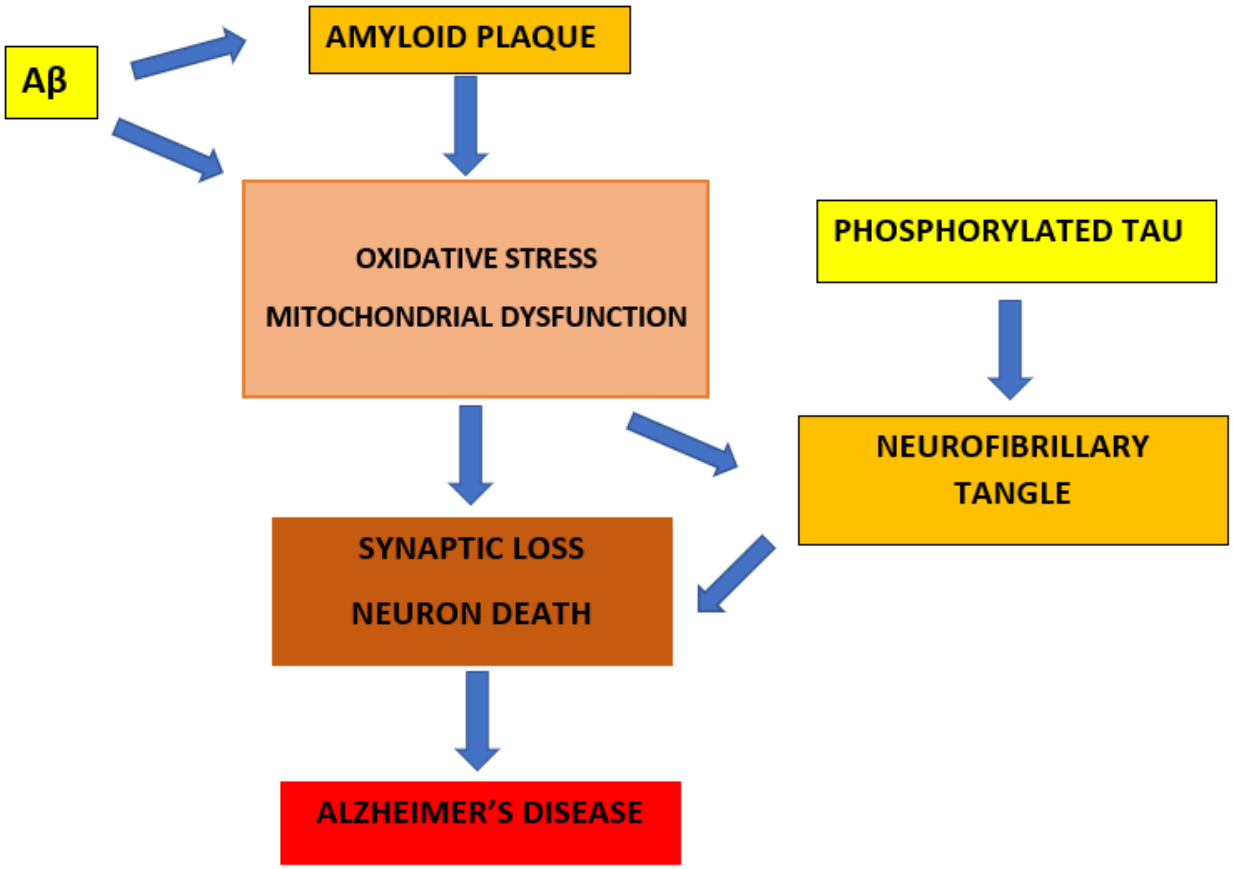


Figure 1. 4. **A chart illustrating the association between amyloid beta, phosphorylated tau, mitochondrial dysfunction, and neuronal death.**

Amyloid plaques and neurofibrillary tangles are well known pathological changes in Alzheimer's disease which are formed from Aβ and phosphorylated tau. Aβ and amyloid plaques in together with oxidative stress and mitochondrial dysfunction result in synaptic damage, neuronal degeneration and death, a process further aggravated by Neurofibrillary

tangles. This neuronal death and synaptic loss results in the observable symptoms of Alzheimer's disease.

1.2: The observable effects of Alzheimer's Disease

Alzheimer's disease is neurodegenerative and generally progresses gradually, possibly for decades. Each individual case presents with different symptoms of varying severity; however as discussed above due to the nature of its pathology, it is possible to broadly generalise, as in Table 1.1.

Table 1. 1. ***An outline of stages and patient presentation of Alzheimer's Disease.***

Source: The progression of Alzheimer's disease. (n.d.). Retrieved March 11, 2020, from https://www.alzheimers.org.uk/about-dementia/symptoms-and-diagnosis/how-dementia-progresses/progression-alzheimers-disease

Stage	Symptoms
Early-Stage AD: 2-4 Years	- Issues navigating the environment - Difficulty with problem-solving and decision making. - Mild personality changes. Social withdrawal.
Moderate Alzheimer's Disease: 2-10 Years (Longest stage of the disease)	- Increased confusion and poor judgement. - Orientation issues. - Difficulty completing complex tasks. - Greater memory loss - More significant personality changes
Severe Alzheimer's disease	- Reliance on others for most aspects of personal care including hygiene, eating and toileting (many patients become incontinent) - Loss of communication: Patients may not be able to speak more than a few coherent sentences. - Loss of motor function: The individual may become unable to mobilise independently. Swallowing can also become impaired (dysphagia).

When looking at the real-world implications of AD upon an individual (Table 1.1), it is possible to see not only the devastating effect the disorder has upon those diagnosed, but also to see the slow progression of the disease. The neurological changes in the brain caused by AD are not normally the primary cause of an individual's death but complications

associated with the disease, such as lack of mobility and dysphagia (swallowing difficulties). Dysphagia can increase the risk of pneumonia and malnutrition (Chouinard, 2000; Kalia, 2003; Secil et al, 2016). As previously discussed, 16.3% of women and 8.7% of men died due to Alzheimer's disease and other dementias in 2017 in the UK making it the leading cause of death for women and the second leading cause for men (England and Wales; Mortality Statistics: Research Agency Registrar General Annual Report 2016).

1.3: Alzheimers Disease: What are the main risk factors?

Many risk factors have been outlined in relation to Alzheimer's disease, of which the most established will be discussed below. As this thesis is focusing solely on sporadic (late onset) AD and aging, the familial forms of AD will not be discussed in detail. A connection has been found between Apolipoprotein (ApoE4) and the development of AD. ApoE4 is one of the genes responsible for the protein that carries cholesterol in the blood and is considered a risk factor for AD (Blennow et al, 1996; Artiga et al, 1998; Bullido et al, 2000). As there are currently no existing preventative or disease-modifying treatments, the identification of modifiable risk factors is of particular interest.

1.3.1: Lifestyle as a risk factor.

There are several environmental and lifestyle related risk factors associated with Alzheimer's disease. This wide and multi-faceted topic is presented here with comparative brevity, mostly focusing on obesity and subsequent cardiovascular issues and smoking.

Mid-life obesity is a well-known risk factor for dementia and AD in epidemiological studies (Anstey et al, 2011) which whilst being a risk factor in itself (Calle et al, 2003; Anstey et al, 2011), is also associated with other risk factors such as cardiovascular disease. Furthermore, several pathological changes associated with obesity, such as insulin resistance, inflammation, or mitochondrial dysfunction, are also associated with AD pathology (O'Brien et al, 2017). Interestingly, late-life obesity is considered to be a protective factor. Weight-loss is known to sometimes pre-date cognitive decline which may explain this obesity paradox regarding AD risk (Pegueroles et al, 2018).

Obesity is also often associated with cardiovascular issues (Bruijn & Ikram, 2014) which have been shown to have a direct influence on amyloid pathology due to accelerating amyloid β production or hampering the clearance of amyloid β (Garcia-Alloza et al, 2011; Iadecola et al, 2013). However, studies which focus upon these pathways remain inconsistent (Jagust et al, 2001; Launer et al, 2008).

Cerebrovascular accidents (strokes), coronary heart disease and heart failure are common amongst the elderly population and are regularly linked to Alzheimer's disease. Traditionally, cerebrovascular accidents are more often associated with vascular dementia than Alzheimer's disease (Leys et al, 2005), however there is important evidence which implicates stroke in the aetiology of AD. Most studies which examine the link between cardiovascular issues and AD focus on asymptomatic cerebrovascular accidents which are often lacunae (a type of ischemic stroke whereby blood flow to one of the arteries deep within the brain becomes blocked). Many studies have shown that the presence of lacunae increases the risk of AD (Troncoso et al, 2008) and, furthermore, white matter lesions,

representing ischemic brain damage, are also associated with both cognitive impairment and Alzheimer's disease (Prins et al, 2004).

Several studies have also noted the relationship between hypertension, (which is a cardiovascular issue often associated with obesity) and brain atrophy, white matter lesions and neurofibrillary tangles (Petrovitch et al, 2000; Van Dijik et al, 2004). White matter lesions and neurofibrillary tangles are both present within AD pathology, and the presence of such abnormalities correlating with hypertension thus further establishes the relationships between cardiovascular issues and AD.

Several longitudinal studies have also found smoking to be a risk factor for Alzheimer's disease. For example, the Honolulu-Asia study (Tyas et al, 2003) found that the number of packets of cigarettes, and the years an individual had smoked for, was related to the amyloid burden in a dose-response manner. Supporting this, the Rotterdam study found that the risk of dementia was significantly higher in smokers than non-smokers (Reitz et al, 2007). It is well-known that tobacco contains neurotoxins which may cause neuronal damage (Treweek et al, 2009) however the exact nature in which smoking affects dementia risk still requires further investigation. In general then, there is evidence to suggest that obesity and smoking increase the risk of dementia, implying that poor cardiovascular health increases dementia risk.

1.3.2: Social networks and social embeddedness: a protective factor in dementia?

Evidence also suggests that social networks and socialisation can act as a protective factor slowing the progression of dementia, or conversely put, that social isolation is a risk factor

for dementia. Protective factors are external influences which are thought to somewhat compensate for neural deterioration and resulting pathology of cognitive abilities in old age (Stern, 2012). Whilst a variety of modifiable protective factors are relatively well established such as physical exercise, diet and social interaction (Baumgart et al, 2015), less is known about the effects of the size and complexity of social networks and social embeddedness (Evans et al, 2018). As discussed below, while the benefits of socialisation are increasingly accepted, it is not yet clear how rich social networks provide benefit. Does the benefit primarily emerge from a boost in cognitive stimulation, or from reduced stress-elicited pathology?

Bennett and colleagues (2006) recruited 89 elderly people without a dementia diagnosis and conducted a yearly clinical evaluation, including information about social network size, which was obtained via structured interview. A brain autopsy was conducted after time of death. Unsurprisingly, they found cognitive function to be inversely related to disease pathology, with individuals displaying lower function at more severe levels of pathology. However, they also found that social network size modified the association between pathology and cognitive function. Even at more severe levels of pathology, cognitive function remained higher for those with larger social networks. This supports the idea that social networks may have a somewhat buffering effect on cognitive function, compensating for neural deterioration and resulting pathology.

Fratiglioni and colleagues (2000) conducted a longitudinal community-based cohort study of 1203 elderly individuals who did not initially have dementia and who were considered to have good cognition. They were followed up on average every three years, during which 176 patients were diagnosed with dementia by their own clinicians.

Information on social networks was obtained at baseline. It was concluded that single people, and those who lived alone, or had no close social ties, were found to have an increased relative risk for developing dementia compared with married people living with their spouse.

Supporting the association between larger social networks serving as a protective factor, a study by Crooks et al (2008) found that larger social networks have a beneficial effect on cognitive ability in elderly women, when controlling for depression and education. Indeed, further research has found that socialising for even just a few minutes (10 minutes) at a time increased performance on tests assessing executive functioning (Ybarra et al, 2008). This increase in performance has been attributed by some to the cognitive stimulation that occurs as a result of interacting with other people (Dodge, Ybarra & Kaye, 2013). The quality of the social networks and support systems have, however, been found to be more imperative in mediating cognitive decline than the sheer quantity of social interactions (Amieva et al, 2010; Holwerda et a, 2012).

Just as larger social networks have been associated with higher cognitive function in those with AD pathology, loneliness has also been associated with dementia risk. Rafnsson et al (2016) recruited 6,677 dementia-free individuals and information regarding loneliness, number of close relationships, marital status and social isolation was analysed in relation to incident dementia over an average of 6.25 years. Two hundred and twenty participants had been diagnosed with dementia at follow-up. They found dementia risk to be positively related to greater loneliness, and inversely related with the number of close relationships and being married. However, no association was found regarding social isolation. Such results strongly indicate that dementia risk may be associated with loneliness and fewer

close relationships as people age and highlights the importance of relationship quality, not simply the sheer size of a social network.

This disparity within the research may be due to many different factors such as differing measures of cognitive abilities such as global measures of cognition (Simning et al, 2014; Shankar et al, 2013). Significantly, the underlying mechanisms between social networks and function remains somewhat unestablished (Ellwardt et al, 2013). In order to better understand the value of social factors as a protective or potential diagnostic measure, it is imperative to first consider its neuronal pathology.

1.3.2.1: Social embeddedness as a protective factor is hippocampus dependent: Animal studies

Rodents reared in a communal nest have been found to have higher levels of hippocampal brain-derived neurotrophic factor (BDNF) within the brain (Branchi et al, 2006). BDNF increases both neurogenesis and synaptic plasticity thus improving cognitive functions (Miranda et al, 2019). This suggests that larger social networks and greater social embeddedness may act as protective factors against cognitive decline via neuronal change in the hippocampus, known to degenerate early in Alzheimer's disease (Bäckman, Small & Fratiglioni, 2001; Ghoshal et al, 2002).

Furthermore, Smith et al (2018) found that 15-month-old female mice had comparatively improved hippocampal functioning when housed in a large group for three months as opposed to mice housed in pairs. Mice living in larger groups showed greater novel object location memory and relied more upon hippocampal-independent processing.

As the hippocampus is known to degenerate at an early stage in AD pathology this evidence of a causal relationship between social networks and the hippocampus supports the idea that neuropathology of the hippocampus may be affected by social embeddedness which in turn acts as a protective factor of cognitive decline.

Although the biochemical and anatomical differences in the brain between humans and rodents must be acknowledged, this is a promising causal link and when paired with human studies which show increased performance and abilities in those with larger social networks, may prove beneficial in early AD diagnosis. This causal relationship between social embeddedness and the hippocampus was of particular interest to the present study, as it offers another hippocampal-dependent function to explore in relation to AD. To address and further explore this relationship, the Social Networks and Embeddedness Questionnaire (SNSEQ), (Chapter 2, Section 2.14) was created.

1.3.3: Stress as a risk factor in Alzheimer's disease

Stress is another risk factor associated with AD. Hydrocortisone or 'cortisol' is a steroid hormone which binds to specific intracellular receptors in the brain, particularly to the regions implicated in cognitive functions (McEwen, 2007; Vogel et al, 2016). Stress is known to affect mood, appetite, sleep, and anxiety along with levels of cognition (Lupien et al, 2007; Copinschi & Caufriez, 2013). Cortisol's association with stress is so well-documented it is often referred to as the 'stress hormone' (Fujiwara et al, 1996; Payne & Nadel, 2004; Stark et al, 2006).

Cortisol dysregulation is commonly found in AD patients (Näsman et al, 1996; Umegaki et al, 2000; Giubilei et al, 2001) and has been related to AD pathology in both humans and animals (Umegaki et al, 2000; Huang et al, 2009; Dong & Csernansky, 2009; Rothman & Mattson, 2010). In patients with AD, elevation in baseline cortisol has even been shown to predict AD progression (Umegaki et al, 2000; Huang et al, 2009). Higher cortisol levels have also been related to increased amyloid beta in the brain (Toledo, Toledo & Weiner, 2012), a pathological hallmark of AD. Such evidence suggests that high cortisol levels, created by chronic stress, act as a risk factor in the development of Alzheimer's disease. Concomitantly, it seems likely that one of the routes by which social embedding reduces Alzheimer's Disease risk is via reducing stress.

Social animals tend to live in groups and communicate and organise this group in a way that ultimately benefits them as an individual. This interaction and co-operation is essential for protection against external threats and is therefore one of the main reasons why establishing a society is so beneficial. Social mammals tend to communicate such threats through visual (Liddell et al, 2005), vocal (Seyfarth & Cheney, 2003) and pheromonal cues (Rottman & Snowdon, 1972; Kikusui et al, 2001). It is therefore possible that individuals feel safe with other members of a group (friends, family etc) because such companionship provides security and protection from environmental threats (Kikusui et al, 2006). Furthermore, the absence of colony members can itself be stressful for mammals and they often show a high stress response when isolated (Hatch et al, 1965; Clancy & McBride, 1975). This is known as 'isolation syndrome' in which animals can show a high level of stress in response to various stimuli when housed individually over a long period of time (Clancy & McBride, 1975; Noble et al 1976). Importantly when discussing AD, social isolation in

humans has been related to physiological and mental pathogenesis (West et al, 1986; Tomaka et al, 2006)

When animals of the same species are together, they have been shown to recover better from negative experiences. This phenomenon is known as social buffering and has been most commonly found in rats, guinea pigs and non-human primates (Davitz & Mason, 1955; Hennessey et al, 2000; Coe et al 1978; Levine et al, 1978) and humans (Thornsteinsson et al, 1998). Social buffering through a greater social network may well prove to be a protective factor in AD pathology, whereas isolation may lead to high levels of stress which may increase cortisol production, the effects of which are discussed above. Thus social integration and a large social network, as discussed above in Section 1.3.2 may be protective by reducing the cumulative effects of excessive cortisol upon the brain. The Social Networks and Embeddedness Questionnaire (SNSEQ) included in the testing of healthy and MCI participants (Chapters 4 and 5) aims to assess the extent to which participants are socially embedded and the potential effect social integration might have upon cognition, as assessed through neuropsychological test scores.

1.3.4: Education as a protective factor in Alzheimer's disease

Lower education is a relatively well-established risk factor for Alzheimer's disease, with higher levels of education being protective. The first indicators of this association came from population studies which found dementia prevalence to be greater amongst those with lower levels of education and less amongst those with higher levels (Dartigues et al, 1991; Kokmen et al, 1993; Precipe et al, 1996; Yamada et al, 1999). The Canadian study of Health

and Aging (1994) is a notable population study which found those with six years or less of education had higher rates of Alzheimer's disease than those with 10 years or more.

Some researchers have also discussed the possibility that education may be indicative of other factors such as bad health habits and occupational exposures such as alcohol use (Fratiglioni et al, 1991), and indeed lower levels of education are often correlated with certain lifestyle choices (smoking, eating habits etc) which may also play a role in Alzheimer's disease (Cobb et al, 1995). For example, DeRonchi and colleagues (1998) found only a residual effect with regards to education after controlling for age, occupation, and smoking. As discussed in Section 1.3.1 above, smoking appears to reliably increase dementia risk, and it is important to consider the possibility that at least some of education's benefits may not be directly cognitive but emerge secondarily via healthier lifestyle choices.

Some benefits of education are, however, likely to be cognitive. One particularly interesting issue with regards to the association between education and AD is the idea of diagnostic bias. For example, education may simply teach an individual the reasoning skills and format of questioning commonly employed by current neuropsychological diagnostic tests (Gilleard, 1997). This explanation is supported by findings that those with lower education tend to have lower neuropsychological test scores whilst suffering no greater functional deficits than higher educated individuals (Swanwick et al, 1999). Should this be the case, it could be suggested therefore, that a higher level of education may not necessarily be a protective factor. Instead it may increase the risk of educated individuals receiving a false negative diagnosis whilst a lower level of education may lead to more false-

positive diagnoses due to the nature and format of neuropsychological tests, which do not adequately control for such educational bias (Gilleard, 2010).

Whilst it is undeniable that those with a lower level of education seem to experience a greater prevalence of dementia, this may also be due to unhealthy lifestyle choices often associated with lower educated populations. The issue of educational bias offers an interesting perspective, potentially highlighting a significant problem within the neuropsychological testing system currently used within clinical practice. This is discussed in more detail in the general methodology chapter of this thesis (Chapter 2) and addressed within the analysis in Chapter 4, which analyses how age and education affects test scores.

1.4: Existing treatment options: Drug Therapies

There is currently no cure for Alzheimer's disease but there are four drugs approved for the treatment of AD, which are thought to temporarily reduce symptoms; three cholinesterase inhibitors (donepezil, rivastigmine, galantamine) and an *N*-menthyl-D-aspartate (NMDA)-receptor antagonist (memantine) (Howard et al, 2012; Hyde et al, 2013). Psychiatric medications utilised to manage behavioural and psychological symptoms such as mood disturbance, sleep problems, hallucinations, and depression but which are not expected to slow disease progression are not discussed here.

As outlined in Sections 1.1.2 and 1.1.3, senile plaques are composed of aggregated Aβ and neurotoxic β-amyloid (Aβ) peptide along with the accumulation of tau composed neurofibrillary tangles and are thought to be the main cause of Alzheimer's disease

pathology. In addition, individuals with AD typically show a reduction in acetylcholine production, resulting in a decreased availability of acetylcholine at the neuronal synapse (Birks, 2006; Birks & Harvey, 2006).

The three approved AChEIs are reversible non-competitive inhibitors of acetylcholinesterase that act to raise the concentration of synaptic acetylcholine by preventing its breakdown. The increased concentration of acetylcholine is thought to lead to increased chances of remembering something, under a model in which high levels of acetylcholine boost initial encoding (Hasselmo, 2006; Easton et al, 2012).

Glutamate is an excitatory neurotransmitter which is released in excessive amounts when brain cells are damaged by AD pathology (Greenamyre, 1986; Danysz & Parsons, 2003), disrupting cellular communication and further contributing to neuronal loss (Areosa et al, 2005). The action of memantine is different from that of galantamine, donepezil and rivastigmine in that it inhibits this destructive, excessive excitatory action of glutamate by reversible antagonism of *N*-methyl-D-aspartate receptors.

Currently, AChEIs have authorisation within the UK for the treatment of moderate and mild AD, whereas memantine has UK authorisation to be used by those with moderate and severe AD. Both drugs propose to improve cognition. There are however side effects to both medications which may limit drug tolerance, A ChEIs can slow heart-rate, cause vomiting, dizziness and nausea. Memantine can cause dizziness, confusion, dizziness, and incontinence. Although the cost of treatment itself is modest relative to many other medications, the sheer amount of those affected, as discussed in Section 1.1.1, and the length of treatment does make both drugs very costly (Casey et al, 2010).

In 2007 The National Institute of Health and Clinical Excellence (NICE) issued guidance regarding the four drugs (Donepezil, Glantamine, Rivastigmine and Memantine) and restricted access in the NHS to the four AChEIs and memantine due to their lack of cost-efficacy, especially with uncertainty regarding efficacy, especially regarding Memantine, the one NMDA (NICE, 2009). Therefore, AChEIs were approved for moderate AD and Memantine was only recommended as part of clinical study. This was then updated in 2010, where the use of AChEIs was extended to all severities of AD and introduced Memantine into clinical practice (NICE, 2011). Although supported by many, there are some criticisms as to this decision, with many attributing the change in guidance to pressure from the media, patient groups and pharmaceutical companies especially as the evidence for their accuracy has changed little since the original guidance (Gilstad & Finucane, 2008).

It is important to note that AChEIs especially have been approved specifically for mild to moderate dementia, however this relies heavily on an early diagnosis. Any potential positive impact of the three approved AChEIs and the NMDA memantine is circumscribed if AD pathology is already relatively advanced before a diagnosis is made, thus as is a main focus within this thesis, a timely diagnosis remains paramount.

1.5: There is a clear need for simple accurate tests to detect early stages of Alzheimer's disease: Screening and diagnostic tools.

As previously discussed, the suffering dementia causes to individuals and their loved ones, and the particularly distressing nature of its later stages, often drawn out over many years, is universally acknowledged. Aside from the anguish it causes, the financial burden on carers

and the healthcare system continues to increase. Detecting Alzheimer's disease (AD) in its earliest stages greatly increases the likelihood that therapeutic agents (e.g. newly developed drugs) and interventions (e.g. improving diet and exercise) can markedly prolong the period of high-quality independent living and reduce the care burden. Drugs and lifestyle changes cannot reverse the disease, but at best can only limit its progression; therefore, these therapies need to be targeted as early as possible to those who need them (Bondi et al, 1994). It is also possible that existing drug therapies would be more effective if utilised at an earlier stage in the Alzheimer's brain pathology. Herein lies the main issue- with a neurodegenerative disease such as AD, time is of the essence and current tools, either in a specialist setting or from a local GP are simply not accurate or sensitive enough to detect AD at an early stage. Due to the global and national scale of the issue, and the numbers of those with the disease only increasing, there is a very high value in tools which have the potential to accurately diagnose the early stages of AD on a national scale i.e. something cost-effective, accurate and easy to administer.

In order to explore this further, it is important to note the distinct differences between screening and diagnostic tools. A screening test is a medical test or procedure performed upon members of an asymptomatic population to assess the likelihood of their members having a particular disease. Generally speaking, screening tests do not diagnose an illness and those who test positively require further investigation with subsequent diagnostic tests. Common examples of screening tests include the pap smear for cervical cancer (Arbyn et al, 2008; Mayrand et al, 2007 and Mammography for breast cancer (Friedwald et al, 2014; Rafferty et al, 2013). In most cases, screening tests need to be benchmarked against an established 'Gold Standard' test (Greenhalgh, 1977). This 'Gold Standard' is generally regarded as definitive and is usually invasive (e.g. biopsy or lumbar

puncture), or possibly too late to benefit the individual (e.g. autopsy). In the case of Alzheimer's disease, there is no clear consensus on a gold standard test and along with the need for screening tests, there is also a need to establish which diagnostic tests best identify AD. This is addressed within the meta-analysis in Chapter 3.

Despite its prevalence, there is currently no routine screening for AD, and this in part has been attributed to the lack of suitable tests. A 2014 review completed by the national screening committee stated 'The 2014 review concluded that cognitive assessment tools for dementia are not sufficiently accurate to be used in primary care or community care settings in the whole population. There was no validated test with agreed cut-off levels and all the cognitive assessment tools exhibited a wide range of sensitivity and specificity scores'.

However, limited access to early diagnostic has been associated with delayed treatment initiation, a delay of provision of services to the individual and their family members, an overall decreased quality of life and an increase of familial burden (Novak et al, 2004). Furthermore, should a successful drug be discovered, current tools would remain unable to identify the disease progression at an early enough stage to be of maximum benefit. Therefore despite the lack of current treatment, there remains a significant benefit in the creation and utilisation of accurate, cost effective and easy to use tools which would be suitable for large-scale screening.

1.6: The problems with current neuropsychological tools commonly used within a primary care setting.

The Alzheimer's disease diagnostic process begins with General practitioners (GPs), who are instrumental in providing both pre and post-diagnostic dementia care and are considered

the gatekeepers to further assessment. While general practitioners (GPs) have a central role to play in the primary care response to identifying cognitive impairment and dementia, some concern has been raised as to the adequacy with which this role is met (Downs et al, 2010; Hansen, 2008). Unfortunately, the early stages of dementia are thought to be extremely underdiagnosed by primary clinicians (Connolly et al, 2011; Boyd, 2013). In 2014 it was estimated that only 44% of those with dementia in the UK receive a diagnosis, leaving around 416,000 people living with the disease undiagnosed (Singh & Adam, 2015). One of the potential reasons for this is the lack of screening tools that are quick to use, cost effective to the NHS whilst also being sensitive to cognitive decline (Lorentz, 2002).

As the identification of dementia at an early stage is important for the initiation of symptom management, life planning and treatment, a referral from a GP to a specialist in order to receive a timely diagnosis is paramount. Despite this, various research and anecdotal evidence indicates that there does not seem to be a clear consensus amongst GPs as to the best tool available to identify cognitive impairment or the need for further investigation in the elderly (Scott & Mayo, 2018). The most commonly used tools include the Montreal Cognitive Assessment (MoCA) 7,6, the ACE III (Hsieh et al, 2013), which is discussed in detail in Chapter 2, Section 2.15. The MoCA and the ACE III are often also used as part of a larger battery if the patient is referred to a specialist memory clinic for further testing.

Despite widespread concern about Dementia, current tests for early stage Alzheimer's disease are inadequate, and as discussed above, the UK National Screening Committee has currently ruled out national screening for Alzheimer's disease for this reason. This thesis aims to compare the ability of three tools; the commonly used ACE III

and two new and recently developed hippocampal dependent tasks to distinguish between Patients with Mild Cognitive Impairment (MCI) and Healthy Ageing (HA) in order to address the lack of quick, effective screening tools (Chapter(s) 4 and 5).

1.6.1: Typical neuropsychological tests used as *diagnostic tools* in the UK.

The diagnostic tools used within specialist memory clinics or hospitals generally consist of neuropsychological testing, Cerebropinal Fluid (CSF) testing, and Neuroimaging. Broadly speaking, the diagnostic problems can be classed as measurement insensitivity in that they are unable to accurately identify those with the disease and a lack of specificity, lacking in the ability to correctly identify those without the disease (true negative rate).

Once a patient has been referred to a specialist from a primary care setting, neuropsychological assessment is widely used as a non-invasive aid in the diagnosis of Alzheimer's disease. Such tests tend to be taken as a battery, with various different tools used to study a patient's short- and long-term memory, attention, concentration, reasoning, ability to learn and retain new information and solve problems. A specialist clinician will administer a battery of various in-depth neuropsychological tests in order to establish a detailed picture of the individual's impairment. The substantial contribution of neuropsychology in the Alzheimer's diagnostic process has been well documented (Pinsker et al, 2018). More detail of commonly used neuropsychological tests is included in Chapter 2.

There has however been some criticism regarding the accuracy of neuropsychological tests, especially tests such as the MMSE and ACE-III, which along with their use as a screening tool, are also utilised by memory services as part of a diagnostic

battery. The most common criticism is that of insensitivity in that they often do not detect a problem in people who actually have AD. Moreover they are non-specific, in that they often do detect a problem in people who do not have AD and who may never develop AD in the future (Kalbe et al, 2004; Nasreddine et al, 2005). Both problems were highlighted by Dr A Mackie of the UK National Screening Committee in April 2015. Dr Mackie particularly highlighted non-specificity, saying:

"The tests are awful. We would be telling an awful lot of people they've got dementia or are at risk of it when they don't, and that's not something you'd wish on anybody."

The non-specificity of current tests for dementia is a serious concern, as there is an increasing number of 'worried well' who are coming forward for testing for dementia due to high profile media campaigns. The Royal College of Physicians observed a four-fold rise in the number of patients seen at specialist Dementia centres from 2010 to 2013. e.g (http://www.dailymail.co.uk/health/article-2989417/Worried-swamping-dementia-clinics-trivial-memory-fears-losingcar-keys-just-absent-minded.html), 11th March 2015.

Although the current thesis' main focus is upon developing tools for use within a primary care setting, with a view to producing potential screening tools, Chapter 3 focuses upon existing neuropsychological tools in order to investigate whether the best neuropsychological tests are currently used within diagnostic batteries. This is investigated through the use of a meta-analysis which looks at how accurate each commonly used test predicts conversion from mild cognitive impairment to Alzheimer's disease. The term mild cognitive impairment (MCI) is discussed in more detail in Section(s) 1.10.1 and 1.10.2. Of course, there are more diagnostic tools available than neuropsychological tests, of which some are outlined in the section below, however many tend to be far more invasive and

expensive. In order to compare the accuracy of traditional neuropsychological tests vs more expensive and invasive procedures, CSF tests were compared to neuropsychological tests within the meta-analysis in Chapter 3.

1.6.2: CSF biomarkers as a diagnostic tool.

Cerebrospinal Fluid (CSF) is a colourless bodily fluid found in both the brain and the spinal cord which is produced by ependymal cells within the choroid plexus of the ventricles of the brain and absorbed into the arachnoid granulations. Cerebrospinal Fluid has many functions including:

1) The provision of immunological and mechanical protection to the brain whilst also helping in the regulation of cerebral blood-flow. It fills the brain ventricles, cisterns, and sulci; along with the spinal cord's central canal.

2) Buoyancy: This allows the brain to maintain its density whilst not being detrimentally affected by its own weight i.e. cutting off blood supply to lower sections (Wright et al, 2012).

3) Homeostasis: CSF assists in the regulation of the distribution of substances between brain cells (Sakka, Coll & Chazal, 2011).

4) Clearing waste: CSF facilitates the removal of waste from the brain and plays a crucial role in the brain's lymphatic system. Metabolic waste products diffuse quickly into CSF and are removed into the bloodstream as CSF is absorbed (Allan, Robert & Brown, 2005).

A large amount of research suggests that early stage AD causes changes in CSF levels of beta-amyloid and tau, which are two proteins that form abnormalities in the brain which are strongly linked to Alzheimer's Disease (Glasko, 1998; Marksteiner et al, 2007; Musiek & Holzman, 2012). There are three core CSF biomarkers used for AD diagnosis: amyloid beta **(**AB42), total tau (T-tau), and phosphorylated tau (P-Tau). Several studies have consistently found an increase in T-tau and P-Tau in those with AD, along with a decrease in Aβ 1-42. A relatively recent meta-analysis conducted by Olsson and colleagues (2016) found the three core CSF biomarkers able to robustly separate AD patients from controls and to discriminate between MCI-AD and stable MCI. The ability of CSF biomarkers to discriminate between stable MCI and MCI-AD converters in comparison to neuropsychological tests is further explored in Chapter 3 of the present thesis.

Although analytes in CSF which are associated with AD pathology such as total tau, p-tau and $A\beta_{1-42}$ are often thought to offer the potential for a more accurate diagnosis, cognitively healthy older individuals have also been found to have altered levels of such CSF AD biomarkers (Peskind et al, 2006; Shaw et al, 2009; Tapiola et al, 2009). This highlights that as with other forms of testing, CSF is not immune to false positives. This was echoed in a 2017 Cochrane review which reviewed the evidence regarding the accuracy of CSF tests in identifying those with MCI who would go on to develop AD or other forms of dementia over time. They concluded that all of the core forms of CSF, used as a single test, lack the accuracy to identify those with MCI who later go on to develop AD. They stated that particular attention should be paid to the risk of misdiagnosis and over diagnosis of dementia as the included studies appeared to have better sensitivity than specificity.

The meta-analysis included in Chapter 3 suggests that despite the recent interest in CSF biomarkers within the field, CSF test accuracy is only equivalent to or possibly lower than that the best neuropsychological tests (Chapter 3). CSF testing is invasive, costly, and requires training at several levels. Its use is restricted to well-funded specialist centres, and it is simply implausible that it could be used on a national scale, given the high demands of an ageing population.

1.6.3: Neuroimaging as a diagnostic tool.

Neuroimaging is a well-researched and versatile tool which allows the analysis of grey and white matter volume, metabolic processes and most recently, the presence of amyloid beta plaques. The following section will discuss some of the most common forms of neuroimaging and their efficacy in diagnosing Alzheimer's disease. The distinction must be made, however, between a high performing neuroimaging technique's efficacy in a research setting and its realistic application to clinical practice. For example, as previously discussed, a diagnostic test must be high performing and sensitive but also cost-effective to be suitable for wide-spread use.

1.6.3.1: Structural MRI: cross-sectional and longitudinal studies

Structural Magnetic Resonance Imaging (MRI) is an imaging technique that examines the anatomy and pathology of the brain. MRI has been used to aid in the diagnosis of AD in clinical practice for many years (DeKosky and Marek, 2003) due to its ability to measure cortical thickness and the volumes of different regions. Cross-sectional studies have shown

that the medial temporal lobe has a reduced volume in patients when compared to healthy controls (Caroli et al, 2007; Glodzik-Sobranska et al, 2005). Decreased hippocampal volume is also a common finding in MRI studies in those with AD compared to healthy controls (Mori et al, 1997; Schulyens et al, 2002).

Atrophy measurements on MRI have also been used to predict the conversion to AD from Mild Cognitive Impairment (MCI) since the 1990s. Most such studies analysed the predictive value of hippocampal volume along with the volume of the entorhinal cortex and other regions (Jack et al, 1999; Grundman et al, 2000). One useful way to evaluate the predictive validity of MRI is through meta-analysis, combining the results of multiple longitudinal studies which explored MCI to AD conversion and the predictive ability of MRI.

One particular meta-analysis conducted by Yuan et al in 2014 which focussed on longitudinal studies tracking progression from MCI to AD, reported that MCI atrophy measures had sensitivity of 72.8% and specificity of 81%, with FDG-PET performing slightly better at 88.8% sensitivity and 84.9% specificity, although this analysis included papers from 2000-2005 only. Positron-emission tomography (PET), is a nuclear medicine functional imaging technique, used to observe the metabolic processes in the body. The development of 2-(^{18}F) Fluoro-2-deoxy-D-Glucose (FDG) in the 1970s was particularly significant in this regard (Revich et al, 1977) as it is a glucose analog that couples fluorine-18 (^{18}F) to glucose. As the brain is reliant on glucose as its primary energy source, Fludeoxyglucose (FDG) is often used to assess glucose metabolism in the brain, within a PET scan. Fludeoxyglucose is typically injected via saline drip into the vein of a patient who is required to fast for at least six hours beforehand and have suitably low blood sugar. FDG is then taken up by cells, phosphorylated by hexokinase and retained by tissues with high metabolic activity. This is

significant as recent research has highlighted which neurons are more likely to resist or to succumb to early Alzheimer's disease (AD) pathology (Morrison & Holf, 1997; Mattson & Magnus, 2006) and large projection neurons with long axons have been shown to be most damaged by AD. One characteristic of such neurons is that they have high metabolic rates and their functionality depends predominantly on the availability of glucose, therefore making them highly visible in FDR-PET.

A meta-analysis by Zhang et al (2012) which included studies from 2009-2011 reported pooled sensitivity of 93% and a pool specificity of 56%, indicating an ability not far more than chance to rule out individuals without AD. As previously discussed, (Section 1.6) a lack of specificity is already an existing issue with current diagnostic tests and the need for tools that correctly diagnose those with AD whilst identifying those who do not have the disease is paramount to avoid unnecessary worry, use of resources and strain on the healthcare system.

A further meta-analysis conducted by Seo et al (2017) also explored the prognostic values of the biomarkers of neurodegeneration measured by MRI and the amyloid burden measured by amyloid positron emission tomography (PET) in predicting MCI to AD conversion. The analysis found that despite some suggesting amyloid PET to be the strongest predictor for conversion from Mild Cognitive Impairment (MCI) to AD (Prestia et al, 2015), the entorhinal cortex atrophy measure on MRI was comparable in prediction value. However, amyloid PET was better at predicting conversion overall.

Repeated use of MRI is not standard within the NHS, with most patients receiving only one single time-point set of images. It may be suggested that the true efficacy of MRI lies in the ability to track the volume and atrophy rate of an individual over time (Ridha et al,

2006). One of the main issues with single-timepoint MRI is the 'noise' associated with normal individual differences in pre-morbid baseline volumes. For example, a patient may present with a small hippocampus, however if their hippocampus has historically always been that size, the relatively small volume is not a sign of neurodegeneration (Scahill et al, 2003). Repeat MRI testing is thought to a somewhat better diagnostic tool, because it can take into account the differences in pre-morbid volumes to produce a patient-specific 'brain shrinkage' score, however, this comes at even greater expense, and the diagnostic gains are modest (Ohnishi et al, 2001). To be an effective predictive tool MRI structural scanning would need to be widespread to generate sufficient numbers of pre-morbid baseline measurements, and this would be financially unfeasible within the National Health Service.

As previously stated, the majority of studies comparing the predictive and diagnostic ability of imaging techniques find MRI to be outperformed in predictive ability, sensitivity and specificity, yet the remaining popularity of structural MRI in clinical practice remains and is understandable. MRI is non-invasive, relatively easily performed and cost effective when compared to imaging techniques such as FTG-PET and Amyloid PET (Section 1.6.3). This continued use of MRI despite this evidence highlights one of the main points this thesis wishes to make; the NHS may not be currently using the most accurate tools with which to diagnose AD.

1.6.3.2: Functional MRI

A functional magnetic resonance imaging scan (fMRI) measures and maps brain activity using the same basic technology as an MRI, however, whilst an MRI scan produces structural

images alone, fMRI produces data regarding blood flow in the brain thus documenting neural activity in multiple brain regions.

fMRI detects neuronal changes involved during the execution of various tasks such as solving problems, moving fingers, reading etc by measuring the changes in blood oxygen level-dependent (BOLD) MR signal (Ogawa et al, 1990; Kwong et al, 1992). When nerve cells are active they consume glucose and oxygen and this consumption leads to a local increase in blood flow. This is because there is a hyperperfusion of the local tissue (more oxygen is provided than necessary), and because blood with and without oxygen have different magnetic susceptibility, signal intensity changes on the images can be detected, the blood oxygen level therefore acting as a proxy for neuronal activation.

The technique has several advantages, particularly for clinical trials, as it is a non-invasive imaging technique that does not require the injection of contrast agent or radiation exposure and can therefore can be repeated many times during a longitudinal study (Atri, et al, 2011) and can be used to find differences in brain regions between AD and healthy controls (Challis et al, 2015).

Alzheimer's disease has an early and specific impact on episodic memory (Albert et al, 2011), discussed in more detail in Section 1.8.1 and so many fMRI studies use different types of memory tests (single and multi-trial presentations, free and cued recall) and stimuli (faces, words, shapes) to detect deficit within this form of memory, especially when testing those with pre-clinical dementia (MCI). Both hypo and hyper activation of the medial temporal lobe has been reported (Mandzia et al, 2009; Hampstead et al, 2011; Jin et al, 2012). This differing result may be dependent on the particular memory process that is assessed, as suggested by a study conducted by Trivedi in 2008 who reported a

hypoactivation of the Para- hippocampal cortices whilst encoding but a hyperactivation of the hippocampus whilst recognition took place. The disparity in study results may also be due to the progression of AD pathology within those MCI participants, for instance Celone et al found that patients with a lower Clinical Dementia Rating score had hippocampal hyperactivation whilst those with a higher score experienced hypoactivation.

A review conducted by Bayram et al in 2018 found fMRI studies which investigated diagnosed AD results to be mostly consistent with medial temporal lobe hypoactivation (Lustig et al, 2003; Golby et al, 2005; Pariente et al, 2005; Peters et al, 2009) and precuneus hyperactivation (Sperling et al, 2003; Patrella et al, 2007). The review concluded that overall, within the studies analysed, fMRI findings suggested that episodic memory tasks lead to medial temporal lobe activation, frontal hyperactivation and reduced precuneus deactivation in those with AD. Although it does also state that the results are not sufficiently consistent yet to provide early diagnosis or act as a disease tracking tool for MCI and, although promising, the area requires further research.

1.6.3.3: FDG-PET

FDG-PET studies have proven to be relatively successful as both a predictor of Mild Cognitive Impairment conversion to AD and as (Prestia et al, 2015). The disease is characterised by a specific regional pattern of the cortical cerebral metabolic rate of glucose (CMRglc) reductions in both the parieto-temporal and posterior cingulate cortex (Hawkins et al, 1983; Silverman et al, 2001; Herholz et al, 2002; Mosconi, 2005), which then progresses onto the frontal association cortices whilst areas such as the basal ganglia, cerebellum,

striatum, and the sensorimotor and Primary visual cortices remain preserved. This distinctive pattern of hypometabolism is found in the majority of AD cases (Silverman et al, 2001) and has been shown to be sensitive in distinguishing AD patients from controls, and from other dementia types (Herholtz et al 2002; Mosconi et al, 2008; Heiss et al, 2012).

The usefulness of FDG-PET is well researched and acknowledged. However, such results have mostly been limited to academic research and well-funded centres, which do not address the practicality aspects of the technique for widespread use. One example of such issues surrounds the fact that the patient is required to fast for 6 hours preceding the scan to ensure suitably low blood sugar. This is problematic for diabetic patients as middle-aged and older adults are at the highest risk of developing and living with type 2 diabetes, (Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2020) thus accounting for a large proportion of the age group also at risk of Alzheimer's disease. Another particularly pertinent issue is that of cost, as has been addressed in Section 1.5, 1.6 and throughout this thesis. A good diagnostic test must of course be sensitive and specific but importantly, in order to truly have an impact on clinical practice and patients' lives, it must also be accessible and far-reaching. Therefore, FDG-PET's high cost and issues of practicality limit its widespread adoption.

1.6.3.4: Amyloid PET

With the successful development and subsequent clinical approval of 18F-Florbetapir, 18FFlorbetaben, and 18F-Flutemetamol, the nuclear imaging community has a set of beta-amyloid aggregate-targeting PET tracers to hand for clinical use. They allow the in vivo

detection, or exclusion, of neuritic beta-amyloid plaques, one histopathological hallmark in the neocortex of patients with AD which so far could only be histopathologically diagnosed post-mortem.

In an amyloid beta (Aβ) PET scan, specialist tracer molecules are injected intravenously. They then travel through the blood stream to the brain and attach to amyloid plaques. As of 2012, three tracers of this type have also been approved by the USA Food and Drug Administration (FDA) for clinical use: 18F-Florbetapir, 18FFlorbetaben, and 18F-Flutemetamol. Such tracers allow the in vivo detection or exclusion of neuritic beta-amyloid plaques, a well-known histopathological hallmark in the neocortex of patients with AD which thus far could only be histopathologically diagnosed post-mortem. The radiation they send out can be used to create a picture showing the density and location of plaques. Tracers of this type are predominantly used in clinical drug trials, where a positive amyloid scan is required prior to enrolment.

Despite being a relatively new development, studies have emphasised the sensitivity of the test and its ability to distinguish those with AD from those without the disease. A meta-analysis by Ossenkoppele et al (2015) used data for 1359 participants with clinically diagnosed AD and 538 participants with non-AD dementia and found that amongst those with dementia, the prevalence of amyloid positivity was associated with age, clinical diagnosis (AD/non-AD type) and APOE genotype. This supports the potential utility of Aβ PET in distinguishing between AD and other forms of dementia.

In a study by Rabinovici and colleagues, which focused on early on-set patients, 18% of subjects that were previously thought to have Alzheimer's disease were found to have negative amyloid scans (Rabinovici et al, 2019). The IDEAS study (Imaging Dementia—

Evidence from Amyloid Scanning), a large multicentre trial (Rabinovici et al, 2019) explored whether a positive (Aβ) PET scan result would affect clinical management and found that clinicians changed their patient management on the basis of these results, in some cases prescribing Alzheimer's disease medications at an earlier stage and in others abandoning an incorrect initial diagnosis of probable Alzheimer's disease. Bouallegue et al (2017) conducted a cross-sectional study including 677 participants. Those suffering from substantial memory complaints and those with MCI patients underwent CSF collection (amyloid $\beta_{1\text{-}42}$, tau and phosphorylated tau) and ^{18}F-florbetapir scans and were followed for 30 ± 16 months. They found amyloid PET to be more powerful than CSF markers for AD grading and MCI prognosis regarding cognitive decline and conversion to AD. Mosconi & McHugh (2011) compared results from FDG and Aβ-PET studies in AD and concluded that more validation studies are needed before Aβ-PET can enter into clinical practice and additional longitudinal studies are needed to establish the strengths and limitations for its clinical use in early AD diagnosis.

A further limitation of Aβ-PET is shared with many imaging techniques and the cost and specialist training involved make it impossible to be used on a national scale, for everyone who is suspected of having Alzheimer's disease. Should Aβ-PET become a feature in future of diagnostic procedure, this would most likely be performed on particularly difficult to diagnose cases which still fails to address the lack of easy to conduct, cost effective diagnostic tools.

1.7: Memory Processes and Systems.

Memory allows humans to acquire, store and retrieve information as needed about differing kinds of knowledge, skills and past experience. An important distinction concerns what has been called procedural memory and declarative memory, with Alzheimer's disease patients like amnesics thought to be particularly impaired at declarative memory. According to Rever & Squire (1998) what predominantly distinguishes declarative memory from procedural memory is that declarative memory supports conscious memory of facts and events whereas procedural memory supports a wide range of phenomena including simple conditioning, priming and habit learning (Rever & Squire, 1998). Within the larger category of declarative memory, Tulving influentially suggested that two further types of memory can be distinguished: semantic memory and episodic memory. Semantic memory refers to the capacity for recalling facts and general knowledge about the world, acting as a 'mental thesaurus' (Tulving, 1972). Episodic memory on the other hand, refers to recalling events that have occurred in the past within particular spatial and temporal contexts; area functionality that is known to be affected in Alzheimer's disease (Schwindt & Black, 2009; Haj & Kessels, 2013).

Memory theorists suggest that episodic and semantic memories do not necessarily act in isolation, but frequently influence each other. For example in his original essay Tulving (1972) observed that the acquisition of a new episodic memory is affected by existing information in semantic memory. This idea has been expanded upon in the SPI model (Serial encoding, Parallel storage, Independent retrieval (Tulving, 1995; Tulving & Marcowitsch, 1998)). This model states that information is encoded in a serial manner and must pass from

the perceptual system to semantic before it can then be encoded into episodic memory. Once information has been encoded, it is then stored in parallel and can be retrieved independently. This model suggests different kinds of interdependencies for encoding, storage and retrieval. Other views such as that by Baddeley (1988) suggest that that semantic memory may represent the 'accumulated residue' of multiple learning episodes, meaning that semantic memory consists of information that has been abstracted and dissociated from the various spatiotemporal contexts within which it has been encountered. Views on the independence or interdependence of episodic and semantic memory vary from theorist to theorist but the early degeneration of the MTL, and more specifically the hippocampus and associated episodic memory impairment in those with AD is well-documented (Desgranges et al, 1996; Gainotti et al, 1998; Petersen et al, 1994; Aggarwal et al, 2005). In contrast, these studies find that semantic memory appears to remain relatively intact until much later in disease progression (Desgranges et al, 1996; Gainotti et al, 1998; Petersen et al, 1994).

1.7.1: Autobiographical Memory

Episodic memories are consciously recalled memories related to personally experienced events, drawing upon mnemonic and non-mnemonic cognitive abilities to reconstruct past events from retrieval cues (Conway, 2009). Autobiographical memories emerge from a memory system consisting of both events and facts from an individual's life, depending respectively upon both episodic memory (personal events) and semantic memory (personal facts). While semantic autobiographical memories involve retrieval of general knowledge,

episodic autobiographical memories involve the retrieval of specific events with stronger subjective experience involving time travel and vivid mental imagery.

Conway (2001) suggests that autobiographical memory retains knowledge over intervals that can be measured from weeks, months to years and across a life-span. Autobiographical knowledge represents experiences of the self (the 'me') and does not necessarily prompt recollective experience. Recollective experience only occurs when this autobiographical knowledge retains access to episodic memories and therefore autobiographical memory provides the context for sensory-perceptual episodic memory. For example, remembering the fact that you had a 21st birthday party then allows you to recall the location, the smell of the room, taste of the cake and conversations you had with the people in attendance.

1.7.2: Recognition Memory: Familiarity and Recollection

Recognition refers to an individual's ability to judge an item or event as something previously experienced. According to dual-process theories, recognition can be subdivided into two component processes: recollection and familiarity (Mandler 1980; Jacoby 1991; Tulving 1985; Gardiner 1988), sometimes referred to as 'remembering' and 'knowing' respectively (Medina, 2008). For example, upon seeing someone's face, the subject may have only a vague sense that they have seen that person before whereas in recollection, the rememberer sees the person's face and may vividly remember details of their previous encounter such as the spatial or temporal context (Mandler et al, 1980; Yonelinas, 2002). It is important to note that whilst this dual-process theory is widely discussed and researched, it is not unanimously endorsed by cognitive scientists. Some have argued that recognition is

a continuous process and that this variance in recognition is associated with the strength or confidence of the memory trace (Donaldson, 1996; Dunn, 2004; Slotnick, 2009).

Many studies suggest that the neural substrates of familiarity and recollection can be dissociated within medial lobe regions (Skinner and Fernandes 2007; Yonelinas et al. 2005; Henson et al. 1999; Diana et al. 2007; Daselaar et al. 2006; Yonelinas et al. 2007). Neuroimaging studies have shown increased activation in hippocampal regions during the encoding of information which was successfully recalled, whereas increased activation was shown in perirhinal regions was associated with items later recognised using familiarity (Ranganath et al. 2004; Daselaar et al. 2006; Eldridge et al. 2000). In a meta-analysis conducted by Diana and colleagues (2007), it was found that across studies increased hippocampal and parahippocampal activation was present during the encoding of information that was successfully recollected, but not with familiarity. This meta-analysis also found perirhinal activation was frequently associated with familiarity, but rarely with recollection.

Overall, research suggests a functional double dissociation between hippocampus and perirhinal areas, with the former appearing associated with recollection and the latter familiarity. This is of particular relevance to the present thesis as the hippocampus is one of the first areas to degenerate in Alzheimer's disease. This would suggest that an early sign of Alzheimer's disease would be an impairment in recollection. The Spatial Sequences Episodic Video Task was partly designed with this rationale in mind. The idea is that in earlier stages of Alzheimer's disease, such as at the 'MCI-due-to-AD' stage, while processes supporting familiarity might still be present, processes supporting recollection of the details of events would be impaired

1.8: Hippocampal dependent tests may be effective in detecting early-stage AD.

The scientific rationale for the use of tests that focus specifically upon episodic memory and topographical spatial memory to detect early-stage AD is based upon two main principles. Firstly, is that the hippocampus and medial temporal lobe (MTL) structures are adversely affected in the early stages of AD. This is evidenced through neuropathological AD studies which show degeneration to initially occur in the trans-entorhinal region. The entorhinal cortex (EC) is located in the medial temporal lobe and functions as a hub in a network for functions such as memory and navigation. The EC is also the main interface between the hippocampus and the neo-cortex (Braack & Braack, 1991; Braack & Del Trecidi, 2015). Neuronal loss within these regions is well observed, even at the very early stages of AD progression (Gomez-Isla et al, 2005). The second is that the hippocampus is critical to both topographical spatial navigation and episodic memory.

1.8.1.: Episodic memory

As previously discussed in Section 1.7, episodic memories are consciously recalled memories related to personally experienced events, drawing upon mnemonic and non-mnemonic cognitive abilities to reconstruct past events from retrieval cues (Conway, 2009). Episodic memory is sometimes confused with autobiographical memory; whilst autobiographical memory does involve episodic memory, this term can include autobiographical knowledge, a form of semantic memory (the recollection of factual and conceptual knowledge) which

involves separate processes (Conway, 2000). For example, an individual may remember visiting Italy, reliving the events they experienced there, seeing in the mind's eye the museums they visited, the sounds heard and the smells they experienced (episodic memory). They may also know that the capital of Italy is Rome and the country has a football team (semantic memory).

While there is a wide consensus that the hippocampus is crucial for episodic memory (Vargha-Khadem etc), the exact nature of its contribution to episodic memory is unclear. However, dominant views propose that the perirhinal and parahippocampal cortices support memory for item and contextual information, whereas the hippocampus performs relational binding of event elements into a unique representation (Cohen & Eichenbaum, 1993; Eacott & Norman, 2004; Diana et al, 2007).

Tulving emphasised that one of the key features of episodic as opposed to semantic memory is that episodic memories have a spatiotemporal context (Tulving, 1983). O'Keefe and Nadel (1978) argued that the addition of a linear temporal component in humans to the basic spatial map in animals provided the basis for an episodic memory system, adding a fourth dimension of time to the three spatial dimensions.

The resolution and robustness of this 'fourth dimension' are weak; people are not very good at estimating temporal context (Friedman, 1993; Wagenaar, 1986; Wells, Morrison & Lindsay, 1993). It is also not clear whether episodic recollection truly relies on a temporal context, and if such a temporal context is a key characteristic of what the hippocampus is contributing to episodic memory. Eacott and Easton (2010, 2012) have argued that episodic memory relies on a sense of 'occasion' rather than a temporal stamp to disambiguate similar episodic memories. In humans, Persson et al (2016), for instance, have argued that while contextual source information can only be retrieved using recollection,

temporal information can be retrieved using either recollection or familiarity processing. A further issue requiring resolution is whether the crucial temporal information is an 'at this time' signal or a 'how long ago' signal. There is recent evidence for both types of signal in the rodent hippocampus (Knierim et al, 2014; Wang et al, 2020). Arguably, the flatness of the theta-frequency-to-speed slope in the rodent hippocampus provides a good clue to how long ago a rat has experienced a context (Wells et al, 2013). Kuruvilla et al (2020) looked at exactly this issue of the 'at this time' vs 'how long ago' signal distinction and concluded that 'how long ago' signals are more accurately retrieved during episodic recall than 'at this time' signals. More research is needed on this issue.

Another approach to the role of the hippocampus to episodic memory is the idea that firstly, the hippocampus is important for remembering sequences, and that secondly, episodic memory often entails remembering sequences. Dede et al (2016) showed that amnesic patients were particularly weak at remembering the sequence of events on an earlier walk. Therefore, a task which focuses upon sequences and events may prove effective in highlight cognitive impairment, which is part of the rationale under which the current Spaces and Sequences Episodic Video Task (SSEVT) was made (details of SSEVT are found in Chapter 2, Section 2.11).

Indeed, this kind of impairment is also amongst the most common early signs of dementia (Backman et al, 2001; Greenaway et al, 2006; Twamley et al, 2006). In a more general sense, neuropsychological studies have shown that episodic learning and recall discriminate between healthy controls and pre-clinical Alzheimer's disease (AD) patients and pre-clinical and probable AD patients well (Collie & Maruff, 2000; Twamley et al, 2006).

The typical neuropsychological assessment purporting to measure a patient's potential episodic memory deficit consists of list learning tasks measuring the patient's

ability to remember a list of unrelated words. Performance on the task is then assessed using various measures (e.g. delayed free recall, cued recall or recognition) (for reviews see Balota et al, 2000; Craik & Jennings, 1992; Luo & Craik, 2008; McDaniel et al, 2008). During delayed free recall, an individual is given a list of items or words to remember during encoding and is then tested by recalling as many words as they can remember after a delay of varying duration (usually 5-30 minutes). The experimenter or clinician records the number of words correctly recalled. In cued recall an individual is given a list of items or words to remember during encoding and then is tested using cues that have been designed to assist them to remember the material, such as the word 'fruit' to assist with the retrieval of 'pear' or the first word of a pair of encoded words. Recognition refers to an individuals' ability to judge whether an event or item has previously been seen. Participants study a list of words and then take an old-new recognition test in which they are asked to judge which word they have previously experienced during the study phase (review: Besson et al, 2013). There are several such verbal learning tests which use these measures. The California Verbal Learning Test (CVLT) (Delis et al, 1987), Rey Auditory Verbal Learning Test (RAVLT) (Rey, 1964), the Free and Cued Selective Reminding Test (FCSRT) (Grober & Buschke, 1988) and the Verbal Selective Reminding Test (vSRT) (Buschke, 1973) are discussed in detail in Chapters 2,3, 4 and 5. The CVLT is currently the most utilised test of this kind in the UK National Health Service whereas tests such as the SRT and FCSRT are more commonly used in the USA, where they are FDA recommended, in private practice and in research settings, due to their time consuming nature.

Such list-learning tests remain the standard approach to neuropsychological testing (Beck et al, 2012), despite bearing little similarity to events that AD patients experience and memorise in daily life (Plancher et al, 2012). Such tests' reliance on verbal ability and the

issue of standardisation across languages are also limiting factors. One of the aims of the meta-analysis in Chapter 3 is to evaluate the diagnostic reliability of neuropsychological tests by evaluating their ability to predict conversion from Mild Cognitive Impairment to Alzheimer's disease.

Currently there are very few tests that target episodic memory in a more ecological way, involving everyday real-world observation of people and events. One highly influential study that did assess the decline of episodic memory in ageing developed a new task called the 'Autobiographical interview', requiring recall of a participant's own memories; this study clearly showed that ageing impaired recall of episodic details (Levine et al, 2002). However, while avoiding verbal lists and relying on real-world memory, the task requires highly complex scoring. Moreover, the 'Autobiographical interview' suffers from the problem that there is no way to systematically check for false or fabricated episodic details produced by the participant. In other words, if the task were to be worked up into a clinical test, sufficiently motivated patients could learn or be taught how to cheat on the test by inventing rich episodic details that were not actually experienced. The main problem with the task, however, is its somewhat open-ended nature and complexity. In summary, Levine et al, 2002's 'Autobiographical interview' is a very useful research tool into cognitive ageing processes but is likely too impractical for the diagnosis of AD.

Virtual reality tasks have become an increasingly popular method with which to test episodic memory in a more ecological way, allowing the researcher to place the participant in a realistic, immersive environment. One experiment conducted in 2012 by Plancher et al placed healthy older adults, MCI and AD patients into two such VR environments: Firstly, as the driver of a virtual car (active exploration) and then, as the passenger of that car (passive exploration. Participants were asked to encode all elements of the environment along with

spatio-temporal context. After the VR immersion, participants' ability to recall and recognise central information, such as the elements of the environment and contextual information such as spatial information was tested. It was found that AD patients' performance was inferior to that of the MCI and even more impaired compared to the healthy group. This form of impairment in episodic memory and the contextual spatial information of where the memory took place reflects allocentric memory impairment, which is discussed in more detail below, in Section 1.9.2. In summary, virtual reality tasks such as those created by Plancher et al are valuable tools in a research setting, allowing the patients to become fully immersed whilst maintaining a standardised, reproducible, and controllable environment. However, especially within the older generation such technology is not always so well tolerated (Manera et al, 2016). As with other techniques discussed, virtual reality remains costly, time consuming and thus inappropriate for widespread clinical use.

It could be argued that an episodic memory task that can be used clinically to contribute towards the diagnosis of AD has to satisfy several criteria. First, it should try to mimic the recall of real world first person memories, under the assumption that such recall provides a more sensitive reliance on the integrity of hippocampal tissue. Second, it should try to avoid over-reliance on education-related variables such as good vocabulary and linguistic skill, as this may penalise the less educated whose episodic memory might actually well be intact, and may underrate the atrophy of the highly-educated. Third, it should be easy to administer, in terms of presentation, procedural simplicity, and ease of scoring. Ideally, a test should be simple enough to be run in a primary health setting, such as by a nurse in a GP surgery, whereby low scores could, for instance, signal the need for referral to a memory clinic.

The episodic video task developed in this thesis project was designed to address these criteria. The need to test episodic recollection, rather than just familiarity, as per the first criterion, makes it non-trivial to keep the task simple. The ability to also test sequence and event recollection may also prove useful e.g. in the recently developed SSEVT used within the current project participants are asked questions such as 'Recall the time you were in the room where you saw the cat being told to leave the bird alone- What event occurred in the room immediately before this? Before choosing from four options. This task is discussed further in Chapter 2, section 2.11.

1.8.2: Spatial memory

The idea that the hippocampus forms memories as they occur in their spatiotemporal context (Burgess et al, 2001; Morris et al, 2003; Kubik et al, 2007) is consistent with the cognitive map theory of hippocampal function (Tolman, 1948; O'Keefe and Nadel, 1978, 1979). The cognitive map theory proposes that the hippocampus of rats represent their environment, the locations within those environments and their contents which in turn provides the basis for spatial memory and flexible navigation. The neural correlates of a cognitive map are thought to be the place cell system in the hippocampus along with grid and boundary cells. Place cells are also important in episodic memory as they contain the contextual spatial information of where the memory took place. Furthermore, place cells show alterations in those with Alzheimer's disease which correlates with a decrease of memory function.

Boundary cells, including boundary vector cells and border cells (Barry et al, 2006; Savelli et al, 2008; Solstad et al, 2008; Lever et al, 2009; Stewart et al, 2014), fire when a

boundary is encountered at a specific distance and direction (Figure 1.5C). Boundary cells respond to different environmental boundaries (Lever et al, 2009; Stewart et al, 2014), for example a tree, wall or cliff edge can all serve as boundary cues. Boundary cells are found in several regions of the hippocampal formation: the subiculum, presubiculum and entorhinal cortex (Poulter et al, 2018).

Grid cells are thought to provide the map with a co-ordinate frame. A grid cell has multiple firing fields (nodes) which fire when the animal moves freely around it's environment (Figure 1.5D) which are roughly equal in size and arranged in a triangular array that covers the entire environment (Moser et al, 2005). How grids are formed is still researched and debated but it is generally thought that they support path integration (Burgess & O'Keefe, 2011; Evans et al, 2016; McNaughton et al, 2006). Path integration is defined as the capacity to use cues generated by the animal's movements, to calculate the position of the animal by monitoring its trajectory in relation to a start location (Gallistel, 1990; Whishaw and Wallace, 2003).

Head direction cells (Taube, 2007) provide the animal with a compass-like sense of direction. In rats, the head direction call encodes the specific direction, relative to the environment, independently of the animal's location (Taube, 2007). Orientation is crucial for a well-functioning spatial network and the orientation of the other spatial cells, including place, boundary and grid cells, depend on head direction orientation (Winter et al, 2015). This process is known as allocentric spatial memory, which is dependent upon hippocampal integrity.

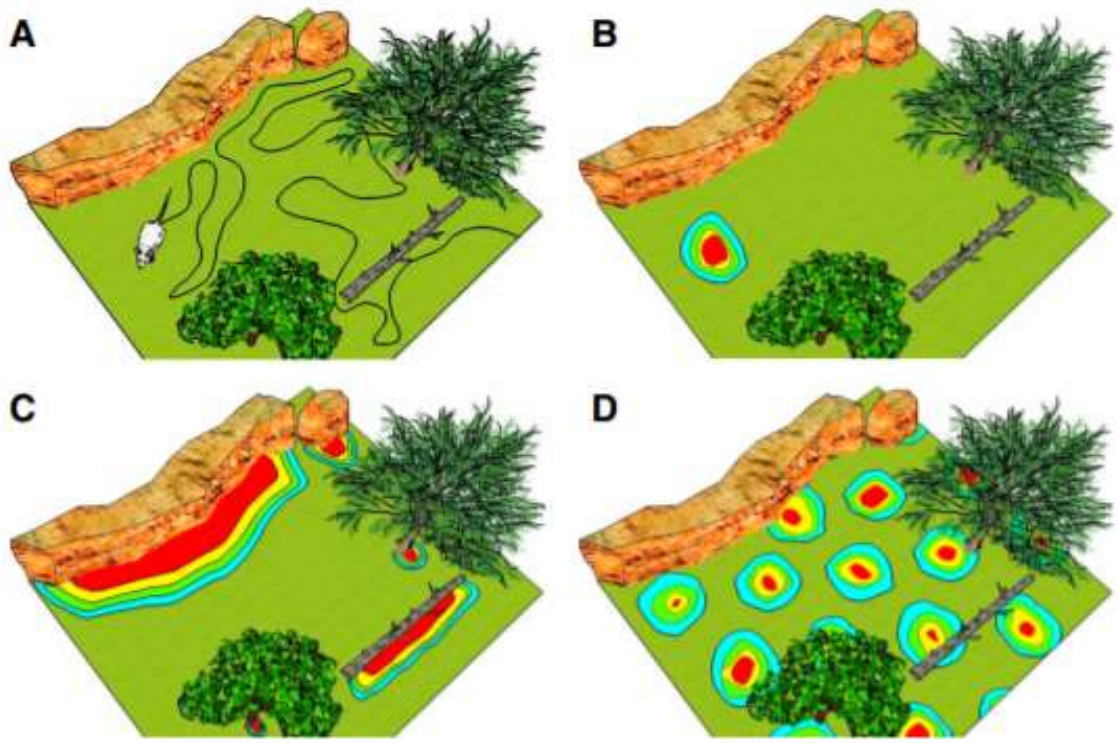


Figure 1. 5. **Schematic illustration of different types of spatial cell in the hippocampal formation.**

Experimenters typically record spatial cells from an animal whilst it continuously forages in a confined two-dimensional space **(A).** Schematic examples of firing maps for a place cell **(B),** Boundary vector cell **(C)** and grid cell **(D).**
(*Source: Poulter, Hartley & Lever, 2018)*

1.9: The hippocampal formation is particularly important in allocentric spatial memory.

1.9.1: Egocentric spatial memory

Before discussing allocentric spatial memory, the distinction must be made between allocentric and egocentric navigation. Egocentric navigation is based upon direction (right-left) responses and actions, independent of environmental cues. Decisions regarding

direction are made at sequential or single choice points but those locations are not used as cues and are still egocentric in nature. For example, memorising a route to the local shops by series of sequential turns would be employing an egocentric strategy (Figure 1.6A). The Virtual Reality Supermarket Trolley Task (VRSTT) is currently the only clinically available test which taps into egocentric spatial orientation (Wong et al, 2015). The test involves the presentation of fourteen short videos within a simulated supermarket, seen from a first-person perspective. From the entrance, participants follow a route throughout the supermarket, making a series of 90 degree turns after which, the participant is asked to point back to the entrance. The response is recorded according to a quadrant (upper and lower right, upper and lower left). The number of correct locations identified is recorded along with number of errors and error type (description from Ritchie et al, 2018). The VRSTT has been shown to distinguish AD from other forms of dementia that also have hippocampal atrophy.

More recent versions of the VVSRT have also been shown to differentiate between egocentric and allocentric navigation. A 2018 study by Ritchie and colleagues, calculated a Dementia Risk Score (DRS) for 188 individuals aged 40-59 and found that whilst a significant negative association was found between DRS and the Four Mountains Test, which taps into allocentric orientation (discussed in detail below), the VVSTT as a test of egocentric spatial processing, did not. The Four Mountains test, and therefore allocentric memory, was found to be a better predictor of risk than the egocentric VVSTT.

1.9.2: Allocentric spatial memory

Unlike egocentric navigation, allocentric navigation utilises external cues and/or landmarks in relation to each other's position to navigate and is independent to self (Figure 1.6B). Using a compass to navigate (North, South, East, West) is an example of allocentric navigation as these cardinal directions are not related to the observer but to the earth and do not change if the individual changes orientation. The cognitive map theory suggests that spatial representations are not centred on the self but are rather allocentric. This is supported by a large amount of studies that provide evidence of allocentric hippocampal dependant memory impairment in patients with early AD, an effect which is not seen in egocentric parietal representation (Maguire & Cipolotti, 1998; Chan et al, 2001; Galton et al, 2001; Kalova et al, 2005; Burgess, 2006). This research suggests that hippocampal degeneration significantly affects those with Alzheimer's disease's ability to maintain an allocentric representation of their surrounding environment. This indicates that tests that target allocentric representations specifically may be valuable tools in diagnosing AD at an early stage.

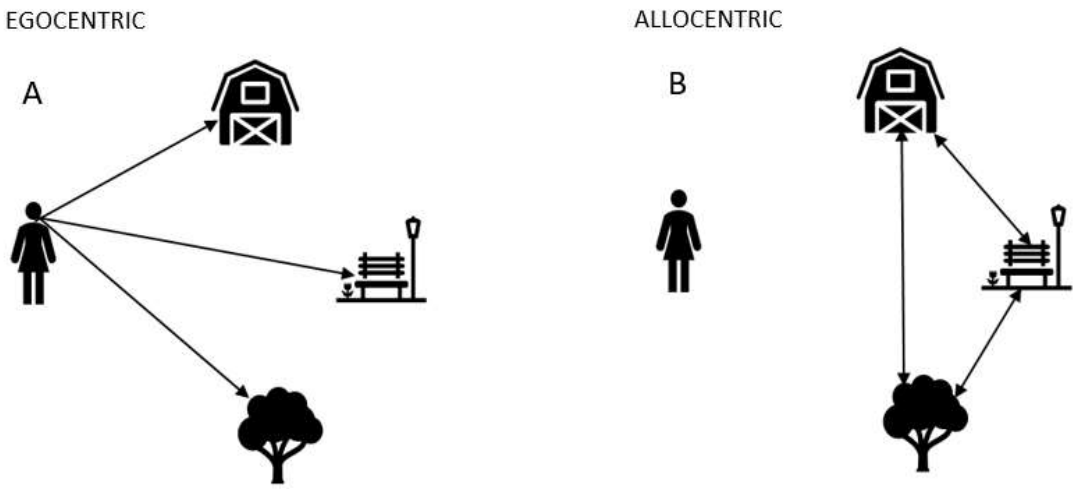


Figure 1. 6. **Schematic of egocentric (A) and allocentric (B) approaches to spatial navigation.**

Egocentric frameworks locate the position of objects/ landmarks to a viewpoint of the subject whereas allocentric frameworks utilise external cues and/or landmarks and locate places with respect to other places, e.g. the Barn's position in relation to the tree and bench.

There are currently very few tasks in existence that test allocentric spatial memory, but they are increasingly being developed. The 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 ability. The test uses computer-generated landscapes containing four mountains where the topography of the landscape (i.e. the geometry of the surface) and its features can be independently varied, such as the time of day and cloud cover (Figure 1.7C). The test assesses an individual's ability to recognise a landscape even when the viewpoint changes (Figure 1.7). Hartley et al (2007) found that all patients tested with damage to the hippocampus showed impaired performance on the Four Mountains whilst showing no impairment non-spatial processing. Further supporting the 4MT hippocampal relationship, Chan et al, 2016 found that 4MT scores correlated with hippocampal volume. which further illustrates the integral role the hippocampus plays in allocentric memory processing (for detail on test administration see Chapter 2, Section 2.10 of the Methods Section).

Bird and colleagues (2010) administered the 4MT to a population diagnosed with mild dementia and found that short-term retention of topographical information was impaired in both AD and Mild Cognitive Impairment (MCI) patient groups, but not in patients with frontotemporal lobar degeneration or subjective memory impairment. This further demonstrated an impaired ability in AD patients to form and retain allocentric representations of large-scale environments. Based upon this evidence, the 4MT could be a helpful tool in the facilitation of AD diagnosis at an earlier stage and is also used within this thesis to assess allocentric memory.

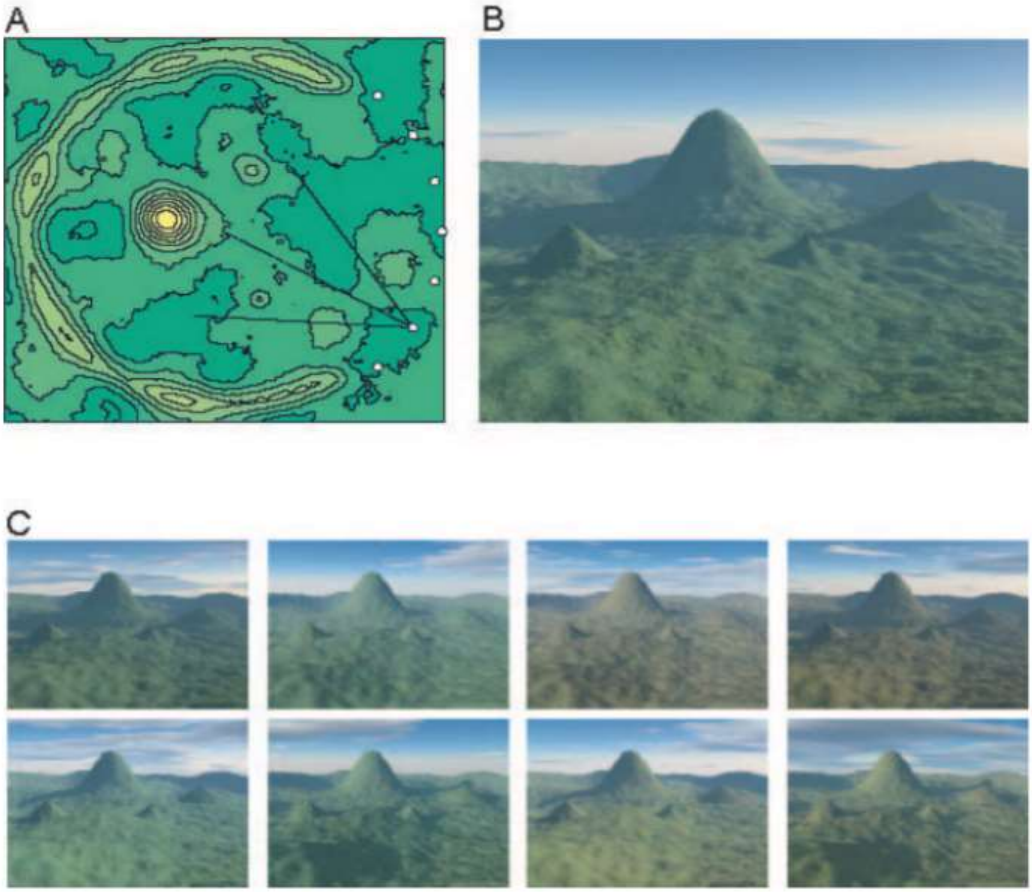


Figure 1. 7. **Stimuli used in the Four Mountains Test.**

(A) Every landscape contains four scattered hills or 'mountains' that vary in shape and size. Each stimulus used a unique configuration of hills. **(B)** An example of the stimulus based upon the topography shown in A. **(C)** The topography shown in A, rendered under the eight different combinations of non-spatial parameters which vary cloud cover, lighting, texture and the colour of vegetation.

1.10: Identifying AD at an early stage: What makes a good screening test?

It is important to note that some decline in cognitive ability naturally occurs in healthily ageing individuals. As is also the case with AD, this decline generally presents as deficits in certain functions which are hippocampus dependent, such as episodic and spatial memory, (Bettio et al, 2017). Supporting this, many of the cognitive deficits seen with ageing have

also been seen in animal models that have bilateral hippocampal damage (Geinisman et al, 1995). Although similar hippocampal alterations occur within both normal and pathological aging, these changes are much exacerbated in conditions such as AD.

A good neuropsychological test should have the ability to differentiate between healthy age-related hippocampal decline and abnormal decline which is indicative of MCI and potentially Alzheimer's disease. Ideally the scores achieved on the two hippocampal tasks included in this project should decrease with age and then appear significantly lower between those with a Mild Cognitive Impairment and healthy ageing participants of a similar age. The relationship between the hippocampal dependent tasks, the questionnaires and age is addressed in Chapter 4. The ability of the hippocampal tasks to differentiate between healthy ageing and MCI participants is within Chapter 5.

Whether used for screening, used within primary care settings or as part of a diagnostic battery, a good test should have the sensitivity to detect everyone who has early-stage AD, while simultaneously having the specificity to not give a 'false alarm' to anyone who shows some age-related impairments in cognition but who does not have early stage AD. Secondly, an ideal test should be cost-effective and simple to administer on a national scale, without requiring extensive training on the part of the testers to set up, run, and interpret. Such a test should also have the ability to detect subtle impairment, as many studies believe AD neuropathology to be present decades before a clinical diagnosis (Villemagne et al, 2011; Ritchie et al, 2015). Based upon the current research outlined above, there seems to be value in looking specifically at episodic and spatial memory for early-stage AD detection. One way to approach this is by looking at pre-defined groups such as those diagnosed with Mild Cognitive Impairment (MCI) to see which tests best predict conversion from MCI to AD.

1.10.1: Mild Cognitive Impairment: an indication of preclinical AD.

Over the last decade there has been an increasing interest in the intermediate state between healthy cognition and Alzheimer's disease, originating from the desire to identify at risk individuals. The term Mild Cognitive Impairment (MCI) is the term most commonly used when referring to this transitional period (Petersen et al, 2001; Winblad et al, 2004;) and is defined by the presence of a memory or cognitive complaint in the absence of dementia and minimal or no deficits in daily living (Petersen, 2003; 2004; Winbald et al, 2004).

There are two main MCI subtypes: amnestic MCI (aMCI) which is associated with memory impairments and non-amnestic MCI (naMCI) which is associated with other cognitive impairment (Albert et al, 2011). Research has also shown that people with aMCI have a greater progression to AD than those with naMCI, however, many MCI cases remain stable (Ganguli et al, 2011). There has been a steady increase in those within the UK diagnosed with MCI, affecting between 5-20% of the population ages 65 or over (Ray & Davidson, 2014). However, as dementia awareness increases along with the amount of memory services, it has been suggested that the rates of referral, assessment and subsequent diagnosis of MCI will continue to increase within the UK (Dean & Wilcock, 2012).

1.10.2: Mild Cognitive Impairment and the risk of conversion to AD.

There is significant research demonstrating the link between MCI and an increased risk of progressing to probable AD (Lopez et al, 2003; Plassman et al, 2008; Manly et al, 2008), with

estimates varying from about 7-16% per annum (Ganguli et al, 2004; Petersen et al, 2005). However, other studies looking at MCI to AD specific conversion (diagnosed and not 'probable' AD) clearly show that not all individuals with MCI go on to develop AD (Bruscoli & Lovestone, 2004; Shiri-Feshki, 2009; Koepsell & Monsell, 2012). For example, Fisk & Rockwood (2007) found that 20-30% of individuals diagnosed with MCI went on to show no cognitive impairment at five-year follow-up. Furthermore, in a population-based sample of older adults 32% of those diagnosed with MCI did go on to convert to AD after five years whilst 15% progressed to non-AD forms of dementia and others recovered (Tuokko et al, 2005). Such results have led some researchers to believe that MCI in fact represents a heterogeneous disorder with different potential outcomes (Petersen et al, 2014).

1.10.3: Defining Mild Cognitive Impairment

One of the overriding issues with the use of MCI as a diagnosis is the heterogeneity in the criteria used to define it. This in turn may contribute to the differing estimates of incidence, prevalence and rate of conversion (Ritchie et al, 2001; Bischkopf et al, 2002). The term Mild Cognitive Impairment (MCI) was first described by Petersen et al (2001) who placed emphasis on the presence of a memory complaint in the absence of cognitive impairment, dementia and deficits in activities of daily living. This criterion has since evolved due to the formation of an international expert working group (Petersen, 2003; 2004; Winblad et al, 2004) to include other types of cognitive impairment beyond just memory in order to reflect the heterogeneous nature of MCI. This impairment is defined by either a self and/or

informant (e.g. family or spouse) report along with evidence from objective measures of cognitive functioning.

Building upon this, the most recent classification of MCI (Albert et al, 2011) also identified three MCI sub-types (1) MCI with memory impairment (amnestic MCI); (2) MCI with impairment in a single non-memory domain (non-amnestic MCI); (3) MCI with impairment in multiple cognitive domains such as language, executive function and visuospatial skills. As previously discussed, there is some evidence that amnestic MCI individuals are more likely to convert to AD (Morris, 2006), whereas non-amnestic MCI individuals have a higher likelihood of progressing to other forms of dementia. Both amnestic and non-amnestic MCI are the most commonly used forms in clinical and research settings and remain a valuable group in the exploration of dementia progression. Within the current project, clinicians were asked to refer MCI patients who were diagnosed according the Albert (2011) criteria.

1.10.4: The main aims of the current project.

The present thesis has four main aims:

1) To assess whether scores on the new and recently developed tasks which focus upon hippocampal dependent function (i.e. allocentric spatial navigation and recollection based episodic memory) are affected by age and education (Chapter 4).

2) To assess whether scores on the new and recently developed tasks which focus upon hippocampal dependent function (i.e. allocentric spatial navigation and recollection based

episodic memory) can accurately identify patients with MCI from healthy ageing controls, and may prove to be effective screening tools (Chapter 5).

3) To identify whether the diagnostic tests currently used within clinical practice are the most effective via a meta-analysis looking at MCI to AD conversion (Chapter 3).

4) To validate the use of two newly developed questionnaires which assess social networks and embeddedness (SNSEQ) and spatial navigation (SAPQ).

Chapter 2: General Methods

2.1: Introduction to general methodology

This chapter describes all of the established and newly developed neuropsychological tests and questionnaires used within the meta-analysis study (Chapter 3), the healthy control testing study (Chapter 4), and the clinical MCI study (Chapter 5).

More details concerning the specific methodology used within each individual study are included in these results-orientated chapters (Chapters 3, 4 and 5).

2.1.1: Included Neuropsychological Tests: Meta-analysis, Healthy control study, and Clinical MCI study.

For ease of at-a-glance reference, table 2.1 summarises all the neuropsychological tests and questionnaires presented and analysed in at least one of the results Chapters 3, 4, and 5. The ticks represent which tests are included within each chapter (meta-analysis, healthy control testing and clinical MCI study). I then describe each test or questionnaire in more detail.

Table 2. 1.

Neuropsychological tests included in each study within this thesis.

Neuropsychological Test	Meta-analysis (Chapter 3)	Healthy control testing (Chapter 4)	Clinical MCI study (Chapter 5)	Designed to test
Mini Multi-State Examination (MMSE)	✓	✗	✗	Multi-domain cognition.
Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG)	✓	✗	✗	Multi-domain cognition.
Free and Cued Selective Reminding Test (FCSRT)	✓	✗	✗	Episodic memory.
Rey Auditory Verbal Learning Test (RAVLT)	✓	✗	✓	Verbal learning and memory.
California Verbal Learning Test (CVLT)	✓	✗	✗	Verbal learning and memory.
Logical memory subtest of the Wechsler memory scale (Logical Memory)	✓	✗	✗	Verbal and working memory.
Trail Making Test B (TMT-B)	✓	✗	✓	Visual attention and task-switching.
Rey–Osterrieth complex figure (ROCF)	✓	✗	✗	Impairments in visuospatial construction.
Four Mountains Test (4MT)	✗	✓	✓	Allocentric spatial working memory.
Spaces and Sequence Episodic Video Task (SSEVT)	✗	✓	✓	Episodic memory.
Buschke Selective Reminding Test (SRT)	✗	✗	✓	Verbal learning and memory.
Spatial Ability and Practices Questionnaire (SAPQ)	✗	✓	✓	Spatial working memory.
Social Networks and Embeddedness Questionnaire (SNSEQ)	✗	✓	✓	Size and complexity of social networks.
Addenbrooke's Cognitive Assessment- III (ACE-III)	✗	✓	✓	Multi-domain Cognition

The table above illustrates all neuropsychological tests included in the thesis, which portion of the thesis they are used within and which functions they aim to test. The ticks in green represent an included test within the chapter at the top of the table whereas the crosses represent tests that were not included in that particular chapter.

Not all neuropsychological tests were used in each empirical study as presented in Table 2.1. above. For example, the Four Mountains Test did not meet the 4-study minimum for inclusion in the meta-analysis but was used with both MCI participants and healthy controls.

2.2: Mini Multi-State Examination (MMSE)

The Mini-Mental State Examination (MMSE) (Folstein & Folstein, 1975) was developed as a brief tool to measure global cognitive function and is divided into two sections. The first section requires only oral responses and measures spatial and temporal orientation, memory (e.g. registration, repetition and recall of three separate objects), and attention (e.g spelling the word 'world' backwards). The second section focusses on language and visuospatial function and requires the patient to name simple objects, physically follow verbal and written commands (e.g. 'Take a paper in your hand, fold it in half and put it on the floor'), write a sentence of their own choice and copy a picture of two intersecting pentagons, as shown in figure 2.1.

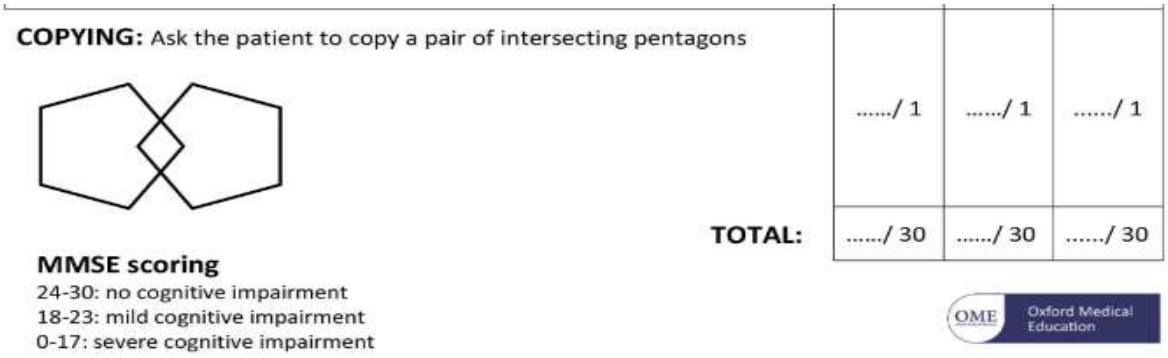


Figure 2. 1. **Figure copying task within the MMSE.**
The participant is asked to copy the above picture of intersecting pentagons. This is to test visuospatial ability. Source: *http://www.oxfordmedicaleducation.com/geriatrics/mini-mental-state-examination-mmse/*

The MMSE is usually administered by a healthcare professional (either doctor or nurse) within a primary care setting and is completely paper-based. It is scored out of 30, with scores below 24 indicating cognitive deficit. The test is quick (taking around 15 minutes), easy to administer, and cost effective.

The test was originally suggested to have reasonable sensitivity and specificity in dementia detection as found by Folstein & Folstein (1975)*;* they found scores significantly differed in 69 patients with dementia, major depressive disorder and major depressive disorder with cognitive impairment. Other studies have also supported the reliability of the MMSE's ability to measure improvement in cognition following treatment of depression (Nelson, Fogel & Faust, 1986).

The MMSE has however, been heavily criticised. When applied to those with mild dementia the test has been shown to lack sensitivity to the early signs and to present 'ceiling effects', resulting in false-negative diagnoses (Simard & Reekum, 1999; Nelson, Fogel & Faust, 1986). As early diagnosis is key in the management of dementia, this is problematic

if the Mini Multi-State Examination remains a 'front line' test used in GP surgeries. Indeed, the findings of a 2015 Cochrane review did not support the use of the MMSE to identify patients with a Mild Cognitive Impairment (MCI) who may develop dementia (Arevalo-Rodriguez, 2015).

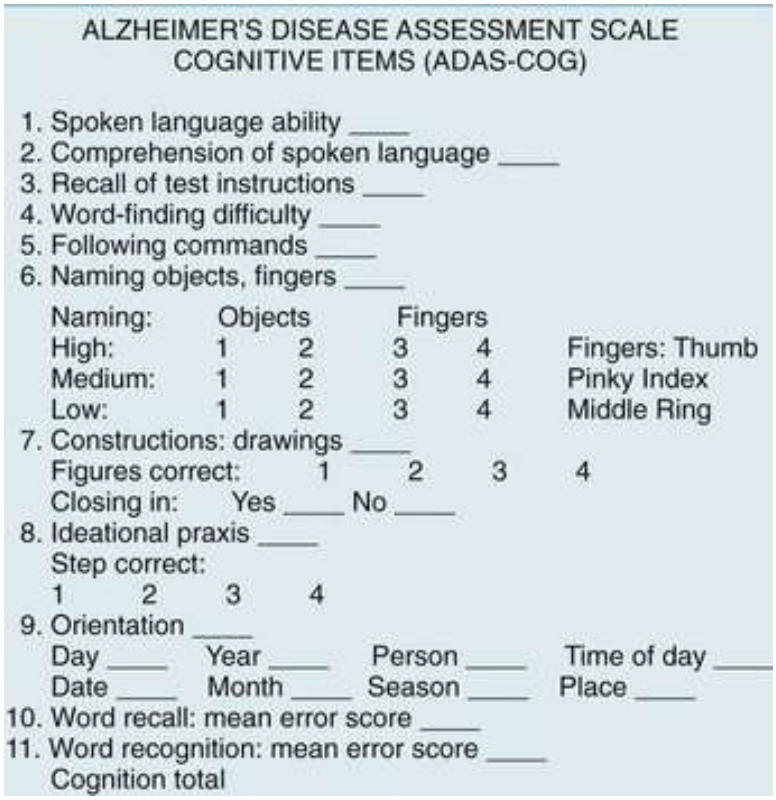
It is now commonly accepted that memory is comprised of many separate yet overlapping systems some of which degenerate earlier in dementia, whilst others may be spared for longer (Simard & Reekum, 1999). The areas that the MMSE focuses upon are fairly limited; working memory, social interaction and abstract abilities, functions known to degenerate in the earlier stages of dementia (Lafleche & Albert, 1995; Huntley & Howard, 2010) are all neglected by the measure.

Due to copyright issues, the MMSE is utilised less and has mostly been replaced by the ACE-III (Hsieh, 2013) within clinical practice, which is described in Section 2.15. However, the MMSE remains widely within research settings, appearing in many studies. The ability of the MMSE to identify patients with MCI that go on to develop dementia is addressed within the meta-analysis in Chapter 3.

2.3: Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG)

The Alzheimer's Disease Assessment Scale (ADAS) is a two-part scale that was designed to assess both the cognitive and non-cognitive symptoms of Alzheimer's Disease (Rosen et al. 1984). The cognitive section (ADAS-COG) is meta-analysed in Chapter 3 and includes tests of language, memory, comprehension and orientation. This cognitive section also tests visuo-

spatial ability such as the drawing of geometric figures and tasks reflecting ideational praxis e.g. folding a sheet of paper and placing it into an envelope. Patients' scores range from 0-70, with higher scores indicating poorer performance, and therefore more cognitive deficit. A sample score sheet is shown in Figure 2.2 below.



ALZHEIMER'S DISEASE ASSESSMENT SCALE
COGNITIVE ITEMS (ADAS-COG)

1. Spoken language ability ____
2. Comprehension of spoken language ____
3. Recall of test instructions ____
4. Word-finding difficulty ____
5. Following commands ____
6. Naming objects, fingers ____

Naming:	Objects		Fingers		
High:	1	2	3	4	Fingers: Thumb
Medium:	1	2	3	4	Pinky Index
Low:	1	2	3	4	Middle Ring

7. Constructions: drawings ____
   Figures correct: 1 2 3 4
   Closing in: Yes ____ No ____
8. Ideational praxis ____
   Step correct:
   1 2 3 4
9. Orientation ____
   Day ____ Year ____ Person ____ Time of day ____
   Date ____ Month ____ Season ____ Place ____
10. Word recall: mean error score ____
11. Word recognition: mean error score ____
    Cognition total

Figure 2. 2. **The cognitive section of the Alzheimer Disease Assessment Scale (ADAS-Cog).**

Source: *Rosen et al, 1984.*

The 11-point cognitive section of the Alzheimer Disease Assessment Scale (ADAS-COG) is designed to measure many important aspects of cognitive function that are liable to deteriorate in Alzheimer's disease. As dementia worsens, patients' responses change from no impairment (where the patient receives 0 points) to severe cognitive impairment (5 points). In short, as dementia worsens, patients accumulate points. Total ADAS-COG scores

for patients with mild-to-moderate Alzheimer disease range from 15 to 25, and as cognitive function declines their scores increase yearly by 6 to 12 points.

This particular cognitive assessment subscale has often been considered the 'gold standard' when assessing the efficacy of anti-dementia treatments (Kueper et al, 2018; Solomon et al, 2019). However, since its development in the 1980s, much research interest has shifted towards pre-dementia symptoms and mild cognitive impairment (MCI) as it is thought that intervening to slow the progression of the disease will be more effective than interventions when there has been more neurological damage and symptoms are more severe (Llano, Laforet & Devanarayan, 2011; Petersen et al, 1993; Mariani, Monastero & Mecocci, 2007). A large amount of research has therefore been conducted in pre-dementia populations such as those diagnosed with MCI (Fleisher et al, 2007; Gaser et al, 2013; Dowling et al, 2016). As the ADAS-COG was originally designed for use in studies where cognitive impairment was more severe there is concern as to whether the test is able to detect changes at the early stages of Alzheimer's disease progression (Podhorna et al, 2016; Raghavan et al, 2013; Aisen, 2015).

2.4: Free and Cued Selective Reminding Test (FCSRT)

The Free and Cued Selective Reminding Test (Buschke, 1973) aims to identify memory impairment that is not secondary to other cognitive deficits such as inattention (Buschke, 1984; Grober & Buschke, 1987). The test begins with a study phase in which participants are asked to examine a card containing pictures of various objects to be memorised (e.g. grapes). Each item has a unique category cue (e.g. fruit). Participants are presented with 16

items to be learned, which tend to be presented four at a time on a card, with one picture in each quadrant (Figure 2.3). The participant is then asked to search each card and name aloud each item (e.g. grapes) in response to its cue (e.g. fruit) which is presented orally. After all 4 cues have been identified correctly, immediate cued recall of just the 4 items is tested by presenting the cues again. Should the participant fail to retrieve any items, they would be reminded by the presentation of the cue and item together (e.g. the fruit was grapes). Once immediate recall for 4 items is completed, the next set of items is presented for study.

The study phase is followed by a test phase that consists of three recall trials, which is preceded by 20 seconds of the participant counting backwards to prevent recall from short term memory. Recall trials consist of two parts; First, participants have 2 minutes to freely recall as many items as possible. Following this, category cues are presented orally for items not retrieved during free recall. If participants still fail to retrieve the item with a category clue, the cue and item are presented together. The sum of the free and cued recall is then calculated in order to find the total recall. The controlled learning stage is designed to redress the mild deficits in retrieval common in many older healthy adults (Grober et al, 1997), but offers little benefit in patients with dementia (Buschke et al, 1995). The FCSRT, therefore, offers a level of discriminative validity for dementia diagnosis that other tests which do not control the learning conditions do not.

In research the FCSRT has been used for various purposes with regards to Alzheimer's disease including; to estimate the prevalence of dementia (Ferris, Aisen & Cummings, 2006; Grober et al, 1988, Petersen et al, 1994), to predict future dementia from healthy populations (Grober et al, 2000; Petersen et al, 1995) and most relevant to the

present study; to identify those with mild cognitive impairment (MCI) who go on to convert to AD (Sarazin et al, 2007; Grober et al, 2008). The ability of the FCSRT to identify patients with MCI that go on to develop dementia is addressed within the meta-analysis in Chapter 3.

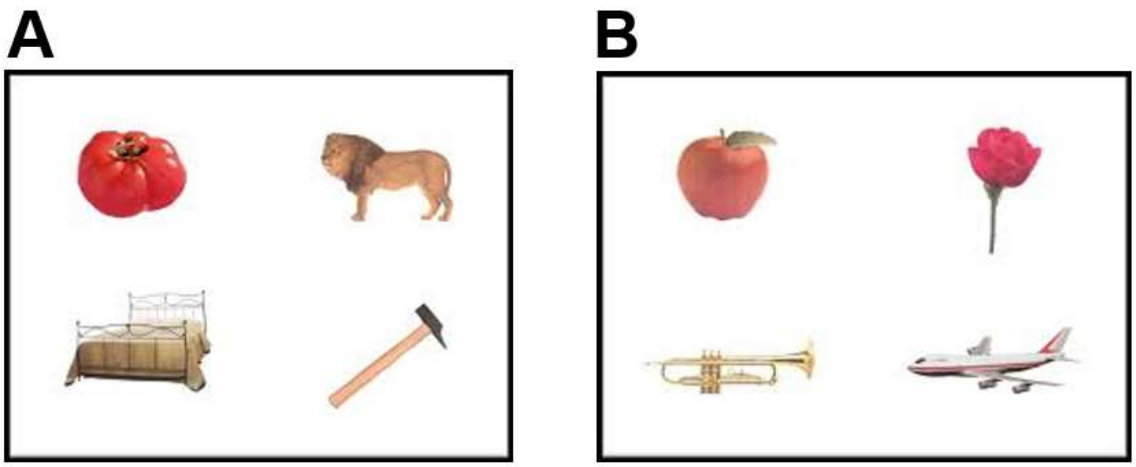


***Figure 2. 3*. Example of the stimuli used in the FCSRT, with 4 items in each quadrant.**
Participants are presented with 16 items to be learned, which tend to be presented four at a time on a card, with one picture in each quadrant. The participant is then asked to search each card and name aloud each item (e.g. grapes) in response to its cue (e.g. fruit) which is presented aurally.

2.5: The Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT (Rey, 1964) evaluates a wide range of functions, including; rate of learning, short-term auditory-verbal memory, learning strategies, retroactive and proactive interference, presence of confabulation of confusion in memory processes, retention of information, and differences between learning and retrieval. The RAVLT requires the participant to learn a list of 15 unrelated words over five trials (Figure 2.4: Sections A1-A5). This is then followed by a second list (Figure 2.4: List B1), designed to serve as an interference to the recall of the original list (Lezak, 1995; Spreen & Strauss, 1991). After a delay of 30 minutes, the

participant is then asked to recall as many words from the first list as they are able to with no prompts. Words can be recalled in any order. Immediate Recall is the total number of words recalled over trails A1-A5, whilst delayed Recall consists of the number of words recalled after the 30-minute delay (A7), also shown in figure 11. Both Immediate and Delayed Recall scores are included in both the meta-analysis (Chapter 3). In particular the delayed recall score is thought to be related to the operation of the medial frontal cortex and the hippocampus (Balthazar et al, 2010) which as previously discussed in Chapter 1 Section 1.8 degenerate early in AD pathology and therefore the delayed recall score is of particular interest to the present study.

Performance on the RAVLT has been shown to be significantly affected by Alzheimer's-type dementia (Mitrushina, Satz & Van Gorp, 1989; Estévez-González et al, 2003; Yagi et al, 2016). However it also has proven useful when assessing pre-clinical dementia and Alzheimer's Disease conversion. Ferreira, Campagna, Colmenarez, and Suarez (2008) found the RAVLT to be the only test able to predict conversion from Mild Cognitive Impairment to Alzheimer's Type Dementia from a wide selection of neuropsychological tests, including Clock Drawing Test, Folstein's Mini Mental State Examination, Trail Making Test, Controlled Oral Association Test, Bender Visual Motor Gestalt Test, Wechsler Adult Intelligence Scale Revised Edition, Wisconsin Card Sorting Test, Weschler's Memory Scale Revised Edition, and Benton Temporal Orientation Test. Furthermore it has been shown to be useful in differentiating AD from other psychiatric disorders (Tierney et al, 1996; Schoenberg et al, 2006; Ricci et al, 2012). However, the test has received some criticism for being affected by variables such as gender, education, IQ, age and cultural differences due to translation and adaptations (Mitrushina et al., 2005; Malloy-Diniz et al., 2007). This is a common criticism of neuropsychological tests as discussed in Chapter 1 Section 1.6.1 and an

issue that the present thesis aims to address within the new tests (Chapter 4). Although there is no clear consensus regarding the magnitude of the effect of such factors, the influence of age is generally thought to be more marked than those of IQ, education or gender (Mitrushina et al, 2005; Van der Elst et al, 2005).

RAVLT SCORING SHEET

Anonymous ID…….

Date……

LIST A	**A1**	**A2**	**A3**	**A4**	**A5**	**LIST B**	**B1**	**A6**	**A7**	
DRUM						DESK				DRUM
CURTAIN						RANGER				CURTAIN
BELL						BIRD				BELL
COFFEE						SHOE				COFFEE
SCHOOL						STOVE				SCHOOL
PARENT						MOUNTAIN				PARENT
MOON						GLASSES				MOON
GARDEN						TOWEL				GARDEN
HAT						CLOUD				HAT
FARMER						BOAT				FARMER
NOSE						LAMB				NOSE
TURKEY						GUN				TURKEY
COLOR						PENCIL				COLOR
HOUSE						CHURCH				HOUSE
RIVER						FISH				RIVER
TOTAL CORRECT										
ERRORS										
PERCENT CORRECT										

Figure 2. 4. **Scoring sheet for the RAVLT.**
The RAVLT requires the participant to learn a list of 15 unrelated words over five trials.
Source: Schmidt (1996) Rey auditory verbal learning test: A handbook

2.6: California Verbal Learning Test – first and second editions (CVLT I & CVLT II).

The California Verbal Learning Test (CVLT) is a widely used standardised measure of verbal learning and memory (Rabin, Barr & Burton, 2005; Rabin, Paolillo & Barr, 2016). The original California Verbal Learning Test (Delis, Kramer, Kaplan, & Ober, 1987) shares many similarities in terms of general format to the RAVLT, however, the CVLT also has the added advantage of presenting the stimuli in an everyday, relatable way, by learning two shopping lists. The CVLT initially evolved from the AVLT and was developed to provide a test ”reflecting the multifactorial ways in which examinees learn, or fail to learn, verbal material. The CVLT's assessment of learning strategies, processes, and errors is designed for use in both clinical and research practice” (Delis, Kramer, Kaplan, & Ober, 1987).

The experimenter begins the CVLT by reading a list of 16 nouns aloud in a fixed order, at one second intervals over 5 learning trials (list A). Following each trial, the participant is asked to recall as many words as they are able, in any order (free recall). An interference list (List B) is then presented that shares two of the categories from list A (e.g. spices and tools) and has two unshared categories (e.g. fish and kitchen utensils). Free and cued recall of the initial list (List A) are tested immediately (short delay), and then again after 20 minutes (long-delay). During cued recall, the experimenter uses the word category to prompt participants.

The final component of the CVLT is a recognition task whereby the experimenter presents the participant with a list consisting of 44 words, to which the participant must indicate whether the word is a ‘target word’ or ‘distractor’. Some of the distractor words

share semantic categories with the target words. The list is presented in the format of a shopping list.

The California Verbal Learning Test-Second Edition (CVLT-II; Delis, Kramer, Kaplan, & Ober, 2000) is an updated version of the original CVLT. It includes an additional forced choice trial which assesses level of effort and not only takes into account the number of correct words recalled but also how many words that were not on the original list. The new word list was intended to be easier, with less educational, cultural and socio-economic bias than the original. The original test had received some criticism regarding bias towards individuals with higher levels of education and functioning (Woods et al, 2006). The 'grocery shopping' list on the original CVLT is discarded in the CVLT-II version and replaced with words taken from four unrelated semantic categories.

Previous research has found the CVLT useful in highlighting a clear pattern of memory deficits (Delis et al, 1991; Kramar, Levin & Delis, 1989), with AD patients presenting with severely impaired learning, high intrusion error rates and poor retention over delay intervals. These characteristics have been shown to be effective in differentiating AD patients from basal ganglia dementia and depression (Delis et al, 1991; Massman et al, 1992), speaking to the potential specificity of the CVLT test. However, the CVLT is reliant on verbal ability, which is associated with an individuals' level of education (Deary et al, 2007) a common limitation of list-learning tests. A higher level of educational attainment may allow individuals to score well on certain tests whilst having the same underlying pathology as someone who has less years of education and scores less. The effect of education upon neuropsychological testing and diagnosis is a key point that this thesis aims to address, and the effect of education upon the two hippocampal tasks (SSEVT and 4MT) is addressed in

Chapter 4. CVLT Short Delay Free Recall and Long Delay Free Recall scores are included in the meta-analysis (Chapter 3) within this thesis.

2.7: Logical memory subtest of the Wechsler memory scale (Logical Memory).

Logical Memory is a subtest from the Wechsler Memory Scale IV that comprises part of the Auditory Memory Index. Participants are read a logically organized story and asked to recall the story immediately after its presentation (Immediate Recall). Approximately 20 minutes later, the participants are again asked to recall the story from memory (Delayed Recall). This delayed recall condition assesses long-term narrative memory. Possible scores for both Logical Memory Immediate and Delayed Recall trials range from 0 to 25, with higher scores reflecting more details recalled.

Advantages of the Logical Memory subtest include that it has been shown to have relatively good inter-rater reliability (Sullivan, 1996) and is quick and easy to administer. However an important disadvantage is that considerable practice effects have been shown to affect the test even when using alternate stories (Dikmen et al, 1999), thus limiting its longitudinal application (Gavett, Ashendorf & Gurnani, 2015). As with many other commonly used neuropsychological tests, the Logical Memory subscale is also heavily reliant on verbal ability. The ability of the Wechsler Logical Memory test to identify patients with MCI that go on to develop dementia is addressed within the meta-analysis in Chapter 3.

2.8: The Trail Making Test B

The Trail Making Test (Reitan, 1958) is one of the most commonly used tests in clinical practice (Rabin, Barr & Burton, 2005), and is thought to be particularly sensitive to brain damage (Reitan & Wolfson, 1994). Part B specifically, as shown in figure 2.5, is thought to effectively determine an individuals' task-switching and visual attention capabilities, and is thought to reflect executive functioning whilst also requiring cognitive abilities such as visual scanning and psychomotor speed (Lezak, Howieson & Loring, 2004).

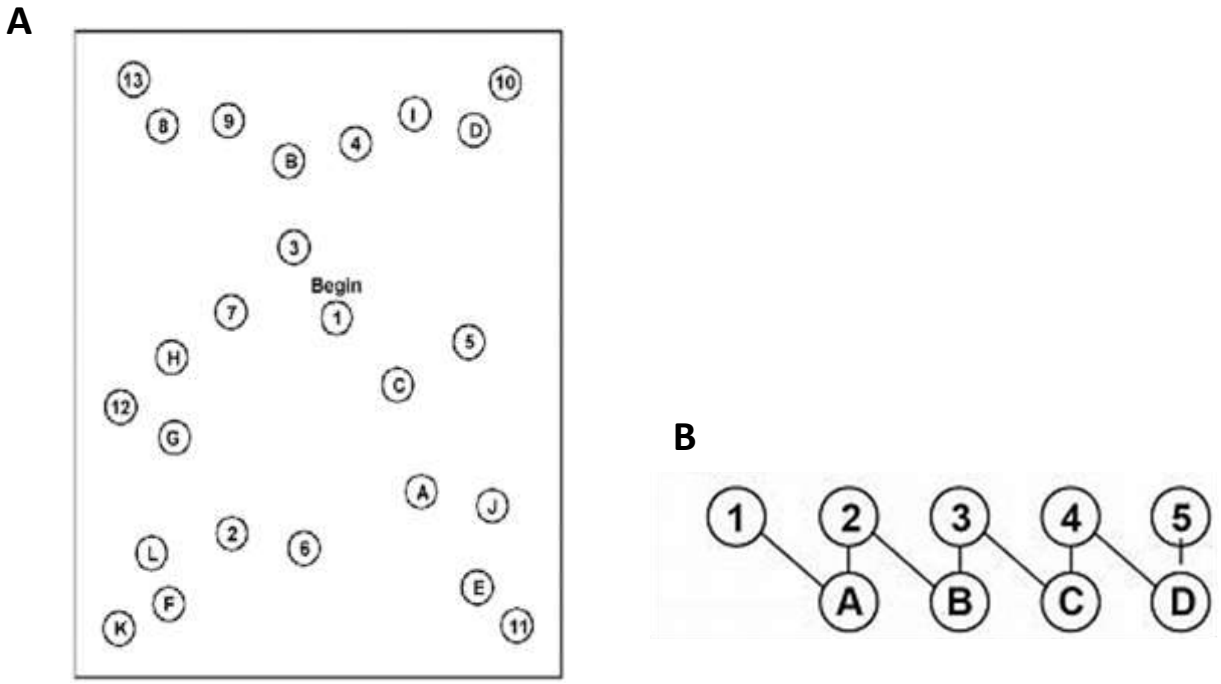


Figure 2. 5. **The Trail Making Test B.**

(A) The sheet used by the participant to make the sequence under timed conditions. The participant is required to connect the circles in ascending order, alternating between numbers and letters. **(B)** A visual aid to better explain the task-switching process the participants are required to complete. *Adapted from Lezak et al, 2004.*

The relationship between increasing age, declining performance and increasing error has been well reported (Kennedy, 1981). However, this has predominantly been shown to exist within 'Part B' and the same effect is not shown in 'Part A'. The majority of research studies, therefore only utilise part B and thus, only this section has been included in the meta-analysis in Chapter 3. A decline in performance with age is also found to occur in the new and recently developed hippocampal tests, as shown in Chapter 4.

This test consists of 25 numbered circles (1-13) and letters (A-L) distributed over a sheet of paper; The participant draws lines to connect the circles in ascending order. Participants are also asked to alternate between letters and numbers (i.e. 1, A, 2, B, 3, C etc) and instructed to connect the circles as quickly as possible, without lifting the pen from the paper (see Figure 2.5 below). Participants are timed, and any mistakes are immediately pointed out by the administrator to allow the participant to correct their mistake. The TMT-B is scored in seconds, with a higher score indicating a greater level of impairment. As previously mentioned, the TMT-B is used extensively in clinics and dementia research (Strauss, Spreen & Sherman, 2006). Longitudinal studies have found that as subjects become older the time required to finish the TMT-B increases significantly, and this time is significantly longer again in those with dementia (Rasmusson et al, 1998).

2.9: Rey-Osterrieth Complex Figure (ROCF)

This test was first proposed by psychologist André Rey in 1941 and standardised by Paul-Alexandre Osterrieth in 1944. The ROCF has three test conditions: Figure copy, Immediate Recall and Delayed Recall. Firstly, the participant is given the Figure stimulus (Figure 2.6 A)

and asked to reproduce it freehand while viewing it as much as they wish. The stimulus is then removed, and the participant is then asked to draw what they remember (immediate Recall). After a 30 minute delay, they are then required to draw the figure once again from memory (Delayed Recall). Results vary depending on the scoring structure used but various aspects of the figure are broken down and scored according to performance (figure 2.6 B). Scores commonly include location, accuracy, and organisation. Each test condition takes around 10 minutes to complete and with the added time of a 30 minute delay, the ROCF test takes around an hour overall. The test evaluates many different cognitive abilities including: attention, memory, visuospatial abilities, planning, working memory, and executive functions.

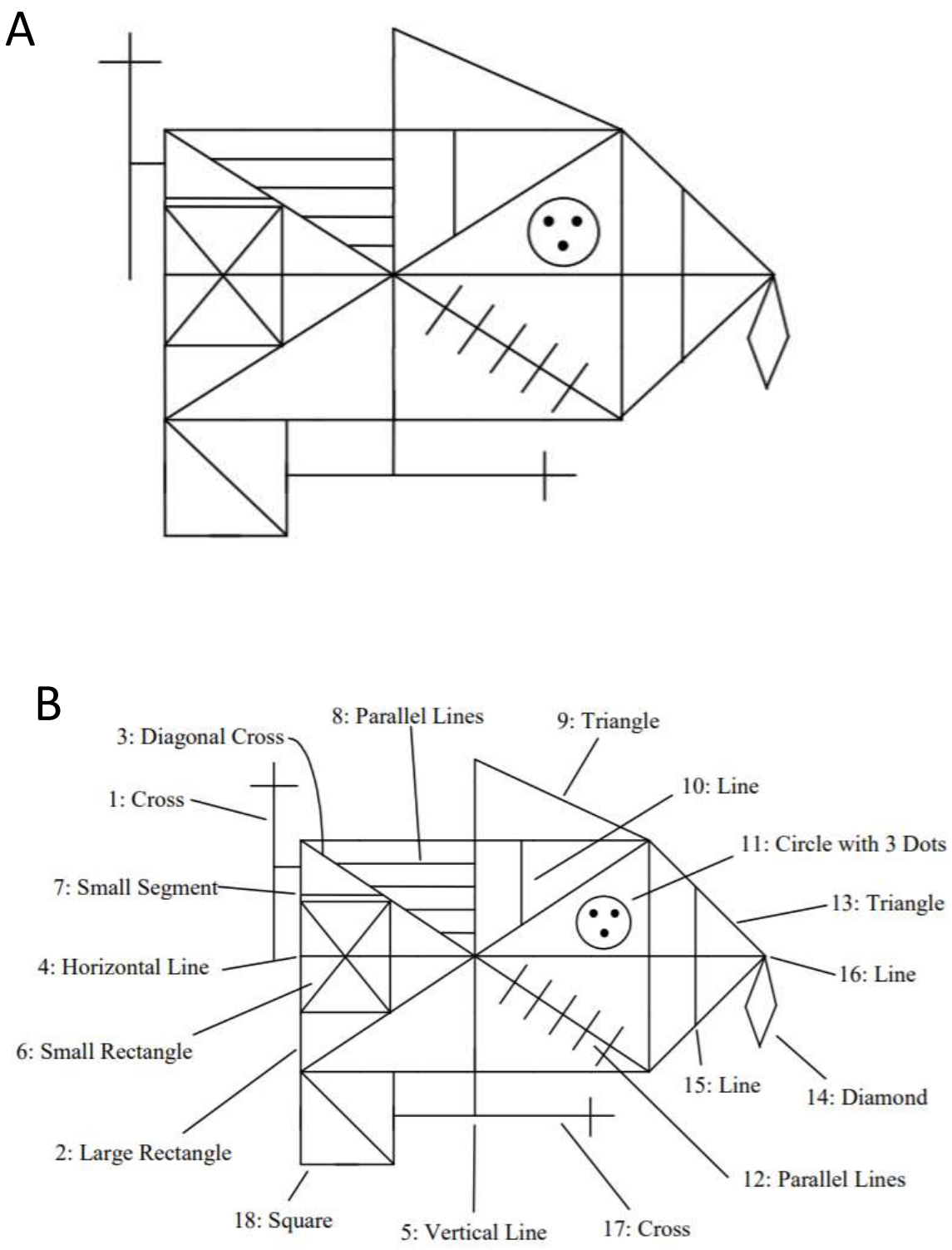


Figure 2. 6. **(A) The Rey-Osterrieth Complex Figure** (**typically 20cm in length).** Source: Dimitrov et al, 2015**. (B) The Osterrieth scoring system**. The various elements of the figure that are used to create an overall score.

Source(s): Dimitrov et al, 2015; Canham et al, 2000.

The visuospatial aspect is of particular interest to the present thesis. As spatial memory is a hippocampus-dependent function, which we know degenerates early in AD. Sowell and colleagues (2001) assessed frontal and medial temporal lobe grey matter volume and memory using the ROCF with 35 young individuals aged 7-16. Results showed a clear association between medial temporal lobe grey matter volume and delayed visuospatial memory on the ROCF. It would therefore be expected that older individuals and those with MCI/ AD would present as impaired upon the same task. In a study by Freeman and colleagues (2000) visuoconstructional ability was assessed by asking those diagnosed with AD to copy a modification of the ROCF and found AD participants performed particularly worse on the visuospatial aspects on the test, as compared to participants with other forms of dementia. Scoring of the ROCF tends to be performed by hand and is therefore subjective in nature. One of the main criticisms of the test is that the individually scored sections tend to have poor inter-rater reliability (Tupler et al, 1995). Both the Immediate Recall and Delayed Recall scores were analysed in Chapter 3's meta-analysis.

2.10: Four Mountains Test (4MT)

The Four Mountains Test (4MT) is a test of working allocentric memory (Chapter 1, Section 1.9.2) that assesses the participants' ability to recall the spatial configuration of a series of computer-generated landscapes from different viewpoints, which is designed to reflect the role of the hippocampus in spatial cognition. The scientific rationale for the 4MT is based upon two main principles. The first principle is that the hippocampus and the related medial

temporal lobe are both structures that are affected early in AD pathology (Chapter 1, Section 1.8) as evidenced from various neuropathological studies of AD (Braack & Braack, 1991; Braack & Del Trecidi, 2015) and severe neuronal loss is clinically-evident even at the earliest stages of the disease (Gomez-Isla et al. 1996). The second principle, as discussed in Chapter 1, Section 1.8.2, is that the hippocampus is critical in spatial memory. This was initially demonstrated through the discovery of the place-related firing activity of hippocampal neurons ('place cells') in freely-moving rats (O'Keefe & Dostrovsky, 1971), which led in turn to the 'cognitive map' theory of hippocampal function (O'Keefe & Nadel, 1978). The further discovery of several other types of spatial cells in mammals including humans has lent more weight to the idea of the hippocampus being important for spatial memory, as have functional imaging studies showing hippocampal activation during spatial memory tasks (reviewed in Burgess, Maguire & O'Keefe, 2002).

Importantly, as discussed in Chapter 1, Section 1.9.2, the hippocampus is particularly crucial in 'allocentric' or 'view-independent' memory, as opposed to egocentric, or view-dependent memory. In open field environments which permit movement in different directions, hippocampal place fields in rodent and human place cells are omnidirectional (Muller & Taube, 1994; Ekstrom et al, 2003). In other words, a place is recognisably the same place even though the subject's viewing direction is altered. A test such as the 4MT, which tests allocentric, view-independent spatial memory, should be highly dependent on the integrity of hippocampal tissue, and thus sensitive to the damage caused by early stages of AD.

The 4MT (Hartley et al., 2007; Bird et al, 2010; Moodley et al, 2015) tests allocentric spatial memory by showing a computer-generated landscape containing four mountains

then, after a 2 second delay a further four pictures, each containing four mountains are shown. These 'pictures' are also computer generated and possible additional viewpoints. The task is to determine which of the four pictures presented is of the original formation of mountains, simply taken from a different place, whilst the others are lures. Figure 2.7 below shows a plan view of the computer-generated landscape, with the seven possible viewpoints shown.

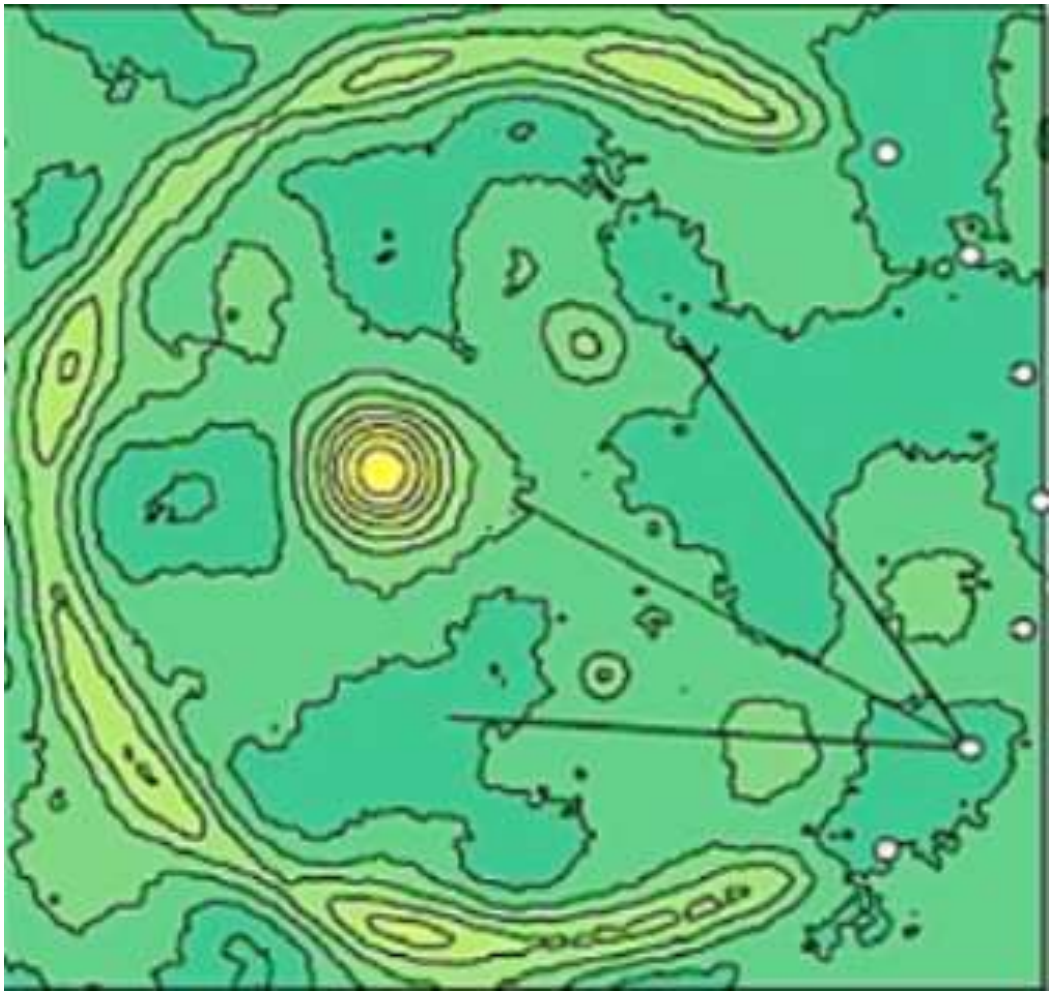
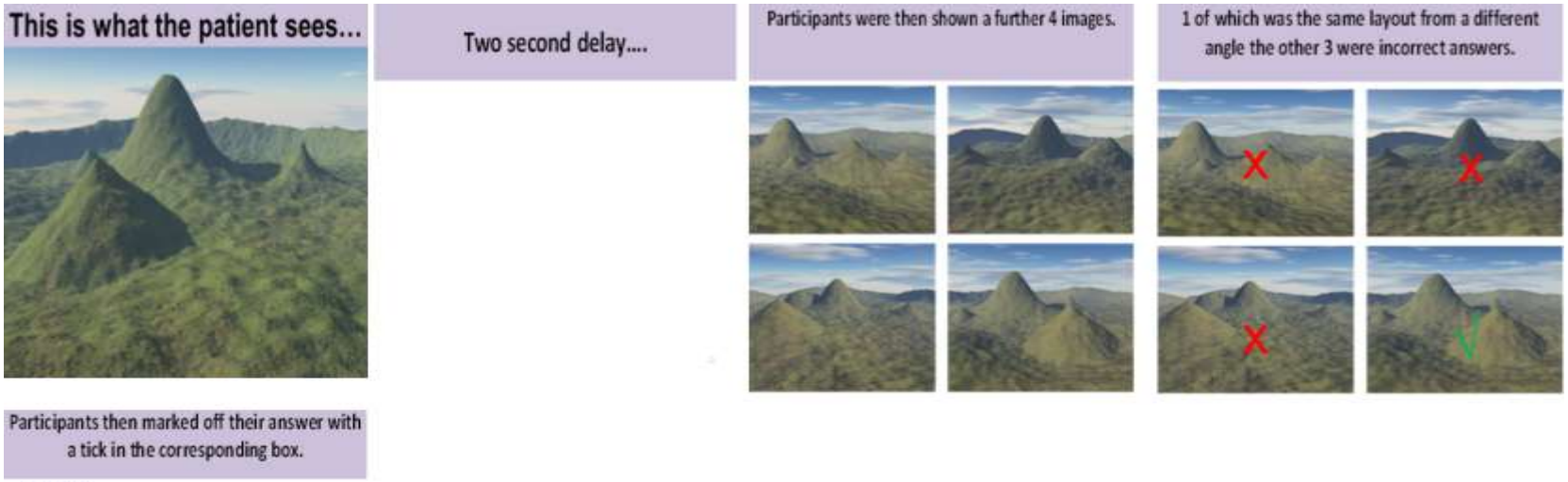


Figure 2. 7. **How the Four Mountains test images are created via virtual camera.**

All 4MT stimuli are based on computer-generated heightfields containing 4 mountains as illustrated by the above map. Images are created using a virtual camera placed at one of the indicated 7 locations, shown as white dots.
Source: *Chan et al, 2016.*

The total test involves 3 practice questions followed by the test itself which showed 15 presentations of the place memory task, each task involving a different computer-generated landscape. Each landscape is made up of similar topographical features; the ground plane with small scale undulations, a semi-circular mountain range, and four prominent mountains which vary in shape and size as can be seen in the contour map in figure 2.7. In order to discourage visual pattern matching strategies, the lighting, landscape colour, textures and weather conditions are varied between the sample and the test images as can be seen in figure 2.8. Each item thus comprises a sample image with one set of nonspatial features, a target image showing the same landscape from a different viewpoint and different nonspatial features and 3 foil images with distinct topography but sharing nonspatial features with the target.



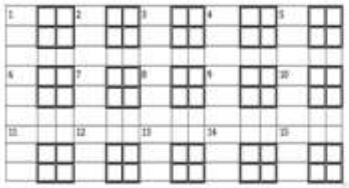


Figure 2. 8.**The Four Mountains Test process (Images have been adjusted for size).**
Sample image is shown for 8 seconds, then turns to a blank page (2 sec), then the four response images are shown for 20 seconds. The participant is asked to indicate their response by pointing to the selected image.

2.11: The Spaces and Sequence Episodic Memory Video Task (SSEVT)

As discussed in the Introduction (Chapter 1, Section 1.8.1), episodic memory impairment is amongst the most common early signs of dementia (Backman et al, 2001; Greenaway et al, 2006; Twamley et al, 2006), as episodic memory is dependent upon the hippocampal formation (Vargha-Khadem et al 1997; Ghoshal et al, 2002; Di Paola et al, 2007; Plancher et al, 2012). Accordingly tasks which can accurately tap episodic memory are likely to be useful in detecting hippocampal damage in early AD, as argued above for allocentric spatial memory. Current standardised neuropsychological assessment measures of episodic memory such as the RAVLT and CVLT (see Sections 2.5 and 2.6 above) generally consist of measuring the patients' ability to recognise and recall lists of unrelated words. As a result of this, scores on these verbal tests are often overly modulated by participants' level of education and linguistic ability (see Chapter 1, Section 1.3.4).

Furthermore, as discussed in the Introduction (Section 1.8.1), there are currently few tests that target episodic memory in a way that is reflective of real-world experiences (Plancher et al, 2012) whilst also being practical for adoption into clinical practice. To reiterate the point made in the Introduction, a good episodic memory test should try to mimic the recall of real world first person memories, under the assumption that such recall provides a more sensitive reliance on the integrity of hippocampal tissue. Secondly, it should try to avoid over-reliance on education-related variables such as good vocabulary and linguistic skill. Thirdly, it should be easy to administer in terms of presentation, procedural simplicity and ease of scoring. Essentially such a test should be simple enough to be run in a primary health care setting.

In order to address this the Spaces and Sequences Episodic Video Task (SSEVT) was developed. The original version of this task was created in 2013, for my undergraduate dissertation by myself and Dr Colin Lever and consisted of a video showing 5 people, 2 rooms and a variety of events occurring. This idea was then developed further to include multiple rooms, events and characters by a team consisting of Dr Colin Lever (Supervisor, Durham University), Georgina Michallat-Bragg (myself, Thesis candidate, Durham) , Dr James Dachtler (2nd Supervisor, Durham University), Sarah Smith (Leeds Beckett University), Christine Wells (Leeds Trinity University), and Sayed Kazmi (Ascentys, Bradford).

The SSEVT is a computer-generated video designed to simulate a participant touring through a house from a first-person perspective. The individual moves through 8 rooms in total which are each visited twice. During the course of the video (4 minutes 16 seconds in duration), the viewer is exposed to seven people (4 women and 3 men) in various rooms. All characters appear at least twice, with 2 female characters appearing 3 times. Each room has a notable colour scheme and decor and within each room, a particular event or activity takes place. Events include: someone watching TV, someone talking about the weather, a character hanging up a picture and so on. As discussed in Chapter 1, Section 1.7.2, the hippocampus is critical for recollection whereas familiarity is dependent on the integrity of the surrounding perirhinal cortex. Therefore, care was taken to ensure that all questions included in the SSEVT were recollective and not answerable by familiarity. For example, all of the person-association questions included in Section 1 e.g. 'Who offered you a snack?' were followed by 4 photographs of characters that all appeared within the video and were therefore all familiar to the participant. Furthermore the pictures of the characters were all set against neutral backgrounds so as to give no contextual clues which may prompt an

answer of familiarity rather than recollection (Figure 2.9). Neutral backgrounds are also used for the object location questions as illustrated below in figure 2.9.

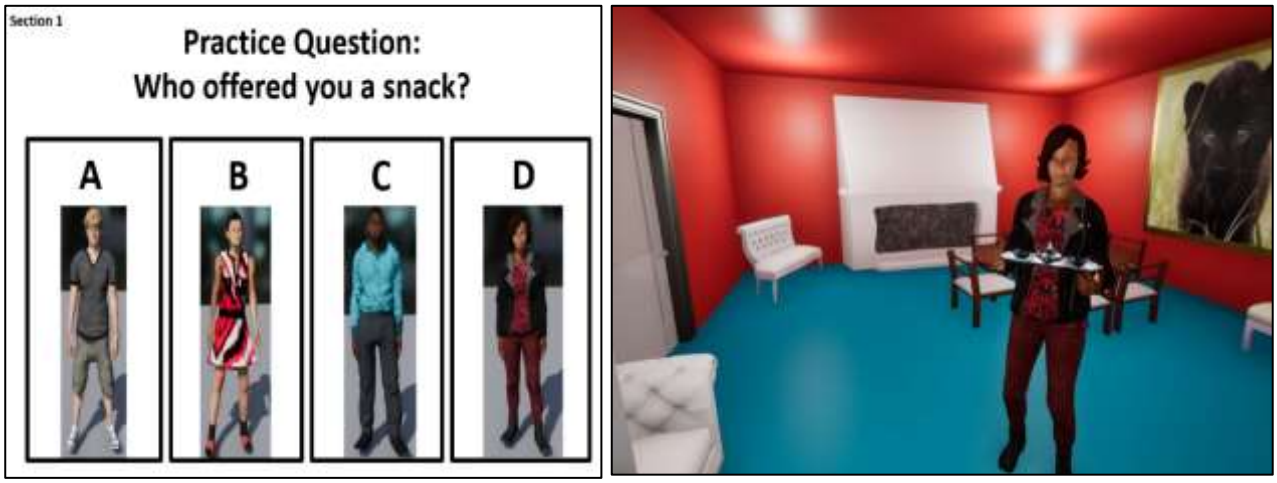


***Figure 2. 9*. The question format in the SSEVT vs the way it appears in the video**.
After the 20-minute delay, the questions were presented via PowerPoint. The objects, rooms and characters were shown in isolation, with no other contextual information which may make the questions answerable by familiarity rather than hippocampal-dependent recollection

In order to further limit the extent to which questions could be answered by familiarity alone 7 of the 9 of the rooms were visited twice, with different events occurring upon each visit.

Before the video begins the experimenter reads the following script:

"The video you are about to watch is presented as if you were walking through a computerised house. The video lasts approximately 4.5 minutes and various things will happen as you walk through the house. Please pay attention to the video and remember what you can as you will be asked questions about the video 20 minutes after it finishes. The questions will assess how well you can remember; the people, the objects, the rooms and the events".

20 minutes after viewing the video the participant is asked to answer 20 forced-choice questions that are divided into 5 sections.

Section 1: Character questions e.g. “who offered you a snack?”.

Section 2: Object-room questions e.g. “in which room did you see this clock?” This section assessed object-room associations, that is, associations between a spatial context and its contents. The idea of this section was to tap the hippocampal support of associations with spatial contexts.

Sections 3-5 examine sequence memory. While it would be expected that spatial sequences depend upon the hippocampus, it was considered important to tap sequence memory that was not necessarily spatially mediated. Evidence from both animals and humans strongly implicate the hippocampus in supporting memories for sequences of events, which are not necessarily reliant on spatial context (e.g. Fortin et al, 2002; Gilbert et al, 2002; Kumaran and Maguire, 2006). For example in a study by Dede et al (2016) patients with Medial Temporal Lobe (MTL) damage were taken for a real-world walk, and the authors reported that the patients “were particularly impaired at remembering the temporal order in which the events occurred” more than they were impaired at recalling spatial details. Sections 3-5 thus all examined sequence memory with different potential reliance upon spatial context. Section 3 questions linked two sequential events to their rooms e.g. “Recall the time you were in the room where you were asked if you liked the painting on the wall. What event occurred in the room immediately before this?”.

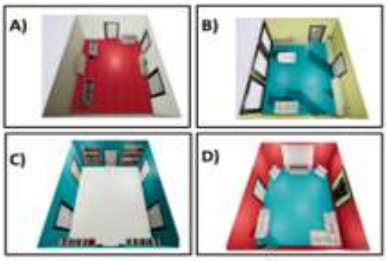
Section 4 event sequence questions were posed without any reference to rooms but consisted of three-step-event order questions e.g. “in which order did these events occur?”,

while Section 5 asked about room visit sequences without reference to the events/contents inside the rooms e.g. “which room did you see first or most recently”.

Each section was preceded by a practice question which gave the participant insight into the up-coming section’s format. Each correct answer was awarded 1 point, with the exception of the final section, within which correct answers were awarded 0.5 points as there were only 2 options to choose from instead of the 4 options on previous questions. The total score was then calculated as the sum of all points from all sections (maximum 17 points). It was intended that subtotals could be taken from overall total, to focus on different forms of memory. Examples of questions and sections can be seen in Table 2.2.

Table 2. 2.

Summary of the Spaces and Sequences Episodic Video Task (SSEVT) including test sections and sample practice questions.

Test section and number of questions	Practice questions included in each section.	Answer format and marking system
Section 1: Person associations. Questions in section: 3	**Practice Question:** **Who offered you a snack?** 	Answered as A, B,C or D as shown on the slide. 1 point awarded per correct answer
Section 2: Object locations Questions in section: 4	**Practice Question:** **In which room did you see this table?** 	 Answer is A, B, C or D as shown on the slide. 1 point awarded per correct answer
Section 3: Event order: Immediately before/ after. Questions in section: 4	**Practice Question:** **Recall the time you were in the room where you were asked if you liked the painting on the wall.** **What event occurred in the room immediately before this?** **A) Two people welcomed you to the house.** **B) You saw a person miss a phone call.** **C) You saw a person watching TV.** **D) You saw a person dancing.**	Answered as A, B, C or D as shown on the slide. 1 point awarded per correct answer. Questions also asked 'What happened immediately **after** this?'
Section 4: Event order: Multiple events. Questions in section: 3	**In which order did these events occur?** **A) You saw a person watching TV; you saw a person dancing; you saw a person miss a phone call.** **B) You saw a person miss a phone call; you saw a person watching TV; you saw a person dancing.** **C) You saw a person watching TV; you saw a person miss a phone call; you saw a person dancing.** **D) You saw a person dancing; you saw a person watching TV; you saw a person miss a phone call.**	Answered as A, B, C or D as shown on the slide. 1 point awarded per correct answer
Section 5: Room order Questions in section: 6	**Which room did you visit first?** 	Answered as A or B as shown on slide. 0.5 points awarded per correct answer.

The above table illustrates each question section, the amount of questions asked and scoring details. Sections focus upon; Person associations, object location, Event order: Immediately before/after, Event order: Multiple events and Room order. Participants noted answers down on paper answer sheets. Questions were asked via PowerPoint.

Overall, the SSEVT aims to assess episodic memory by requiring the participant to access memory of contextual, spatial, and temporal features after a 20-minute delay. Unlike many tests discussed above, the SSEVT places less focus upon verbal ability, which could affect the participant score, whilst not reflecting an actual cognitive deficit. The task was specifically designed to require recollective memory as this is hippocampus dependent, and avoid answers based upon familiarity.

The computerised nature of the SSEVT allowed us to shape and reshape the environment repeatedly to suit our memory testing design needs. For instance, it was important, for as many rooms as possible, to generate two visits into each room. This allowed us to increase interference by having more than one set of associations tied to each room. This was straightforwardly achievable in the virtual world. Secondly, we wanted the sequence of rooms to be different from the first to the second set of room visits. This required the rooms to have multiple doors to other rooms, in all the right places. Such a requirement is unlikely to be met in most real architectures, but is straightforwardly done in the virtual world. Another example is that the virtual walkthrough occurs 'in a single take' of around 4.5 minutes. It would not be easy to film a real walkthrough through a house in a single take. There would be too many mistakes from the actors and the filmmakers. Just focusing on voices, for instance, it was notable that the amateur actors voicing the voiceovers required many takes to achieve one acceptable voice recording.

It is worth discussing the distinction between this virtual task and 'virtual reality' that whilst the task is computerised and mimics characters and environments it is not 'virtual reality' (VR) in that it is not an immersive experience, however there is a virtual element to the task. There have been concerns raised regarding older adults and those with MCI and

dementia's tolerance to VR (Manera et al, 2016), which was further discussed in Chapter 1, Section 1.8.1. However, there is also recent evidence which saw minimal or no ill-effects in those populations when using VR (Kim, Park & Lim, 2020; Appel et al, 2020). Unlike the Four Mountains Test (4MT) where some participants complained about the speed of the slides and the overall difficulty, there were no complaints regarding the material noted during testing upon the SSEVT or it's virtual nature.

When using a virtual computerised task there is a generational component that must be considered, older adults such as those tested in the current project may have had less exposure to computerised stimuli which may lead to less engagement with the material and thus, lower scores than the younger participants tested. However, healthy older participants were age matched with MCI patients (Chapter 5, Section 5.3.1) in order to address the potential issue of generational differences and technology familiarity. Nevertheless, it is possible that MCI patients were more unfamiliar than healthy aged, matched participants with the virtual nature of the SSEVT.

2.12: The Buschke Selective Reminding Test (SRT)

The Buschke Selective Reminding Test (SRT) involves reading the subject a list consisting of 12 unrelated words at a rate of 2 seconds per word, and then having them immediately recall as many of those words as possible. The words used are as follows: Bowl, Passion, Dawn, Judgement, Grant, Bee, Plane, County, Choice, Seed, Wool and Meal. After the first repetition every subsequent trial involves selectively repeating only those words that the subject did not recall on the previous trial. The selective reminding trials continue in this

way until the subject has correctly recalled all of the 12 words for three consecutive trials, or until 12 trials have been completed. By only assessing the recall of words that are not given, the selective reminding test is believed to distinguish between retrieval from short-term recall (STR) and long-term storage (LTS).

The total Recall (TR) score refers to the number of words recalled over 12 trials. If a word is recalled on two successive trials without the researcher providing a reminder it is assumed to have entered Long Term Storage (LTS). After recalling the word on two trials, it is still scored as LTS on all following trials, even if it is not retrieved on subsequent trials. A word is scored as Long-Term Retrieval (LTR) when the subject recalls a word that has entered LTS. Consistent Long-Term Retrieval (CLTR) refers to consistent recall of this particular word on all succeeding trials. If the subject recalls a word that has not entered LTS, it is then scored as STR. Multiple Choice items (MCR) includes the number of recognised words on the multiple-choice portion of the test and Delayed Recall (DR) contains the number of words the subject recalls after the 30 minute delay. Additionally Masur et al (Masur, Fuld, Blau, Crystal, & Aronson, 1990; Masur et al, 1994) have found the delayed recall measure, specifically from the Buschke selective reminding test (SRT), to be an effective predictor of conversion to dementia.

2.13: The Spatial Abilities and Practices Questionnaire.

Given the early degeneration of the hippocampus in AD pathology as discussed in Chapter 1 Section 1.8, a questionnaire which investigates putatively hippocampal-dependent spatial abilities and practices could prove beneficial in highlighting spatial deficits arising from early

AD. Such a questionnaire could act as a pointer to more formal testing of spatial cognition and memory. In principle, for example, a non-stressful straightforward questionnaire administered and scored by a Nurse in a GP surgery could help to indicate a marked deficit that could trigger a referral to a Memory Clinic for more rigorous testing.

With this kind of motivation in mind, the Spatial Abilities and Practices Questionnaire was developed by members of a collaborative team, including Dr Colin Lever (Supervisor, Durham University), Georgina Michallat-Bragg (myself, Thesis Candidate), Dr Dennis Chan (University College London) and Dr David Howett (University of Cambridge). The Spatial Abilities and Practices Questionnaire (SAPQ) aims to assess the participant's spatial memory and navigational ability in the real world. We intended a questionnaire assessing presumptive hippocampal-dependent spatial cognition in both familiar and unfamiliar environments.

Overall, the test consists of 15 questions (Figure 2.9) assessing different kinds of spatial ability, in the form of statements to endorse using a Likert scale, e.g. 'I have difficulty accurately visualizing in my mind's eye the local walking routes (e.g. to shops, pubs, parks, restaurants) to and from my home.' Reverse scoring is indicated in Figure 2.9 in bold font.

Hippocampal degeneration and a subsequent decline in navigational ability also occurs as people healthily age. In order for the newly developed SAPQ to be a useful tool to gage spatial ability and AD in its earliest 'preclinical' stages, it should also be sensitive to the changes that occur as people age that may become further exacerbated as such individuals convert to AD.

In a study by Harris et al, 2014, younger (mean age: 21.8 years) participants were found to be more able to navigate when required to create a novel shortcut through a

virtual reality (VR) city environment than older participants (mean age: 68.7 years). The use of a novel shortcut is considered to be a hallmark measure of a complex mental allocentric map complete with landmarks (O'Keefe & Nadel, 1978). The ability to create shortcuts through an environment is assessed through question 14: ' On an outing or holiday, having walked around visiting several locations (e.g. coffee shop, museum) I can generally calculate a shortcut route back to my starting point without consulting signs and maps'. The ability to generate a new route or shortcut is also tested via question 8: 'I stick to major walking routes, and avoid minor paths and shortcuts, to avoid getting lost.' And question 6: 'I stick to major walking routes, and avoid minor paths and shortcuts, to avoid getting lost'.

In general, older adults tend to perform less well than younger individuals during navigational tasks. This inferiority is presumably multifactorial. One contributory factor is thought to be older adults' tendency to be less effective at integrating distal landmarks into a stable spatial framework when learning new environments (Rodgers, Sindone & Moffatt, 2012; Head & Isom, 2010; Montefinese et al, 2015). This ability is tested through questions within the SAPQ such as question 10: 'It is difficult for me to find my bearings in a new town/city'. Accordingly, we predict older individuals to perform worse than their young counterparts. This is explored in Chapter 4.

There is an already-existing questionnaire on broadly allocentric spatial cognition, the Santa Barbara sense of direction scale (Hegarty et al, 2002). The Santa Barbara sense of direction scale is a questionnaire designed to test an individual's spatial and navigational abilities, preferences and experiences through a Likert scale e.g. 'My 'sense of direction' is very good'. The Santa Barbara sense of direction scale has been found to have good re-test validity and to correlate with measures of spatial knowledge that involve orienting oneself

within an environment, rather than estimating distances or map drawing (Hegarty et al, 2002).

Such orientation is only one aspect of cognitive mapping likely affected by hippocampal damage, and thus we attempted to create a more wide-ranging questionnaire in the present project. For example, while questions 1, 2 and 3 assess sense of direction, questions 4 and 5 assess visualisation 'in the mind's eye', which might speak to connectivity between hippocampus and its efferents. Question 15 assesses spatial ability in darkness, which might index path integration ability, thought to depend upon entorhinal cortex, which contains grid cells, and its connections with the hippocampus.

We also considered that the Santa Barbara sense of direction scale requires quite a lot of self-reflection upon general questions. We considered that more specific questions might be friendlier to answer for cognitively ageing participants. Thus the questions often contain examples, such as 'when I walk out of a large shop or shopping centre', and 'local walking routes (e.g. to shops, pubs, parks, restaurants)', designed to try to jog typical memories and knowledge of habits from the participant's mind.

Another difference from the Santa Barbara sense of direction scale concerns changes in ability over time. Due to the inevitable decline that is associated with AD, considering and evaluating change is crucial when considering spatial ability in those with MCI. Therefore, in our Spatial Ability and Practices Questionnaire, every question is followed up with a further 'Has this ability changed within the last 12 months?' to potentially gauge decline. It is expected that spatial ability differs across different people, and below average performance does not necessarily imply decline. Accordingly, as described above, after each of the 15 questions there was a standard Likert scale question asking whether there has been a

change in the last 12 months, and in which direction. This secondary question indexing change was scored from -2 to +2 and then added or deducted from the original score to give an adjusted final score. The spatial questionnaire with the added secondary questions indexing change can be seen in Appendix A.

Above I talked about prompting typical memories and habits within the participant's mind. One potential drawback associated with the use of self-report questionnaires is the issue of Illness insight. Insight is a critical issue to consider when discussing self-report measures in MCI and AD as insight into disease declines as the disease progresses (Migliorelli et al, 1995; Starkstein et al, 1996). Lack of disease insight, commonly referred to as 'anosognosia', is defined as the loss in ability to give details on the experience of the disease, understand that the symptoms of the disease are pathological or understand the effect such symptoms have upon daily life (Horning, Melrose & Sultzer, 2014). This would affect the way in which disease-affected individuals would answer questionnaires tapping abilities such as spatial navigation. Participants may feel their navigational abilities to be far better than they are. In order to mitigate this in the present study, participants also specified whether they answered the SAPQ alone, or with someone else's help (partner, family member, or other carer).

Number	Question
1	I am good at recognising a place (eg. town square, building) even when I approach it from a new direction.
2	When leaving or returning home, I generally have a good idea of the direction between my home and destination.
3	**When I walk out of a large shop or shopping centre, I sometimes find I am taking the wrong direction from the one I intended.**
4	**I have difficulty accurately visualizing in my mind's eye the local walking routes (e.g. to shops, pubs, parks, restaurants) to and from my home.**
5	I find it easy to visualize in my mind's eye the routes to places further afield (e.g. to nearby towns).
6	**When a walking route I usually take is completely blocked off (e.g. for maintenance, treefalls), I find it difficult to work out a new route**
7	I find it easy to remember precisely where the car is parked.
8	**I stick to major walking routes, and avoid minor paths and shortcuts, to avoid getting lost.**
9	**When visiting new places, I prefer to be with people I know and follow them, rather than find my way myself as I feel that if I am alone, I may become lost**.
10	**It is difficult for me to find my bearings in a new town/city.**
11	**As a passenger in a car, I usually have to take the same route many times to remember it.**
12	Before I go somewhere, I tend to visualise the different points along the journey where I need to make a decision (e.g. where I will need to go straight, left or right).
13	I can tell quite quickly that I am approaching a place I have been to before, even if I have only been there once or twice.
14	On an outing or holiday, having walked around visiting several locations (e.g. coffee shop, museum) I can generally calculate a shortcut route back to my starting point without consulting signs and maps.
15	I can find my way around places when travelling in the dark.

Figure 2. 10. **The Spatial Abilities and Practices Questionnaire: Statements to be endorsed**

Questions assess the participants' self-reported ability to navigate in both familiar and unfamiliar environments (and whether this ability has changed in the last 12 months, not shown). Questions that require reverse scoring in **bold.**

2.14: Social Networks and Social Embeddedness Questionnaire (SNSEQ).

Limited social networks and low-quality social contacts have been shown to increase the risk of dementia (Fratiglioni et al, 2000). The emphasis on social networks as a protective factor in dementia has become increasingly popular. As discussed in more detail in Chapter 1 Section 1.3.2, rodents in a communal nest have been found to have higher levels of hippocampal brain-derived neurotropic factors within the brain (Branchi et al, 2006) which increases neurogenesis and synaptic plasticity, in turn improving cognitive function. This supports the argument for social embeddedness and larger social networks acting as a somewhat protective factor against cognitive decline due to neuronal changes within the hippocampus, an area to which degeneration is linked at the disease's earliest stages (Backman et al, 2001; Ghoshal et al, 2002).

Furthermore, larger social networks are thought to provide a form of 'social buffering' (Chapter 1, Section 1.3.2) which acts as a protective factor against AD pathology (Davitz & Mason, 1955; Coe et al, 1978). Social isolation on the other hand can lead to cortisol dysregulation (Fujiwara et al, 1966; Payne & Nadal, 2004; Stark et al, 2006) which is commonly found in AD patients. The effects of social isolation are discussed in more detail in Chapter 1, Section 1.3.3. It may therefore be suggested that a questionnaire which evaluates the size and complexity of an individual's support network may prove valuable for highlighting those who may be at greater risk of converting from MCI to AD.

With this motivation in mind, the Social Networks and Social Embeddedness Questionnaire (SNSEQ) was developed by Georgina Michallat-Bragg, Dr James Dachtler, and Dr Colin Lever at Durham University. It aims to assess the extent to which the participant is

socially motivated and socially embedded. It consists of 16 questions in the form of statements (Figure 2.10) to endorse using a Likert scale (1. Strongly disagree, 2. Disagree, 3. Neither agree not disagree, 4. Agree, or 5. Strongly agree) and scored 1-5 accordingly. Statements that are reverse scored can be found in bold in figure 2.10.

As with the Spatial Abilities and Practices Questionnaire considered above, after each question the SNSEQ includes an additional secondary question aimed at establishing if there has been any change in the given social measure in the last 12 months. Thus, after each of the 16 questions, there is a standard Likert-scale question asking whether there has been a change in the last 12 months and in which direction. The overall idea is to examine if levels or changes in sociability and social embedding may modulate conversion to AD (For the questionnaire in full please see Appendix B).

Similar questionnaires which address social networks do exist, of which the Lubben Social Network Scale (LSNS) is one of the most utilised (Lubben, 1988; Lubben & Gironda, 2004; Lubben et al, 2006). The LSNS is a brief instrument designed to measure the perceived social support by friend and family in older adults, as shown in full in figure 2.11 (6 item version). The LSNS exists as a 6, 12 and 18 version test, although the 6 item test is most commonly seen in within research. The LSNS has shown good internal consistency (Lubben, 2006; Chang et al, 2018; Myagmarjav et al, 2019) and is frequently used in research settings to determine the social support of both affected participants and care givers (Cascado & Sacco, 2012; Albright et al, 2016).

Number	Question
1	I would describe myself as very sociable.
2	I find it easy to meet new people.
3	There are people outside of my family that I can talk to about personal matters.
4	**On an average week, I will only interact with my spouse and/or children.**
5	I have friends outside of family members that I see on at least a fortnightly basis.
6	**I can sometimes feel lonely**
7	**I have less desire to meet new people than I used to.**
8	If I were to have a party, I can think of more than 5 people aside from family members that would attend
9	**I tend to avoid social situations unless they are with my immediate family**
10	**I'd rather stay at home than have day trips out.**
11	**I've fallen out of touch with many of my closest friends.**
12	I enjoy socialising outside of my home environment.
13	**I would avoid going to a new place if there were a lot of people I didn't know there.**
14	**If a situation arises where I need to speak to someone new, e.g. a new neighbour, I prefer my partner/family member to lead the conversation.**
15	I am actively involved in my community.
16	**I think I would find things less stressful if I had more social contact with people.**

***Figure 2. 11*. The Social Networks and Social Embeddedness Questionnaire: Statements to be endorsed.**

This figure only includes the statements asked within the questionnaire. Each statement is followed by a Likert scale choice of answers (and a further question to detect change within the last 12 months, not shown). Questions that are reverse scored are in **bold.**

The Lubben Social Network Scale does not take some more nuanced changes in socialisation and social networks into account, which we aimed to address through our own Social Networks and Embeddedness Questionnaire (SNSEQ). For instance, factors such as patient motivation are not addressed in the LSNS despite evidence that as the disease progresses social withdrawal and a lack of social motivation may occur (Burke et al, 2015; Van der Wee et al, 2019). Thus, the current questionnaire contains statements such as 'I have less desire to meet new people than I used to'. Adolphs, for instance, has commented on the complexity of brain processes required to both initiate and maintain social relationships and networks (Adolphs, 2009). It is not difficult to imagine that these brain processes might have been compromised, or the effort required to maintain networks has become too much for the patient.

Another point that is addressed in our SNSEQ is that of a patient preference for their caregiver or partner to take the lead in social situations, indicating a reliance on others to initiate social interaction. This phenomenon does not yet have much of a research backing but was discussed so frequently with caregivers, family members, clinicians, and patients themselves that we felt it warranted further investigation. This preference for another to lead social interaction was addressed through statements such as

'If a situation arises where I need to speak to someone new, e.g. a new neighbour, I prefer my partner/family member to lead the conversation.'.

As weak social integration is often thought to accelerate or worsen AD (Zunzunegui et al 2004; Read et al, 2019), a short questionnaire which specifically focuses upon social networks may prove useful. It may also offer some insight into how social networks may change as individuals age or develop MCI. This is explored in Chapter(s) 4 and 5.

As with the Spatial Navigation and Practices Questionnaire, the general drawback of insight, as discussed above, also applies to the present questionnaire. In order to mitigate this we again asked participants to record whether the participant was taking the questionnaire alone or with someone who knows them well.

FAMILY: Considering the people to whom you are related by birth, marriage, adoption, etc.

1. How many relatives do you see or hear from at least once a month?
   ☐ none ☐ one ☐ two ☐ three or four ☐ five thru eight ☐ nine or more

2. How many relatives do you feel at ease with that you can talk about private matters?
   ☐ none ☐ one ☐ two ☐ three or four ☐ five thru eight ☐ nine or more

3. How many relatives do you feel close to such that you could call on them for help?
   ☐ none ☐ one ☐ two ☐ three or four ☐ five thru eight ☐ nine or more

FRIENDSHIPS: Considering all of your friends including those who live in your neighborhood

4. How many of your friends do you see or hear from at least once a month?
   ☐ none ☐ one ☐ two ☐ three or four ☐ five thru eight ☐ nine or more

5. How many friends do you feel at ease with that you can talk about private matters?
   ☐ none ☐ one ☐ two ☐ three or four ☐ five thru eight ☐ nine or more

6. How many friends do you feel close to such that you could call on them for help?
   ☐ none ☐ one ☐ two ☐ three or four ☐ five thru eight ☐ nine or more

To score responses and interpret the results:
The LSNS-6 total score is an equally weighted sum of these six items. Each LSNS-6 question is scored from 0 to 5 and the total score ranges from 0 to 30.
The answers are scored: none = 0, one = 1, two = 2, three or four = 3, five thru eight = 4, nine or more = 5. A score of 12 and lower delineates "at-risk" for social isolation.

***Figure 2. 12*. The 12 Item Lubben Social Network Scale.**
The Lubben Social Network Scale is a self-report measure of social engagement including family and friends. Source: Lubben, 1988

2.15: ACE-III

The Addenbrooke's Cognitive Examination (ACE) was originally developed as a theoretically motivated extension of the Mini-Mental State Examination (Folstein & Folstein, 1975), which is described above in Section 2.2. The ACE-III (Hsieh et al, 2013), was developed to remove MMSE elements from the ACE and ACE-R as the MMSE was no longer open access in the year 2001 (Seshadri et al, 2015). The ACE-III also attempted to improve the screening process and address some neurological elements omitted by the original and is now considered superior to the MMSE in diagnostic utility (Hodges & Larner, 2016).

The ACE-III has been widely adopted within memory clinics and dementia research fields as it is relatively quick (15-20 minutes) and cost effective (Hsieh et al, 2013). Due to this widespread use, the ACE-III has also been included in the testing battery of MCI patients and healthy controls in the present project. The test is paper-based and includes items assessing the domains of attention, memory, fluency, language (figure 2.12B) and visuospatial function, which are scored individually before collectively giving a score out of 100. The threshold at which a diagnosis of dementia is considered are usually 82 or 88/100 (Beishon et al, 2019).

Further supporting its use the subtests of the ACE-III have been demonstrated to significantly correlate with other neuropsychological tests (Hsieh et al, 2013; Matias-Guiu et al, 2017), namely the FCSRT and the RAVLT (discussed in Sections 2.4 and 2.5 respectively). It does, however, fall victim to the issues discussed in Chapter 1, Section 1.3.4 regarding educational bias. The level of education has been observed to have an effect on the accuracy of the ACE-III in the diagnosis of dementia (Jubb & Evans, 2015; Wang et al, 2017).

Jubb & Evans (2015) administered the ACE II to 59 patients prior to any diagnosis. Thirty-three participants (55.9%) of which 56.3% were diagnosed with AD. They found that the number of years of full-time education had a significant positive relationship to total ACE III scores (r=0.697, p<0.001) for the no-dementia group. This may be due to education allowing a certain amount of 'cognitive reserve' where participants still perform well in neuropsychological tests due to their level of education whilst having the same amount of AD pathology as a lesser educated individual who may score poorly (Wilson et al, 2019; Gilleard, 2010; Swanwick et al, 1999). The role of education in AD is discussed in detail in Chapter 1, Section 1.3.4. Lower scores on the ACE III due to education may be due to the use of irregular words, phonemic verbal fluency (Silva et al, 2004) or naming task, as illustrated in figure 2.13A.

Ideally tests that are designed to identify cognitive decline should not be affected by education, as cognitive reserve which may lead to higher scores may simply lead to a false negative diagnosis, potentially delaying a diagnosis until a much later stage. Creating tests that are not affected by education was a key focus within this thesis. The effect of education upon the two hippocampus dependent tests is analysed in Chapter 4.

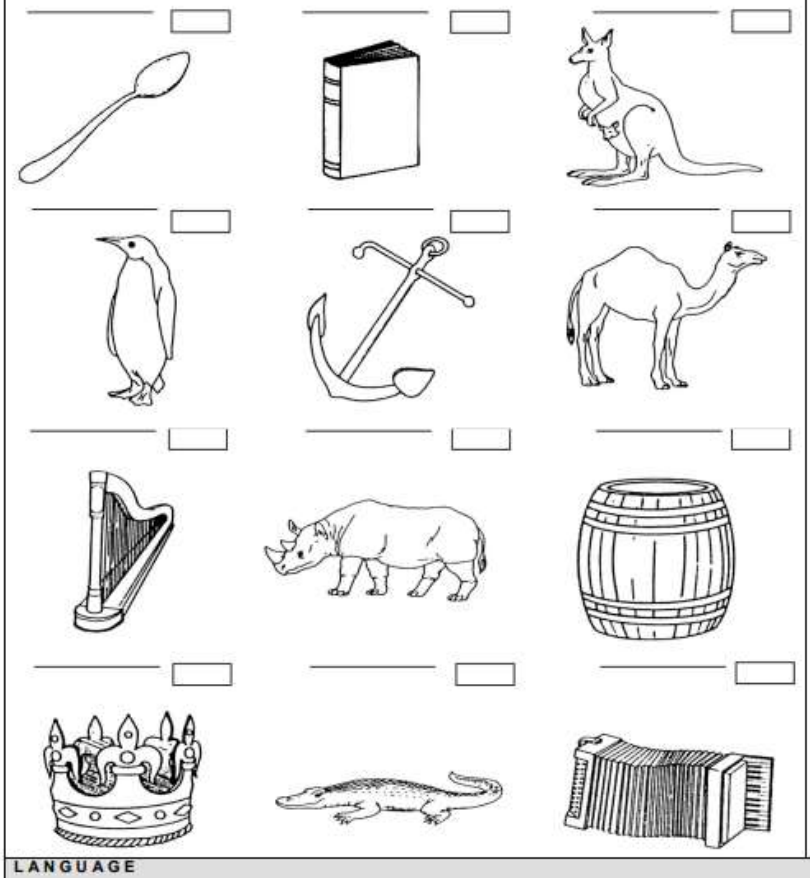
A

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

B

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

Figure 2. 13. **The Language task and overall scoring for the ACE-III.**

(A) The language section of the ACE III. Some questions may be overly affected by levels of education. Thus, knowing that a kangaroo is a marsupial may correlate more with educational levels than avoidance of cognitive ageing. **(B)** Each domain included in the ACE-III and the amount of points awarded to each.

Source: http://dementia.ie/images/uploads/site-images/ACE-III_Administration_(UK).pdf

Chapter 3: Meta-analysis of Neuropsychological tests and Cerebrospinal Fluid (CSF) tests.

Table 3. 1.

The neuropsychological tests used within each of the separate studies in this thesis.

Neuropsychological Test	Meta-analysis (Chapter 3)	Healthy control testing (Chapter 4)	Clinical MCI study (Chapter 5)	Designed to test
Mini Multi-State Examination (MMSE)	✓	✗	✗	**Multi-domain cognition.**
Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG)	✓	✗	✗	**Multi-domain cognition.**
Free and Cued Selective Reminding Test (FCSRT)	✓	✗	✗	**Episodic memory.**
Rey Auditory Verbal Learning Test (RAVLT)	✓	✗	✓	**Verbal learning and memory.**
California Verbal Learning Test (CVLT)	✓	✗	✗	**Verbal learning and memory.**
Logical memory subtest of the Wechsler memory scale (Logical Memory)	✓	✗	✗	**Verbal and working memory.**
Trail Making Test B (TMT-B)	✓	✗	✓	**Visual attention and task-switching.**
Rey–Osterrieth complex figure (ROCF)	✓	✗	✗	**Impairments in visuospatial construction.**
Four Mountains Test (4MT)	✗	✓	✓	Allocentric spatial working memory.
Spaces and Sequence Episodic Video Task (SSEVT)	✗	✓	✓	Episodic memory.
Buschke Selective Reminding Test (SRT)	✗	✗	✓	Verbal learning and memory.
Spatial Ability and Practices Questionnaire (SAPQ)	✗	✓	✓	Spatial working memory.
Social Networks and Embeddedness Questionnaire (SNSEQ)	✗	✓	✓	Size and complexity of social networks.
Addenbrooke's Cognitive Assessment- III (ACE-III)	✗	✓	✓	Multi-domain Cognition

The table above illustrates all neuropsychological tests included in the thesis, which portion of the thesis they are used within and which functions they aim to test. The ticks in green represent an included test within the chapter at the top of the table whereas the crosses represent tests that were not included in that particular chapter. The tests included in the Meta-analysis are highlighted in **bold.**

3.1: Meta-analysis: overview and rationale

As outlined in Chapter 1, Section 1.1.1, Alzheimer's disease will continue to impose a high health economic impact upon society, and there is an urgent need for high-performing predictive diagnoses of AD, in order to more effectively target therapeutic interventions such as pharmaceutical agents, exercise and lifestyle changes (e.g. Sloane et al, 2002; Hebert et al, 2003; Laske et al, 2015). Since giving therapy to an entire aged population is infeasible, it is important to identify the individuals most at risk and focus resources upon those individuals. Secondly, for treatment to be propitious, it is crucial that these therapeutic interventions occur sufficiently early in the disease timeline, since most currently envisaged treatments are unable to actually reverse the disease process (e.g. Laske, 2014; Laske et al, 2015). Together, these considerations make it vital to establish which tests provide the best predictive diagnoses of Alzheimer's disease.

Whilst Chapters 4 and 5 focus upon new and recently developed tests, it is also important to assess the efficacy of neuropsychological tests and biological tools that are currently used within clinical practice and AD research. The tests included in each section of the thesis is included in table 3.1. One clear way to do this is by assessing the ability to detect conversion from MCI to AD, i.e. the ability to predict a future diagnosis of AD.

3.1.1: Meta-analyses as a way to assess predictive diagnostics.

A common approach to assay predictive diagnostics for Alzheimer's disease is to conduct longitudinal studies examining which tests/biomarkers best predict which patients with Mild Cognitive Impairment (MCI; Petersen et al, 1999) do or do not subsequently 'convert' to

Alzheimer's disease (AD). Cross-sectional studies are useful in developing diagnostics but have the limitation that they do not mimic the conditions of a predictive diagnostic test. Here, I selected neuropsychological tests for evaluation because the best neuropsychological tests are among the best candidates for testing and potentially screening on national scales, due to resource and cost considerations (e.g. Laske et al, 2015). Accordingly, I conducted meta-analysis of those conversion studies employing neuropsychological tests, in order to estimate the effect size (Hedge's g) of the converters-vs-nonconverters discrimination produced by different neuropsychological tests.

This kind of meta-analysis is also helpful for benchmarking reasons because Alzheimer diagnostics are of course not static but develop. A meta-analytic based quantitative understanding of what the 'best-in-class' diagnostic tests can achieve, currently, provides valuable benchmarking to guide development of the diagnostic tests of the future. To give just one line of reasoning, the neuropsychological tests that are useful for diagnosing Alzheimer's disease are generally memory tests for verbal lists (Chapter 1, Section 1.6.1). However, it may turn out that testing in other domains offers advantages over verbal material. These advantages could potentially include being more easily standardised across different countries/languages, being quicker-to-administer, or being more amenable to repeat testing and thus longitudinal assessment. For instance, to re-iterate points made in the Introduction, because the hippocampal formation degenerates early in Alzheimer's disease (e.g. Braak and Braak, 1991; 1993; Gomez-Isla et al, 1996; Scheltens, 1992), and the hippocampal formation supports allocentric (i.e. viewpoint-independent) spatial memory, as previously described in Chapter 1, Section 1.8.2 (Muller et al, 1994; King et al, 2002; Hartley et al, 2007; Lever et al, 2009; Hartley et al, 2014; Poulter et al, 2018), allocentric spatial memory tests may help diagnose Alzheimer's disease (Coughlan et al, 2018). Indeed spatial

memory tests such as the Four Mountains test (Hartley et al, 2007), which has been used within the present project (Chapters 4 and 5), Sea Hero Quest (Coughlan et al, 2018), virtual water maze (Nedelska et al, 2012; Possin et al, 2016) and others (e.g. Pengas et al 2010) show promise for detecting Alzheimer's disease, including in its earlier stages (Bird et al, 2010; Pengas et al 2010; Moodley et al, 2015; Wood et al, 2016; Coughlan et al, 2018). Clearly, however, to have widespread potential for Alzheimer diagnostics, these spatial memory tests need to be at least as accurate as existing diagnostic tests. This begs the question, just how accurate are existing diagnostic tests? What, precisely, are the standards that future tests must equal or better? The need to answer this comparative question is a major motivation for the present study/chapter.

Meta-analyses often become analyses of very few high-quality studies, due to the stringent exclusion criteria that is usually applied. This approach dominates the meta-analysis literature. My overall approach to the meta-analysis was to be inclusive, under the idea that a larger sample is an interesting alternative approach to estimating diagnostic accuracy as practiced rather than a relative paucity of high-quality samples. Each approach answers different questions, and in my view, both have strengths and limitations. Accordingly, I did not apply quality-of-study thresholds, though I did eliminate studies with duplicated samples. Similarly, most analytical criteria were not identified *a priori*, as often occurs in meta-analysis studies (see Section 3.2 below). This was not possible, since the overall aim was to establish which are the better predictive tests, i.e. an open question, and not, what are the results of tests X and Y, i.e. a closed question.

Publication dates for studies were required to be on or before 31st December 2016 for studies involving neuropsychological tests. Searching of CSF literature was conducted in

order to have comparators for neuropsychological tests (Section 3.1.2 below), and thus proceeded after the neuropsychological test searching. Accordingly, the end date for the period of publication of these studies was later, i.e. approximately a year after the final date for the neuropsychological tests. Publication dates for studies of CSF (and their within-study accompanying MMSE data) were required to be on or before 31st January 2018. Details of all included tests can be found in Chapter 2.

3.1.2: Neuropsychological tests vs CSF biomarkers

A second comparative question expands the terms of comparison. 'How good are the best-performing neuropsychological tests not just relative to other neuropsychological tests but relative to other kinds of tests and markers including neurobiological markers?' This is a question with many implications including for national health economics. In which domains (e.g. neuroimaging, molecular, neuropsychological) should a country's Alzheimer's-related medical resources and research funding be focused? This important question embraces many diagnostic domains. For instance, structural MRI-based volummetrics of hippocampal formation (Chapter 1, Section 1.6.3) including the hippocampus and entorhinal cortex (e.g. Dickerson et al, 2001; Devenand, 2007; Du et al, 2004; Ewers et al, 2012), PET-imaging (Chapter 1, Section 1.6.3.) of beta-amyloid load (Villemagne, 2011), FDG-PET (e.g Yuan et al, 2009; Prestia et al 2015), SPECT e.g. Yuan et al, 2009;), (Chapter 1, Section 1.6.3), genetics (Denk et al, 2015) brain-specific proteins in blood (Olsson et al, 2016; Blennow 2017) and cerebrospinal fluid markers of tau and beta-amyloid (e.g. Blennow & Hampel, 2003; Diniz et al, 2008; Ritchie et al, 2017), (Chapter 1, Section 1.6.2), have all been considered for use as

predictive diagnostics. Accordingly, definitively answering this wide-ranging question is not trivial. Certainly, a comprehensive, up-to-date comparative analysis of all these biomarkers was well beyond the resources and scope of the present study. Here, as a first-pass addressing of this question, I evaluated the ability of cerebrospinal fluid markers, often considered a gold-standard in Alzheimer's diagnostics (e.g. Diniz et al, 2008; Alberts et al, 2011; Sperling et al, 2011; Dubois et al, 2007; 2014; Herruka et al, 2016; Jack et al, 2018), to predict conversion from MCI to Alzheimer's disease.

As we shall see, interestingly, perhaps surprisingly, albeit with some caveats, this chapter suggests that cerebrospinal fluid markers are not superior to the best neuropsychological tests at predicting conversion from MCI to Alzheimer's disease as typically clinically assessed. Accordingly, the best neuropsychological tests may have particular utility for Alzheimer's diagnostics for reasons extending beyond cost and convenience.

3.2: General Methods

The overall approach was to sample across a wide range of neuropsychological tests and three CSF tests. A systematic review is typically performed on one or a small selection of *a-priori*-selected tests. Such systematic reviews are invaluable, but typically offer limited across-test and across-domain comparability, and given the continuing pace of Alzheimer's related research, they date quickly. My approach was purposely not *a priori*, but allowed for the idea that certain tests would emerge from searches as usefully diagnostic of conversion to Alzheimer's type dementia, and that I should focus my analysis upon those tests.

Importantly, such an approach enabled the kind of insights that can emerge from a large, wide-ranging survey, but carried the limitation that I was not able to conduct systematic review, with all the methodological conventions that term implies, to each of the individual tests. Applying the methods of a systematic review to around 30 tests/assays relevant to Alzheimer's diagnosis would have been far beyond the scope and resources of a PhD project.

3.2.1: Strategy and procedure of search and analysis

In order to survey and then analyse the ability of neuropsychological tests to predict conversion from MCI to AD, a two-phase system was used. As there are a large amount of existing neuropsychological tests which aim to assess AD, it was first important to identify candidate **tests** to consider further. This general survey phase is referred to as **Phase 1.** This phase identified 23 candidate neuropsychological tests that were used in studies predicting conversion from MCI to AD.

Phase 2 involved narrowing down the 23 candidate neuropsychological tests to a smaller number of tests that appeared to reliably predict conversion, and then ensuring search was comprehensive and studies were appropriate. This was done according to a set of criteria that were not established *a priori*, but which reflected the better tests in the initial survey phase. This resulted in 11 tests. These criteria were that tests needed to have been used in at least four studies, involve at least 300 patients, and show promising effects which we operationalised as showing a minimum effect size of Hedges' g = 0.40 from preliminary searches. Details of tests excluded are given in further detail below. I then conducted more extensive searches and examined studies carefully to exclude inappropriate studies. This then

led to a database to be analysed of 55 studies and 11 neuropsychological tests. Further details are provided below.

3.3: Phase 1: The identification of Neuropsychological tests.

Searches for neuropsychological tests were performed via the three main search engines: Google Scholar, ISI Web of Knowledge and PubMed. The following terms were used separately and together: Mild Cognitive Impairment, Conversion to dementia, Progression to dementia, Conversion to Alzheimer's disease, Progression to Alzheimer's disease, Neuropsychology, Neuropsychological test. Through conversations with Clinical Psychologists we also specifically searched for tests we knew were commonly used clinically or in a research setting such as the RAVLT, CVLT, MMSE, ACE-III, ADAS-COG and CANTAB-PAL.

Altogether, 23 candidate neuropsychological tests and sub-tests emerged from the phase one searches. (References and descriptions of many of these tests have been provided in the previous chapter). In alphabetical order, these were: Addenbrooke's Cognitive Evaluation III (ACE-III); Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG); Boston naming test; Cambridge Neuropsychological Test Automated Battery- Paired Associates Learning (CANTAB-PAL); Cambridge Cognition Examination (CAM-COG); CLOCK DRAWING TEST; Hopkins Verbal Learning Test; California Verbal Learning Test: Short Delay Free Recall (CVLT:SDFR); California Verbal Learning Test II (Second edition); California Verbal Learning Test: Long Delay Free Recall (CVLT: LDFR); Digit Span; Free and Cued Selective Reminding Test: Total Recall (FCSRT:TR), (i.e. including both free and cued recall); Logical Memory Immediate Recall (LM:IR); Logical Memory Delayed Recall (LM:DR); Mini Multi-State Examination

(MMSE); Montreal Cognitive Assessment (MOCA); The New York University Paragraph Recall Test (NYU Paragraph); The Rey Auditory Verbal Learning Test: Delayed Recall (RAVLT:DR); The Rey Auditory Verbal Learning Test: Immediate Recall (RAVLT: IR); Rey–Osterrieth Complex Figure: Immediate Recall (ROCF:IR); Rey–Osterrieth Complex Figure: Delayed Recall (ROCF:DR); Buschke Selective Reminding Test (SRT); Trail Making Test-B (TMT-B).

3.3.1: Phase 2: 23 Candidate tests identified: 11 tests remained, 12 were excluded.

Eleven neuropsychological tests were excluded from final tabulation and analysis for two reasons, as shown in figure 3.1. One, the following seven tests did not satisfy the 'four studies minimum' criterion: Addenbrooke's Cognitive Evaluation III (ACE-III); Cambridge Cognition Examination (CAM-COG); Cambridge Neuropsychological Test Automated Battery- Paired Associates Learning (CANTAB-PAL); Montreal Cognitive Assessment (MOCA); The New York University Paragraph Recall Test (NYU Paragraph); Hopkins Verbal Learning Test; Selective Reminding Test (SRT, not to be confused with the FCSRT, which is included).

Two, initial exploratory analyses of the following five tests (which are not generally considered classic tests for specific diagnosis of Alzheimer's disease) suggested that these tests produced too small an effect size (Hedge's $g < 0.4$) to be worth more detailed examination (in alphabetical order): Boston naming; Clock drawing; Digit Span; Stroop; Rey-Osterrieth Complex Figure Copy (note that two subtests of ROCF, the Immediate Recall and Delayed Recall tests are both included in the meta-analysis).

Considering subtests separately, there were 12 neuropsychological tests included for final tabulation and analysis, as follows: Alzheimer's Disease Assessment Scale-cognitive subscale

(ADAS-COG); The Free and Cued Selective Reminding Test (FCSRT); California Verbal Learning Test Free Recall at Short Delay (CVLT:SDFR); CVLT Free Recall at Long Delay (CVLT:LDFR); Logical Memory Immediate Recall (LM:IR); Logical Memory Delayed Recall (LM:DR); The mini-multi-state examination (MMSE); RAVLT Delayed Recall; RAVLT Immediate Recall; Rey-Osterrieth Complex Figure: Immediate Recall (ROCF: IR); Rey-Osterrieth Complex Figure: Delayed Recall (ROCF:DR); Trail making test B (TMT-B).

3.3.2: Subtests and test variants.

Where a test (e.g. RAVLT, CVLT) had *subtests*, I only selected the best-performing one or two subtests for analysis, and analysed subtests separately: for instance data from CVLT Free Recall *at Short Delay* were analysed independently from CVLT Free Recall *at Long Delay*. Any subtests and tests were excluded that did not meet the following criteria:

a) ≥300 participants over all included studies which included the test;
b) Used in at least 4 studies
c) Showing a mean Hedge's g of ≥0.4.

Where different *variants* of the same test or subtest were considered only minor these were analysed together; thus the CVLT and CVLT2 were analysed together (Delis, Kramer, Kaplan, & Ober, 1987; Delis, Kramer, Kaplan, & Ober, 2000).

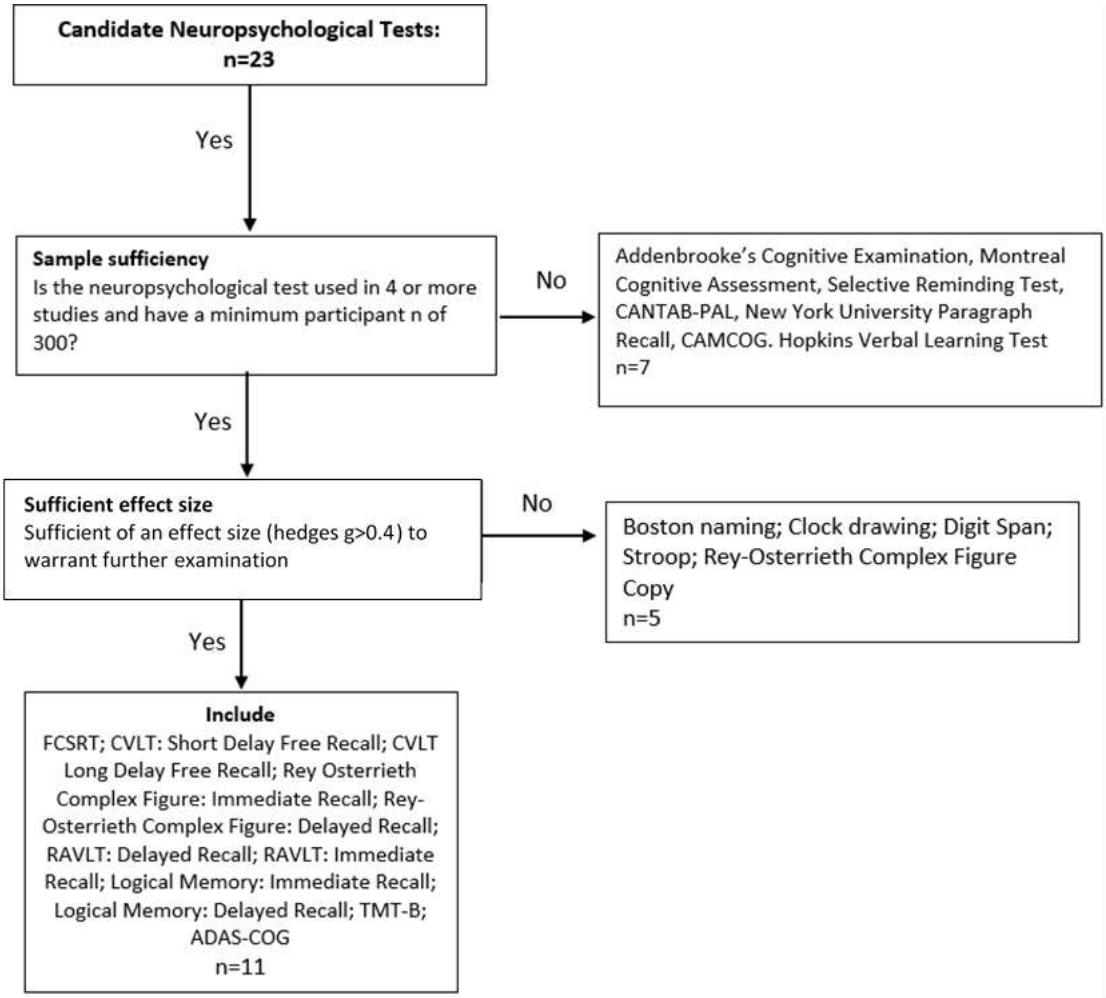


***Figure 3.1*. Phase 2: Neuropsychological test inclusion/exclusion flowchart.**

Flowchart outlining the inclusion/exclusion process for the neuropsychological tests included in the meta-analysis. Note: Due to the wide administration of the MMSE only a sub-set of the MMSE studies were analysed and we were therefore able to take advantage of within-study comparisons. This brings the total amount of studies up to 12 from the calculated 11 shown above.

3.4: Phase 2: Candidate Study search strategy and identification.

After phase 1, I attempted exhaustive inspection in phase 2 of the available records of a given test by the following means. The inspection of a set of records for a given set of search terms (described below) was first performed in Google Scholar, and was terminated when at least 50 consecutive records were consulted that did not yield a single paper obeying the parameters of the inclusion and exclusion criteria, which is outlined below. Inspection of records then continued along the same lines with the same test using a different set of search terms. Finally, when all search terms had been applied to a given test, the overall search for that test was terminated. Search terms included: 1) the full and abbreviated name of a test, and related terms (e.g. Trail making test, TMTB, TMT-B); 2) conversion, progression, and related terms; 3) mild cognitive impairment, and related abbreviations (e.g. MCI, aMCI); 4) Alzheimer's disease. This was then supplemented by further inspection of articles: a) found from searching on ISI Web of Knowledge and PubMed; b) referenced by candidate studies from all other searches. After the initial search, 124 studies which used the 11 included neuropsychological tests emerged as potential candidates for inclusion.

3.4.1: Phase 2: 86 candidate studies identified, 55 remained, 31 were excluded.

My approach towards study inclusion/exclusion was based upon the following criteria;

a) studies must be longitudinal, not cross-sectional;

b) studies must have an MCI patient sample at the initial timepoint, who are then followed up to evaluate their conversion status (i.e. to AD or stable);

c) at least 75% of the dementia in a given study must be of the Alzheimer's disease type;

d) included studies must compare the test performance of MCI participants who did convert to AD at follow-up with those that did not;

e) the raw data and standard deviation must be given (figure 3.2).

f) I excluded overlapping samples (see next section).

g) I excluded studies where a given single test was evaluated as part of a composite score.

Exclusion criteria c above states that at least 75% of the dementia in a given study had to be of the Alzheimer's disease type. It should be emphasised however that the number of participants who converted to non-AD forms of dementia was very much lower than 25%, with the most affected meta-analysis containing 5.5% of converters that did not convert to AD. The meta-analyses affected were Logical Memory: Delayed Recall, RAVLT: Immediate Recall, RAVLT: Delayed Recall, CVLT: Short Delay Free Recall, CVLT: Long Delay Free Recall. The only studies which contained non-AD converters were Alegret et al (2012), Mauri et al (2012), Quaranta et al (2016), Pozueta et al (2011) and Garcia-Herranz et al (2015). Table 3.2 shows the percentage of conversions that were to AD.

Table 3. 2

The percentage of participants who converted to AD within each test included in the meta-analysis.

Neuropsychological Test	Total Converters: Participant n	Non-AD Converters: Participant n	% AD conversion
TMT-B	1112	0	100%
ROCF: Immediate Recall	191	0	100%
ROCF: Delayed Recall	251	0	100%
Logical Memory: Immediate Recall	629	0	100%
Logical Memory: Delayed Recall	449	9	98%
RAVLT: Immediate Recall	212	10	95.3%
RAVLT: Delayed Recall	965	19	98%
CVLT: Short Delay Free Recall.	110	6	94.5%
CVLT: Long Delay Free Recall.	132	6	95.5%
FCSRT	110	0	100%
ADAS-COG	1141	0	100%
MMSE	2516	25	99%

Table outlining the total amount of participants who converted to dementia in each of the included meta-analyses, the number of participants who converted to other forms of dementia (Non-AD Converters) and the overall percentage of those who converted specifically to AD.

the same institutions/authors. Here, two rules were applied.

First, where there was a high overlap in the patient sample across two studies, I excluded the earlier of the two studies (e.g. excluding Gomar et al, 2011, while retaining Gomar et al, 2014, see Table of Exclusions (Figure 3.2 'High sample overlap: earlier study').

Second, where there was a high overlap in the patient sample within a single study using two follow-up periods, I excluded the data from the shorter follow up period (e.g. excluding the 1

year follow up dataset, while retaining the 3 year follow up dataset, e.g. Gaser et al, 2013, see Table of Exclusions (figure 3.2) 'High sample overlap: shorter follow-up').

All together 55 neuropsychological studies were included across 11 neuropsychological tests. 54 of which also included the MMSE and so were included within the constrained MMSE (described in detail below, Section 3.6.4).

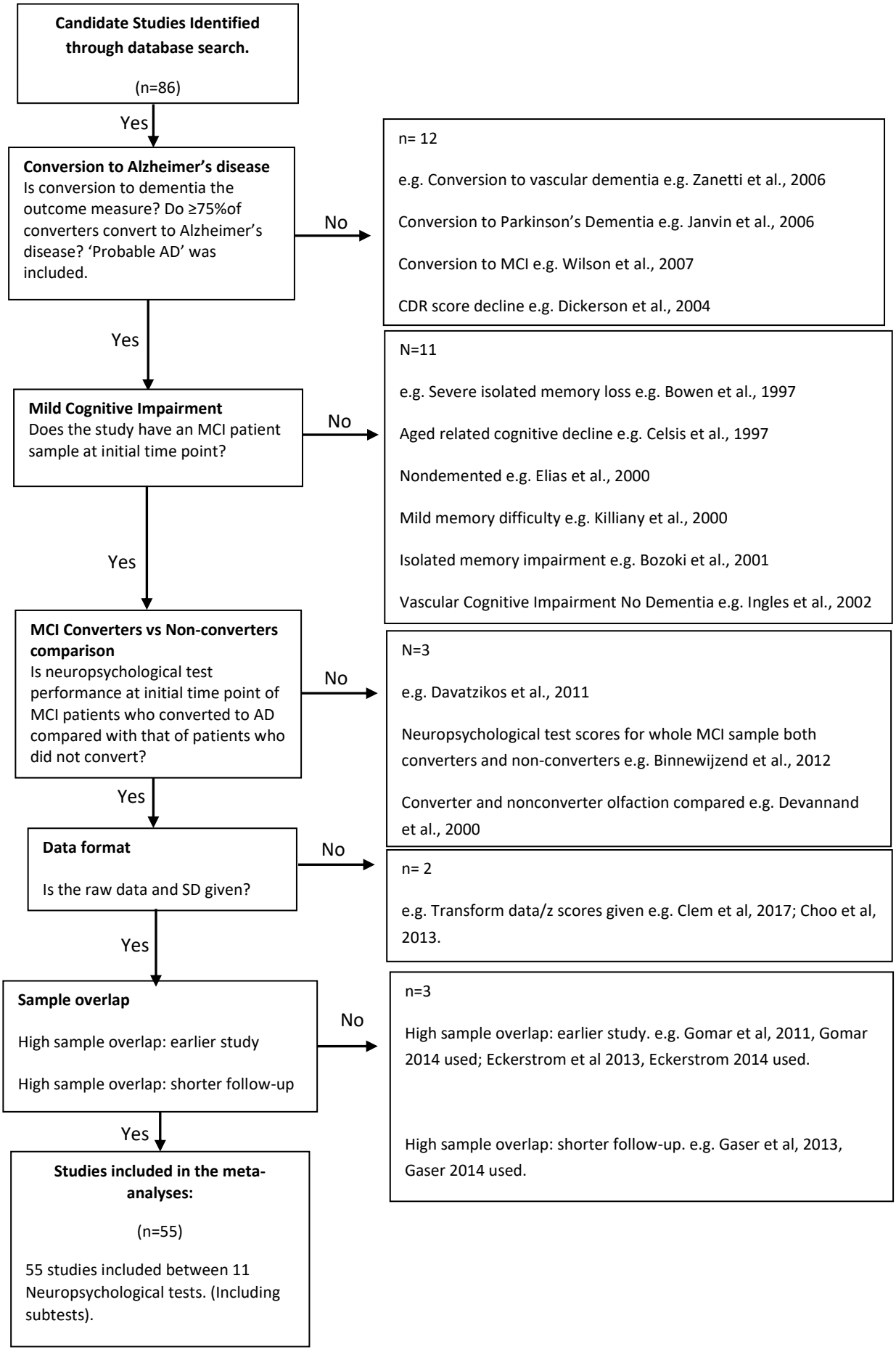


Figure 3. 2. **Phase 2: Flowchart to illustrate inclusion/exclusion procedure of studies included the 11 Neuropsychological tests (12 including MMSE).**

3.5: Statistical analysis.

3.5.1: Forest plots

Both forest and funnel plots were used in order to investigate the predictive ability of each of the tests. A forest plot is a graph which shows results in terms of effect sizes from different studies addressing the same question In this case that question was which neuropsychological tests or biomarkers best predicted conversion from MCI to AD. When a test/biomarker is good at predicting conversion then the difference between the converters and the non-converters, i.e. the effect size of the prediction, is large. I extracted from each study the values of the mean, the standard error of the mean the sample sizes of the two groups assessed in that given study: the converters and the non-converters. This permits calculation not only of the effect size for each individual study, but also of the weighted average effect size across all the studies. This weighted average effect size is represented by the diamond at the bottom of every forest plot shown within this meta-analysis.

Studies included in the forest plots in this thesis are presented in chronological order on the Y axis of each plot whereas the hedge's g between converters and non-converters is on the X axis. The centre of each square box indicates the effect size of the difference between the converters and the non-converters for a given individual study. The length of the blue horizontal line running through each square box indicates the magnitude of the confidence interval. The longer the lines, the wider the confidence interval and thus generally the less reliable the estimate of the effect size. The width of the diamond at the bottom of the plot also indicates the confidence interval, but of the weighted average mean.

The weight that the individual study contributes to the weighted average effect size is indicated via the area of the box. Studies with a larger sample size and smaller confidence intervals are shown via a larger size box as they contribute to the pooled effect size to a greater degree than smaller studies with larger confidence intervals.

Finally, forest plots are able to demonstrate to what extent effect size estimates from the different studies addressing the same question overlap with each other. Effect size estimates that do not overlap well are termed heterogeneous and considered less conclusive. If the results are suitably similar across the studies, the distribution of the effect sizes is said to be homogenous and is generally considered more conclusive. Heterogeneity is indicated via the I2, as is shown in table 3.3. Heterogeneity of less than 50% is thought to be low and suggests a greater degree of similarity between the study data whereas an I2 value above 50% indicates more dissimilarity.

3.5.2: Funnel plots

Funnel plots are used to assess the potential role of publication bias. Publication bias is more likely to be due to smaller-scale and negative trials not being published. Funnel plots graphically represent the standard error, and thus the size of sample in trials, against the effect sizes that they report. As sample sizes increase effect sizes are likely to converge around the true underlying effect size. If there is no publication bias it would be expected that there would be an even scattering of studies either side of this true underlying effect, creating a triangle shape. When visually examining a funnel plot for asymmetry we may typically identify asymmetry by noting a relatively fewer or even no studies on the lower corner of the left side of the funnel plot and a corresponding greater number of studies in the opposite corner. Such a pattern could suggest that smaller studies with unfavourable

results were not published. This is discussed in further detail below in relation to the specific tests included. There is no consensus on a metric for detection of publication bias based on funnel plots, and even if there were, any such metric would likely require much higher sample sizes than seen here.

Effect sizes indicate how much one group differs from another, in this case the difference in test scores between those diagnosed with MCI who converted to AD (converters) and those who did not (non-converters). There are several measures of effect size, including the commonly used Cohen's d, Hedge's g and Glass's delta. Hedge's g and Glass's delta are both measures used within this thesis. The measure of effect size used is dependent on the data. The unit of these effect sizes is standard deviations. Simply put, if Cohen's D or Hedges g has a value of say 1.5, then the means of the two groups differ by 1.5 standard deviations. Cohen's d (Cohen, 1988) has been shown to have a slight bias in small studies, for which it overestimates the effect (Hedges 1981). Cohen's d is determined by calculating the mean difference between two groups (M_1= mean scores of converters and M_2=mean scores of non-converters), in this case the mean difference in neuropsychological test scores between those who converted to AD and those who did not, and then dividing the result by the pooled standard deviation ($(M_1-M_2)/SD_{pooled}$). In order to compute the pooled SD from two groups, the difference between each value (scores achieved by participants in each group in individual studies) and it's group mean (mean score achieved by participants in the converters/ non-converters group) is calculated, those differences are then all squared, added together ($s1^2+ s2^2$), in this case all those who converted and those who did not, ($s1^2$=converters: the difference between each value, scores achieved by this group, and the group mean, squared. $S2^2$= non-converters: the difference between each value, scores achieved by this group, and the group mean, squared) and divided by the

number of degrees of freedom ($\sqrt{(s1^2 + s2^2) / 2}$). Hedge's g is similar to Cohen's d but is best suited to a sample size below 20, as is the case with many of the tests included below in the meta-analysis. Hedge's g is calculated much the same as Cohen's d in that it is calculated as the difference between the means of one group (converters) and another (non-converters) and is then divided by the pooled standard deviation ($g = M_1 - M_2)/SD_{pooled}$). However, unlike Cohen's *d*, Hedge's *g* then multiplies this result by a correction factor, correcting for the upward bias in small samples (under 50) seen in Cohen's *d*.

Medcalc 18.5 was used to derive the Hedge's g (of the effect size of the difference between scores of converters and non-converters) and associated confidence intervals, heterogeneity (I2) and the Forest and Funnel Plots. Medcalc was also used for the paired samples t-test used to compare the Hedge's g of CSF biomarkers and the MMSE in those studies where both these tests were used to predict conversion. I conducted the meta-analyses with the random-effects model rather than fixed-effects model because this is a more conservative approach and is necessary to appropriately take into account both between and within study variability. For instance demographic factors could vary across patient samples, and moreover heterogeneity was often observed across the studies within a meta-analytic table.

Average weighted estimates of effect size (Hedge's g) with 95% confidence intervals were calculated for each test/subtest, with a higher Hedge's g indicating better predictive ability of each neuropsychological test to predict conversion from MCI to AD. Forest and Funnel plots for the 12 neuropsychological tests were created and visually inspected, as shown above.

3.6: Results: Neuropsychological Tests

Eleven neuropsychological tests were selected for analysis along with the constrained MMSE. MMSE procedure differed from the rest of the included neuropsychological tests and is described below. Broadly speaking, selected tests can be categorised based upon the functions they aim to test.

3.6.1: Test of Executive Functioning and Speed of processing

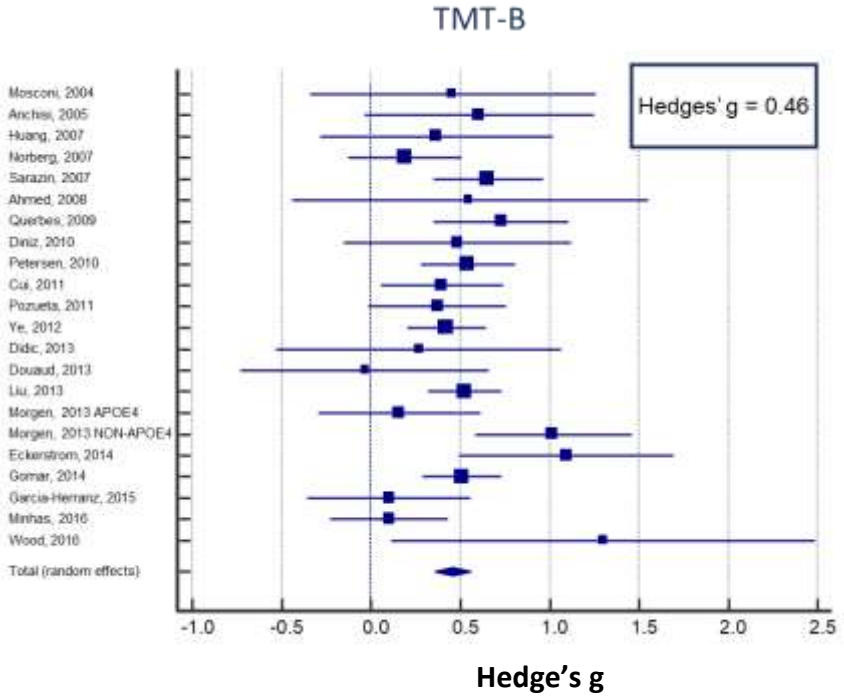
Executive functioning is an umbrella term which refers to a wide range of active cognitive processes, allowing adaptive, appropriate responses to environmental stimuli. More specifically, executive functioning includes verbal reasoning, multi-tasking, cognitive flexibility, resistance to interference and the ability to cope and adjust to novelty (Stuss & Benson, 1986; Shallice, 1988; Grafman & Litvan, 1999; Burgess et al, 2000). TMT-B is thought to be particularly sensitive to executive functioning as multiple abilities are required to complete it such as task-set inhibition, cognitive flexibility and the ability to maintain a response pattern (Abuthnott & Frank, 2000; Kortte, Horner & Windhan, 2002).

3.6.1.1: Trail Making Test B (TMT-B)

The Trail Making Test consists of part A and B. The consensus is that part B is a better test of cognitive decline in AD as it is more cognitively demanding (Arbuthnott & Frank, 2000; Karimpoor et al, 2017; Barbosa et al, 2017; Wei et al, 2018). Therefore, the majority of tests

which look at MCI to AD conversion specifically look at part B, which is included in the current meta-analysis. Scoring is determined by the number of seconds it takes to complete the test, an average score is 75 seconds, and a deficient score is greater than 273 seconds according to the TMT directions for administration. The TMT-B is explained in greater detail in Chapter 2, Section 2.8. Twenty-one papers were included within the TMT-B meta-analysis. When all studies were combined, a small effect size was found between MCI participants that did convert to AD and those who did not when TMT-B was. The Hedge's g (±95% confidence intervals) value for TMT-B was 0.46 (0.36- 0.57). The TMT-B produced the smallest effect size as compared to the other neuropsychological tests included in the current meta-analysis. The included studies can also be seen in the forest plot (Figure 3.3A). One of the inclusion criteria of the meta-analysis was that at least 75% of converters had to convert to AD in any given study. All of the participants that converted to dementia in the studies included in the TMT-B converted to Alzheimer's disease. The funnel plot shown in 3.3B looks broadly symmetrical suggesting no publication bias.

A



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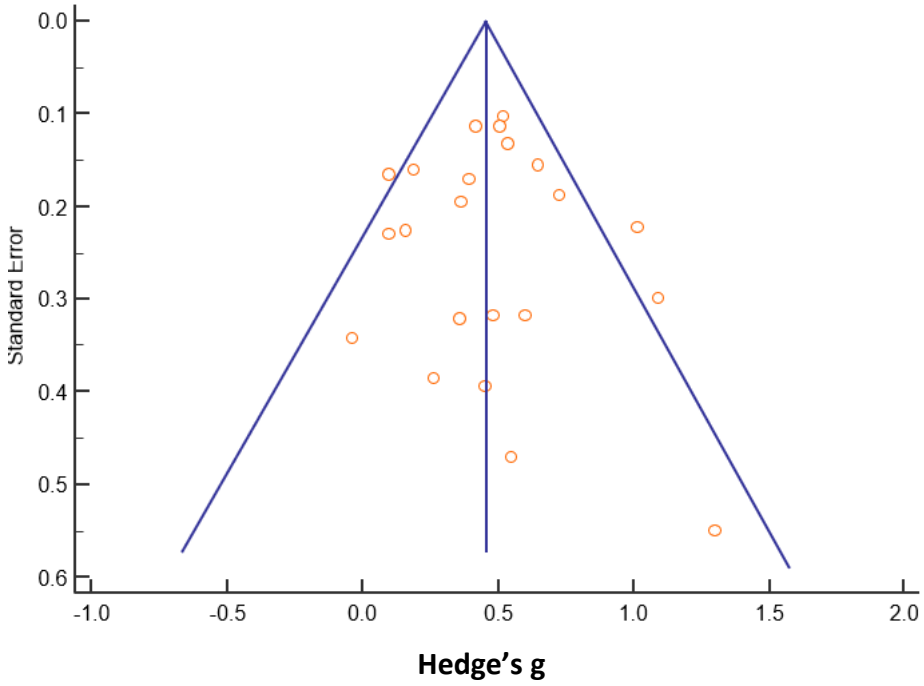


Figure 3. 3. **(A)** Forest Plot for the 21 studies included in the TMT-B meta-analysis. Studies included in all forest plots in this thesis are presented in chronological order on the Y axis of each plot. The hedge's g between converters and non-converters is on the X axis. The centre of each square box indicates the effect size of the difference between the converters and the non-converters for a given individual study. The length of the blue horizontal line running through each square box indicates the magnitude of the confidence interval. The longer the lines, the wider the confidence interval and thus generally the less reliable the estimate of the effect size. The width of the diamond at the bottom of the plot also indicates the confidence interval, but of the weighted average mean. The weight that the individual study contributes to the weighted average effect size is indicated via the area of the box. Studies with a larger sample size and smaller confidence intervals are shown via a larger size box as they contribute to the pooled effect size to a greater degree than smaller studies with larger confidence intervals. **(B)** Funnel plot for all studies included in the TMT-B meta-analysis. Funnel plots graphically represent the standard error, and thus the size of sample in trials, against the effect sizes that they report. As sample sizes increase effect sizes are likely to converge around the true underlying effect size. If there is no publication bias it would be expected that there would be an even scattering of studies either side of this true underlying effect, creating a triangle shape. When visually examining a funnel plot for asymmetry we may typically identify asymmetry by noting a relatively fewer or even no studies on the lower corner of the left side of the funnel plot and a corresponding greater number of studies in the opposite corner. Such a pattern could suggest that smaller studies with unfavourable results were not published. This is discussed in further detail within the methods text above.

3.6.2: Test of Spatial Ability.

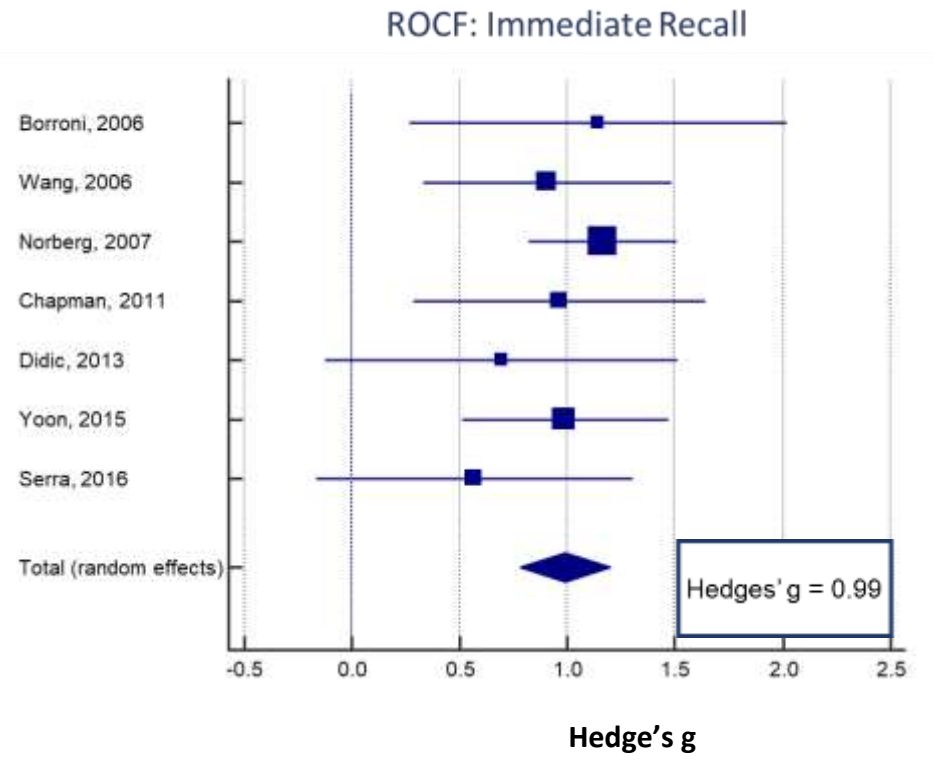
The importance of spatial navigation and its relationship with the hippocampus is discussed at length in Chapter 1, Section 1.8.2 and explored later in this thesis when assessing the Four Mountains task in Chapters 4 and 5. The Rey-Osterrieth Complex Figure (ROCF) requires visuospatial attention and ability in order to recreate the figure stimulus given (more details given below). The immediate and delayed recall conditions of the ROCF are associated with the functions of the hippocampus (la Torre et al, 2013), which degenerates early in AD.

3.6.2.1: Rey-Osterrieth Complex Figure: Immediate Recall

In the immediate recall condition of the ROCF, the participant is given the figure stimulus and asked to reproduce it after a 30-minute delay. The figure is then scored according to location, accuracy and organisation. Seven studies which included the ROCF: Immediate Recall test were included in the meta-analysis. The figure which participants are required to copy and further explanation of the ROCF is given in Chapter 2, Section 2.9. The forest plot showing the results of the included seven studies is figure 3.4A. The Hedges g (± 95% confidence intervals) value for ROCF:IR was 0.99 (0.79-1.20). In other words, Hedges g was essentially around unity. The results can thus be interpreted as follows. At the time of testing, MCI patients who subsequently received a diagnosis of AD (converters) performed about one standard deviation worse on this test than MCI patients who remained broadly stable (non-converters). As we shall see, a Hedges g value of 0.99 is somewhat above the average of the neuropsychological tests assessed in this meta-analysis and can be regarded as offering good performance.

Importantly, all of the participants within the studies included in the meta-analysis for Rey's Complex Figure: Immediate Recall who progressed to dementia converted to AD. No other kinds of dementia were included. Although there are relatively few studies in the dataset to comment on, the funnel plot shows no obvious signs of publication bias (Figure 3.4B).

A



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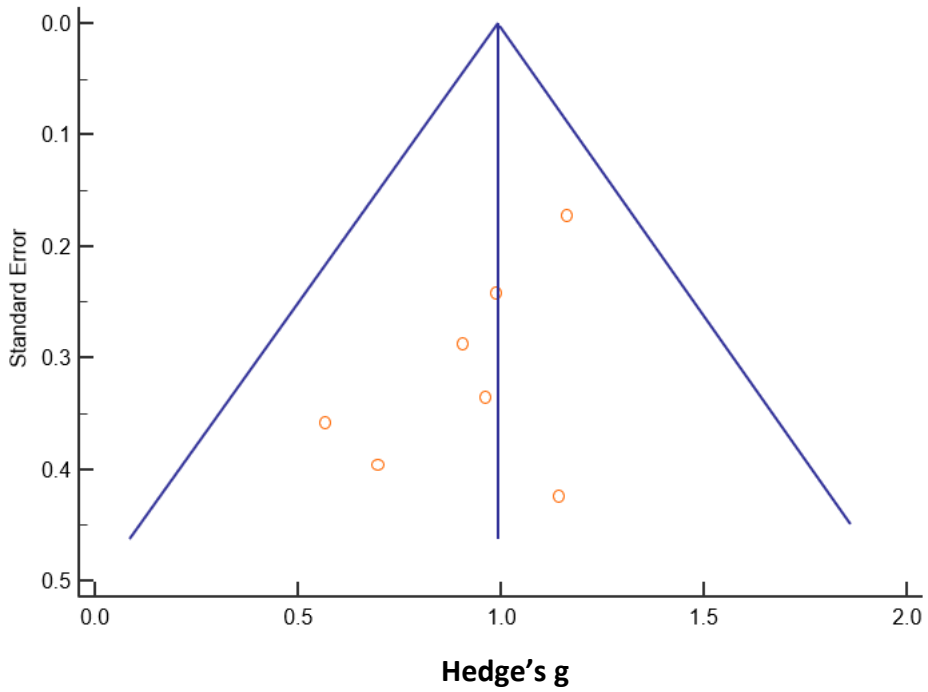

Figure 3. 4. **(A)** Forest Plot for the 7 studies included in the ROCF: Immediate Recall meta-analysis. **(B)** Funnel plot for all studies included in the ROCF: Immediate Recall meta-analysis.

3.6.2.2: Rey-Osterrieth Complex Figure: Delayed Recall

In the delayed recall condition of the ROCF, the participant is given the figure stimulus and asked to reproduce it after a 30-minute delay. The figure is then scored according to location, accuracy, and organisation. More details are included in Chapter 2, Section 2.9. Eleven studies were included within the meta-analysis. The forest plot showing the results from the included studies is shown in figure 3.5A. The Hedges g (± 95% confidence intervals) value for ROCF: DR was 0.67 (0.48-0.86). Interestingly, this Hedges g value was appreciably lower than that obtained for immediate recall on the same test.

Importantly, all participants who converted from MCI within the eleven studies included in the meta-analysis progressed to AD specifically and no other kinds of dementia. Although there are relatively few studies in the dataset to comment on, the funnel plot below (figure 3.5B) is potentially consistent with publication bias. That is, there is some sign of fewer studies on the bottom left of the plot, where one might to expect to see a couple more higher-standard error, low-effect size studies.

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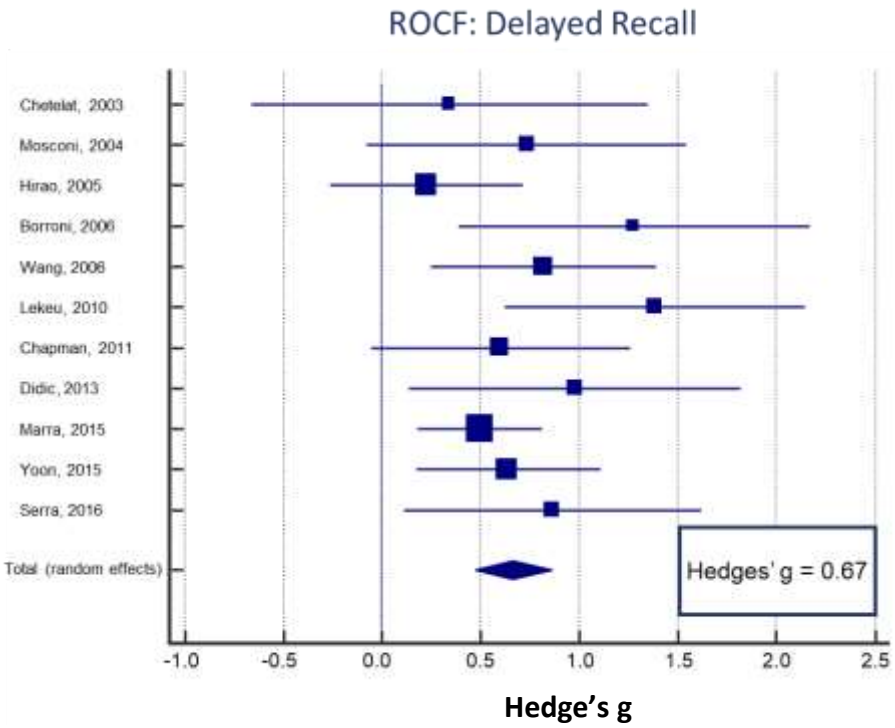

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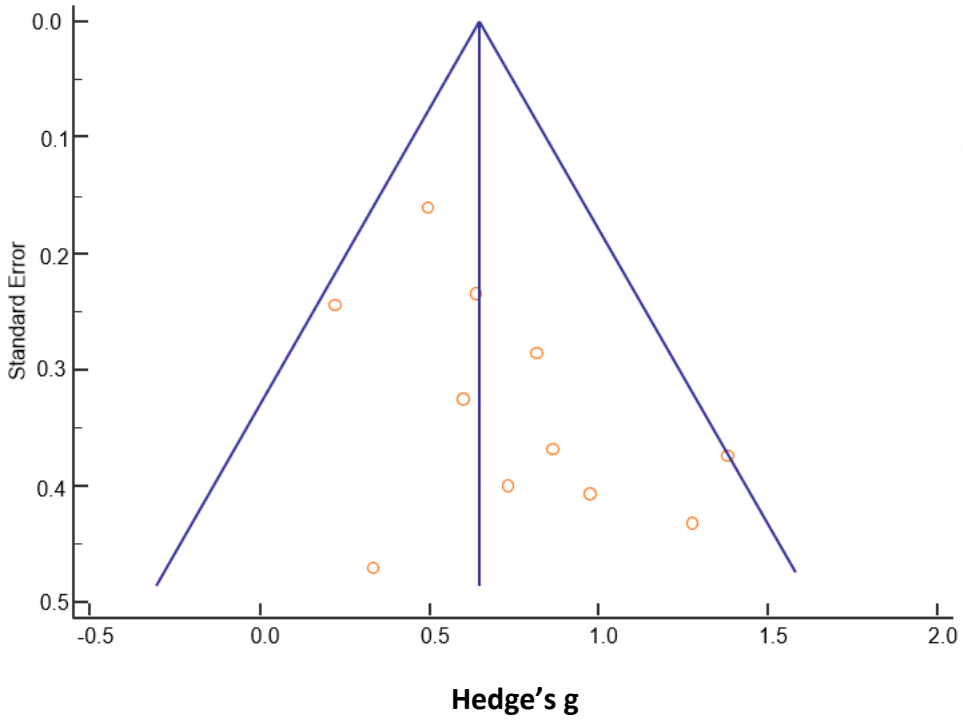


***Figure 3. 5*. (A**) Forest Plot for the 11 studies included in the ROCF: Delayed Recall meta-analysis. **(B)** Funnel plot for all studies included in the ROCF: Delayed Recall meta-analysis.

3.6.3: Verbal Memory tests

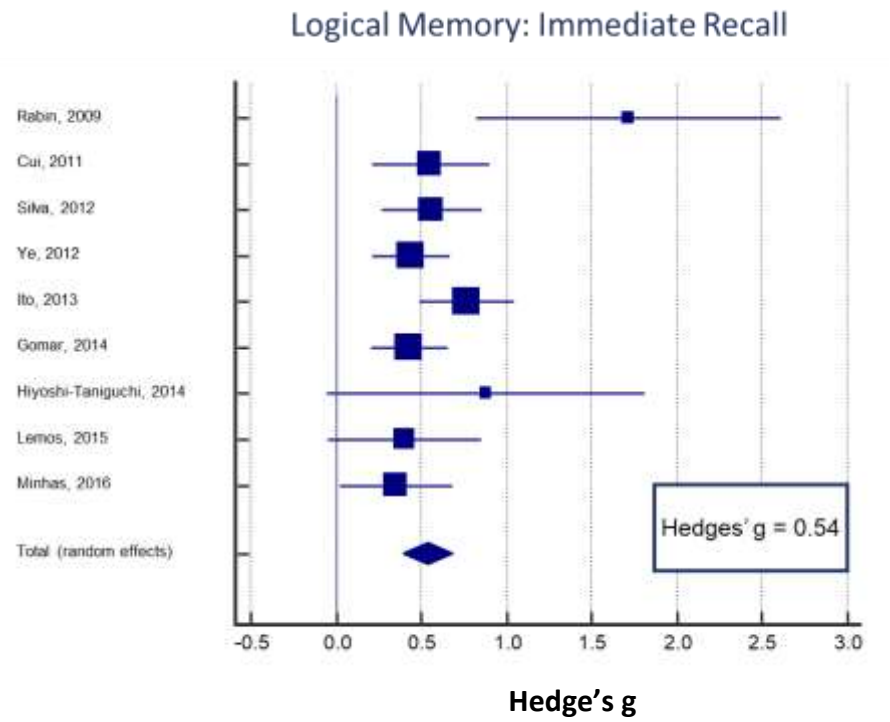
Verbal memory tests typically involve learning a story or list of words before recalling the information after a period of time. Episodic memory deficits are associated with impairment when encoding contextual information and consolidating new verbal material (Belleville et a', 2013; Wang & Zhou, 2002). Therefore, it is often suggested that a lower score on tests of episodic verbal memory, such as the list-learning verbal memory tests within the meta-analyses below, may indicate future decline to AD (Almkvist et al, 1998; Blacker et al, 2007; Rabin et al, 2009). This is unsurprising given that episodic memory is hippocampal-dependent, an area of the brain known to degenerate at the early stages of AD pathology as discussed in Chapter 1, Section 1.8.1.

3.6.3.1: Logical Memory: Immediate Recall

Logical Memory is a subtest from the Wechler Memory Scale IV, which comprises part of the Auditory Memory Index. Within the immediate recall condition, participants are required to read a story and recall its contents immediately after its presentation. Logical memory: Immediate recall is scored between 0-25, with higher scores reflecting more details from the original story recalled. The Hedge's g (±95% confidence interval) value for Logical Memory: Immediate Recall was 0.54 (0.40-0.690). Nine studies were included within the meta-analysis, as can be shown below in figure (3.6A). In all 9 included studies all included participants converted to AD. Ito, 2013 did find that some participants converted to non-AD dementia but excluded them from the study as they were specifically looking for progression to AD. Although there are relatively few studies in the dataset to comment on,

the funnel plot does seem somewhat asymmetrical, with a comparative absence of data in the bottom left of the plot which may indicate publication bias. However, this may also be due to the small number of studies included, with only two studies on the right side of the plot (higher standard error, higher effect size).

A



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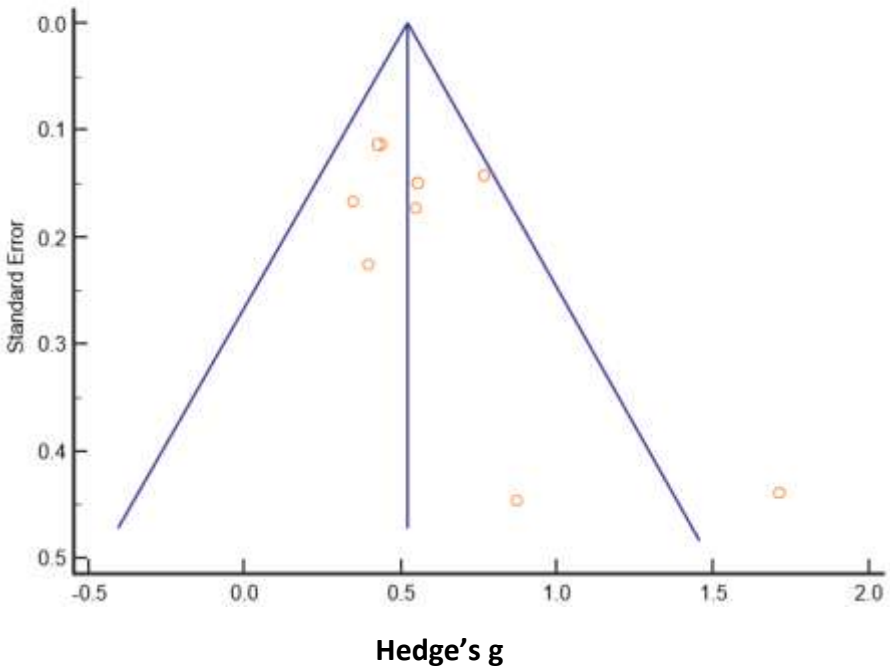


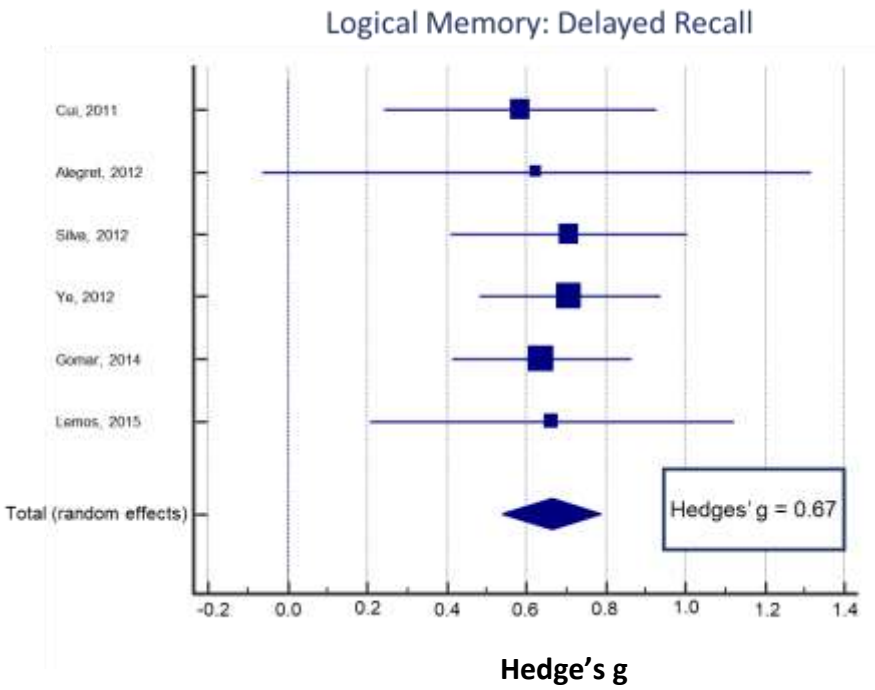
Figure 3. 6. (A) Forest Plot for the 6 studies included in the Logical Memory: Immediate Recall meta-analysis. **(B)** Funnel plot for all studies included in the Logical Memory: Immediate Recall meta-analysis.

3.6.3.2: Logical Memory: Delayed Recall

Within the delayed recall condition of Logical Memory, participants are required to read a story and then recall as many details as they are able after a 20-minute delay. As with the Immediate recall condition, scores range from 0-25 depending on the amount of detail recalled. Six studies were included within the current meta-analysis with a combined medium effect size. The Hedge's g (± 95% confidence intervals) value for Logical Memory: Delayed Recall was 0.67 (0.54-0.79), which whilst larger than Logical Memory: Immediate recall, was still relatively low compared to other included neuropsychological tests. The inclusion criteria states that studies must have at least 75% conversion to AD to be included. In Alegret, 2012, out of 58 participants who converted, 85% of participants converted to AD and 15% of participants converted to other kinds of dementia. The remaining five studies all stated 100% conversion to AD. Therefore, out of 449 participants who converted to dementia in this LM:DR meta-analysis as a whole, 440 converted to AD and 9 converted to other kinds of dementia (2% of all included participants who converted to dementia).

Fewer studies were included in Delayed Recall than in the Immediate recall meta-analysis. The Logical Memory delayed and immediate recall meta-analyses shared 5 studies; Cui, 2011; Silva, 2012; Ye, 2012; Gomar 2014 and Lemos, 2015, sharing 1177 participants. One study was included within Logical Memory: Delayed Recall that was not included in Logical Memory: Immediate Recall, Alegret, 2012 which had a relatively small sample size of 37 participants, leading to large confidence intervals as shown in the forest plot below (Figure 3.7A). Considering the very small amount of publications included, the funnel plot (figure 3.7B) does not seem to indicate publication bias.

A



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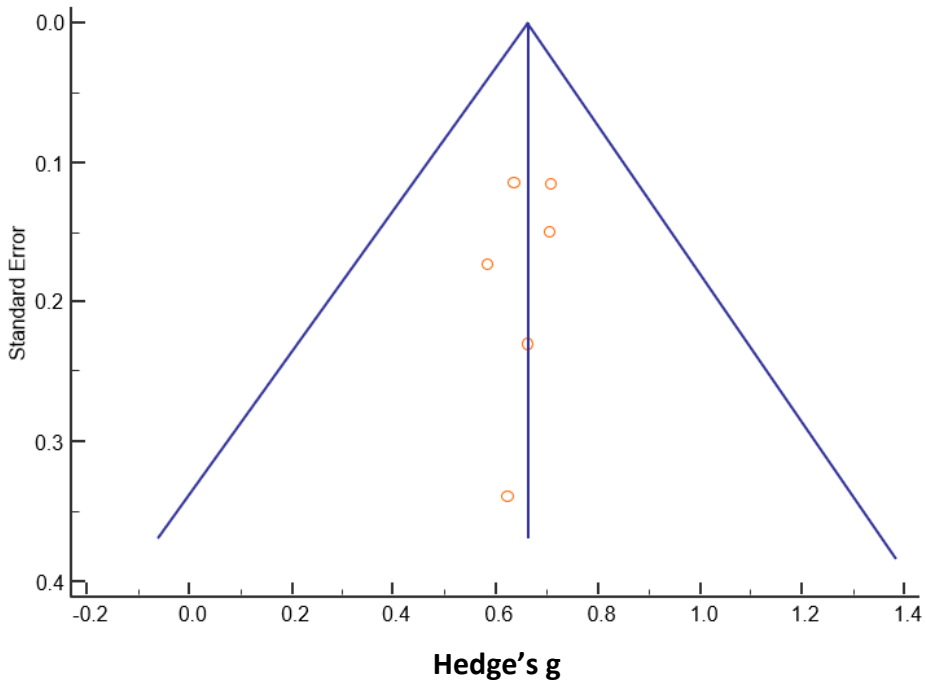
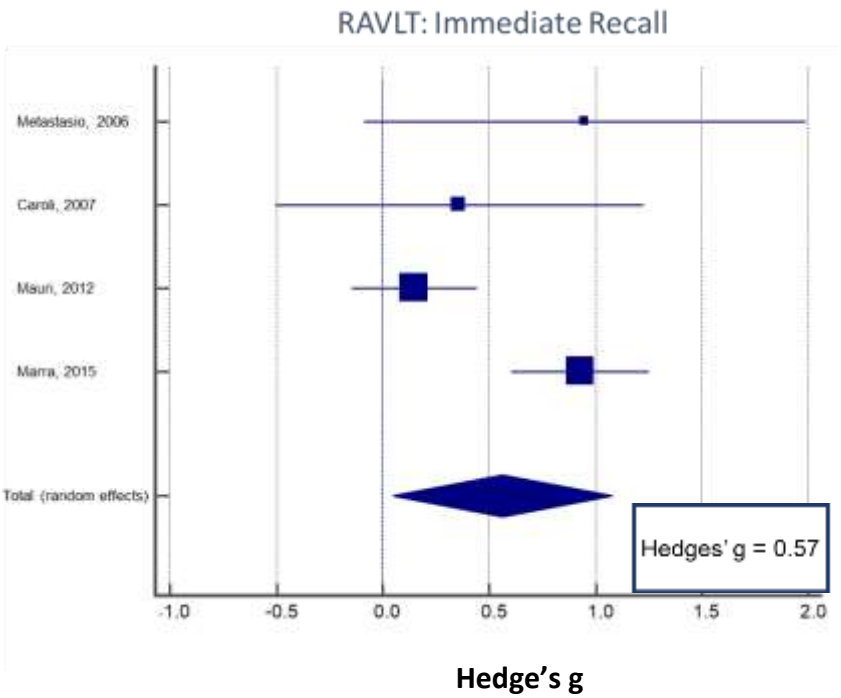


Figure 3.7. **(A)** Forest Plot for the 6 studies included in the Logical Memory: Delayed Recall meta-analysis. **(B)** Funnel plot for all studies included in the Logical Memory: Delayed Recall meta-analysis.

3.6.3.3: Rey's Auditory Verbal Learning Test: Immediate Recall

The RAVLT requires the participant to learn a list of fifteen unrelated words over five trials. The list of words are repeated five times and the Immediate recall score is generated by how many of the words the participant can recall immediately after the list has been read by the examiner. Four studies that included the RAVLT: Immediate recall were included within this meta-analysis. The Hedge's g (±95% confidence intervals) value for RAVLT: Immediate Recall was 0.57 (0.05-1.08), much lower than the RAVLT: Delayed Recall and the third lowest Hedge's g overall. The forest plot showing results from the included studies is shown in figure 3.4C. Immediate recall is scored out of seventy-five. All participants that converted from MCI to dementia included in Metastasio, 2006, Caroli, 2007 and Marra, 2015 were classified as converting to AD. However, whilst 93% of participants who converted in Mauri, 2012 converted to AD (133 participants), 7% progressed to 'degenerative/vascular' dementia. Therefore, of the 212 participants who are included as 'converters' with the RAVLT: Immediate Recall meta-analysis, 10 (4.72%) did not convert to AD. Whilst some included participants did progress to other kind of dementia, it is unlikely that this significantly affected the results of the meta-analysis. The inclusion criteria of 75% AD conversion allowed for a larger and more inclusive analysis, in the case of Mauri, 2012, another 133 AD participants. As the RAVLT: Immediate Recall only includes 4 studies the funnel plot must be treated with caution, however there is no clear indication of publication bias.

A



B

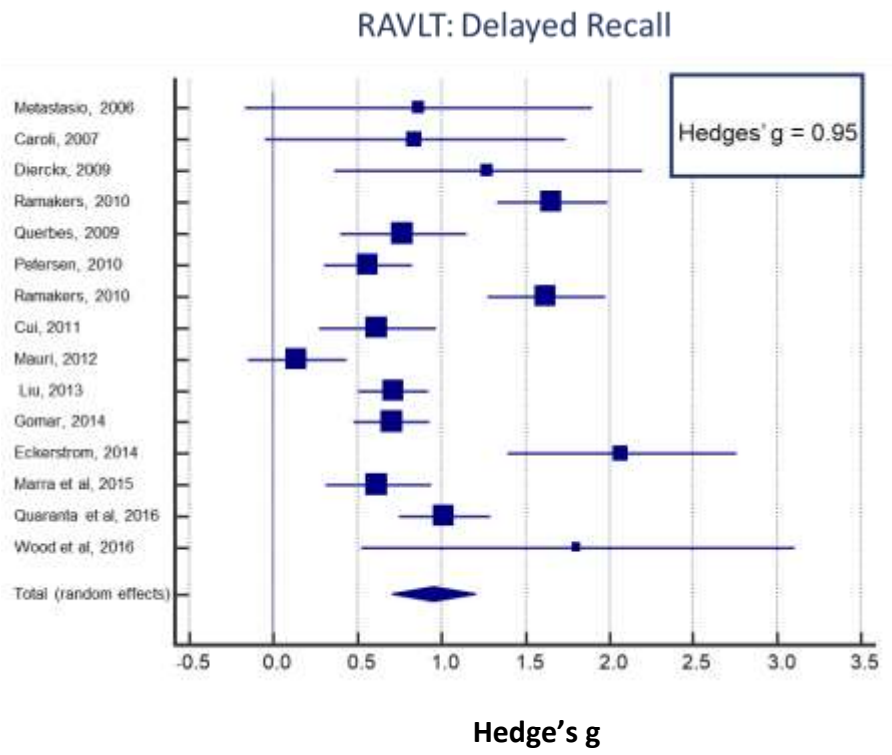
Figure 3. 8. **(A)** Forest Plot for the four studies included in the RAVLT: Immediate Recall meta-analysis. **(B)** Funnel plot for all studies included in the RAVLT: Immediate Recall meta-analysis.

3.6.3.4: Rey's Auditory Verbal Learning Test: Delayed Recall

Following immediate recall, a second list is read to act as an interference to the recall of the original list. After a delay of 30 minutes, the participant is asked to recall as many words as they can from the first list. Words can be recalled in any order and is scored by how many words they remember out of fifteen. Fifteen studies were included in the meta-analysis and the forest plot showing the results of the included studies is in Figure 3.9A, a large effect size was found. The Hedge's g (± 95% confidence intervals) value for RAVLT: Delayed Recall was 0.95 (0.71 to 1.20), placing it in the top 5 performing neuropsychological tests within the present meta-analysis. The Hedge's g was also much larger than that of the RAVLT: Immediate recall condition.

As part of the inclusion criteria, a study was included if 75% or more converters progressed specifically to AD. As discussed above, in Mauri et al (2012) 10 participants who converted to dementia did not convert to AD. Quaranta, 2016 consisted of 71 patients who converted to AD, 4 mixed dementia and 5 'non-AD type'. Eckerstrom, 2014 did find that 16 participants out of 34 progressed to other forms of dementia but the 18 participants that converted to AD were analysed separately, and only these results were included in the current analysis. Therefore, only 19 participants out of 965 who are included in the RAVLT: Delayed Recall meta-analysis as 'converters' converted to non-AD type dementia, 1.97%. There does appear to be some asymmetry within the funnel plot (figure 3.9B) with a comparative absence of studies from the bottom left of the plot which may suggest that there may be some publication bias.

A



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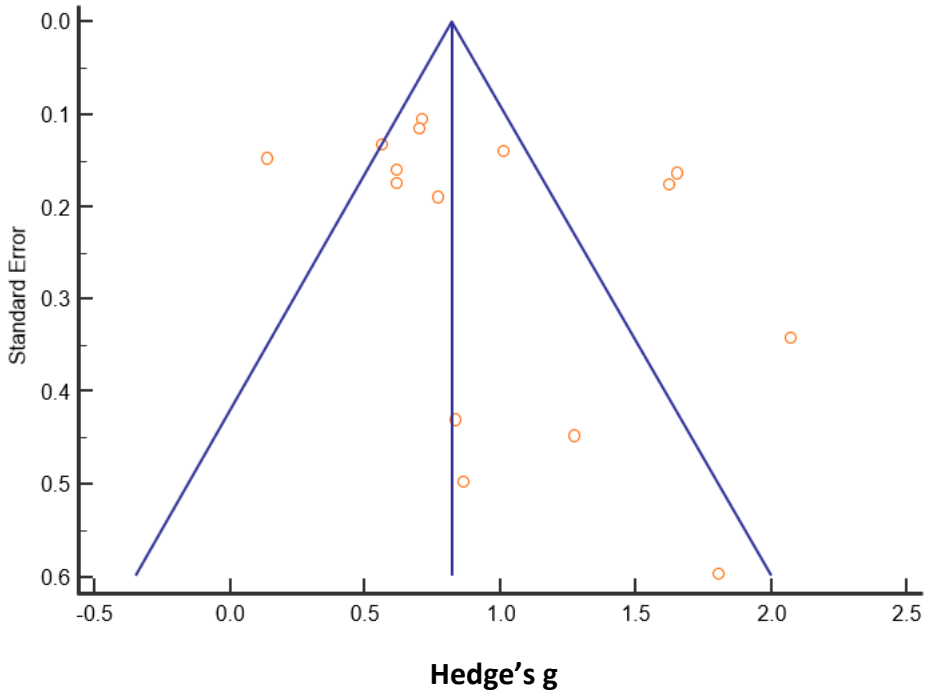

Figure 3. 9. **(A)** Forest Plot for 15 studies included in the RAVLT: Delayed Recall meta-analysis. **(B)** Funnel plot for all studies included in the RAVLT: Delayed Recall meta-analysis.

3.6.3.5: California Verbal Learning Test: Short Delay Free Recall

The CVLT and CVLT 2 claim to measure key functions such as repetition learning, serial position effects, episodic verbal learning, semantic organisation and proactive interference (Elwood, 1995). In many ways the CVLT is similar to the RAVLT in its general format in that it is a list-learning task. However, it has the added advantage of presenting words drawn from four semantic categories (tools, fruits, clothing, spices/ herbs). The examiner reads a list of 16 nouns aloud over 5 learning trials. After each trial, the subject is asked to recall as many words as they are able in any order. Following this, an interference list is presented (List B). List B shares two categories from list A (e.g. clothing and fruits) and two unshared categories. Free and cued recall of list A are tested immediately following List B (Short Delay Free Recall). CVLT 2 also includes Short Delay Free Recall and Long Delay Free Recall including the same delays and number of words. The words are not drawn from a 'shopping list' as with the original CVLT but from four unrelated semantic categories. Due to their similarity in scoring and utilisation in research both CVLT and CVLT 2 were analysed together within this meta-analysis. All studies except Rabin, 2009 tested using the original CVLT whereas Rabin, 2009 used the CVLT 2. Garcia-Herranz et al (2015) tested using the original CVLT described as the 'Spanish version'. The CVLT is described in more detail in Chapter 2, Section 2.6.

Altogether, 5 studies that had used the CVLT/ CVLT 2 were analysed within the meta-analysis. The Hedge's g (±95% confidence intervals) value for CVLT: Short Delay Free Recall was 1.20 (0.89-1.58), making it the second best performing included neuropsychological test, after the FCSRT.

One possible limitation of the current meta-analysis may be the inclusion of studies within which converters did not all convert to AD. The requirement was that at least 75% of converters converted to AD. This occasionally led to the inclusion of participants who did not convert to AD specifically, but to other forms of dementia (fronto-temporal, vascular etc) which may affect the extent to which the CVLT: Short Delay Free Recall is able to predict conversion to AD specifically. Looking at the included studies, Rabin et al (2009) found that all converters converted to 'probable AD'. Similarly, Lekeu et al (2010) found that all participants who converted to probable AD and Mielke et al, 2012 found that all participants who converted progressed to AD. However, Pozueta (2011) found that out of the individuals who converted to AD at follow-up, 50 progressed to AD whereas 4 converted to other forms of dementia. In the study by Garcia-Herranz (2015), out of 24 participants, 2 were classified as having mixed dementia, described as 'AD with vascular component' whilst 22 converted to AD. In summary, therefore, of the 110 converters included in the CVLT: Short Delay Free Recall meta-analysis, only 6 participants were not diagnosed with AD at follow-up (5.5%). The inclusion of such a small percentage of non-AD participants is unlikely to affect the meta-analysis to a significant extent.

Furthermore, we can note that four studies showed very similar results with Hedges g values averaging a little above unity, with (Mielke et al, 2012) being the outlier with a much higher g value above 2.5. As this outlier study contained only AD converters, and the other studies had similar values with and without pure AD converter samples, there is little sign that the relatively mild impurity of the dementia conversion sample shaped the Hedges g values. In conclusion, then, the CVLT Short Delay Free Recall test appears effective at predicting conversion to AD, with all studies exhibiting a Hedges g value of at least around unity.

As with other included tests the small amount of studies included make the funnel plot difficult to interpret however it does not seem to indicate any obvious publication bias.

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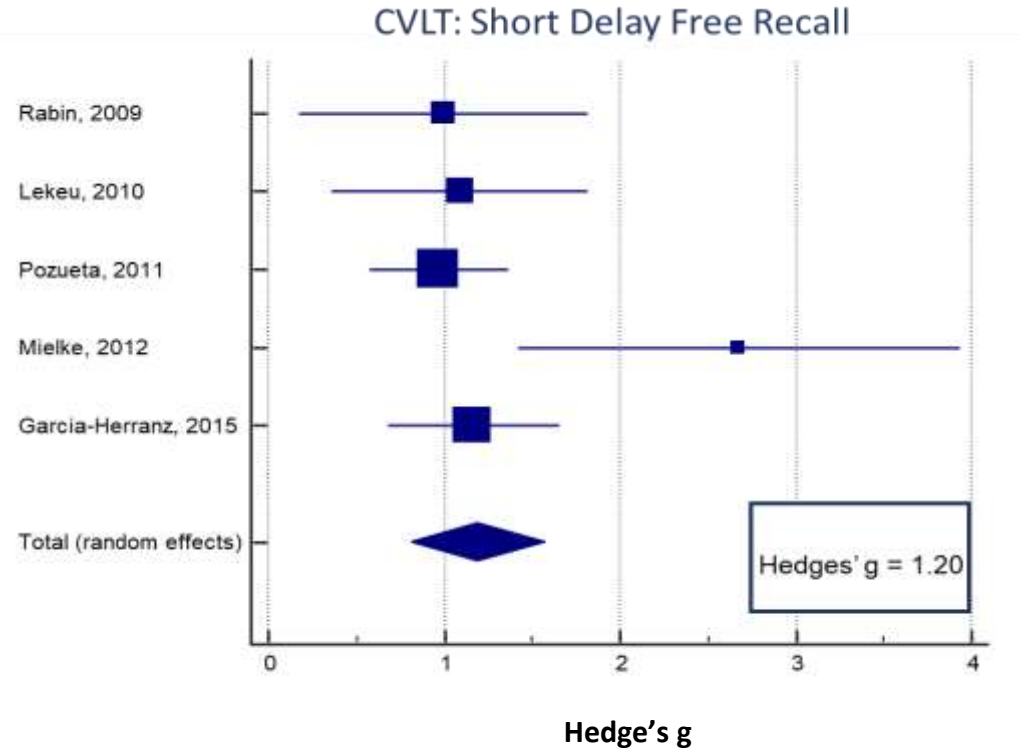

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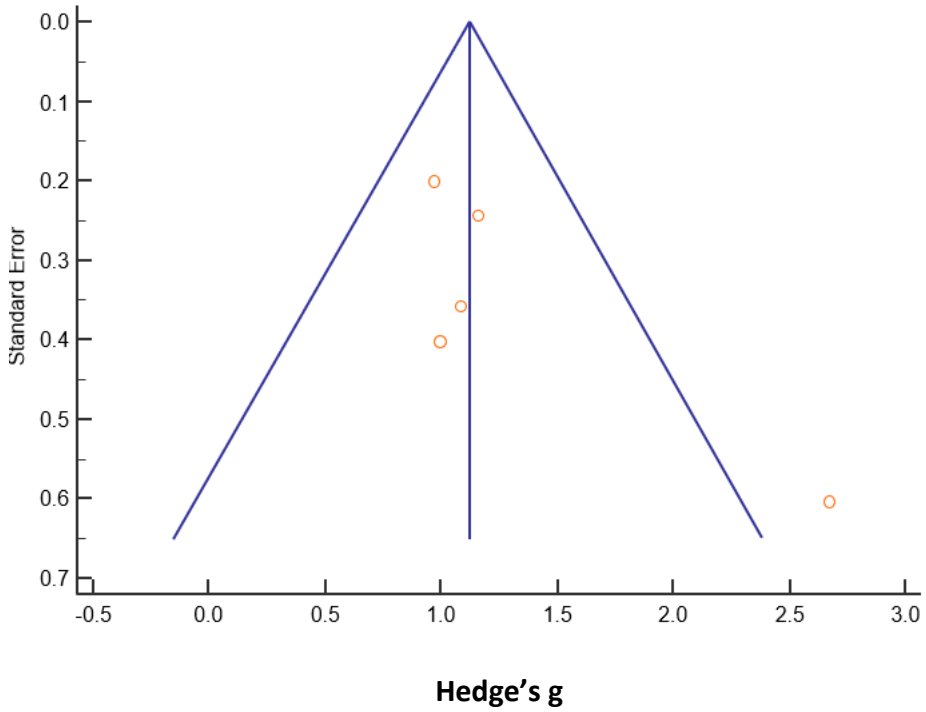


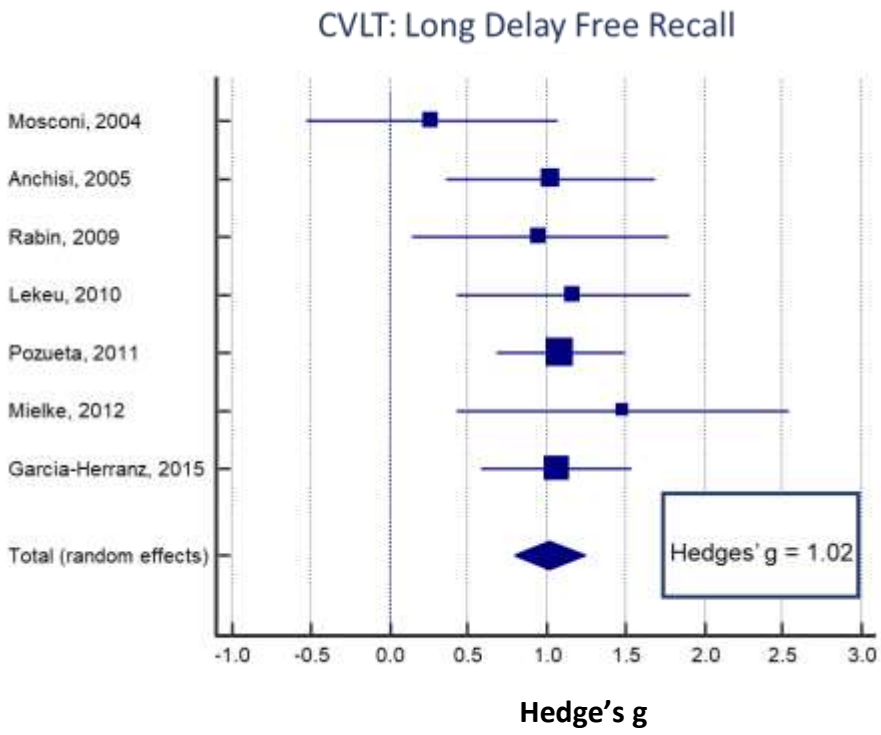
Figure 3. 10. **(A)** Forest plot for all five studies included in CVLT: Short Delay Free Recall. **(B)** Funnel plot for all studies included in in CVLT: Short Delay Free Recall.

3.6.3.6: California Verbal Learning Test: Long Delay Free Recall

Following the Short Delay Free Recall condition, the participant is asked to recall list A again after a 20-minute delay (Long Delay Free Recall). Seven studies were included within the meta-analysis with all but Rabin, 2009 using the original CVLT. The Hedge's g (±95 confidence intervals) value for the CVLT: Long Delay Free Recall was 1.02 (0.79-1.25), making it the third highest of the included neuropsychological test albeit with a slightly lower Hedge's g than the CVLT: Short Delay Free Recall. There were two studies included within CVLT: Long Delay Free Recall which were not included within the CVLT: Short Delay Free recall meta-analysis; Mosconi, 2004 and Anchisi, 2005. Neither of these studies contained participants who converted to another form of dementia besides AD. As with CVLT Short Delay Free Recall, Garcia-Herranz, 2015 and Pozueta, 2011 were included and so 6 participants out of 132 included within this meta-analysis who converted to other forms of dementia. Therefore 4.5% of participants included converted to dementia of a non-AD type, too small a percentage to dramatically affect the Hedge's g.

In summary, the CVLT Long Delay Free Recall test was quite effective at predicting conversion to AD, with all studies except (Mosconi et al, 2004) exhibiting a Hedges g value of at least around unity. The funnel plot appears to be broadly symmetrical, with no clear indication of publication bias.

A



B

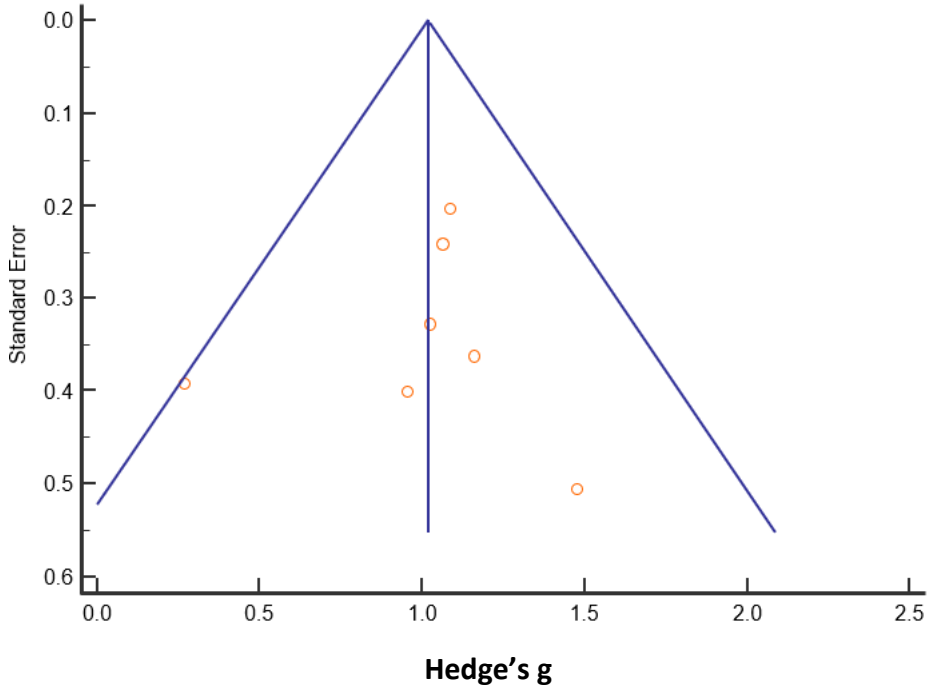


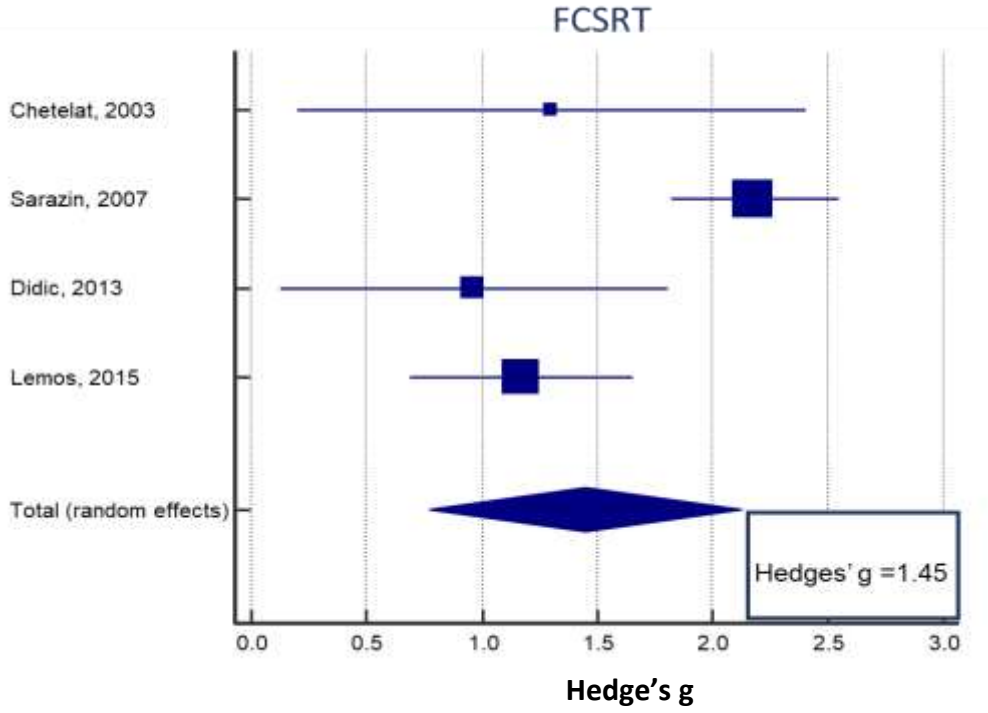
Figure 3. 11. **(A)** Forest plot for all seven studies included in the CVLT: Long Delay Free Recall meta-analysis. **(B)** Funnel plot for all studies included in CVLT: Long Delay Free Recall.

3.6.3.7: Free and Cued Selective Reminding Test

The Free and Cued Selective Reminding Test (FCSRT) requires participants to search for items in response to their category cues. The same category cues are given later in order to elicit the recall of items that the participants were unable to recall on the free recall trial. A detailed description of the FCSRT is provided in Chapter 2, Section 2.4. There are many scoring procedures that can be used with the FCSRT including free recall, total recall and cue efficiency. However, the measure used in the studies that fit my inclusion/exclusion criteria and which is widely used generally is 'total recall' which is calculated as the sum of free and cued recall. The Hedge's g (±95% confidence intervals) value for the FCSRT was 1.45 (0.77 to 2.13), making it the best performing included neuropsychological test within the meta-analysis. Although there were only four studies in this meta-analysis, it is notable that this test performed very well at predicting conversion to AD, with the study with the lowest Hedges g value (Didic et al, 2013) still exhibiting a g of around unity. It is not obvious why this task is not more used, given this good performance. I note that using a broadly similar task in my MCI patient sample (Chapter 5 of the present thesis), ie Buschke's pictureless Selective Reminding test (Buschke (1973)), the patients find it somewhat stressful.

The 110 participants who converted to dementia within the five studies included in the FCSRT meta-analysis all converted to AD specifically. Given the small amount of studies included in the FCSRT meta-analysis, the funnel plot (Figure 3.12B) appears to give no indication of clear publication bias.

A



B

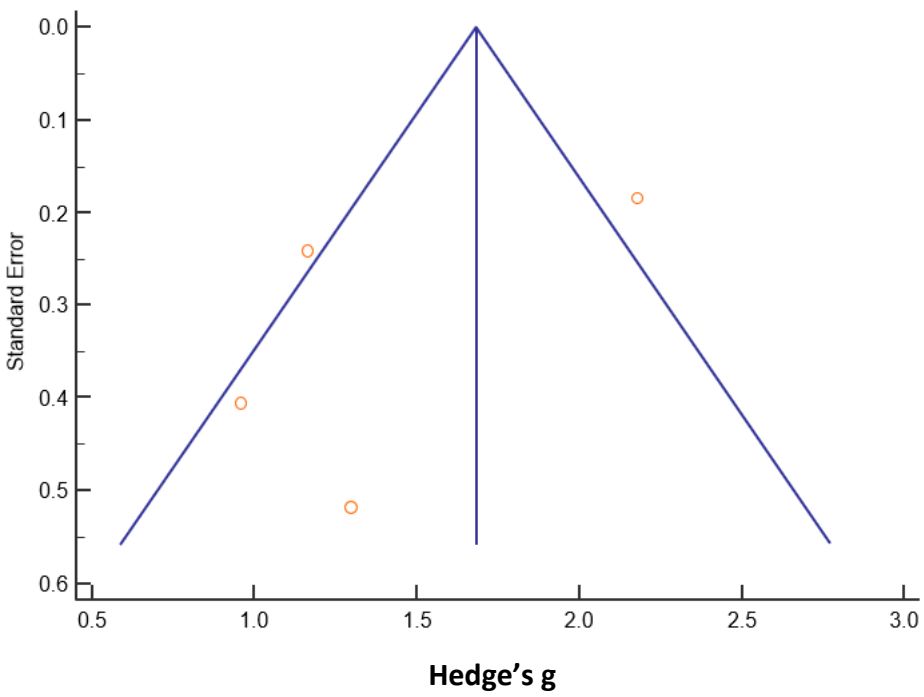


Figure 3. 12. **(A)** Forest plot for the four studies included in the FCSRT meta-analysis. **(B)** Funnel plot for all studies included in the FCSRT meta-analysis.

3.6.4: Multi-Domain Cognitive Tests

Multi-domain cognitive tests were designed to test the five main cognitive domains; attention, executive function, memory, visuospatial function and language. Such tests aim to give an overview of an individuals functioning and are very often used in primary care setting due to how quickly they can be administered, their cost effectiveness (the vast majority are paper-based) and easy scoring.

3.6.4.1: Alzheimer's Disease Assessment Scale- Cognitive Subscale (ADAS-COG)

The Alzheimer's Disease Assessment Scale is a two-part scale that was designed to test the symptoms of Alzheimer's Disease. The meta-analysis below however, purely focuses on the Cognitive subsection of the test (ADAS-COG). As with other multi-domain tests, the ADAS-COG tests multiple functions such as language, memory, comprehension and orientation. This cognitive section also tests visuo-spatial ability such as the drawing of geometric figures and tasks reflecting ideational praxis e.g. folding a sheet of paper and placing it into an envelope. Patients' scores range from 0-70, with higher scores indicating poorer performance, and therefore more cognitive deficit. A detailed explanation of the ADAS-COG is given in Chapter 2, Section 2.3.

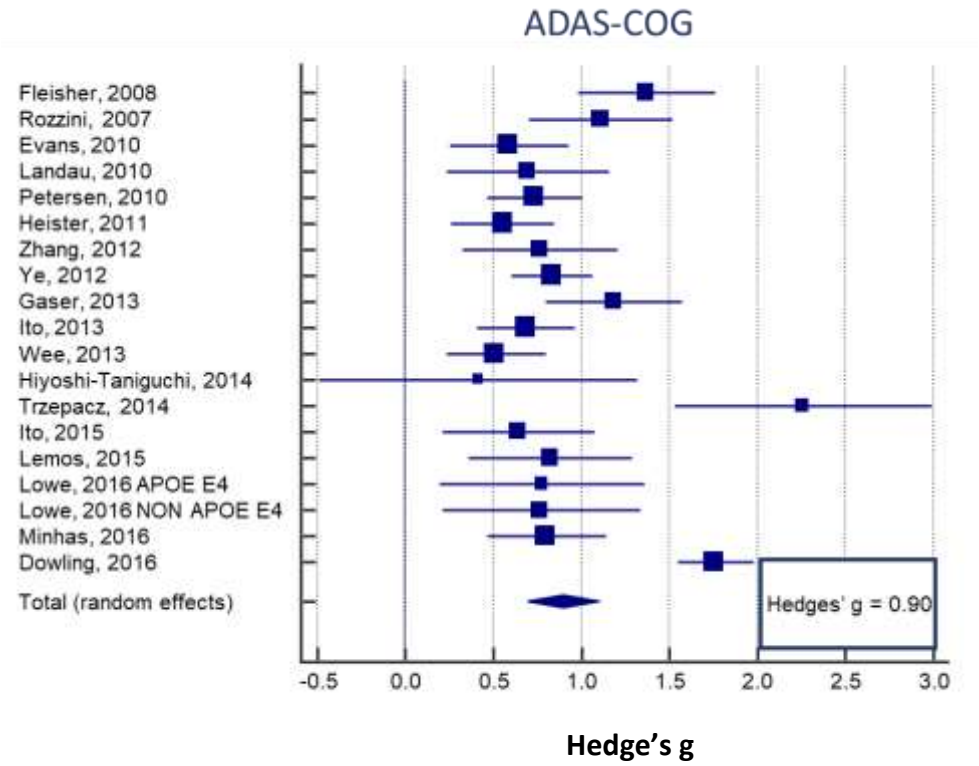
18 studies were included within the ADAS-COG meta-analysis with a combined average Hedge's g of 0.90, which can be seen in the forest plot below (figure 3.13A). The Hedge's g (± 95% confidence intervals) value for the ADAS-COG was 0.90 (0.70-1.10).

Unusually, Ito was included at 2013 and 2015 as there was no cross-over between participant groups, unlike other studies that occurred in different years. All 18 studies included in the

ADAS-COG meta-analysis had 100% conversion to AD, with no one converting to any other forms of dementia.

The distribution of datapoints in the funnel plot (Figure 3.13B) looks a little unusual, with several datapoints outside the funnel, but there is no sign of strong publication bias. There are two studies with very high effect sizes outside the funnel, but also several studies on the left side of the plot.

A



B

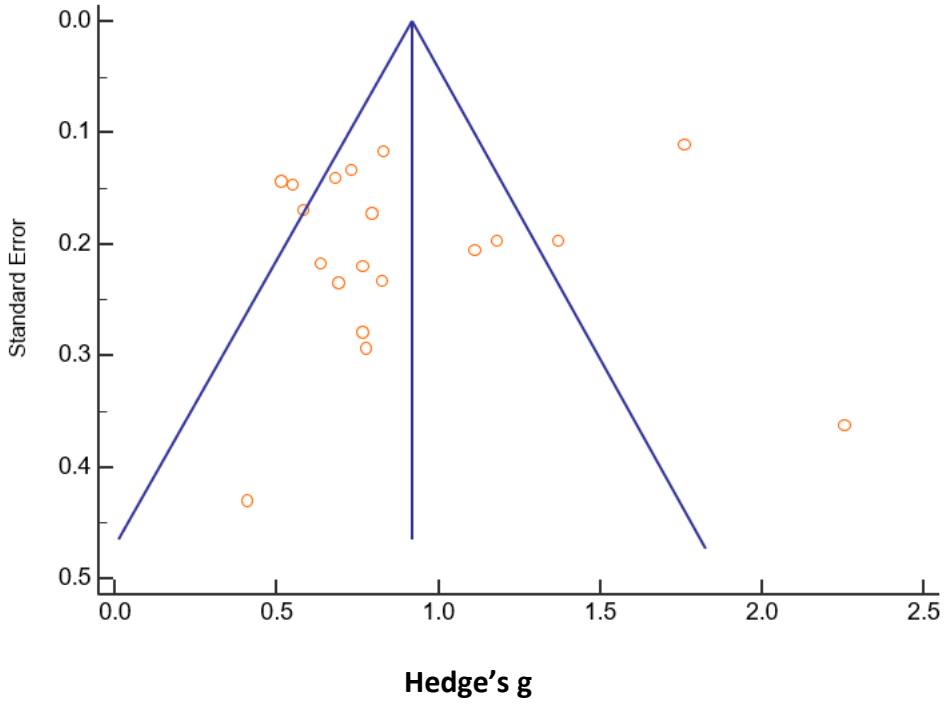


Figure 3. 13. **(A)** Forest plot for all 18 studies included in the ADAS-COG meta-analysis. **(B)** Funnel plot for all studies included in the ADAS-COG meta-analysis.

3.6.4.2: Constrained MMSE

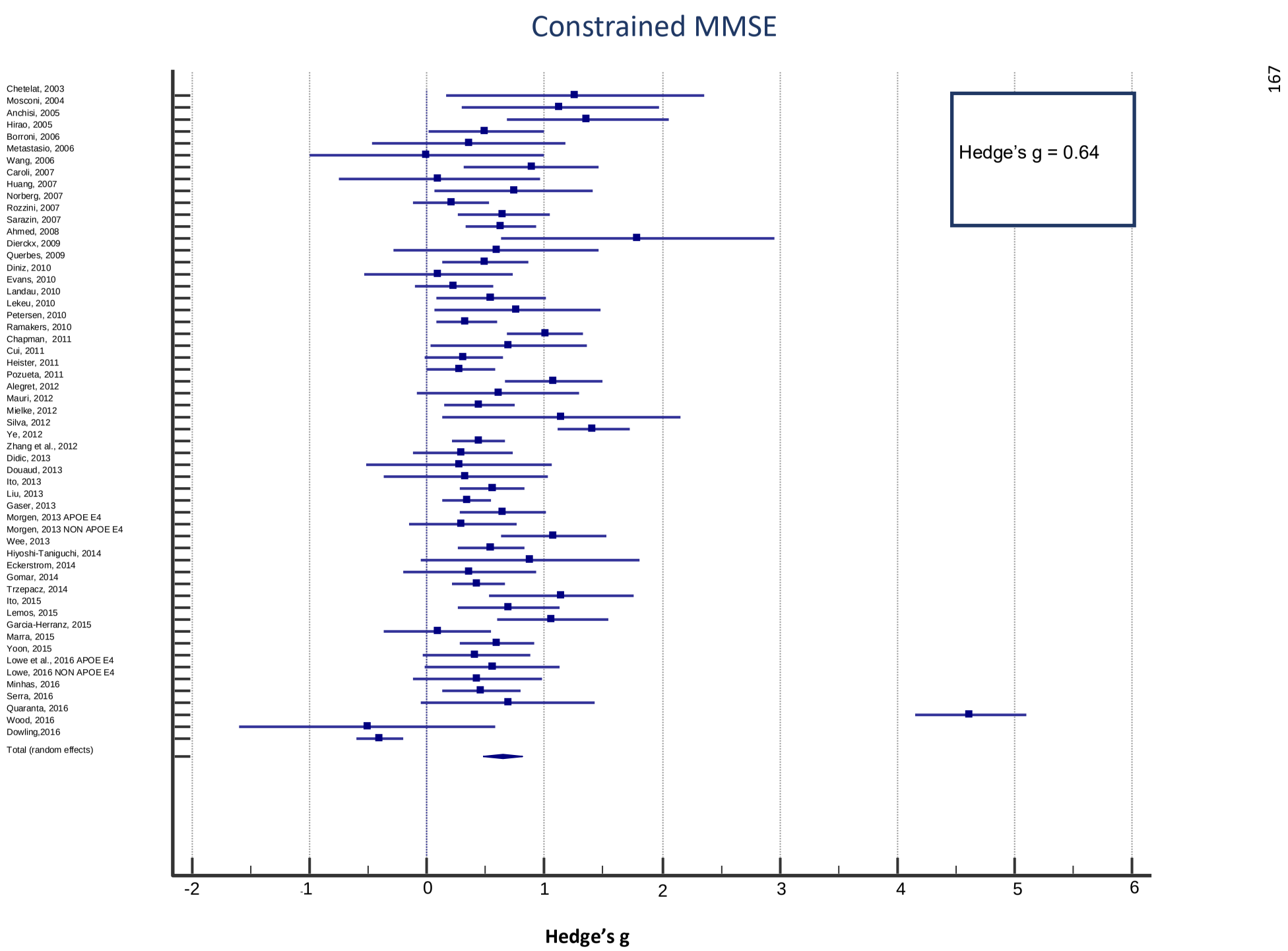
The MMSE remains one of the most commonly used neuropsychological tests and as such, most literature which focuses upon MCI to AD conversion includes MMSE scores as a baseline classification. Due to the copious amounts of research including the MMSE, we only included MMSE data from a study where that study simultaneously provided data for one or more of the other 11 neuropsychological tests or subtests.

Tabulation and analysis of the MMSE proceeded differently from other neuropsychological tests in that we only analysed a subset of MMSE studies. This was done because the MMSE is so widely administered that we were able to take advantage of within-study comparisons. We considered that the most useful between-test comparisons were drawn from studies where tests were given to the same patient sample, thus controlling for variability associated with demographic, follow-up and other factors. Accordingly, first, to make the standalone MMSE table as part of the neuropsychological test analysis, we only included MMSE data from a study where that study simultaneously provided data for one or more of the other 11 neuropsychological tests. Second, for direct comparison between the MMSE and Cerebrospinal Fluid markers, we selected studies incorporating the MMSE and one or more of the three CSF markers, and conducted paired t-tests (MMSE vs CSF marker) for each of the CSF markers.

The MMSE is another multi-domain cognitive test which measures orientation, attention, memory, language and visuo-spatial skills. The MMSE is quick (taking around 15 minutes), easy to administer, and cost effective. Scores range from 0-30, with scores below 24 indicating cognitive deficit. A detailed description of the MMSE is included in Chapter 2, Section 2.2. Altogether, 54 studies were included in the constrained MMSE meta-analysis,

with a weighted average Hedge's g of 0.64 (0.48-0.81) (shown in forest plot below, figure 3.14A). The forest plot appears broadly symmetrical (figure 3.14B), with some indication of more datapoints outside the funnel on the right-hand side, but publication bias does not seem pronounced.

A


Constrained MMSE
Chetelat, 2003
Mosconi, 2004
Anchisi, 2005
Hirao, 2005
Borroni, 2006
Metastasio, 2006
Wang, 2006
Caroli, 2007
Huang, 2007
Norberg, 2007
Rozzini, 2007
Sarazin, 2007
Ahmed, 2008
Dierckx, 2009
Querbes, 2009
Diniz, 2010
Evans, 2010
Landau, 2010
Lekeu, 2010
Petersen, 2010
Ramakers, 2010
Chapman, 2011
Cui, 2011
Heister, 2011
Pozueta, 2011
Alegret, 2012
Mauri, 2012
Mielke, 2012
Silva, 2012
Ye, 2012
Zhang et al., 2012
Didic, 2013
Douaud, 2013
Ito, 2013
Liu, 2013
Gaser, 2013
Morgen, 2013 APOE E4
Morgen, 2013 NON APOE E4
Wee, 2013
Hiyoshi-Taniguchi, 2014
Eckerstrom, 2014
Gomar, 2014
Trzepacz, 2014
Ito, 2015
Lemos, 2015
Garcia-Herranz, 2015
Marra, 2015
Yoon, 2015
Lowe et al., 2016 APOE E4
Lowe, 2016 NON APOE E4
Minhas, 2016
Serra, 2016
Quaranta, 2016
Wood, 2016
Dowling,2016
Total (random effects)
Hedge's g = 0.64
-2
-1
0
1
2
3
4
5
6
Hedge's g

B

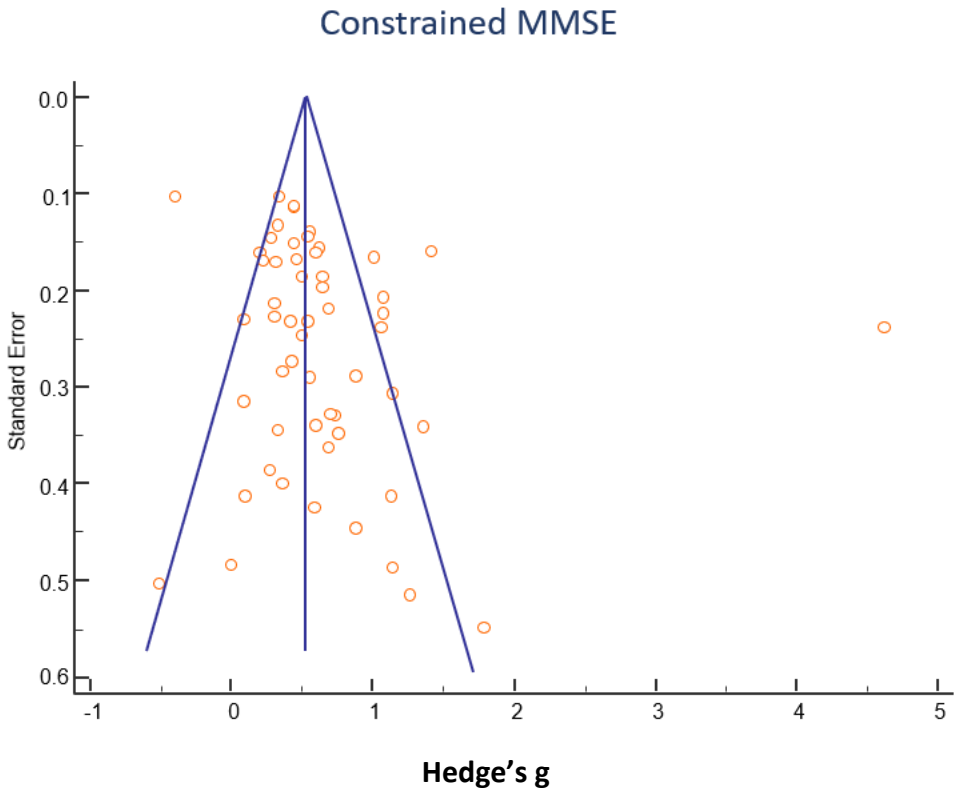


Figure 3. 14. (A) Forest plot for all 54 studies included in the Constrained MMSE meta-analysis. **(B)** Funnel plot for all studies included in the Constrained MMSE meta-analysis.

3.7: Neuropsychological tests: Summary

The overall analysis of neuropsychological tests suggests that there are six tests which appear to be superior to the MMSE, which is the most commonly used assay for age-related cognitive decline and Alzheimer's disease, especially within research settings. There six tests are, in order of Hedge's g: FCSRT, CVLT: Short Delay Free Recall, CVLT: Long Delay Free Recall, Rey-Osterrieth Complex Figure: Immediate Recall, RAVLT: Delayed Recall, ADAS-COG, Rey-Osterrieth Complex Figure: Delayed Recall and Logical Memory: Delayed Recall. All included studies and results are included in table 3.3.

Based upon these results, it may be tempting to suggest that they should be used more frequently in AD diagnostic work-ups. However, a degree of caution may be required when coming to definitive conclusions in this regard, especially as the best performing five

neuropsychological tests contained a relatively small amount of studies. There may also be practical reasons as to why such tests are not commonly used within clinical practice such as copyright issues and the associated expense, which remains more of an issue in the UK national health service than for example, clinics within the US. The FCSRT was found to perform the best out of the included neuropsychological tests and is FDA recommended in the USA. It is unclear why so few longitudinal studies have used the FCSRT when assessing MCI conversion to AD but the present thesis suggests it may prove a valuable tool for early AD detection.

Table 3. 3

Included neuropsychological test information in descending order of Hedge's g

Test	Total Studies	Total Participants	Mean Follow-up	Age of non-converters (Years)	Age of converters (Years)	I^2	Hedge's g (95% CI)
FCSRT	4	348	3.12	69.31	71.65	80.63%	1.45 (0.77 to 2.13)
CVLT: Short Delay	5	303	2.58	71.66	74.12	45.58%	1.20 (0.89 to 1.58)
CVLT: Long Delay	7	388	2.13	69.90	73.24	0.00%	1.02 (0.79 to 1.25)
ROCF: Immediate Recall	7	416	2.91	70.31	72.34	0.00%	0.99 (0.79 to 1.20)
RAVLT: Delayed Recall	15	2605	3.10	70.72	73.28	85.27%	0.95 (0.71 to 1.20)
ADAS-COG	18	3508	2.36	73.85	73.99	83.44%	0.90 (0.70 to 1.10)
ROCF: Delayed Recall	11	624	2.55	69.84	72.53	14.62%	0.67 (0.48 to 0.86)
Logical Memory: Delayed Recall	6	1177	2.83	72.73	73.21	0.00%	0.67 (0.54 to 0.79)
Constrained MMSE	54	7122	2.56	71.04	73.14	89.06%	0.64 (0.48 to 0.81)
RAVLT: Immediate Recall	4	454	2.65	71.99	73.56	77.29%	0.57 (0.05 to 1.08)
Logical Memory: Immediate Recall	9	1551	3.00	72.32	72.50	41.67%	0.54 (0.40 to 0.69)
TMT-B	21	2953	2.48	69.46	72.42	35.14%	0.46 (0.36 to 0.57)

3.8: Cerebrospinal Fluid tests to predict conversion from MCI to AD.

Up to this point in this chapter, the analysis has in effect been addressing the question: *'Which are the world's best-performing neuropsychological tests for predicting conversion from MCI to AD, and just how good are they?'*. The analysis, summarised in Table 3.3, suggests that there are half a dozen tests which are effective in this regard and appear to be superior to MMSE, the most widely used assay for age-related cognitive decline and Alzheimer's disease. However, of course neuropsychological tests are not the only type of tests used in AD related

study and may be considered to be in competition with other types of test, as listed more fully above in Section 3.1.2.

Accordingly, it is also important to address the following question: 'How good are the best-performing neuropsychological tests not just relative to other neuropsychological tests *but relative to other kinds of tests and markers including neurobiological markers?*' This is an important question globally. As outlined in Section 3.1.2, there are many candidates for other tests, and one has to be selective for practical reasons of time and resources. For this thesis, I examined CSF tests as comparators for neuropsychological tests, as they are considered gold standard tests and in principle could be given to larger groups of people than some of the very expensive forms of beta-amyloid-based neuroimaging (e.g. Pittsburg compound).

The three core AD CSF biomarkers include total tau (t-tau), phosphorylated tau (p-tau) and the 42 amino acid forms of beta-amyloid ($A\beta_{1-42}$). Beta-amyloid plaques are formed from beta amyloid, which is created when amyloid precursor protein (APP) is cut by two enzymes, beta and gamma secretase. This cutting of APP can occur at many locations along the APP sequence and therefore there are several kinds of Aβ which form, of which the most toxic is $A\beta_{1-42}$. Research has shown a negative relationship between $A\beta_{1-42}$ levels in the brain and in CSF. This is due to $A\beta_{1-42}$ becoming trapped in plaques, allowing less of it to leave the brain to enter CSF. Therefore, CSF $A\beta_{1-42}$ measurements in AD patients tend to be lower in AD patients than healthy individuals (Nostrand et al, 1992; Reddy & Beal, 2007; Niemantsverdriet et al, 2017). The tau proteins are a group of six highly soluble protein isoforms that are produced via alternative splicing from the microtubule-associated protein tau (MAPT) gene. Their main role is maintaining the stability of microtubules in axons. In those with AD tau thought to have become neurofibrillary tangles which contribute to AD. Increases in total tau protein, along with phosphorylated tau are also often seen in the CSF of those with MCI and AD. Due to the

increasing interest in the use of CSF biomarkers, often considered a gold standard in AD diagnostics (e.g. Diniz et al, 2008; Alberts et al, 2011; Sperling et al, 2011; Dubois et al, 2007; 2014; Herruka et al, 2016; Jack et al, 2018), I evaluated the three core biomarker tests' ability to predict conversion from MCI to AD.

3.8:1: Search Strategy: Cerebrospinal Fluid tests.

A literature search was conducted using Google Scholar, PubMed and ISI Web of Knowledge for studies published up to 31st January 2018. The following search string was used: 'Alzheimer's disease or AD' and 'Mild Cognitive Impairment' or 'MCI' and 'CSF' or 'cerebrospinal Fluid' and the terms 'predict', 'progress' or 'convert' and 'tau' or 'total tau' or 'beta-amyloid or 'phospo-tau' or 'p-tau' or 'phosphorylated tau'. More studies were identified using the reference lists of already identified studies.

3.8.2: CSF Tests: Study inclusion criteria and method.

The same inclusion used for inclusion for the analysis of neuropsychological tests (Figure 3.2) was also applied to CSF study inclusion/ exclusion (Figure 3.4.). All-together 30 studies were included between Phosphorylated tau (P-Tau), Amyloid Beta 1-42 (Aβ1-42) and Total tau (T-tau), this is illustrated below in figure 3.15. As I was only examining $A\beta_{1-42}$, P-Tau and Total Tau, the exclusion process purely involved studies which looked at conversion using these three core biomarkers.

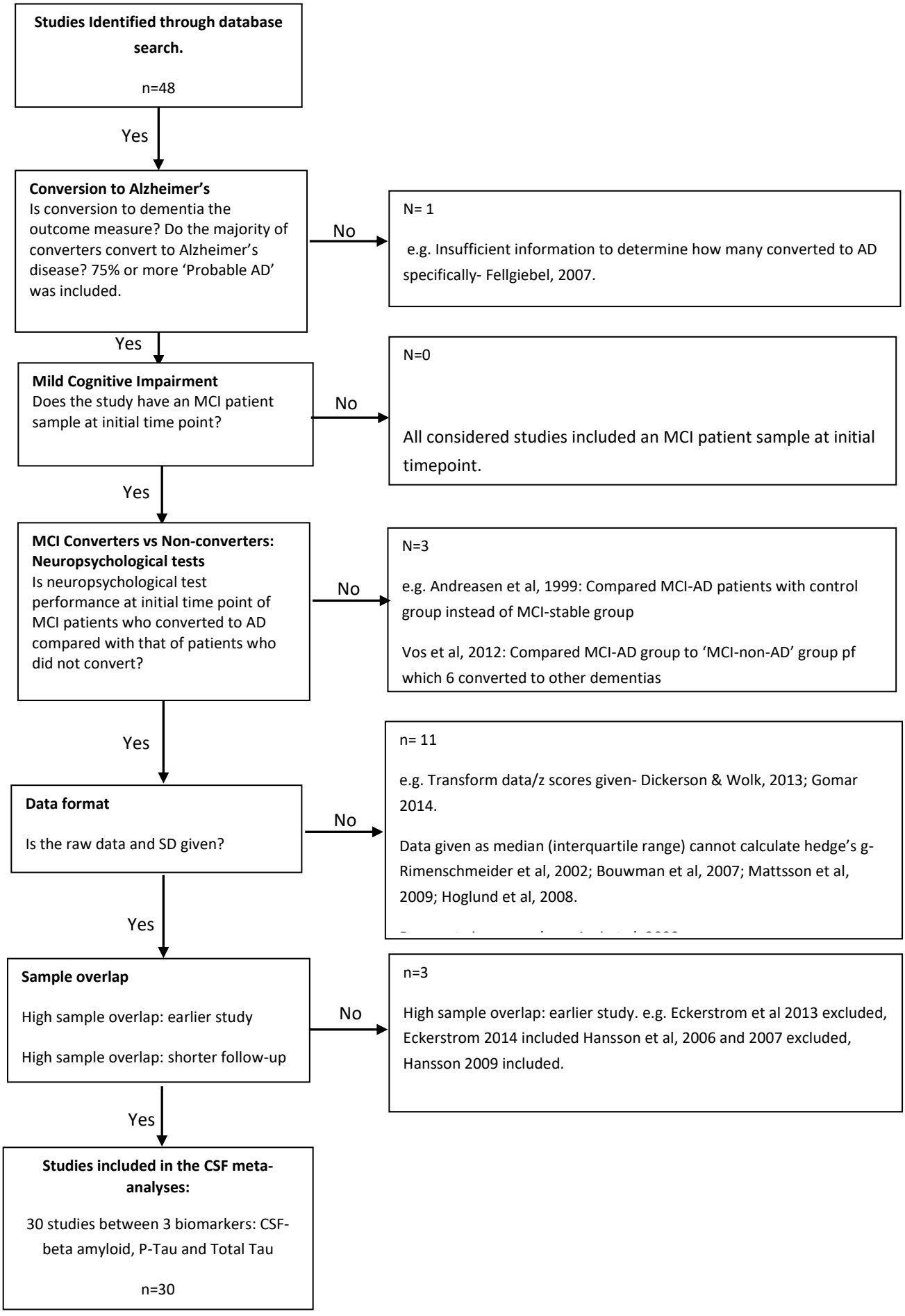


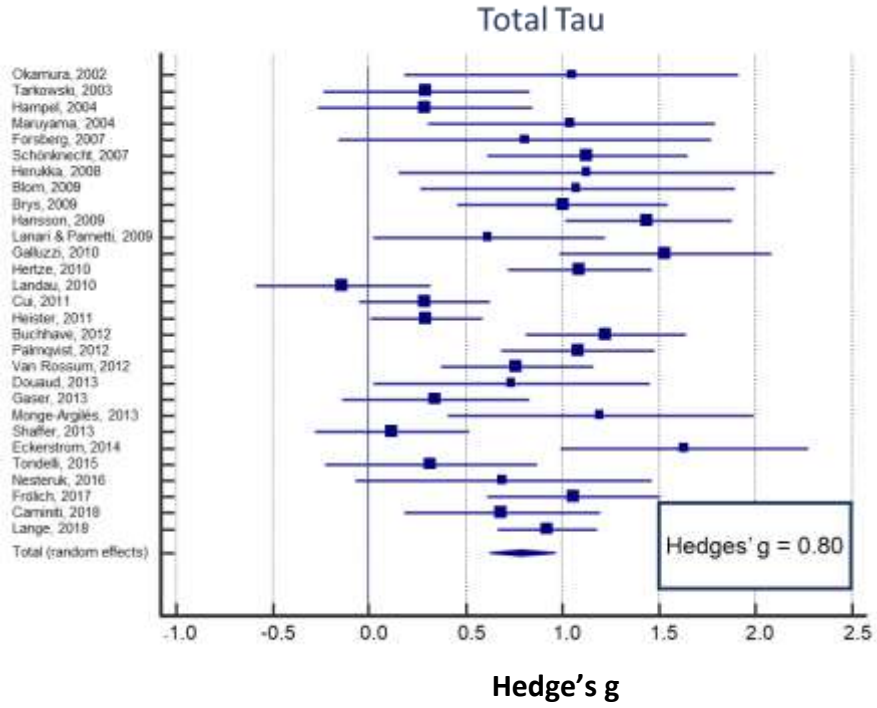
Figure 3. 15. **Flowchart illustrating the inclusion/ exclusion procedure of studies which used CSF $A\beta_{1-42}$, P-Tau and Total Tau.**

3.8.3: Results: CSF Biomarkers

3.8.3.1: Total Tau

Total Tau (T-Tau) is generally measured in picograms per millilitre (pg/ml). To give an 'at a glance' example, Okamura, 2002 measured non converters to have an average of 251 pg/ml whilst converters had an average score of 566 pg/ml. An increased level of tau is often seen in the CSF of those with MCI and AD and so a higher level of total tau in those who converted to AD shows the predictive ability of the test. Twenty-nine studies were included in the T-Tau meta-analysis. The Hedge's g (±95% confidence intervals) value for t-tau was 0.80 (0.62-0.97), as can be seen in the forest plot below (Figure 3.16A). The asymmetry of the funnel plot, specifically relating to the absence of studies from the bottom left part of the plot in figure 3.16B, suggests possible publication bias. Notably, there are five studies with appreciably higher-than-average effect sizes in the bottom (high-standard error region) of the plot, which have no counterparts on the left side (ie. high-standard error region but with low effect sizes).

A



B

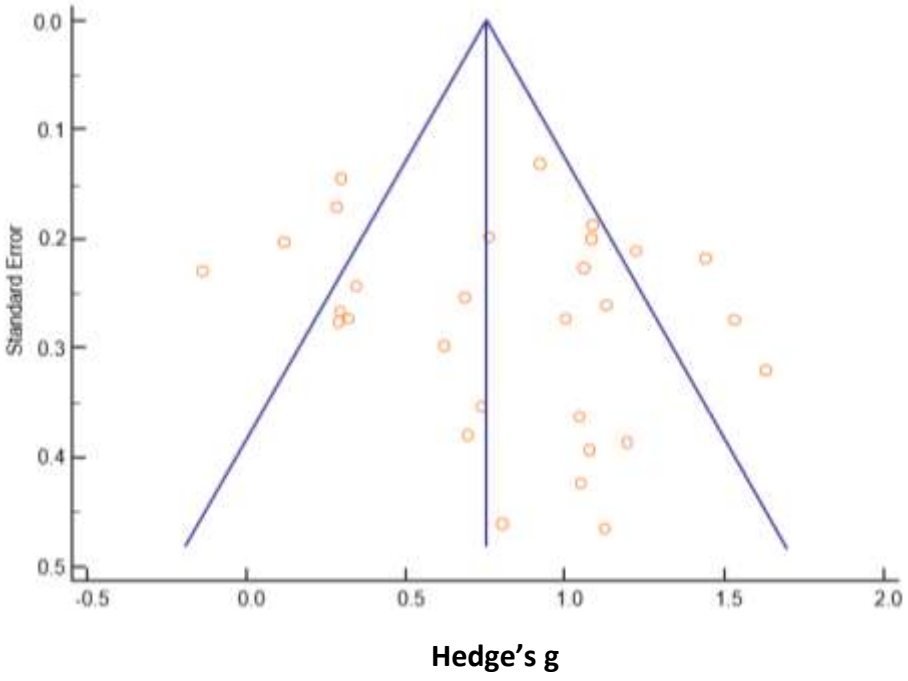


Figure 3. 16. **(A)** Forest plot for all 29 studies included in the T-Tau meta-analysis.

(B) Funnel plot for all studies included in the T-Tau meta-analysis.

3.8.3.2: Phosphorylated Tau

P-Tau is also measured in pg/ml and as with T-Tau, a higher level of total phosphorylated tau in those who converted to AD shows the predictive ability of the test. Twenty-three studies were included in the P-Tau meta-analysis, the Hedge's g (±95% confidence intervals) value was 0.84 (0.66-1.02), as can be seen in the forest plot below (Figure 3.17A). The funnel plot appears symmetrical, suggesting no publication bias.

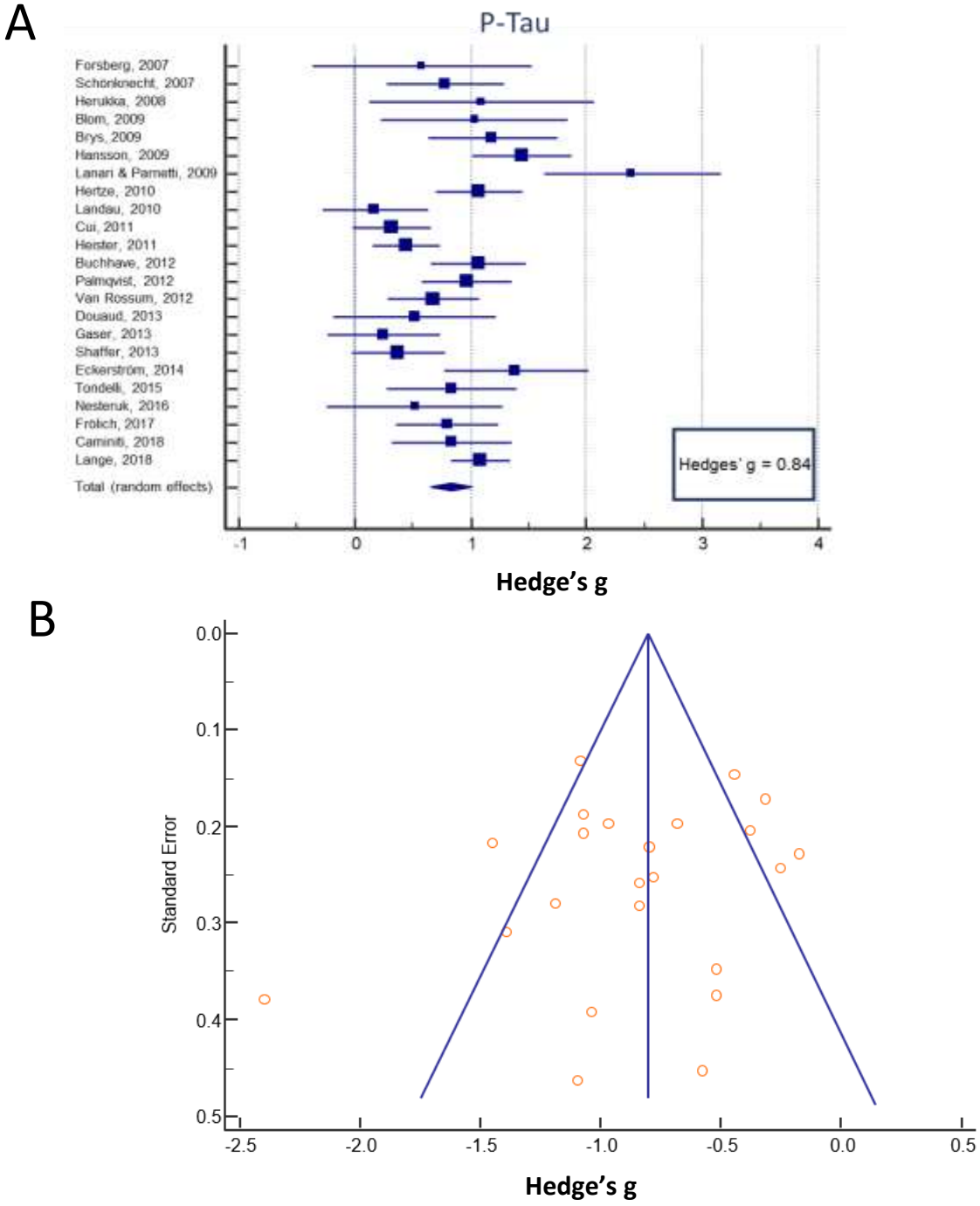


Figure 3. 17. **(A)** Forest plot for all 23 studies included in the P-Tau meta-analysis. **(B)** Funnel plot for all studies included in the P-Tau meta-analysis.

3.8.3.3: Amyloid beta ($A\beta_{1-42}$)

As with T-Tau and P-Tau, $A\beta_{1-42}$ is also measured by pg/ml but unlike T-Tau and P-Tau, AD pathology leads to a decrease in amyloid beta due to $A\beta_{1-42}$ becoming trapped in plaques, allowing less of it to leave the brain to enter CSF. Twenty-seven studies were included in the $A\beta_{1-42}$ meta-analysis, the Hedge's g (±95% confidence intervals) value was 0.88 (0.68-1.09), as can be seen in the forest plot below (Figure 3.18A). The funnel plot appears relatively symmetrical (Figure 3.18B), albeit with some right-sided bias, suggesting only a relatively mild publication bias.

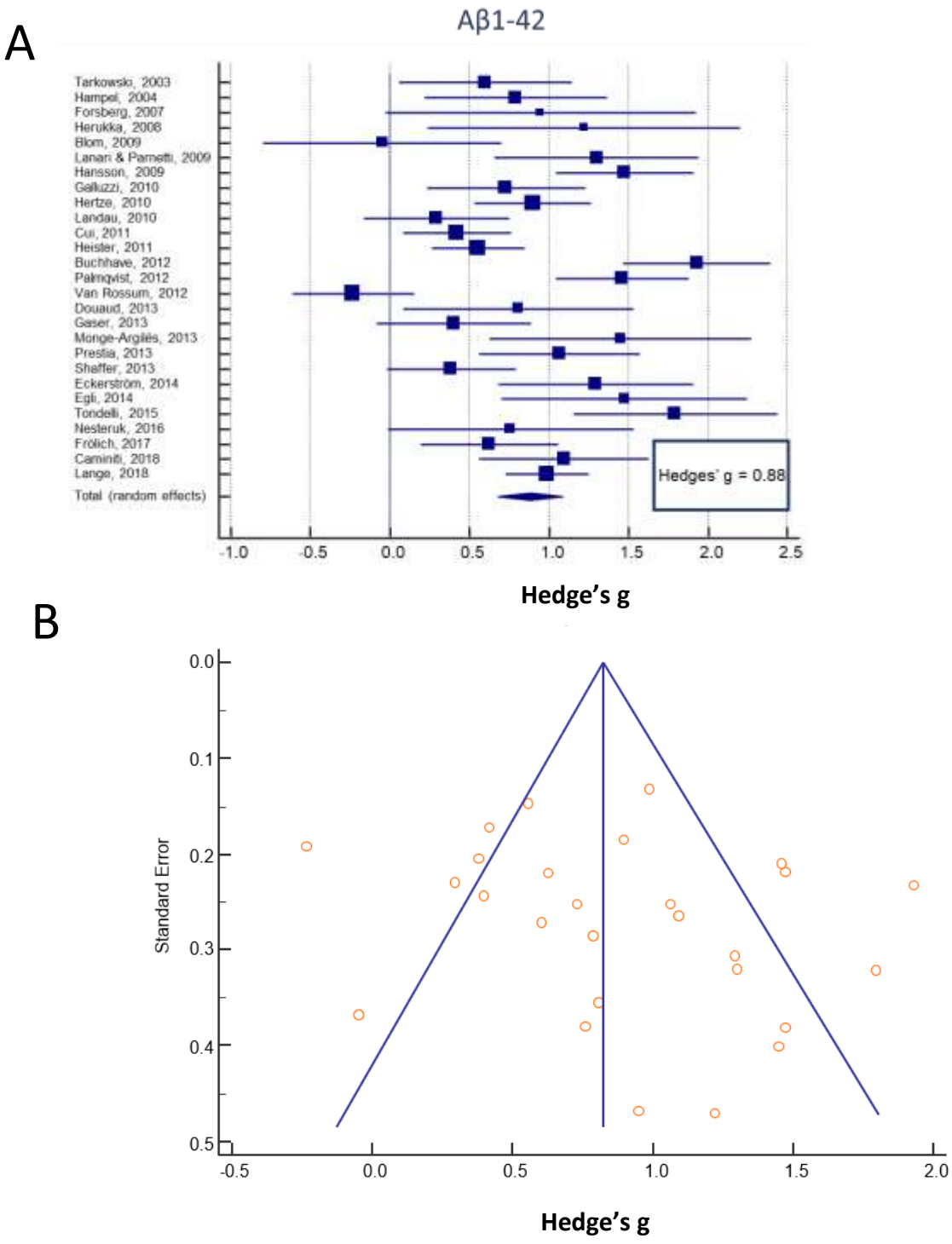


Figure 3. 18. **(A)** Forest plot for all 27 studies included in the $A\beta_{1\text{-}42}$ meta-analysis.

(B) Funnel plot for all studies included in the $A\beta_{1\text{-}42}$ meta-analysis.

3.9: CSF tests vs the MMSE

Studies which employed both CSF markers and the MMSE afforded direct comparison of these different diagnostic approaches. Although the MMSE's imperfections as a diagnostic tool are well established (Simard & Reekum, 1999; Nelson, Fogel & Faust, 1986; Arevalo-Rodriguez, 2015) its widespread use, as in the studies highlighted in the present meta-analysis, afford some within-study comparison. Across-test evaluations are best made in a within-study manner. Within-study comparisons do not of course necessarily mean that expertise is of a similar quality across domains; the neuropsychological testing might conform less to best international standards than CSF analysis, and vice versa. However, use of exactly the same patient sample means that such studies do at least control for:

a) demographic variables (e.g. age, education, region);

b) follow-up variables (e.g. follow up period, and quality of Alzheimer's diagnosis).

As it turned out, the beta amyloid and t-tau CSF tests were not significantly better than the MMSE at predicting conversion, and the p-tau tests produced very similar results to the MMSE.

One point of potential superiority is likely the lower variance of the CSF tests, with the variance of the P-Tau test less than that of the MMSE (*F* test variance ratio=2.992, *p*=0.025). It is not obvious that this indicates superiority, but it could suggest it is easier in practice to achieve standardisation across CSF tests than the MMSE.

Table 3. 4

Summary of neuropsychological and CSF test information in descending order of Hedge's g.

Test	Total Studies	Total Participants	Mean Follow-up	Age of non-converters (Years)	Age of converters (Years)	Hedge's g
FCSRT	4	348	3.12	69.31	71.65	1.45 (0.77-2.13)
CVLT: Short Delay	5	303	2.58	71.66	74.12	1.20 (0.89-1.58)
CVLT: Long Delay	7	388	2.13	69.90	73.24	1.02 (0.79-1.25)
ROCF: Immediate Recall	7	416	2.91	70.31	72.34	0.99 (0.79-1.20)
RAVLT: Delayed Recall	15	2605	3.10	70.72	73.28	0.95 (0.71-1.20)
ADAS-COG	18	3508	2.36	73.85	73.99	0.90 (0.70-1.10)
$A\beta_{1-42}$	27	2370	2.76	68.99	71.99	0.88 (0.68-1.09)
p-tau	23	2193	2.88	68.92	71.89	0.84 (0.66-1.02)
t-tau	29	2469	2.71	69.63	72.04	0.80 (0.62-0.97)
ROCF: Delayed Recall	11	624	2.55	69.84	72.53	0.67 (0.48-0.86)
Logical Memory: Delayed Recall	6	1177	2.83	72.73	73.21	0.67 (0.54-0.79)
Constrained MMSE	54	7122	2.56	71.04	73.14	0.64 (0.48-0.81)
RAVLT: Immediate Recall	4	454	2.65	71.99	73.56	0.57 (0.05-0.69)
Logical Memory: Immediate Recall	9	1551	3.00	72.32	72.50	0.54 (0.40-0.69)
TMT-B	21	2953	2.48	69.46	72.42	0.46 (0.36-0.57)

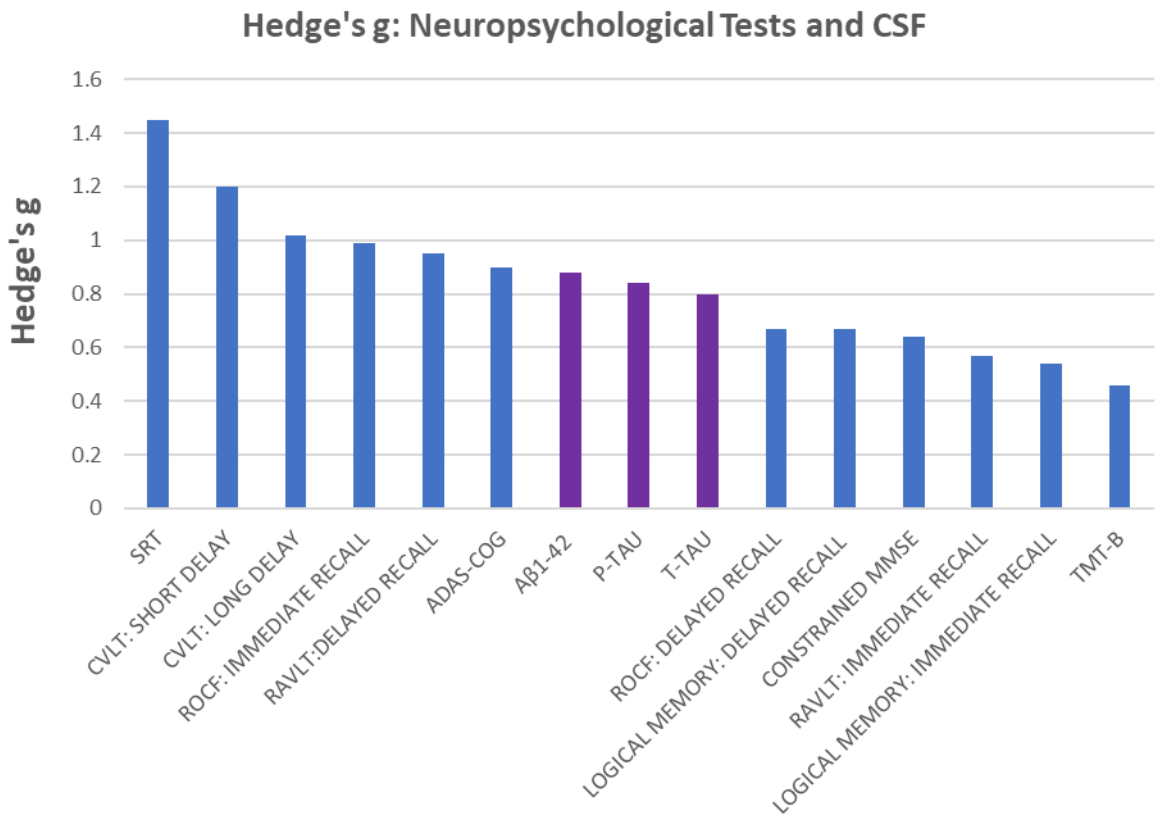


Figure 3. 19. **Bar chart of average Hedge's g: Included Neuropsychological and CSF tests.**

3.10: Meta-analysis discussion

In summary, I conducted a meta-analysis of the ability of twelve neuropsychological tests and three CSF biomarkers to predict conversion from Mild Cognitive Impairment (MCI) to Alzheimer's disease. The twelve neuropsychological tests, in ascending order of effect size, were as follows: Trail making test B (g = 0.46); Logical Memory Immediate Recall (g = 0.54); Rey Auditory Verbal Learning test Immediate Recall (g = 0.57); Constrained MMSE (g = 0.64); Logical Memory Delayed Recall (g = 0.67); Rey's Complex Figure Delayed Recall (g = 0.67); ADAS-COG (g = 0.90); Delayed Recall of the Rey Auditory Verbal learning test (g = 0.95); Rey's

Complex Figure Immediate Recall (*g* = 0.99); CVLT Long Delay Free Recall (*g* = 1.02); CVLT Short Delay Free Recall (*g* = 1.20); Free and Cued Selective Reminding test (FCSRT) (*g* = 1.45). Effect sizes for the 3 CSF biomarkers, from smallest to largest, were as follows: t-tau (*g* = 0.80); p-tau (*g* = 0.84); $A\beta_{1\text{-}42}$ (*g* = 0.88). In summary, there was no evidence from these weighted average effect sizes that the best CSF biomarker ($A\beta_{1\text{-}42}$) was superior to that of the best six neuropsychological tests, all of which produced average effect sizes greater than 0.90. The weighted average effect sizes in predicting conversion from MCI to AD of both CSF and neuropsychological tests from largest to smallest is shown in figure(s) 3.18 and 3.19.

Some potential signs of publication bias can be seen from the funnel plots of Logical Memory: Immediate Recall, RAVLT: Delayed Recall, ROCF: Delayed Recall, $A\beta_{1\text{-}42}$ and T-Tau. Again, there was no superiority here of the CSF tests over the neuropsychological tests. Two of the three CSF tests (the $A\beta_{1\text{-}42}$ and T-Tau) showed some sign of potential publication bias, i.e. a lower-than-expected number of studies with high standard error studies and small effect sizes. It should be acknowledged that it is difficult to judge this issue. The best neuropsychological tests (FCSRT, CVLT: Short Delay Free Recall, CVLT: Long Delay Free Recall, ROCF: Immediate Recall) had only 4, 5, 7 and 7 studies included respectively. As a rule of thumb, 10 studies or more should be used when looking for funnel plot asymmetry as when there are fewer studies the power of the tests may be too low to distinguish asymmetry from chance (Sterne et al, 2011). The remainder of the neuropsychological and biomarker tests had relatively minimal asymmetry at the high-standard-error region of the funnel. Accordingly, my summary and discussion here focuses upon the random effects estimates of the average effect size of the predictive converters-vs-nonconverters discrimination.

3.10.1: Age and Follow-up period

Is it possible that differences in age and follow-up period across the CSF tests could explain these results? For instance, it could be the case that the CSF tests involved younger patients and shorter follow-up times compared to those in the neuropsychological tests. Looking over Table 3.3, it can be seen that there is no systematic variation in this direction. Notably, for instance, comparing the top ranking neuropsychological test (FCSRT) with the top-ranking CSF biomarker ($A\beta_{1-42}$), the average age and follow-up times were rather similar (**FCSRT:** Non-Converters' age: 69.3 ± 1.3 years; Converters' age: 71.7 ± 3.3 (S.D) years; Follow-up: 3.1 ± 2.0 years; $A\beta_{1-42}$ CSF: Non-Converters' age: 69.0 ± 4.7 years; Converters' age: 72.0 ± 4.0; Follow-up: 2.8 ± 1.8 (S. D) years).

3.10.2: Limitations of the present meta-analyses

While it may be tempting to suggest that the diagnostic performance of the best six neuropsychological tests rivals that of the CSF biomarkers, the limitations of these findings must be acknowledged.

First, it is not straightforward to compare absolute values of effect sizes across testing domains because the patient samples may be different across the set of studies evaluating neuropsychological tests, and the set of studies evaluating CSF biomarkers. Further studies are needed where one or more of the best neuropsychological tests is directly compared to either/both of the p-tau and $A\beta_{1-42}$ CSF biomarkers. Our dataset did not permit sufficient direct comparison of the candidate neuropsychological tests, and the CSF biomarkers. However, we were able to compare CSF biomarkers vs MMSE test scores. Importantly, despite

a fairly large sample in terms of studies and patients, the beta amyloid and t-tau tests were not significantly better than the MMSE at predicting conversion.

Secondly, importantly, a key limitation was that total sample size was smaller in the three best-performing neuropsychological tests than the CSF tests. For the three top-ranking neuropsychological tests (FCSRT, CVLT Free Recall Short Delay, CVLT Free Recall Long Delay), analyses were based on a total sample of patient numbers in the 100s (n = 348 for SRT, n = 303 & 388 for the two CVLT tests). This is in contrast to the total sample in the 1000s for the three CSF biomarkers (n = 2370 for $A\beta_{1-42}$, n = 2193 for p-tau; n = 2469 for t-tau). Accordingly, caution is certainly merited before concluding that SRT and CVLT offer *superior* diagnostic performance to CSF tests.

Nevertheless, concluding that these tests are at least as diagnostic and robust as the p-tau and $A\beta_{1-42}$ CSF biomarkers seems plausible for the following reasons: 1) the three tests produced higher effect sizes than the three CSF biomarkers; 2) no single conversion study using any of the three top-ranking neuropsychological tests obtained a lower effect size than 0.956 (CVLT Free Recall Long Delay: 0.956; CVLT Free Recall Long Delay: 0.968; SRT: 0.961), i.e. the lowest-obtained single-study effect size was higher than that obtained from the average of any of the CSF biomarkers, including the highest performing one ($A\beta_{1-42}$: 0.88); 3) the RAVLT: Delayed Recall and ADAS-COG, producing an effect sizes of 0.95 and 0.90 respectively, had sample sizes (n = 2605 and 3508 respectively) larger than all three CSF tests (n = 2502 for t-tau; n = 2543 for p-tau; n = 2347 for $A\beta_{1-42}$). Taken together, these considerations suggest that sample size alone cannot discredit the apparent efficacy of the six best-performing neuropsychological testing.

Perhaps less important, it may also be considered a limitation that we did not consider CSF biomarker combinations (e.g. tau/$A\beta_{1-42}$ ratios or $A\beta_{1-40}$ and $A\beta_{1-42}$ combinations).

Combinations of CSF biomarkers may turn out to be more accurate for diagnosis than singly applied biomarkers (Ritchie et al, 2017; O Hansson et al, 2009; Blennow et al, 2001). Currently, however, there are relatively few reports with data whereby tau/A$\beta_{1\text{-}42}$ ratios predict conversion (Ritchie et al, 2017). Combinations of tests would be worth exploring in future meta-analyses. Importantly, however, just as CSF biomarker values can be combined to improve diagnostic accuracy, so can scores from neuropsychological tests (e.g. Pozueta et al, 2011; Lepeleire et al, 2005). Accordingly, there is nothing in the analytic approach that is biased against CSF biomarkers. My focus here was upon identifying the best neuropsychological tests and CSF biomarkers, considered singly, in the belief that this may contribute to decision-making about which tests to use and combine in future studies.

3.10.3: Combining tests may be beneficial

Regarding combining different neuropsychological tests, it is interesting that FCSRT and CVLT delayed free recall may have different sensitivity/specificity profiles for predicting conversion. CVLT delayed free recall tends to produce higher sensitivity than specificity for predicting conversion to Alzheimer's disease (Anchisi et al, 2005; Rabin et al, 2009, Pozueta et al, 2011), e.g. 97% sensitivity and 59% specificity in Anchisi et al (2005). On the other hand, while producing the highest diagnostic performance of any tests reviewed here, the FCSRT tends to show higher specificity than sensitivity for predicting conversion (Tabert et al, 2006; Sarazin et al, 2007; Didic et al, 2013), e.g. 80% sensitivity and 90% specificity in (Sarazin et al, 2007). It is plausible that combinations of tests with different sensitivity/specificity profiles may help to increase diagnostic accuracy. Our findings that that FCSRT offers the most accurate performance in predicting conversion to Alzheimer's disease supports the recommendation

of this task by the International Working Group for New Research Criteria for the Diagnosis of Alzheimer's Disease (Dubois et al, 2007; 2014).

3.10.4: The best performing neuropsychological tests may well be hippocampus dependent.

It is particularly interesting that the top five performing neuropsychological tests within the meta-analysis were tests of episodic memory (FCSRT, CVLT: Short Delay Free Recall, CVLT: Long Delay Free Recall and RAVLT: Delayed Recall) and Spatial Ability (Rey's Complex Figure Recall: Immediate Recall). Episodic memory impairment is amongst the most common early signs of AD type dementia (Backman et al 2001; Greenaway et al, 2006; Twamley et al, 2006) and other neuropsychological studies have shown that episodic learning and recall discriminate between healthy controls and pre-clinical AD participants (Collie & Maruff; Twamley et al, 2006).

The ROCF has been found to be sensitive to medial temporal lobe damage (Spreen, 1998; Lezak, 1995) and specifically associated with hippocampal functioning (Babiloni; Snaphaan et al, 2008), integrity (Carlesimo et al, 2010; Van Norden et al, 2012), and volume (den Heijer et al 2010; 2012). The relationship between spatial memory and AD is well established (Cherrier et al, 2001; DeIpolyi et al, 2007; Bird et al, 2010) as discussed in Chapter 1 Section 1.8.2. As hippocampal degeneration occurs at an early stage of AD, it is perhaps unsurprising that the tests which best predicted MCI to AD conversion are likely assaying hippocampal function, at least in part. This further supports the ability of neuropsychological tests which tap hippocampal function to identify early decline. This is further explored in the new and recently developed tests included within this thesis, which focus upon episodic and spatial memory (Chapters 4 and 5).

3.10.5: What is the status of neuropsychological tests for a disease that is increasingly biologically defined?

The National Institute on Ageing and Alzheimer's Association (NIA-AA) 2018 framework suggests that Alzheimer's disease, for research purposes at least, should be biologically defined (Jack et al, 2018; Silverberg et al, 2018). For example, Figure 1 of Silverberg et al 2018 suggests that "the current recognised biomarkers are positive 20-30 years prior to symptoms". Arguably, this kind of claim can better be seen as a campaigning slogan, rather than illustrating a proven principle. The specificity of the claim applies in at least two respects. Firstly, these data rest on characterising patients with highly genetically driven versions of Alzheimer's disease, and such patients represent a small minority of Alzheimer's disease population. The application of these data to the development of neurodegeneration and symptomology in sporadic AD is not straightforward. Secondly, neuropsychological tests for earlier stages of Alzheimer's disease are relatively undeveloped. As this thesis notes, there may be particular advantage in using ecologically-valid tests of spatial memory and episodic memory, designed with the neurobiological substrate in mind, in diagnosing early AD, and these kinds of tests seem promising despite their relative novelty. A recent study used a test of spatial memory (path integration), designed specifically to test the integrity of the entorhinal cortex, and distinguished excellently between MCI+ and MCI- subjects (Howett et al, 2019).

As mentioned in the Introduction above, there is increasing research effort on developing diagnostic tests tapping spatial cognition. Allocentric spatial representations are known to depend on regions early affected in Alzheimer's disease, notably the hippocampal formation including the entorhinal cortex and hippocampus (Hartley et al, 2014; Poulter et al,

2018). There are encouraging, if preliminary, signs that predisposition to AD can be seen with purely cognitive testing well before symptoms become apparent. For instance, performance on the video game 'Sea Hero Quest', testing spatial cognition, is poorer in APOE e4 carriers in midlife (Coughlan et al, 2019). Accordingly, it seems highly plausible that such development of cognitive testing, motivated and constrained by knowledge of the cellular and regional neurobiological underpinnings of cognition, will greatly improve predictive accuracy in what is typically regarded as 'pre-symptomatic' stages of Alzheimer's disease. Furthermore, because such neuropsychological testing may be more practical, neuropsychological diagnostics can also benefit from heavily-sampled population norms (helping to recognise age age-normalised patient deficits), and repeated within-subject testing (e.g. helping to recognise declines in patient scores across time).

While some question marks may remain regarding the accuracy of medical diagnosis of Alzheimer's disease at follow up, without *post-mortem* confirmation, these findings point to the utility of neuropsychological testing at the MCI stage to diagnose 'MCI due to Alzheimer's disease'. Applied to the future, and to earlier stages of Alzheimer's disease, the findings suggest it may be possible that a combination of tests including biomarkers that specifically include neuropsychological tests may be more efficacious than biomarkers alone, in detecting classically 'pre-clinical' Alzheimer's disease.

Chapter 4: Neuropsychological testing of healthy participants.

Table 4. 1

Neuropsychological tests included in each study within this thesis. Neuropsychological tests included in the current chapter (Chapter 4) shown in bold.

Neuropsychological Test	Meta-analysis (Chapter 3)	**Healthy control testing (Chapter 4)**	Clinical MCI study (Chapter 5)	Designed to test
Mini Multi-State Examination (MMSE)	✓	✗	✗	Multi-domain cognition.
Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG)	✓	✗	✗	Multi-domain cognition.
Free and Cued Selective Reminding Test (FCSRT)	✓	✗	✗	Episodic memory.
Rey Auditory Verbal Learning Test (RAVLT)	✓	✗	✓	Verbal learning and memory.
California Verbal Learning Test (CVLT)	✓	✗	✗	Verbal learning and memory.
Logical memory subtest of the Wechsler memory scale (Logical Memory)	✓	✗	✗	Verbal and working memory.
Trail Making Test B (TMT-B)	✓	✗	✓	Visual attention and task-switching.
Rey–Osterrieth complex figure (ROCF)	✓	✗	✗	Impairments in visuospatial construction.
Four Mountains Test (4MT)	✗	✓	✓	Allocentric spatial working memory.
Spaces and Sequence Episodic Video Task (SSEVT)	✗	✓	✓	Episodic memory.
Buschke Selective Reminding Test (SRT)	✗	✗	✓	Verbal learning and memory.
Spatial Ability and Practices Questionnaire (SAPQ)	✗	✓	✓	Spatial working memory.
Social Networks and Embeddedness Questionnaire (SNSEQ)	✗	✓	✓	Size and complexity of social networks.
Addenbrooke's Cognitive Assessment- III (ACE-III)	✗	✓	✓	Multi-domain Cognition

The table above illustrates all neuropsychological tests included in the thesis, which portion of the thesis they are used within and which functions they aim to test. The ticks in green represent an included test within the chapter at the top of the table whereas the crosses represent tests that were not included in that particular chapter. The tests included in Chapter 4 are shown in **bold.**

4.1: Participants and Recruitment

'Healthy' participants were recruited over the course of 3 years by myself and also by teams of students supervised by Dr Colin Lever and I. The test battery was not as extensive as for the MCI study with only the ACE-III, Four Mountains Test, Episodic Video Task (SSEVT) and the Spatial (SAPQ) and Social (SNSEQ) questionnaires included. Participants were all over the age of 18 and were recruited through various mediums including; word of mouth, local clubs and online posts. For those tested by undergraduate or MSc groups the upper age limit was 74, but those tested by myself could be over 75 due to requirements for additional ethical and DBS clearance. In order to ensure that there were no other cognitive factors which may affect performance, the following same exclusion criteria was applied except that, in addition, participants should have no diagnosis of dementia or MCI.

1. Presence of significant neurological condition such as Traumatic Brain Injury, Epilepsy, Stroke, Multiple Sclerosis, Brain tumour, Encephalitis, Meningitis, Parkinson's disease or visual impairment severe enough to hamper processing of visual test stimuli.

2. Major psychiatric disorder, such as schizophrenia, bipolar disorder and personality disorders such as a borderline personality disorder. Participants with severe (but not mild or moderate) clinical depression, and severe (but not mild or moderate) anxiety were also excluded.

3. The use of cognitive enhancing drugs e.g. Cholinesterase inhibitors

4. A history of alcohol excess, i.e. has received external assistance and/or previously had functional issues due to a reliance on alcohol or excess of illicit drug use within the last 5 years.

5. A diagnosis of MCI or Dementia.

There was some variation in the number of individuals who took each test. Details of participant numbers, age, sex and education are given in Section 4.5 and 4.6. The tests given in relation to other thesis study chapters is given in Chapter 2 table 2.1.

Education was categorised according to the highest level of educational qualification participants achieved, which is explained in table 4.2.

Table 4. 2

Categorisation of participants' education level.

Education Score	Level of Education
0	No formal qualifications
1	GCSE or equivalent
2	A-Level or equivalent
3	Undergraduate degree
4	Postgraduate qualification

Education was categorised according to the highest level of education achieved by the participant.

4.2: Materials

The Social Network and Embeddedness Questionnaire (SNSEQ), Spatial Abilities and Practices Questionnaire (SAPQ) and the ACE-III were purely pen and paper based. The 4MT and the Spaces and Sequence Episodic Video Task (SSEVT) required a computer for which a 15’ Dell laptop was used, results were then recorded on score sheets.

Table 4. 3

Testing Procedure

Test	Duration (minutes)	Delay (minutes)	Materials	Scoring details
Four Mountains Test (4MT)	15	NONE	Laptop (Dell 15') and pen and paper.	0-15, with higher scores indicating greater allocentric spatial memory. Error *type* was also recorded.
Spaces and Sequence Episodic Video Task (SSEVT)	5	20	Video-Laptop (Dell 15')	0-17, with higher scores suggesting greater episodic memory.
Social Network and Social Embeddedness Questionnaire (SNSEQ)	10	NONE	Paper based	0-80, with higher scores indicating more social embedment and a larger social network.
Answers to Spaces and Sequence Episodic Video Task (SSEVT)	10- 15	None	Laptop and paper	0-17, with higher scores suggesting greater episodic memory.
Spatial Ability and Practices Questionnaire (SAPQ)	10	NONE	Paper based	15-75 for SAPQ score, with higher scores suggesting greater spatial ability. -15 - +15 for SAPQ change, with positive scores indicating an improvement in spatial abilities within the last year and negative scores indicating a decrease in spatial abilities, and the degree of overall positivity and negativity indicating the magnitude of the change.
ACE-III	10	NONE	Paper based	Overall: 0-100, with higher scores indicating greater cognition. Attention: 0-18, Memory: 0-26, Fluency: 0-14 Language: 0-26, Visuospatial: 0-16

A table outlining the tests used within the healthy study including the duration, any delay, materials used and scoring details.

Testing was conducted by myself and various undergraduate researchers. I did however, spend considerable time with testing groups to ensure consistency and accuracy in the way they were administered. This consisted of several practice sessions, instruction on the delivery of testing scripts to ensure that instructions were given in a standardised way and advice on how to answer any questions they may experience from participants. Specific details on each test are given in Chapter 2 and summarised in table 4.3. As with the MCI study discussed in Chapter 5, the testing environment varied. Some people were tested within rooms within Durham university whilst others were tested in community halls or in their own homes. Participants were advised that a quiet environment free from distractions, with a table on which to work would be necessary prior to meeting. All groups received ethics approval and lone working was supervised by Dr Colin Lever and Dr Stephen Evans.

4.4: General overview of analysis: rationale regarding age and education

I first characterise (further) two tests that were created with a view to developing better early diagnosis of Alzheimer's disease in its prodromal or even 'preclinical' phases. These two tests are: 1) the Four Mountains Test (4MT), which was first introduced in 2007; and 2) the Spaces and Sequences Episodic Video task (SSEVT), developed for this project. In the Introduction (Section 1.8) and General Methods (Sections 2.10 and 2.11), I made the general point that a key characteristic of a neuropsychological test for Alzheimer's type dementia, which involves early pathological changes to hippocampal tissue, is that the test should be hippocampal-dependent. Exactly with this rationale in mind, both tasks were designed to probe the functional integrity of the hippocampus, the 4MT by tapping allocentric spatial

memory, the SSEVT by tapping recollective, episodic memory, because both these functions are thought to be reliant upon the hippocampal formation.

Importantly, hippocampal tissue integrity and volume declines in healthy ageing (e.g. Zimmerman et al, 2008; Barnes et al, 2009; Fotuhi et al 2012; Kurth et al 2015; Ezzatti et al, 2016), and this decline is faster than for many other brain regions (Raz et al, 2004; Raz et al, 2005; Raz et al, 2010). For instance, hippocampal volume declines with age appreciably faster than volume in Insular cortex, Orbitofrontal cortex, Inferior Parietal Cortex, Primary visual cortex, and the caudate nucleus (Raz et al, 2004; Raz et al, 2005; Raz et al, 2010). This hippocampal volume shrinkage is consistent for instance with Levine et al (2002)'s highly-influential finding that episodic detail is impaired in ageing, but not semantic detail, under the logic that episodic memory is highly hippocampus-dependent. It follows that performance on a hippocampus-dependent task useful for diagnosing early AD will also be expected to decline with age over the lifespan even in those who are healthily ageing. If this relationship is statistically significant or strong, this does not of course guarantee that the task will be highly sensitive to AD. However, it is clear that the relationship between task success and age is expected to be negative, whether weakly or strongly so, and certainly not positive. Accordingly, for both the 4MT and SSEVT, I examine to what extent older age is associated with lower scores on these 'hippocampal' tasks. Along with examining participants over the age of 45, I also further explore the impact of age related decline by looking at the difference in test scores between young, middle and older age groups on the SSEVT, 4MT and the ACE III.

In discussing ideal characteristics of a task diagnosing early AD (Chapter 1, Sections 1.8.1 and 1.3.4), I noted that one of these characteristics was that education should not be

an overly influential asset in successful task performance. If it is, such a task becomes vulnerable to false positives whereby the less-educated perform worse than expected, and to false negatives whereby the highly educated are able to mask their neurological deficits. It seems straightforward to argue that an ideal task is one in which education levels make no contribution to predicting task scores. However, it is perhaps difficult to entirely rule out the counter view that education should positively predict scores on an Alzheimer's-disease relevant task since several studies have found that low education is associated with increased risk of dementia (Chapter 1, Section 1.3.4). With these considerations in mind, for both the 4MT and SSEVT, I examine to what extent higher levels of education predict better scores on these tasks.

4.4.1: General overview of analysis: rationale re Questionnaires.

Importantly, unlike the two cognitive tasks (4MT & SSEVT), the two Questionnaires were not designed with equivalent intentions. We designed the Spatial Abilities and Practices Questionnaire (SAPQ) as part of this project to see if it could function as a useful screen for deficits in spatial ability and thus AD. As part of this investigation, it may be useful to examine to what extent the SAPQ taps abilities supporting successful performance in the 4MT. Accordingly, I examine if scores on the 4MT and SAPQ are positively correlated.

We designed the Social Networks and Social Embedding Questionnaire (SNSEQ) as part of this project to further test the hypothesis that rich social networks may play a protective role in dementia, or conversely put, that poor social networks elevate risk of dementia. This question is considered in Chapter 5 with reference to the MCI patients,

where I cross-sectionally test the prediction that MCI patients will have weaker social networks than age-matched healthy controls. In this Chapter, I test the prediction that weaker social networks predict lower scores on the two cognitive tasks in healthy ageing. To further appreciate the characteristics of both questionnaires, I also test how their scores are predicted by age and education. In all of the tests included within the analysis, no significant difference was found between sexes in scores.

4.5: Participant demographics for those aged 45+

Education was categorised according to the highest level of educational qualification participants achieved, as set out in Table 4.2. The age, gender, educational attainment, and the number of participants aged 45+ that took each test is summarised in Table 4.4.

Table 4. 4

Descriptive Statistics for HC group aged 45 +.

	Male n	Female n	Participant n	Age Minimum	Age Maximum	Age M ± SD	Education M ± SD
4MT	55	87	142	45	89	60.4 ± 8.8	2.2 ± 1.2
SSEVT	41	72	113	45	84	59.7 ± 8.6	2.5 ± 1.1
SNSEQ	43	72	115	45	89	60.4 ± 9.3	2.4 ± 1.1
SAPQ	42	72	114	45	89	60.5 ± 9.3	2.5 ± 1.1
ACE III	31	56	87	45	84	59.7 ± 9.0	2.5 ± 1.1

Descriptive statistics for all the tests used: Four Mountains Test (4MT), Spaces and Sequence Episodic Video Task (SSEVT), Spatial Abilities and Practices Questionnaire (SAPQ), Social and Embeddedness Networks Questionnaire (SNQ) and the ACE-III. Participant N differs between groups. Education and Age is given as mean ± standard deviation.

4.6: The relationship between age and 4MT and SSEVT in participants over the age of 45.

A Pearson correlation was used to investigate the relationship between age and test scores in the 4MT and SSEVT. A negative correlation was found between age and Four Mountains Test score (r=-0.22, p=0.009), shown in Figure 4.1A. A negative correlation was also found between age and SSEVT score (r= -0.26, p= 0.006) as shown in Figure 4.1B. The moderate negative correlations between age and both 4MT and SSEVT tests fall in line with expectations as both the tests are designed to be dependent upon the hippocampus, an area known to decline with age, even within those who are healthily ageing.

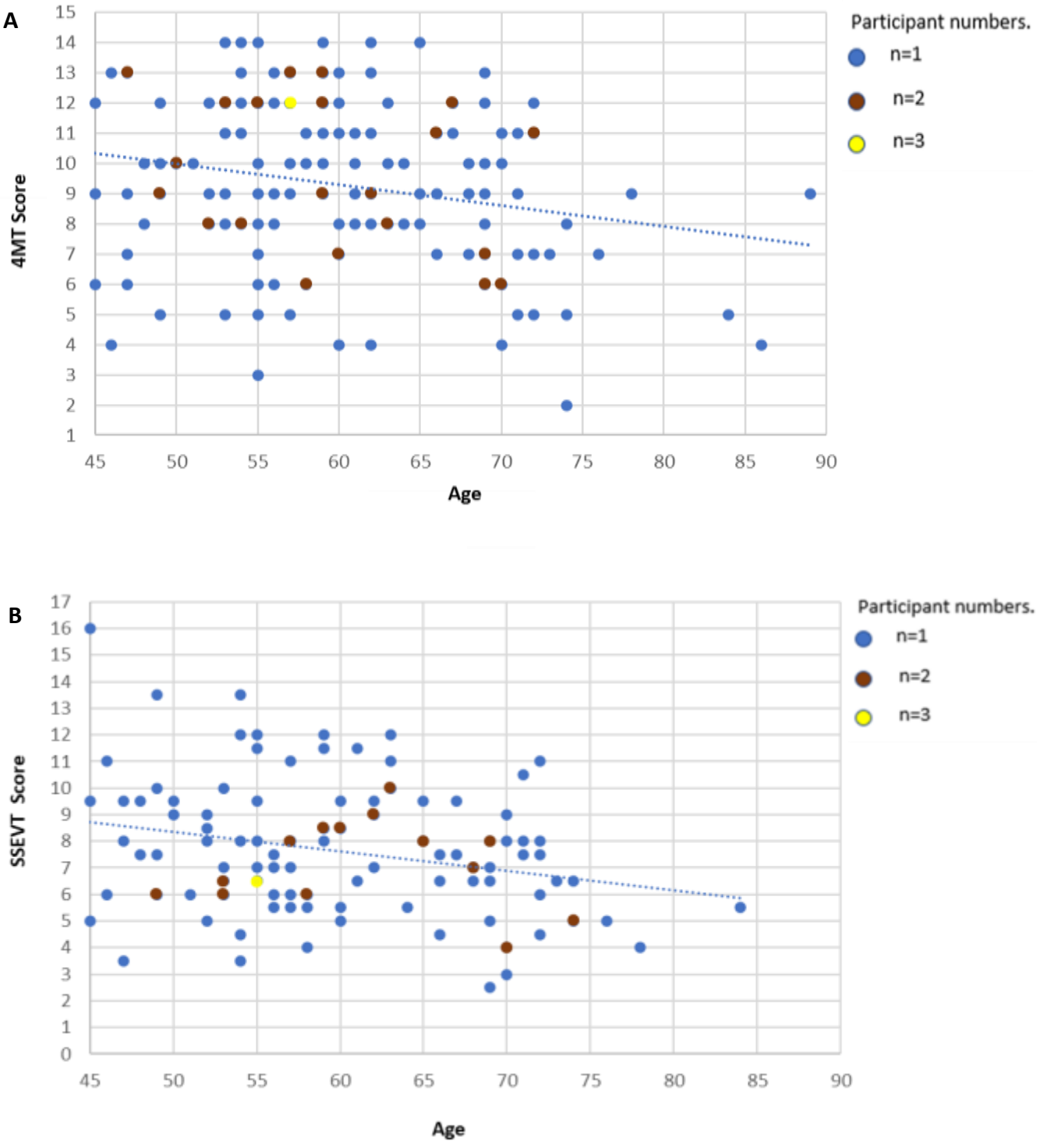


Figure 4. 1. **Scatterplot of the relationship between age and SSEVT and 4MT scores.**

Dotted line illustrates the line of best fit. Key to the right of each graph indicates how many participants each coloured point represents. Participants were aged between 45 and 84.
(A) The 4MT has a maximum score of 15. A negative correlation was found between age and 4MT test scores (r= -0.22, p=0.009). **(B)** The SSEVT has a maximum score of 17. A negative correlation was found between age and SSEVT scores (r= -0.26, p=0.006).

4.7: The SSEVT and 4MT are better able to differentiate between younger, middle and older participant group scores than the ACE III.

In order to further explore whether episodic and spatial memory ability declines with age the data was divided into 3 groups: Young (18-34), Middle (45-64) and Older (65+). The younger group 18-34 group ages were chosen to reflect the youngest age tested up to adulthood. Middle (45-64) was chosen to reflect slightly older people. It is thought that relatively little decline occurs until individuals are around 50 years old (Albert & Heaton, 1988), and this group was created to capture this. The older group of 65+ was chosen to encapsulate older individuals who possibly may be at retirement age. The number of participants that took each test differed as can be seen in Table 4.5 A, B and C.

Table 4.5 A

4MT group averages

Age group	Age M ± SD	Participant n	Sex	Education M ± SD	4MT Score M ± SD
Young (18-34)	23.1 ± 3.8	113	59 F: 54 M	2.3 ± 0.7	11.1 ± 2.3
Middle (45-64)	55.5 ± 5.1	97	62 F: 35 M	2.4 ± 1.1	9.7 ± 2.7
Older (65 +)	70.8 ± 5.1	45	25 F: 20 M	1.8 ± 1.2	8.4 ± 2.7

Table 4.5 B

SSEVT group averages.

Age group	Age M ± SD	Participant n	Sex	Education M ± SD	SSEVT Score M ± SD
Young (18-34)	23.5 ± 3.9	87	48 F: 39 M	2.5 ± 0.64	9.0 ± 2.5
Middle (45-64)	54.9 ± 5.1	76	49 F: 27 M	2.7 ± 0.9	8.1 ± 2.5
Older (65 +)	70.3 ± 3.8	37	23 F: 14 M	1.9 ± 1.3	6.7 ± 2.0

Age, Education and Score are represented as mean ± standard deviation. Sex is given as n of Females (F) and Males (M) Education was categorised according to the highest level of education the participant had achieved at the time of testing: 0= no formal education, 1= GCSE or equivalent, 2= A-Level or equivalent, 3= undergraduate degree, 4= postgraduate qualification**. (A)** Four Mountains Test (4MT) group averages. (**B)** Spaces and Sequence Episodic Video Task (SSEVT) group averages. (**C)** Addenbrooke's Cognitive Examination III (ACE III) group averages.

Table 4.5 C

ACE III group averages.

Age group	Age M ± SD	Participant n	Sex	Education M ± SD	ACE III Score M ± SD
Young (18-34)	23.5 ± 4.2	69	42 F: 27 M	2.4 ± 0.7	93.8 ± 4.4
Middle (45-64)	54.5 ± 5.2	58	39 F: 19 M	2.8 ± 0.8	94.6 ± 5.0
Older (65 +)	70.3 ± 4.3	29	17 F: 12 M	2.0 ± 1.4	92.6 ± 6.0

All group averages and standard deviations are summarised on table 4.5A, B and C above. A one-way independent groups ANOVA was conducted to compare the effect of age group on 4MT scores. Effect sizes were also calculated in order to quantify the size of the difference between group scores (young, middle and old). Hedge's g was chosen to measure effect size between group scores due to the differing participant sample sizes. Glass's delta was also analysed to control for any significant difference in standard deviation between group scores as it only uses the standard deviation of the control group.

There was a significant effect of age group on 4MT scores, ($F(2, 252) = 20.292$, $p<0.001$ as illustrated in Figure 4.2A. An independent samples t-test found a significant difference in the scores achieved by the young group (M= 11.1, SD=2.3) and the middle group (M=9.7, SD=2.7) on the 4MT ($t(208) = 4.159$, $p= 0.000047$), with the middle group scoring significantly lower than the young group. A medium effect size was found between young and middle groups using Hedge's g (0.58) and Glass's delta (0.63).

A significant difference was also found in the middle group (M = 9.7, SD = 2.7) and older group (M = 8.4, SD = 2.7) on 4MT scores ($t(140) = 2.577$, $p = 0.011$), with the older group scoring significantly lower than the middle group. A medium effect size was also seen between these two groups (Hedges g = 0.46, Glass's delta = 0.47)

A one-way independent groups ANOVA was also run to compare the effect of age group on SSEVT scores. A significant effect of age group on SSEVT Score ($F(2,197) = 12.258$, $p = 0.00001$) as shown in Figure 4.2B, as the average age of the group increased, the average score achieved decreased. An independent samples t-test found a significant difference between the young group (M = 9.0, SD = 2.5) and the middle group (M = 8.1, SD, 2.5) scores on the SSEVT, with the middle group scoring significantly lower than the young group (t

(161) = 2.359, p = 0.020. However only a small effect size was seen between participants in the young and middle groups' SSEVT scores (hedge's g = 0.37, glass's delta = 0.37). The older group was also found to score significantly lower than the middle group (M = 6.7, SD = 2.0), (t (111) = 2.962, p = 0.004), with a medium effect size found using both hedge's g and glass's delta, 0.59 and 0.56 respectively.

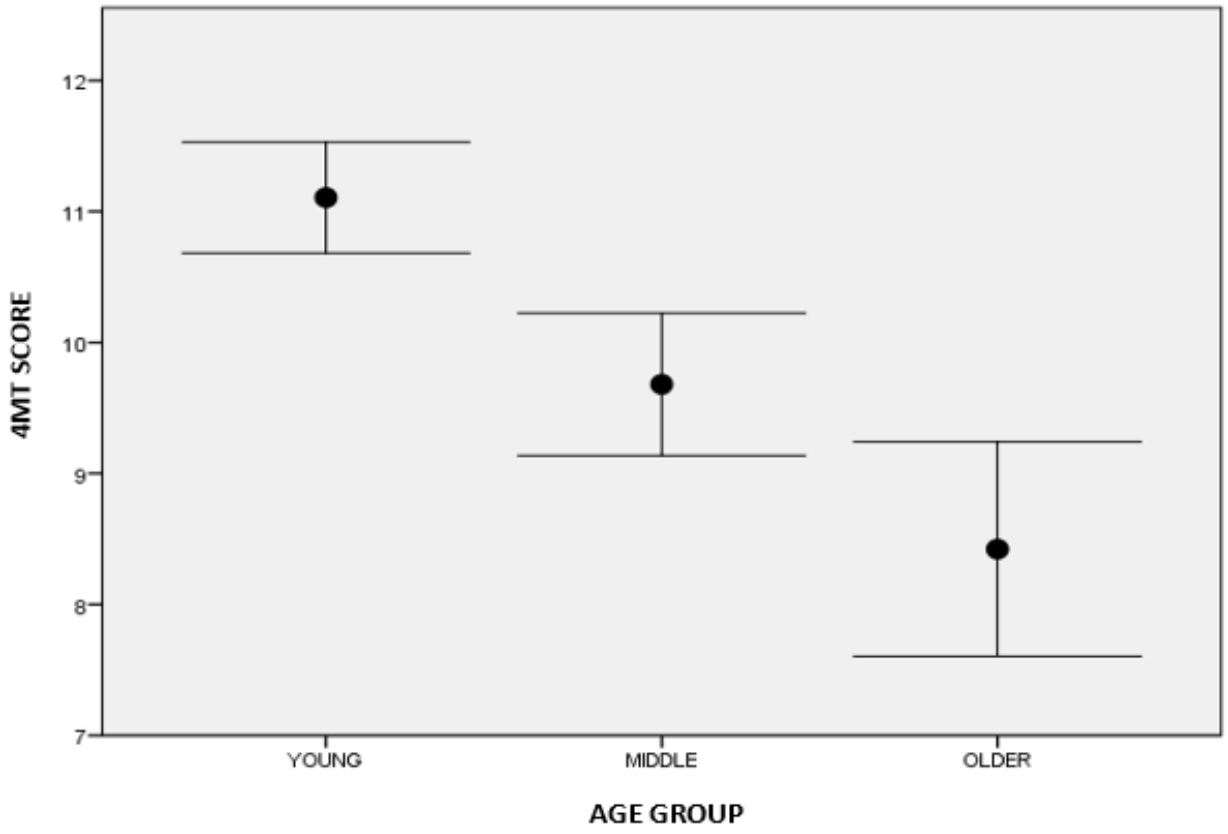
Upon looking at the ACE-III scores, one participant's results were excluded as at the age of 33 they scored 62 which is indicative of memory impairment (Hsieh et al, 2013). This exclusion criterion was applied after looking at the data. For a 33-year-old individual to score at a level which suggests impairment more befitting of MCI is highly unusual and may suggest either some form of cognitive impairment, a lack of effort, possible malingering or a testing error, all of which would make those scores an unreliable representation of how a healthy 33-year-old may perform when taking these tests. Therefore it was deemed inappropriate for this participant to be analysed along with the rest of the healthy control group. Note that if this participant was included the findings below suggesting the relative insensitivity of ACE-III to cognitive ageing would be even clearer.

No significant difference was found in the group scores on the ACE III (F (2,153) = 1.688, p = 0.188), as can be seen in Figure 4.2C. Unsurprisingly an independent samples t-test found no significant difference in the scores achieved by the young group (M = 93.8, SD = 4.4) and the middle group (M = 94.6, SD = 5.0) when taking the ACE III (t (125) = -1.006, p = 0.317. A small effect was found between these two groups (Hedge's g = 0.18, Glass's delta = 0.19). Similarly, an independent t-test found no significant difference between the middle group (M = 94.6, SD = 5.0) and the older group (M = 92.6, SD = 6.0) scores on the ACE III (t (85) = 1.685, p = 0.096). As with the young and old groups a small effect size was seen

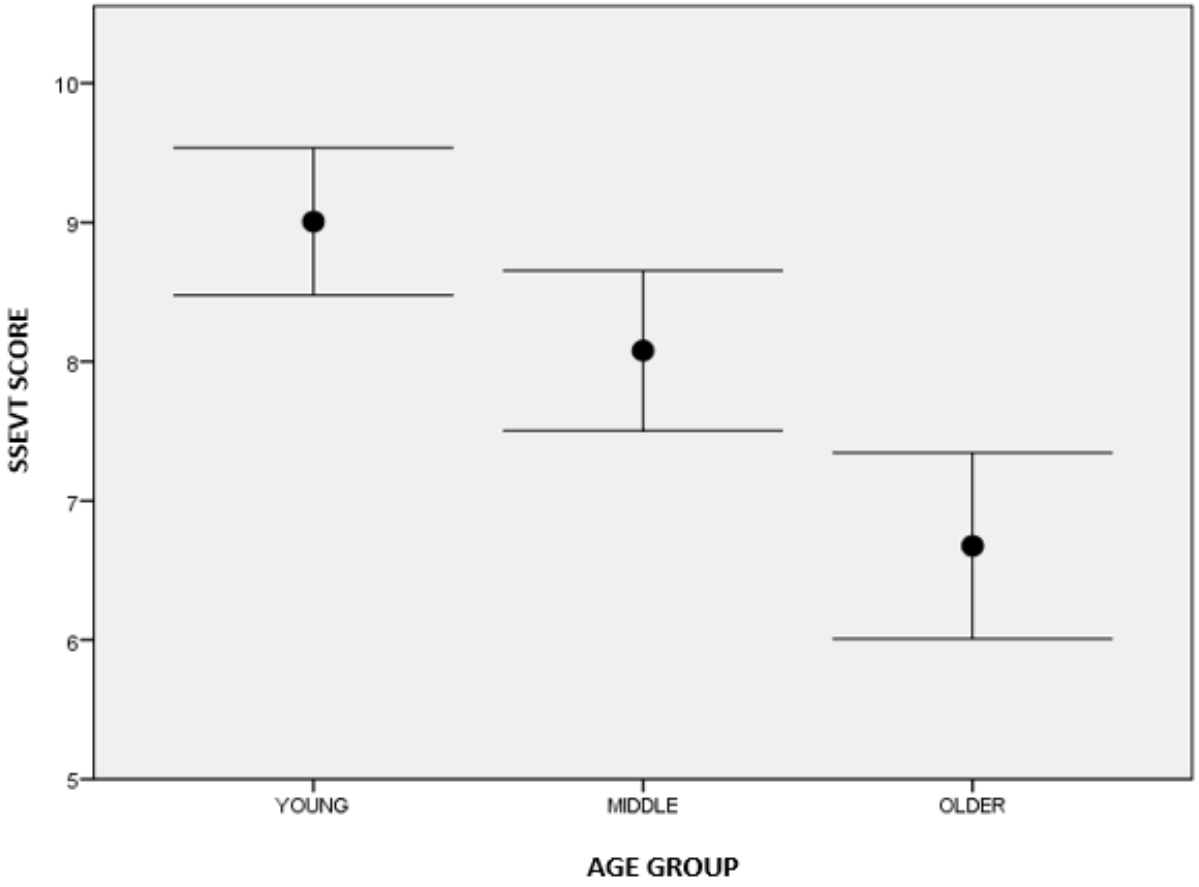
between the scores achieved on the ACE III between middle and older age groups (Hedge's g = 0.38, Glass's delta = 0.41).

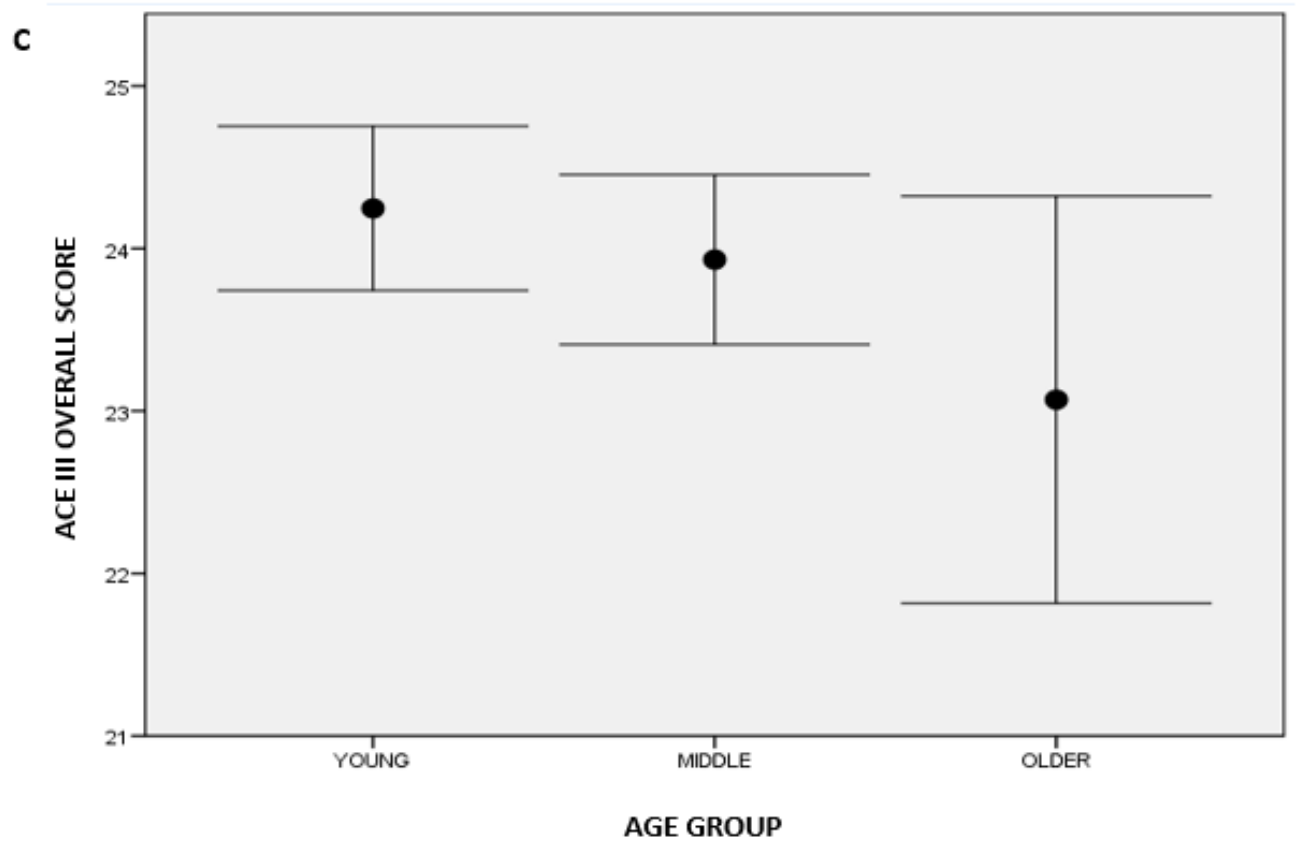
The seemingly blunt insensitivity of the ACE-III to cognitive ageing was surprising. Accordingly, I re-analysed the test, examining scores only on the memory sections of the ACE III. There was still no effect of age group upon memory section (F (2,153) = 2.611, p=0.077). This is shown in Figure 4.2D. ACE III scoring details can be found in Table 4.3 and a detailed description of the ACE III overall and the ACE III memory section is included in Chapter 2, Section 2.15.

A


12
11
10
9
8
7
4MT SCORE
YOUNG
MIDDLE
OLDER
AGE GROUP

B


10
9
8
7
6
5
SSEVT SCORE
YOUNG
MIDDLE
OLDER
AGE GROUP



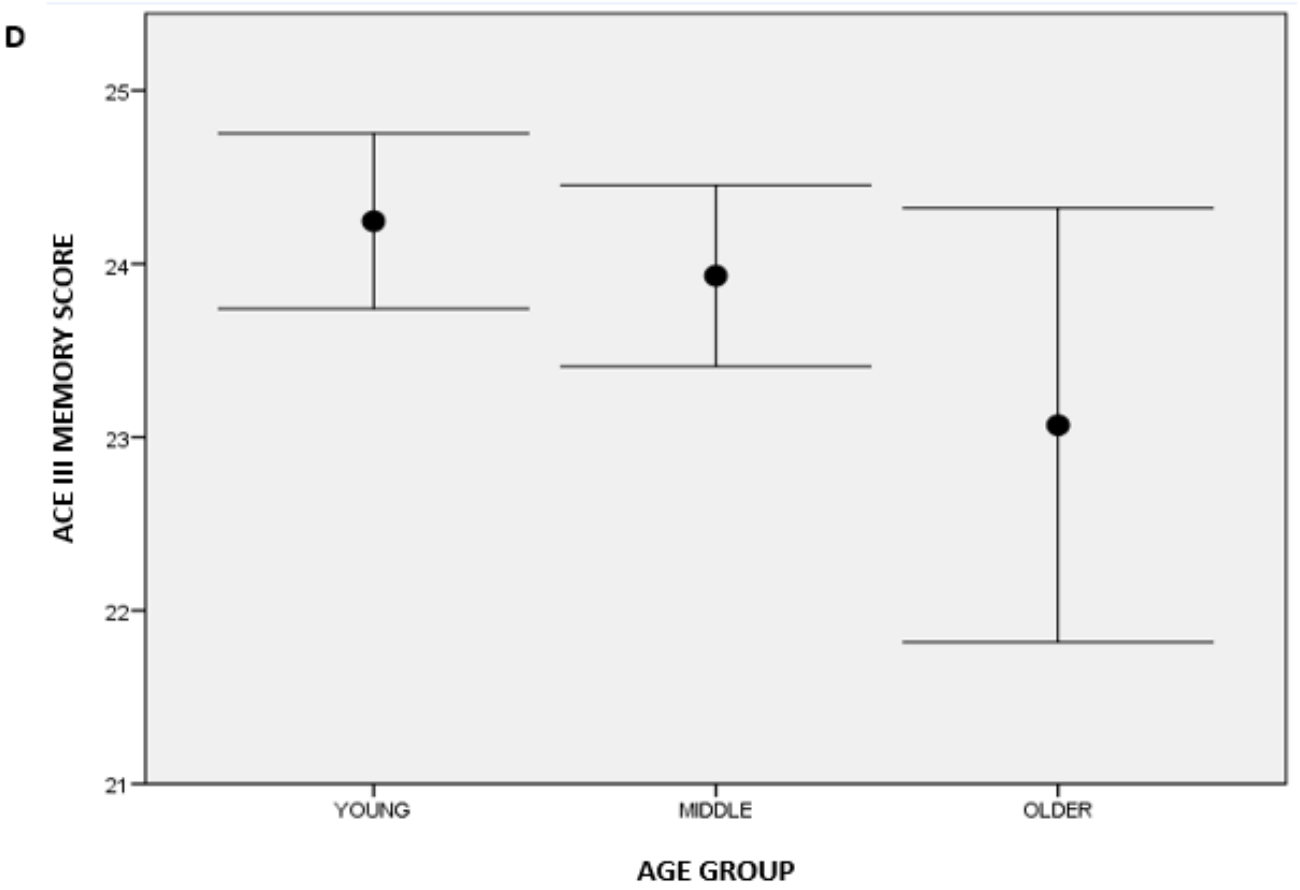
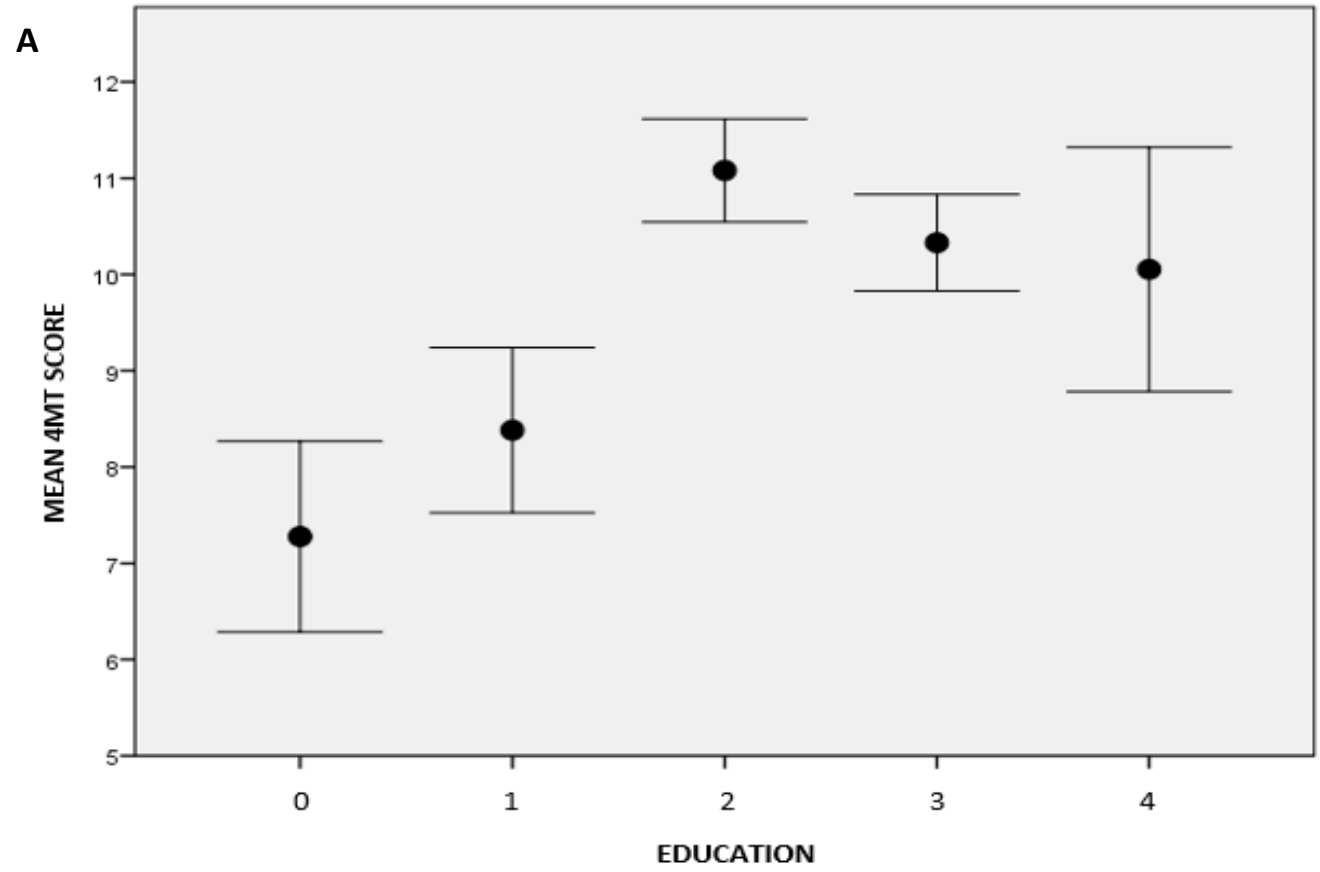


Figure 4. 2. **Relationship between age group and test scores.**

Error bars represent +/- 1 standard error of the mean**. (A)** Significant effect found between age groups and 4MT scores, (F (2, 252) =20.292, *P*= <0.001 **(B)** Significant effect found between age groups and SSEVT scores (F (2,197) =12.258, *P*=0.000010) **(C)** No significant difference was found in the group scores on the ACE III (F (2,153) =1.688, *P*=0.188) **(D)** No significant difference was found in the group scores on the memory section of the ACE III, which was scored out of 26 (F (2,153) = 2.611, *P*=0.077).

To investigate the relationship between education and test scores on the two hippocampal dependant tasks, the 4MT and the SSEVT, a Pearson correlation was used. A positive correlation was found between the participants' level of education and the amount of correct answers they acquired on the 4MT (r=0.345, p=0.000027), illustrated in Figure 4.3A. As discussed in Chapter 1, education should ideally not be an overly influential asset in successful task performance. However, education could potentially predict test scores on Alzheimer's disease relevant tasks such as the 4MT. Studies have linked education to dementia risk.

Education level did not correlate with SSEVT test scores (r=0.075, p=0.428), shown in Figure 4.3B. This lack of educational influence may be considered advantageous in a neuropsychological test in order to avoid false positives whereby less educated participants perform worse than expected and highly educated individuals are better able to mask neurological deficit. This is explained in more detail in Chapter 1, Section 1.3.4.



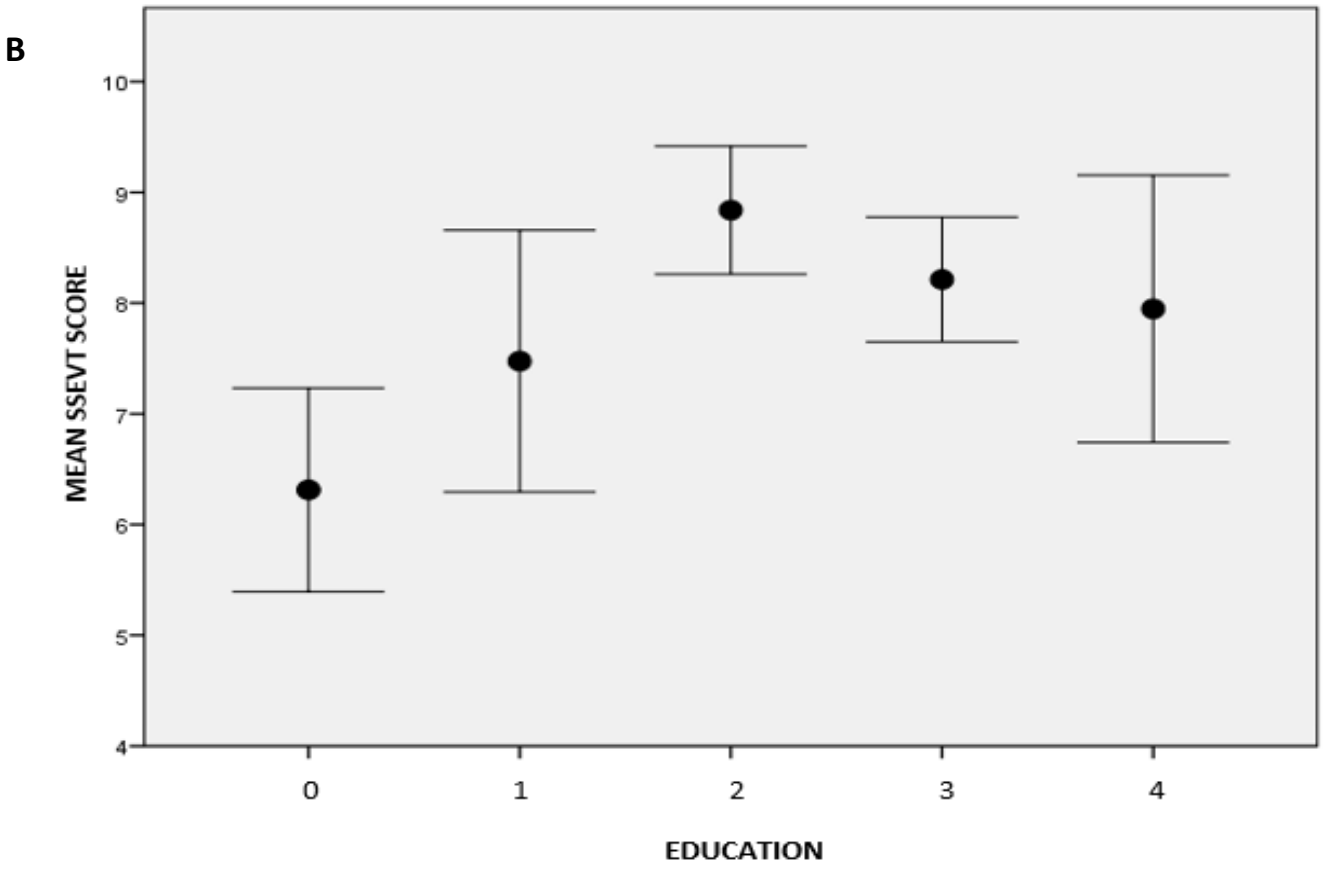


Figure 4. 3. **Relationship between test scores and education level.**

Error bars represent +/- 1 standard error of the mean. Coding for education level can be found in table 4.2. **(A)** Relationship between education and 4MT scores. Individuals who had achieved a higher level of qualification generally achieved higher 4MT scores (r=0.345, *P*=0.000027). **(B)** Relationship between education and SSEVT scores. Education level did not correlate with SSEVT test scores (r=0.0.075, *P*=0.43).

4.9: To what extent do higher levels of education predict lower scores on the two cognitive tasks (4MT and SSEVT) in healthy aging (45+)?

In order to see if age or education could predict the scores achieved by participants in either the 4MT or SSEVT, a linear regression was used. Since none of the VIF values were above 3 the assumption of multicollinearity was met. Durbin-Watson statistics fell within the expected range, indicating that the assumption of no autocorrelation of residuals has also been met. Finally, the scatterplot of standardised residual on standardised predicted value did not appear to funnel out or curve and therefore the assumptions of linearity and homoscedasticity have also been met for both the 4MT and SSEVT.

Both education and age were entered into the multiple linear regression analysis and a significant model emerged F (2,139) = 10.937, p = 0.000039. This regression analysis found that whilst age did not predict 4MT scores (β= -0.136, p=0.098), education appeared to be positively predictive (β=0.308, p=0.000248), in that those with a higher level of education tended to score higher on the 4MT.

Linear regression analysis of the SSEVT found age to be negatively predictive of scores, F (2,110) =3.908 (β= -0.258, p= 0.009). Education was found to not predict participants' scoring (β= -0.003, p= 0.976), which indicates that scores achieved on the SSEVT are not influenced by an individual's level of education, a desirable characteristic of a neuropsychological test.

4.10: To what extent do age and education predict scores on the two questionnaires?

Both the SNSEQ and the SAPQ were scored using a Likert scale. Answers on the main questions were calculated along with the 'change' score to give an overall result. Detailed scoring information is included in Chapter 2, Sections 2.13 and 2.14. Both education and age were entered into the multiple linear regression analysis and a significant model emerged F (2,112) = 6.498, p= 0.002. The analysis found that whilst education was positively predictive of Social Networks Questionnaire score (β= 0.273, p=0.005), age was not (β= -0.107, p=0.260). Another multiple linear regression was run to analyse whether age and education predict SAPQ scores F (2, 111) = 1.252, p=0.290. The analysis found neither age (β=-0.041, p=0.679) nor education (β=0.131, p=0.189) predicted spatial questionnaire scores.

4.11: Do Social Networks predict scores on the two cognitive tests?

The SNSEQ was developed in order to further test the hypothesis that larger and richer social networks may play a protective role in dementia, whilst poor social networks increase risk (Chapter 1, Section 1.3.2). As the hippocampal formation is closely related to AD (as discussed in Chapter 1, Section 1.8) and the SSEVT and 4MT have been designed to tap hippocampal function, it would be beneficial to consider whether an individual's social network is reflective of their performance on hippocampal tasks.

Accordingly, a linear regression analysis was used to assess whether the SNSEQ could predict scores on the 4MT and SSEVT. The analysis found that the Social Networks and

Embeddedness Questionnaire did not predict scores on either the 4MT *F* (1,111) =2.966. (β=0.161, *p*=0.88) nor the SSEVT *F* (1,111) = 1.926, *p*=0.168. (β=0.131, *p*=0.168). Exploratory analyses were run to see if any social network questions predicted 4MT or SSEVT scores. After Bonferroni-type correction for multiple comparisons, no significant correlations were found. However, certain questions within the SNSEQ were found to correlate with overall scores; Question four 'On an average week, I will only interact with my spouse and /or children' (*r*=0.226, *p*=0.016), Question Thirteen 'I would avoid going to a new place if there were a lot of people I didn't know there' (*r*=0.225, *p*=0.016) and Question Fourteen 'If a situation arises where I need to speak to someone new, e.g. a new neighbour, I prefer my partner/ family member to lead the conversation.' (*r*=0.193*, p*=0.041). There was no significant difference found between those that took the questionnaire alone or with someone who knew them well.

4.12: Is the SAPQ a useful screen for spatial ability?

The SAPQ was developed to see if it could act as a useful screen for spatial ability and therefore Alzheimer's Disease. To examine the extent to which the SAPQ taps abilities relevant to a good performance on the 4MT, a Pearson correlation between the SAPQ and the 4MT was run. No correlation was found between 4MT and SAPQ scores (*r*=0.114, *p*=0.099) and therefore no overall relationship between test scores on the SAPQ and the 4MT could be established. However, an itemised correlation analysis of the individual SAPQ questions and the 4MT found that question 6 'When a walking route I usually take is completely blocked off (e.g. for maintenance, treefalls), I find it difficult to work out a new

route' was strongly correlated with overall 4MT score (r= 0.312, p= 0.001). Question 8, 'I stick to major walking routes, and avoid minor paths and shortcuts, to avoid getting lost' was also found to correlate with overall 4MT score (r=0.249, p= 0.008) along with question 10 ' When visiting new places, I prefer to be with people I know and follow them, rather than find my way myself as I feel that if I am alone, I may become lost.' (r= 0.296, p=0.001).

4.13: Overall summary of Healthy Ageing participants analysis.

As predicted, performance on the two presumed hippocampus-dependent tasks (the 4MT and SSEVT) showed some tendency to decline with age, but this effect was much more reliable for the SSEVT than 4MT. This was shown both through a negative correlation between age and test scores on both tasks in participants over the age of 45. However, when age and education were both entered as predictor variables in a multiple regression in the 45+ age group, age did not significantly predict 4MT scores (age beta = -0.136, p = 0.098), while age still predicted SSEVT scores (age beta = -0.258, p = 0.000248). The basic decline with age was further supported by the use of a one-way independent groups ANOVA which compared Young (18-34), middle (45-64) and older (65+) healthy ageing participants which again illustrated how performance on the two hippocampal tasks decreased with age in healthy ageing participants. This supports the idea that hippocampal integrity and volume declines in healthy ageing. Somewhat surprisingly, the ACE III was found to be seemingly insensitive to cognitive ageing and no correlation was found between ACE III score and age in the 45+ participant group. An independent t-test found no

significant difference between age scores and age group (Young, Middle, Old). There was still no effect of age group when only the memory section from the ACE III was tested.

As discussed in Section 4.4 and Chapter 1, Sections 1.3.4, education should ideally not be overly influential in successful task performance. The reasoning behind this ideal is to avoid false positives should less educated individuals perform worse despite having no AD pathology or false negatives should highly educated individuals perform well, potentially masking AD pathology. A Pearson correlation found that education did not correlate with SSEVT test scores, and this was underscored when the linear regression showed education did not significantly predict SSEVT scores whilst age did.

In contrast, the 4MT did show a positive correlation between test scores and level of education. The above linear regression analysis (Section 4.9) also found that whilst education was able to predict scores on the 4MT, age could not. Education was found to be positively predictive of SNSEQ scores, with those with a higher level of education appearing to be more socially embedded. However, age was found to not be predictive of SNSEQ scores across the ages of 45-89. Neither age not education was found to predict spatial questionnaire scores.

A linear regression found that the Social Networks Questionnaire did not predict scores on either the 4MT or the SSEVT. Despite the SNSEQ's inability to predict SSEVT scores overall, certain questions within the SNSEQ (Q 4,13 and 14) were found to correlate with overall SSEVT scores. A Pearson correlation found no relationship between SAPQ and 4MT scores, however a positive correlation was found between question 6, 8 and 10 of the SAPQ and overall 4MT score, this is discussed in more detail below

4.14: Healthy Ageing participants discussion

4.14.1: Interpretation of 4MT performance 4MT decreasing with age.

The hippocampal formation houses spatial cells which integrate inputs to create a neural reconstruction of the world, which is critical for the formation of allocentric spatial memories (Moffatt, Elkins & Resnick, 2006; Lithfous, Dufour & Despres, 2013; Wenger, Schaefer Noack, 2012). Age-related reduction in hippocampal volume could negatively affect the encoding of the location of landmarks (Kimura et al, 2019), in this case the mountains within the 4MT. Conversely, neuroimaging studies have found that increased activation in hippocampal cortical areas is associated with better recall of the spatial layout of an environment (Moffatt, Elkins & Resnick, 2006).

Age-related decline in navigational skills are relatively well-documented in humans (Kirasic et al, 1992; Moffat et al, 2002; Tanila et al, 1997). Age-related decline in allocentric spatial navigation specifically is supported by studies such as Moffatt et al (2006) who tested 51 participants (30 young and 21 old), using an fMRI to scan participants whilst they completed a virtual reality navigation task. They found substantial age-related alteration in the neural networks supporting allocentric navigation. In comparison to the 'Young' group, the elderly participants showed reduced activation in the posterior hippocampus, parahippocampul gyrus, retro-splenial cortex and regions of the parietal lobe. This reduced activation in elderly participants in some of the neural systems that support navigation within the younger group suggest that neural changes may underlie impairment. This was further supported by the analysis conducted within the study that found increased

navigational accuracy to be associated with increased activation in the same neural regions, including the hippocampus. Several other studies have also found a similar reduced activation of posterior and medial temporal regions in older individuals during episodic memory tasks such as that of allocentric spatial memory (Cabeza et al, 1997; Grady et al, 2000; Gutchess et al, 2005).

As previously discussed, place cells within the rodent hippocampus (Knierim et al, 1995) change their response characteristics with age. This change in response may contribute to the well-researched spatial deficits present in aged mammals (Barnes et al, 1997; Shen et al, 2000; Tanila et al, 1997). Notably for the present project, the medial temporal region, including the hippocampus, atrophies as humans age and is one of the first regions affected by Alzheimer's disease. Such age-related hippocampal degeneration is shown by the decrease in 4MT performance. More specifically, a decrease in 4MT performance with age is in agreement with other studies which show that a difference in navigational ability between young and older adults may be one of flexibility (Harris & Wolbers, 2014; Harris, Wiener & Wolbers, 2012; Zancada-Menendes et al, 2015; Allison & Head, 2017). Due to the neurological changes outlined above, older adults often show more difficulty adjusting to environmental changes, which suggests that they find it more difficult to reorient to a known route or environment when it is approached by them from a less well-known vantage point (Kimura et al, 2019) such as is required by the 4MT when the participant is asked to identify the same layout of mountains from a different orientation.

The Spatial Navigation and Practices Questionnaire (SAPQ) was found to not predict 4MT score. However, all of the individual questions within the SAPQ that were found to correlate with scores achieved on the 4MT related to the participants ability to adjust to

spatial change and their flexibility in navigational ability (Q6: 'When a walking route I usually take is completely blocked off (e.g. for maintenance, treefalls). I find it difficult to work out a new route.'; Q8: I stick to major walking routes, and avoid minor paths and shortcuts, to avoid getting lost.'; Q10: 'It is difficult for me to find my bearings in a new town/city'). Further supporting that older adults have more difficulty adjusting to environmental changes. This difficulty in adjusting to new environments can affect the way in which older individuals navigate the world. Existing survey research indicates that that over time elderly individuals develop behavioural patterns in order to avoid unfamiliar routes (Burns, 1999) which is also reflected in question 8 'I stick to major walking routes, and avoid minor paths and shortcuts, to avoid getting lost'. This behavioural adjustment due to age related hippocampal decline is not only limited to conscious navigation of one's environment.

A review by Colombo et al (2017) reported an age-related performance gap in conditions which required allocentric strategies whilst showing preserved egocentric abilities in older adults within twenty studies. Furthermore, a review by Adrienne, Li & King (2019) concluded that the fifteen included studies offered support for age-related reductions in hippocampal and para hippocampal gyrus volume and activity that corresponds with old age performance on allocentric or 'hippocampus dependent' tests. Three of the included studies found a significant association between performance and the right hippocampus, thought to support specific memory relating to location and environment (Burgess et al, 2002; Maguire et al, 1997). Furthermore, the same review found 3 out of 5 fMRI studies found increased striatal activation in older adults accompanying their bias towards egocentric navigational strategies (Adrienne, Li & King, 2019). From this, it is plausible to hypothesise that an old age performance gap may indicate a shift away from allocentric strategies towards egocentric, proximal landmark based

strategies which becomes apparent when such individuals take a test which requires allocentric processing. This shift towards extra-hippocampal strategies (ego-centric navigational strategy) is a result of the previously discussed age-related degeneration of hippocampal areas.

Despite an individuals' hippocampal pathology, a decline in spatial abilities may not be noticeable in behavioural presentation until an advanced stage due to the behavioural avoidance of new routes and egocentric strategic compensation when navigation is required. This point further reinforces the value in a test which taps allocentric navigational abilities such as the 4MT, and a questionnaire which specifically asks about an individuals' ability to reorient themselves such as the SAPQ. Such hippocampal degeneration occurs at an early stage and hippocampal shrinkage accelerates at an abnormal rate during Alzheimer's disease, a test which is sensitive enough to identify age-related decline i.e. the 4MT may prove to be beneficial in identifying when healthy ageing becomes indicative of AD pathology and therefore prove to be an effective screening tool. This is discussed in detail in Chapter 5.

4.14.2: Interpretation of performance on the SSEVT decreasing with age.

As discussed in Chapter 1, Section 1.8.1, the hippocampus and related structures in the medial temporal lobe have long been associated with episodic memories (Squire, Stark & Clark, 2004; Eichenbaum, Yonelinas & Raganath, 2007). Functional brain imaging studies have further confirmed the involvement of MTL regions during both encoding and retrieval of new episodic memories (Wagner et al, 1998; Zeineh et al, 2003; Maass, Schutze & Speck,

2014). Evidence from longitudinal and cross-sectional studies suggest that semantic memory and procedural memory appear to be maintained throughout much of a human being's lifespan, however episodic memory begins to decline as we age (Nyberg et al, 1996; Park et al, 2002; Nilsson et al, 2003). A large-scale cross-sectional study of episodic face-name encoding and retrieval conducted by (Salami, Eriksson & Nyberg, 2012) showed a decline in hippocampal function during the course of an adult's lifespan, with a more significant reduction after the age of 65. Participants over the age of 65 were also found to perform significantly worse than their younger counterparts on the SSEVT test of episodic memory within the current project, further supporting this. Of course, allocentric spatial navigation is also thought to play a key role in episodic memory, which has been discussed in detail above and in Chapter 1, Section 1.7.1.3, providing contextual spatial information of where a memory took place.

The episodic memory impairment that occurs as people age has often been described as an impairment of recollection, coupled with preserved familiarity (Yonelinas et al, 2002). This is of particular relevance to the SSEVT as the questions asked in relation to the video were all carefully designed to tap recollection and steps were taken to ensure that questions could not be answered based upon familiarity alone. A detailed description of this is included in Chapter 2, Section 2.11 and discussed in Chapter 5, Section 5.7.4. The age-related decrease in SSEVT score supports how recollection-based episodic memory declines as individuals age due to a decline in hippocampal tissue integrity and volume. As such hippocampal decline occurs at an early stage in AD, the ability of the SSEVT to detect age-related decline suggests that it may also be sensitive to preclinical AD. This is further explored in Chapter 5.

4.14.3: The effect of education upon performance on the two hippocampal tasks.

Education was found to predict scores on the 4MT. Longitudinal studies have shown that individuals who experienced higher levels of education in earlier life are at lower risk of dementia as they age (Stern et al, 1994; Ott et al, 1995; Letenneur et al, 1999). Therefore it follows that a test which taps hippocampal ability would elicit a lower score from those with lower levels of education. There are various explanations why education is thought to protect against dementia-related pathology. Education is related to socio-economic status, healthy lifestyle choices and advantages and less exposure to possible environmental toxins. Education may also affect the way an individual may use verbal ability when taking the 4MT, prior knowledge in mathematics and shapes may assist in accuracy during the task. For example, when surveying the 4 mountains some individuals may remember their location in relation to each other by shape e.g. 'The conical mountain is placed next to gaussian shaped mountain'.

Alternatively, it has been suggested that those with higher levels of education may functionally compensate for underlying neuropathology, allowing more educated individuals to possess what is often referred to as the 'cognitive reserve' hypothesis (Katzman, 1993; Stern, 2002,2006; Valenzuela et al, 2007). The cognitive reserve hypothesis states that more pathology is necessary in those with higher levels of education to show symptoms which would be considered clinically indicative of dementia than their lesser educated counterparts. A study by Roe et al (2007) found that the overall risk of AD diagnosis was decreased by 0.82 to 0.87 with each additional year spent in education. They found that whilst AD pathology was not reduced by education, a decline in cognitive function remained undetectable in those with higher levels of education. Such individuals' ability to withstand

pathology that would affect those with less education has also been supported through various other studies (Sando et al, 2008; Bennett et al, 2005). A pathological study by Bennett et al (2005) found that 22 years of education reduced the effect of amyloid deposition on cognitive function more than 18 years of schooling, suggesting that education may be directly dose-dependent on cognition.

The specifics of how this protective effect of education occurs remains unclear. However, it has been suggested that cognitive reserve may be based upon larger brain size and/ or increased synapse count (Sando et al, 2008). Alternatively, pre-existing cognitive processing acquired through the completion of challenging tasks such as are required within education may allow the brain to make use of more efficient neural networks, or a greater ability to recruit alternative networks to compensate (Stern et al, 2006). Both hypotheses are not mutually exclusive and may play a role in why education appears to offer some form of 'cognitive reserve'.

However, when cognitive decline does occur, it appears to be more rapid in those with higher levels of education (Stern et al, 1999), this is possibly due to an increased cognitive reserve resulting in a delay in the onset of clinical symptoms. Far from providing a positive effect, higher levels of education may mean that AD pathology is effectively missed until later stages of decline. Therefore, a test which appears unaffected, such as the SSEVT may prove beneficial in detecting AD pathology at an early stage. The SSEVTs ability to detect subtle cognitive decline in healthy ageing adults offers insight into its sensitivity which may prove beneficial when assessing when healthy ageing becomes abnormal AD pathology.

4.14.4: Education level was correlated with SNSEQ but not with age.

Education was found to be predictive of SNSEQ scores, indicating that a higher level of education is associated with larger social networks and more social embeddedness. There is limited research that focuses upon the association between education and social network size but it is plausible that attending different institutions and the travel associated with occupations that follow a higher level of education may lead to a more wide and varied social network. More specifically, higher education levels are associated with more diverse and less family-based networks (Krause & Borawski-Clark, 1995; Wenger, 1995; McPherson et al, 2001). This may be due to the greater resources and skills that are necessary to both develop and sustain social relationships (Broese van Groenou & van Tilburg, 2003). In the current project, age was found to be non-predictive of SNSEQ scores, however Kubzansky et al (1998) found that amongst older participants aged 70-79 years, lower levels of education were associated with larger social networks. The relationship between education and social embeddedness remains unclear, but it may be the case that educational attainment simply offers a different kind of social network of 'quantity over quality' with more widespread variation and less close family relationships (Ajrouch et al, 2005).

Age was found to not be predictive of scores on the SNSEQ, suggesting that there is no difference in social networks and embeddedness as people age. Social networks and social embeddedness may not decline as we age healthily. Instead it has been suggested that the way social networks are defined and perceived as people age is much more nuanced, with older individuals placing more value on established, close relationships rather than many interactions and a large-scale network.

Age is positively correlated with higher quality relationships, tending to interact more with close supportive systems and a kin-centred network (Marsden, 1987; Schnittiker, 2007; Shaw et al, 2007). Supporting this, some research suggests that as people age, they shed less meaningful, superficial contacts in favour of emotionally close relationships (Fredrickson & Carstensen, 1990). Essentially older individuals have denser, rather than wider social networks. Furthermore, it is thought that it is specifically the lack of close, high quality relationships that increases dementia risk (Fratiglioni et al, 2000; Rafnsson et al, 2017).

This may explain why some of the SNSEQ questions correlated with the SSEVT. The SNSEQ was found to not predict age but certain questions did correlate with the hippocampus dependent SSEVT, which has been shown to be associated with age. (Section 4.14.2). Question 4 'On an average week, I will only interact with my spouse and/or children', Question 13 'I would avoid going to a new place if there were a lot of people I didn't know there' and Question 14 'If a situation arises where I need to speak to someone new, e.g. a new neighbour, I prefer my partner/family member to lead the conversation' all show a preference for a smaller social network with established close relationships.

A small social network size in older people may prove to be a risk factor in AD (Zunzunegui et al, 2003). The Honolulu ageing study (Saczynski et al, 2006) found that those whose social network size declined from mid-life to late-life had the highest risk of dementia. Suggesting that low social engagement in later life may be a prodromal symptom of dementia. This is supported by the findings of Chapter 5.

4.15: Healthy Ageing study: Overall conclusions.

The ACE III was designed in order to identify cognitive impairment in conditions such as AD and not to measure cognitive decline in healthy ageing. However, the seemingly blunt insensitivity of the ACE III and ACE III memory section to cognitive decline in healthily ageing participants was surprising. Of course, the ability of a test to identify subtle cognitive decline does not necessarily mean that the ACE III is also insensitive to identifying AD. However, it does suggest that it may not be sensitive to identifying abnormal decline at an early stage and would be unsuitable for use as a screening tool to monitor an individual as they age. In contrast, SSEVT and to a lesser extent the 4MT were shown to be sensitive to the changes that occur in healthy ageing which could reflect a decline in the integrity and functioning of hippocampal tissue. This, along with their relative ease of use and low cost may indicate that the two new and recently developed tests may be suitable for use as a screening tool. The ability of the 4MT, SSEVT and ACE III to identify MCI participants from healthy controls is explored in Chapter 5.

Chapter 5: Neuropsychological testing of patients with Mild Cognitive Impairment vs Healthy Controls.

Table 5. 1

Neuropsychological tests included in each study within this thesis. Neuropsychological tests included in the current chapter (Chapter 5) shown in bold.

Neuropsychological Test	Meta-analysis (Chapter 3)	Healthy control testing (Chapter 4)	**Clinical MCI study (Chapter 5)**	Designed to test
Mini Multi-State Examination (MMSE)	✓	✗	✗	Multi-domain cognition.
Alzheimer's Disease Assessment Scale-cognitive subscale (ADAS-COG)	✓	✗	✗	Multi-domain cognition.
Free and Cued Selective Reminding Test (FCSRT)	✓	✗	✗	Episodic memory.
Rey Auditory Verbal Learning Test (RAVLT)	✓	✗	✓	Verbal learning and memory.
California Verbal Learning Test (CVLT)	✓	✗	✗	Verbal learning and memory.
Logical memory subtest of the Wechsler memory scale (Logical Memory)	✓	✗	✗	Verbal and working memory.
Trail Making Test B (TMT-B)	✓	✗	✓	Visual attention and task-switching.
Rey–Osterrieth complex figure (ROCF)	✓	✗	✗	Impairments in visuospatial construction.
Four Mountains Test (4MT)	✗	✓	✓	Allocentric spatial working memory.
Spaces and Sequence Episodic Video Task (SSEVT)	✗	✓	✓	Episodic memory.
Buschke Selective Reminding Test (SRT)	✗	✗	✓	Verbal learning and memory.
Spatial Ability and Practices Questionnaire (SAPQ)	✗	✓	✓	Spatial working memory.
Social Networks and Embeddedness Questionnaire (SNSEQ)	✗	✓	✓	Size and complexity of social networks.
Addenbrooke's Cognitive Assessment- III (ACE-III)	✗	✓	✓	Multi-domain Cognition

The table above illustrates all neuropsychological tests included in the thesis, which portion of the thesis they are used within and which functions they aim to test. The ticks in green represent an included test within the chapter at the top of the table whereas the crosses represent tests that were not included in that particular chapter. The tests included in chapter 5 are shown in **bold.**

Overall, 10 patients diagnosed with Mild Cognitive Impairment (MCI) took part in the study (age range: 62-84, mean: 72, standard deviation: 8.47, consisting of five males and five females). All participants had received a diagnosis of MCI within the previous three months. All were asked via a participant information sheet about their qualifications, age and occupation. Three had no formal qualifications, three had GCSE equivalent qualifications and four had at least Bachelor's degree or equivalent. All were retired or not currently working. Their highest level of educational achievement was coded as shown in Table 5.2 below.

Table 5. 2.

Highest level of education achieved by the MCI participants.

Highest level of Education	MCI Participant n
0 (No formal Qualifications)	3
1 (GCSE or Equivalent)	3
2 (A level or Equivalent)	0
3 (Bachelor's Degree or equivalent)	3
4 (MSc, PhD or equivalent)	1

Education score was established using a coding system 0: No formal qualifications, 1: GCSE or equivalent, 2: A-Level or equivalent, 3: Bachelor's degree or equivalent, 4: MSc or PhD or equivalent.

5.1: The recruitment process, inclusion and exclusion criteria and testing procedure.

After receiving approval from the Health Research Authority and the Durham University Ethics Committee, participants were recruited from four different clinics: Tees Esk and Wear Valleys NHS Foundation trust, Cumbria Partnership NHS Foundation Trust, Leeds and York Partnership NHS Foundation Trust and South Tees Hospitals NHS Foundation Trust. The number of participants recruited from each trust is shown in Table 5.3. The researchers travelled to individual clinics to present the study, gain support and to ensure that those recruiting understood the inclusion and exclusion criteria.

Table 5. 3

The number of participants referred from each trust.

Trust	Number of participants provided
Tees Esk and Wear Valleys NHS Foundation trust	1
Cumbria Partnership NHS Foundation Trust	5
Leeds and York Partnership NHS Foundation Trust	3
South Tees Hospitals NHS Foundation Trust	1

Participants were recruited from four different trusts via the communication protocol in Figure 5.1. Nine participants opted to be tested in their own homes, with just one tested in their local clinic.

Study eligibility was restricted to those who had been diagnosed as having Mild Cognitive Impairment (MCI) by clinicians in accordance with the four core clinical criteria of Albert et al (2011). Briefly, these are: 1) Evidence of change (worsening) in cognition; 2)

Impairment in one or more cognitive domains greater than expected for age/education; 3) Preservation of independence in functional abilities; 4) No current dementia.

A key criterion was that participants had to have previously received a diagnosis of MCI within three months prior to testing, in order to ensure that patients' cognition had not appreciably declined further in the interim between diagnosis and testing.

Exclusion criteria were:

1) The presence of a significant neurological condition such as Traumatic Brain Injury, Epilepsy, Stroke, Multiple Sclerosis, Brain tumour, Encephalitis, Meningitis, Parkinson's disease or visual impairment severe enough to hamper processing of visual test stimuli.

2) A major psychiatric disorder, such as schizophrenia, bipolar disorder or personality disorders such as borderline personality disorder. Severe (but not mild or moderate) clinical depression was also excluded and severe (but not mild or moderate) anxiety.

3) The use of cognitive enhancing drugs e.g. Cholinesterase inhibitors.

4) A history of alcohol excess, i.e. has received external assistance and/or previously had functional issues due to a reliance on alcohol or excess of illicit drug use within the last five years.

The diagnosis of any form of dementia also excluded a participant as, by definition, this would conflict with the Albert criteria outlined above.

Figure 5.1 below sets out the steps in the recruitment process, which was followed by clinical staff at the four NHS clinics.

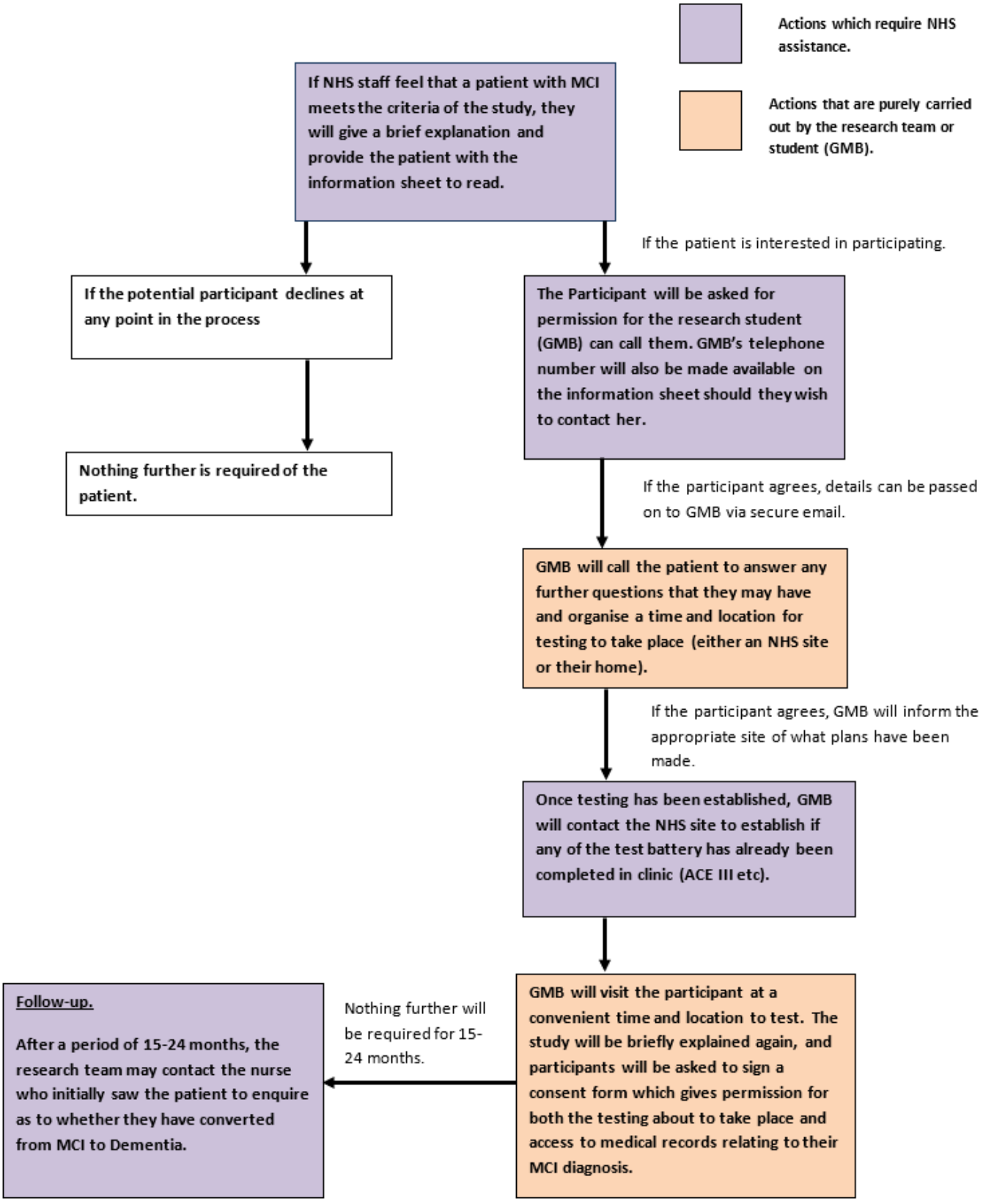


Figure 5. 1. Recruitment and Communication Protocol

Flowchart outlining the recruitment process and the actions to be undertaken by either NHS staff or

procedure, which varied slightly from trust-to-trust. Discussions between the referring site and myself were therefore needed to establish which tests included in the project battery (e.g. ACE-III, RAVLT) the patient had already completed, so as to prevent unnecessary duplication and/or practice effects. It was decided that testing could be conducted either in clinics or at the participant's home, taking care to implement safety guidelines in accordance with risk assessments, and NHS and Durham University lone working policies.

5.1.1: The Recruitment process

'Initially this study aimed to have 40 participants with a diagnosis of MCI with a view to conduct a longitudinal conversion study, such as those included in the meta-analysis in Chapter 3. This was based upon potentially overgenerous initial estimates given in an optimistic vein from trusts. The first stage of this process included preparing all study documents and completing a research application form on the Integrated Research Application System (IRAS). Due to the recruitment of those with a diagnosis of MCI, myself and both of my supervisors attended a Research Ethics Committee (REC) meeting and answered all questions surrounding potential ethical issues. A letter advising us that the study had been approved then followed. The next period of time was spent presenting to various locations and trusts regarding recruitment in which I presented the proposed study and garnered support. After this period of time had passed, the two years needed to

provide a follow-up in a longitudinal study was no longer feasible within a PhD project timeline.

As it turned out, in the end, only 10 patients were recruited from Tees, Esk and Wear Valley NHS Foundation Trust, Cumbria Partnership NHS Foundation Trust, Leeds and York Partnership NHS Foundation Trust, South Tees Hospitals NHS Foundation Trust. There were several factors which may have limited recruitment. Despite trust Research and Development (R&D) teams' support, many healthcare professionals' time is limited in day to day working life which may have limited the amount of prospective patient's that were approached. Another limiting factor may have been the study's lack of Portfolio funding which provides some funding to the NHS trusts, to enable specific individuals to oversee, manage and aid. However, the 10 participants that were recruited were due to the hard work and interest of professionals at each trust.

Following MCI diagnosis potential participants were identified by the local NHS site clinical staff and provided with an information sheet regarding the project, with a number to call if they would like to be included. A follow-up letter was then sent to the potential participants' home address, and the experimenter would call by telephone to ascertain if they were still interested. Before testing began informed consent was sought from the patient for use of their data, comprising: 1) the previous clinical data, notably the results from the NHS site-specific psychological test and questionnaire battery; 2) results from our additional tests; 3) any diagnostic changes at a future time by clinicians. The signed informed consent forms were then stored appropriately in accordance with GDPR guidelines.

Participants were given the choice to either be tested in their own homes or in their local clinic. Nine participants opted to be tested in their own homes for comfort and transportation reasons, with only one participant choosing to be tested in clinic. Participants were advised in advance that a quiet environment free of distractions, and a table on which to work, would be necessary.

5.1.2: Test order and materials used

Both established and newly developed tests were used in this study. For already-established neuropsychological tests the Consultant Clinical Psychologist supervisor (Dr Stephen Evans) trained me on the appropriate procedures to administer the four established neuropsychological tests, namely: the Rey Auditory Verbal Learning Test (RAVLT), Addenbrookes Cognitive Examination (ACE III), Verbal Selective Reminding Test (vSRT) and the Trail Making Test B (TMT-B). A detailed explanation of each of the tests used can be found in Chapter 2: General Methods.

The project-specific battery consisted of the following tasks in the following order, although in many cases the ACE III had already been administered and was therefore not repeated: The Free and Cued Selective Reminding Test (FCSRT); The Four Mountains Test (4MT); Spaces and Sequence Episodic Video Task (SSEVT); Trail Making Test B (TMT-B); Social Network and Social Embeddedness Questionnaire (SNSEQ); Rey's Auditory Verbal Learning Test (RAVLT); Spatial Ability and Practices Questionnaire (SAPQ); and the Addenbrookes Cognitive Examination (ACE III), as can be seen below in Table 5.4. Whilst

many tests were purely pen and paper based, a computer was required for the 4MT and the SSEVT for which a 15' Dell laptop was used.

Table 5. 4.

MCI Test Battery

Test order	Test	Duration (minutes)	Delay (minutes)	Materials	Scoring details
1	Buschke vSRT	20	30	Paper based	Scoring the SRT is more complex than other tasks, and a full explanation is given in the SRT section, Chapter 2, Section 2.12. However, only Total Recall (TR) and Delayed Recall (DR) were used in the current analysis. DR was scored out of a possible 12 whilst TR was scored out of a possible 144
2	4MT	15	NONE	Laptop (Dell 15') and pen and paper.	0-15, with higher scores indicating greater allocentric spatial memory. Error *type* was also recorded.
3	vSRT delayed recall	5	NONE	Paper-based	Scored out of 12, higher score indicates batter retrieval.
4	Spaces and Sequence Episodic Video Task (SSEVT)	5	20	Video- Laptop (Dell 15')	0-17, with higher scores suggesting greater episodic memory.
5	Trail Making test B (TMT-B)	10	NONE	Paper based- stopwatch also needed.	Results for TMT-B are reported as the number of seconds required to complete the task; higher scores reveal greater impairment.
6	Social Networks and Embeddedness Questionnaire (SNEQ)	10	NONE	Paper based	0-80, with higher scores indicating more social embedment and a larger social network.
7	Answers to SSEVT	10- 15	None	Laptop and paper	0-17, with higher scores suggesting greater episodic memory.
8	RAVLT	15	20 minutes	Paper based	Total number of words recalled was reported after each trail. Immediate recall (Trials I-V): Maximum score 75. Interference task: Maximum score 15. Delayed recall: Maximum score 15.
9	Spatial Ability and Practices Questionnaire (SAPQ)	10	NONE	Paper based	15-75 for SAPQ score, with higher scores suggesting greater spatial ability. -15 - +15 for SAPQ change, with positive scores indicating an improvement in spatial abilities within the last year and negative scores indicating a decrease, and the degree of overall positivity and negativity indicating the magnitude of the change.
10	ACE-III	10	NONE	Paper based	Overall: 0-100, with higher scores indicating greater cognition. Attention:0-18, Memory:0-26, Fluency:0-14 Language: 0-26, Visuospatial:0-16
11	RAVLT: Delayed Recall	10	NONE	Paper based.	Delayed recall score (maximum 15) was recorded. Higher score indicates better cognition.

5.1.3: Procedure

All participants read the Participant Information Sheet and General Data Protection Plan before signing the consent form. It was made clear to participants that they could withdraw at any time, and that should they proceed breaks would be provided as testing was rather lengthy (around 1.5-2 hours). They also filled out a General Information form detailing their age, gender, level of education, and whether they met any of the exclusion criteria (although this had also been checked beforehand by their NHS referral site). Upon test completion participants read a debrief sheet and were offered the opportunity to address any questions they may have had to the researcher (myself). Participants could not receive their personal results but they could receive a 'banding' of their performance should they so wish (above average, average, below average). The clinical supervisor (Dr Stephen Evans) was also available should any participants feel in any way concerned after testing.

Table 5.4 details which tests were used, and in which order. Three of the tests included a 'delay' task (SRT, RAVLT, SSEVT), whereby a certain amount of time had to pass before the participant was asked to recall information from the previous task. These delays were filled with unrelated, quicker tasks (e.g. questionnaires). Should the participant take longer on the shorter task than the delay allows (e.g. they were still only half-way through a questionnaire when it was time to recall the list from the RAVLT task), a questionnaire could be left and referred back to at the end of testing.

5.2: General overview: Healthy Ageing vs MCI.

This Chapter is focused upon patients who received a diagnosis of Mild Cognitive Impairment, and presents, broadly speaking, two sets of results. The first set of results I provide are essentially stand-alone descriptive statistics describing the characteristics of this MCI patient sample. The first set of results includes scores on tests such as the RAVLT and SRT which the ageing controls did not take. MCI participant demographics and test scores can be found in table 5.5.

The second set of results is comparative: I compare the patient group to a sample of matched healthily-ageing controls (HA). After checking for any potential differences in age and education between the two groups, this second set of results compares performance of the two groups (MCI vs HA) on three cognitive tasks (4MT, SSEVT, ACE-III) and the two project-specific questionnaires (SAPQ and SNSEQ). An important goal of the present thesis is to examine whether the 'hippocampal' tasks (4MT and SSEVT) can discriminate the MCI-vs-HA group distinction, and if so, whether they are at least as effective as the ACE-III. The ACE-III, discussed in Section 2.15, is a brief cognitive screening test that takes around 15 minutes to administer and encompasses five major cognitive domains: attention, memory, language, visuospatial function and verbal fluency (Hsieh, 2013; Velayudhan, 2014). It comprises of 21 cognitive tasks and has a total score of 100, the common cut-off for dementia is 82 and 88 for MCI patients. The ACE III was developed in order to address some of the weaknesses identified by its predecessor, the ACE R including ceiling effects to questions and translation

difficulties (Hsieh, 2013; Velayudhan, 2014). The ACE III was chosen as a comparator test because it is currently the most commonly used tool in the NHS for assessing dementia, and more generally, cognitive ability in ageing-related patients. As we shall see, it transpired that hippocampal' tasks (4MT and SSEVT) clearly differentiated the MCI vs HA groups, while the ACE-III did not.

The patient and control sample demographics greatly overlap but are not identical across the three tests. Accordingly, I then re-analyse the group differences across the three tests looking only at patients and controls who underwent all three tests. This helps to ensure that any apparent group differences across the tests are not due to lack of homogeneity in the sample. This analysis further confirms that the 4MT and SSEVT were, and ACE-III was not, effective at discriminating the two groups.

Finally, I examine the MCI and HA groups' scores on the SAPQ and SNSEQ questionnaires. One of the key research goals of this thesis project was to create a social questionnaire capturing variation in social networks sufficiently so as to be able to better predict future cognitive decline (e.g. conversion to dementia status). As applied to my cross-sectional analysis here, I test the prediction that MCI patients will have weaker social networks than the healthy controls. As we shall see, this prediction was confirmed in this thesis' dataset.

Of course, the patients in an MCI group likely include at least some patients who do not have MCI due to AD. A task or questionnaire that distinguishes well between MCI and matched healthy control cross-sectional samples is not necessarily one which will be accurate at diagnosing earlier stages of AD. However, one can be confident of the converse: that a task or questionnaire that consistently fails to distinguish MCI and HA groups is

unlikely to be a useful diagnostic for early AD. In the Discussion, I consider the limitations of ACE-III, and the potential promise of the 4MT, SSEVT and SNSEQ as contributing to an AD diagnostic armoury.

Table 5. 5.

MCI Patient Sample demographics and test scores.

	Participant n	Sex n	Age (years) M ± SD	Education M ± SD	DR M ± SD	TR M ± SD	Overall Score M ± SD
4MT	10	5 F: 5 M	73.3 ± 8.5	1.6 ± 1.5		-	6.2 ± 2.7
SSEVT	7	4 F: 3 M	77.6 ± 5.9	1.7 ± 1.3		-	4.8 ± 0.5
ACE III	10	5 F: 5 M	73.3 ± 8.5	1.6 ± 1.5		-	88.0 ± 12.0
SAPQ	10	5 F: 5 M	73.3 ± 8.5	1.6 ± 1.5		-	45.9 ± 15.8
SNSEQ	10	5 F: 5 M	73.3 ± 8.5	1.6 ± 1.5		-	51.0 ± 8.1
vSRT	9	4 F: 5 M		1.4 ± 1.5	4.8 ± 2.3	75.3 ± 27.21	-
RAVLT	10	5 F: 5M	73.3 ± 8.5	1.6 ± 1.5	6.8 ± 3.9	34.1 ± 17.1	-

Data are represented as a mean ± standard deviation except 'Sex' which is the number of male and female participants n=5(M): 5(F),. DR refers to delayed recall score, TR refers to total recall score. Participant n is given as the number of participants has some variation. Fewer patients took the SSEVT due to the delay between the beginning of testing and the SSEVT's revisions being finalised. One participant declined completion of the vSRT (verbal Selective Reminding Test). MCI = Mild Cognitive Deviation, HC= Healthy Controls. 4MT- Four Mountains Test, SSEVT-Spaces and Sequence Episodic Video Task, ACE III- Addenbrookes Cognitive Examination III, SAPQ- Spatial Abilities and Practices Questionnaire, SNSEQ- Social Networks and Embeddedness Questionnaire, RAVLT- Rey Auditory Verbal Learning Test.

Table 5. 6.

MCI and HA demographics for participants aged 65+

	MCI					HC				
	Participant n	Sex	Age M ± SD	Education M ± SD	Score M ± SD	Participant n	Sex	Age M ± SD	Education M ± SD	Score M ± SD
4MT	10	5 F: 5 M	73.3 ± 8.5	1.6 ± 1.5	6.2 ± 2.7	45	25 F: 20 M	70.8 ± 5.1	1.8 ± 1.3	8.4 ± 2.7
SSEVT	7	4 F: 3 M	77.6 ± 5.9	1.7 ± 1.3	4.8 ± 0.5	37	23 F: 14 M	70.3 ± 3.8	1.9 ± 1.3	6.7 ± 2.0
ACE III	10	5 F: 5 M	73.3 ± 8.5	1.6 ± 1.5	88.0 ± 12.0	29	17 F: 12 M	70.3 ± 4.3	2.0 ± 1.4	92.6 ± 6.0
SAPQ	10	5 F: 5 M	73.3 ± 8.5	1.6 ± 1.5	45.9 ± 15.8	39	24 F: 15 M	71.2 ± 5.4	1.9 ± 1.3	52.4 ± 8.0
SNSEQ	10	5 F: 5 M	73.3 ± 8.5	1.6 ± 1.5	51.0 ± 8.1	39	24 F: 15 M	71.2 ± 5.4	1.9 ± 1.3	57.9 ± 9.8

Data are represented as mean ± standard deviation. MCI = Mild Cognitive Deviation, HC= Healthy Controls. Education was categorised by score: 0= no formal education, 1= GCSE or equivalent, 2= A-Level or equivalent, 3= undergraduate degree, 4= postgraduate qualification. Participant n is given as the number of participants that took each test varied.

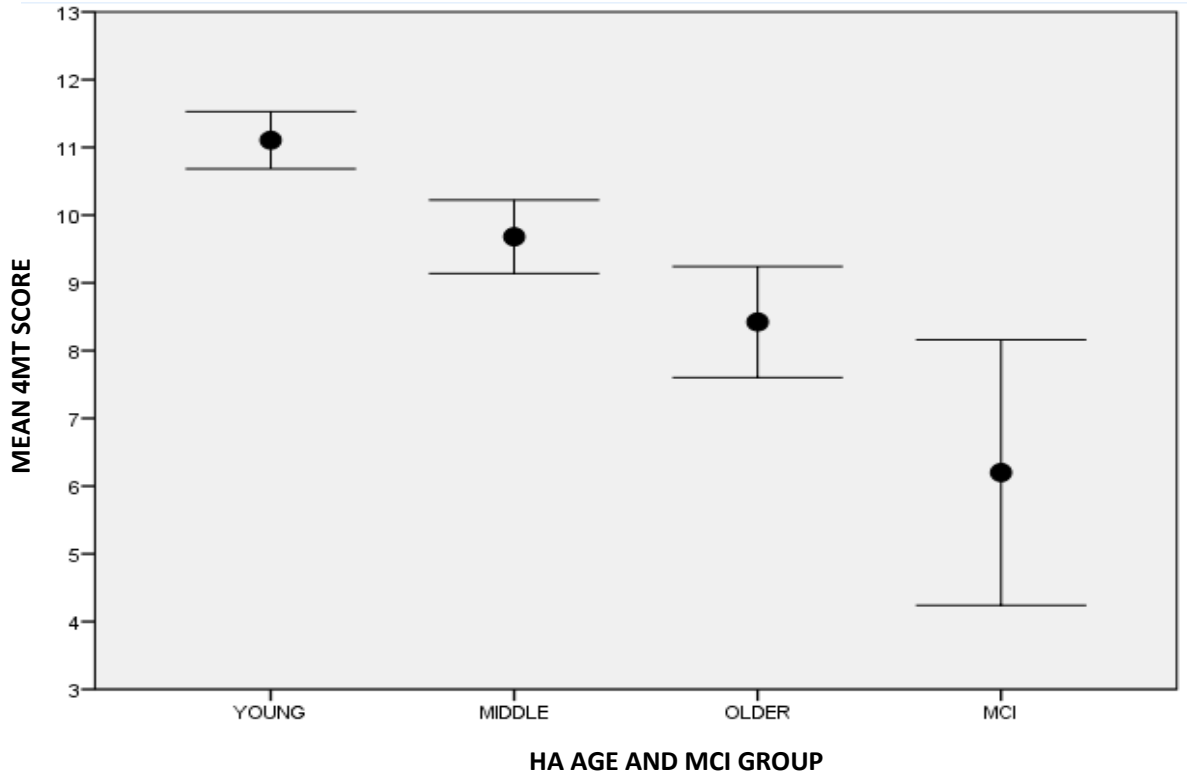
5.3: MCI patients scored significantly worse on the 4MT and SSEVT that the Healthy Ageing controls; the ACE III did not distinguish these two groups.

In order to assess whether there is a significant difference between MCI and HA scores on the 4MT, SSEVT and the ACE III, a t-test was used. The MCI group (M=6.2, SD=2.74) obtained significantly lower scores on the 4MT compared to Healthy Controls (M=8.42, SD=2.73),(t (53)=2.33, p=0.024). This indicates that the 4MT is successful in differentiating between the HA and MCI groups. The MCI group also obtained lower scores (M=4.8, SD= 0.48) compared to HA when using the SSEVT (t (39.1)=5.00, p= 0.000012 (Levene's correction applied)). This difference between older participants and MCI patients is of particular importance as it shows both the new and recently developed hippocampal tasks included in the battery, the 4MT and SSEVT, have the ability to highlight scores of individuals with cognitive deficit as they score significantly lower than those who are healthy aging. This is valuable in the development of an effective neuropsychological test.

As discussed in Section 5.2, the ACE III is widely used within the NHS for assessing cognitive ability in ageing-related patients. However, no significant difference in scores were found when comparing HA older adults (M=92.55, SD=6.01) to MCI patients (M=88.0, SD=11.20), (t (37)=1.57, p=0.124). The ACE-III was unable to distinguish between HA participants and those with diagnosed MCI. The ACE III 'memory' section (scoring details in Table 5.4, test description in Chapter 2, Section 2.15) was also tested in isolation and found to also be unable to distinguish between older HA participants and MCI patients (t (37)=1.84, p=0.075).

The difference in performance between young, middle and older healthy groups on the 4MT, SSEVT and the ACE III has been previously discussed on Chapter 4. Figures 5.2A, B, C and D below reiterate the mean scores achieved by the young, middle and older groups, as shown in figure 4.2, along with the addition of the mean score achieved by MCI patients on the same tests. Figure 5.2 illustrates how scores decline with age and then further significantly decline in those with MCI in both the 4MT (Figure 5.2A) and the SSEVT (Figure 5.2B) and how this is not the case in ACE III (Figure 5.2C) or the ACE III memory section (5.2D).

A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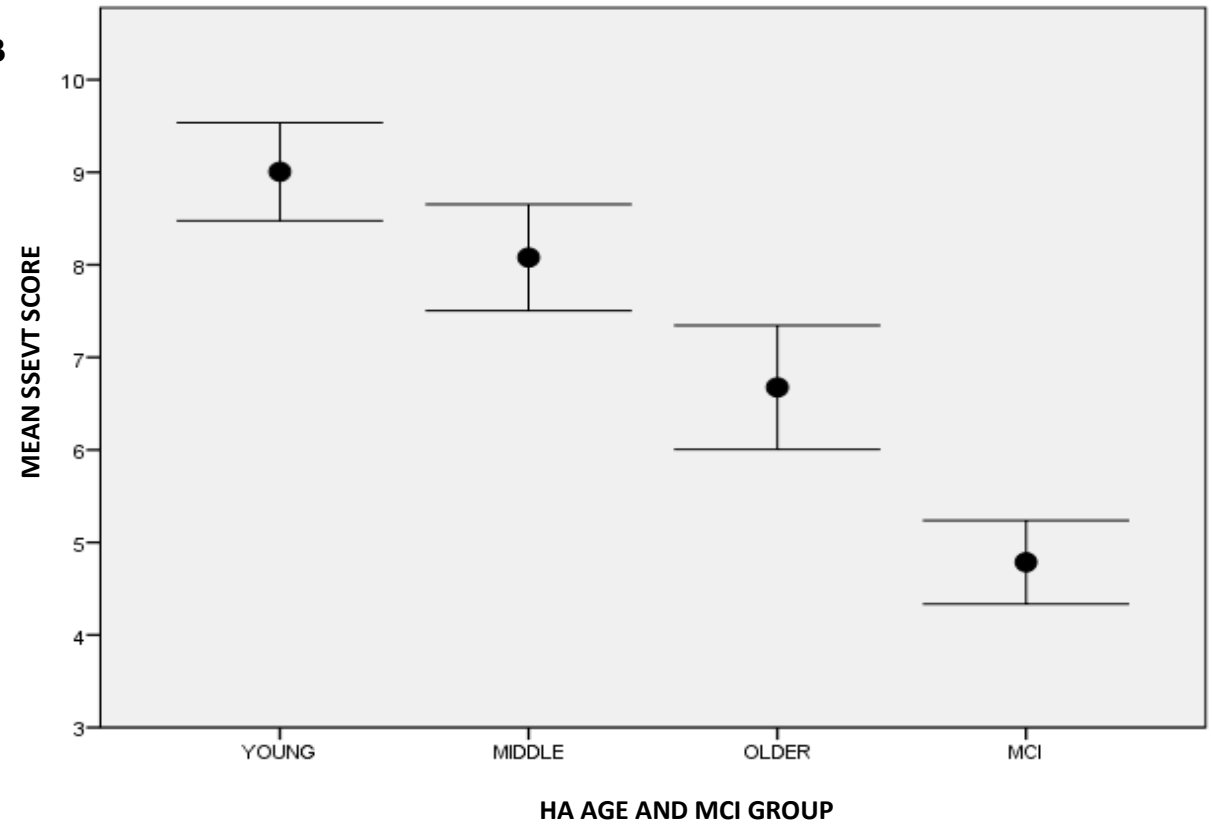
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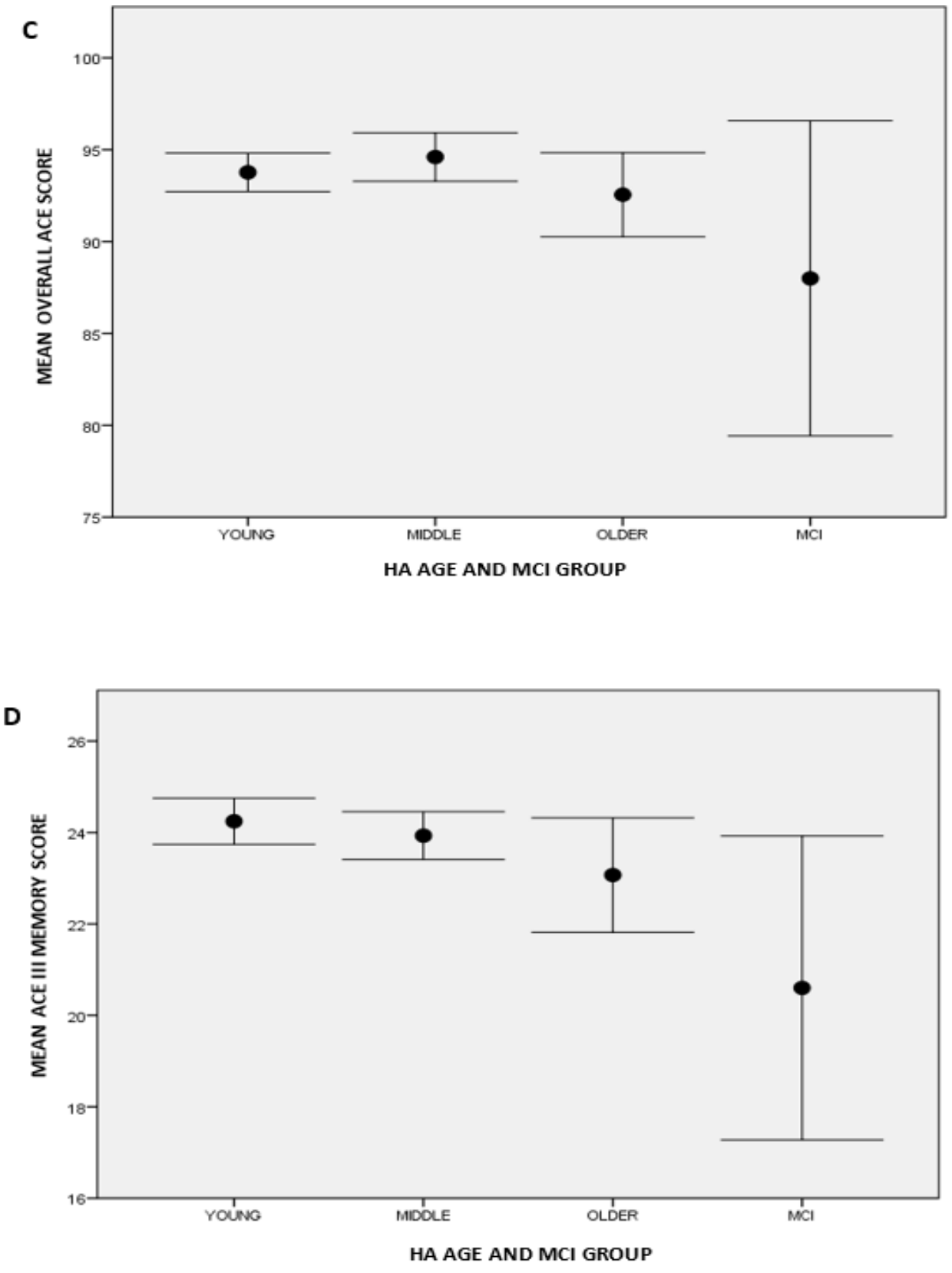

Figure 5. 2. **Mean scores for each age group.**

Error bars represent +/- 1 standard error of the mean. Age groups split into Young (18-34) Middle (45-64), Older (65+) and MCI. The initial analysis of the difference between healthy ageing groups is given in chapter 4, section 4.7, the figure above shows these results with the addition of the scores achieved by MCI patients. Details of test scoring in Table 5.4. **(A)** A significant difference was found between scores achieved by MCI and Older HA participants on the 4MT (T)=2.33, *p*=0.024. **(B**) A sig. difference was also found between MCI and Older HA scores on the SSEVT *t* (39.1) =5.00, *p*=0.000012. **(C**) No sig. difference was found between MCI and Older HA scores on the ACE III *t* (37) = 1.57, *p*=0.124**. (D)** There was also no sig. difference between MCI and Older HA scores on the ACE III Memory section *t* (37) =1.84, *p*=0.075.

However, whilst classic t-tests suggest that the 4MT and SSEVT have the ability to differentiate between MCI and HA participants, whilst the ACE does not, it is important to also interpret these results in terms of magnitude. As previously discussed in Chapter 3, effect size shows how much one group differs from another, in this case the difference in test scores (ACE III, SSEVT and 4MT) between those diagnosed with MCI and healthy ageing participants (HA). Hedges' g was chosen to measure effect size between group scores due to the small sample size (<20). Glass's delta was also provided to control for any significant difference in standard deviation between group scores as it only uses the standard deviation of the control group. A large effect size was found between MCI and HA scores on both the 4MT and the SSEVT when using either Hedges' g or Glass's delta (Table 5.7) whereas only a medium effect was found on both the overall and memory section scores of the ACE III (Table 5.7).

Table 5.7.

Summary of t-test results and effect sizes between MCI and HA scores on the 4MT, SSEVT, ACE III and ACE III Memory section.

	HA		MCI				
Test	**Participant n**	**M ± SD**	**Participant n**	**M ± SD**	**Hedges' *g***	**Glass's *delta***	***t*-test**
4MT	45	8.4 ± 2.7	10	6.2 ± 2.7	0.81	0.82	t (53) =2.33, p=0.024
SSEVT	37	6.7 ± 2.0	7	4.8 ± 0.5	1.01	0.94	t (39.1) =5.00, p= 0.000012*
ACE III	29	92.6 ± 6.0	10	88.0 ± 12.0	0.58	0.76	t (37) =1.57, p=0.124
ACE III Memory	29	23.1 ± 3.3	10	20.6 ± 4.6	0.67	0.75	t (37) =1.84, p=0.075

*Levene's correction applied

5.3.1: The difference in HA and MCI scores on the SSEVT remains significant when participant groups are matched in age.

The healthy participant group above were aged 65+ in order to age-match with the MCI sample. Whilst there was no significant difference between MCI and HA ages in the 4MT and ACE III, this was not the case for the SSEVT. As some MCI participants did not complete the SSEVT the average age was higher than those who took part in the 4MT and ACE III. A t-test was therefore re-run between MCI and HA test scores on the SSEVT, where the minimum age was raised to 72, thus creating no significant difference between MCI and HA ages. Both Glass's delta and Hedge's g were also calculated in order to quantify the size of the difference between MCI and HA group scores. As with the above analysis, a significant difference in SSEVT test scores was found between MCI (M=4.8, SD=0.49) and HA (M = 6.2, SD = 1.9), (t (13.3) = -2.43, p = 0.03) albeit limiting the HA to a much smaller sample (MCI: n = 7, HA: n = 12). A large effect size was again found between SSEVT test scores achieved by MCI and HA participants (Hedge's g = 0.90, Glass's delta = 0.74) when aged- matched. This further reinforces the ability of the SSEVT in distinguishing between healthy ageing individuals and those with MCI.

Although the analysis above is useful in showing how MCI participants perform significantly worse than HA individuals, as discussed in Chapter 1, Section 1.6, a good diagnostic test must be sensitive in that it identifies those with cognitive impairment whilst also having the specificity to correctly identify those without impairment (true negative rate).

A receiver operating characteristic curve (ROC curve) is often used to demonstrate the trade-off between sensitivity and specificity at various cut-offs of a diagnostic test and is

also able to tell the reader the overall accuracy of a given test via the area under the curve (AUC). In this instance, the true positive rate or 'sensitivity' is the amount of people with MCI who are correctly identified as such whereas the false positive rate refers to the number of individuals inaccurately identified as MCI when they are not and is calculated as '1 minus specificity'. The ability of the ROC to demonstrate the trade-off between sensitivity and specificity for given threshold values is especially relevant in tests where the initial measures are not simply binary in outcome but on a continuum such as scores on the SSEVT, 4MT and ACE III.

An individual may be identified as having an MCI or not, depending on where this score 'cut off' is placed, for example 'anyone who scores under 8/15 on the 4MT indicates MCI. Where this cut-off threshold is placed changes the false positive and false negative rate. For example, if the threshold was moved in order to reduce the false positive rate, this may in turn increase the amount of false negatives. Conversely, if the threshold was moved to minimise false negatives this may in turn increase the amount of false positives. In summary, different cut-off points for different sensitivities and specificities have different false positive and false negative rates.

ROC curves can be used to determine a cut-off point which optimises the trade-off between sensitivity and specificity. As can be seen in the figures below (5.3-5.7), sensitivity is plotted on the Y axis and can also referred to as the true positive rate, the proportion of those with MCI correctly identified as such by the given test. The false positive rate, that is 1 minus specificity, is plotted along the X axis. The false positive rate is the proportion of participants incorrectly categorised by the test as having MCI despite being healthy ageing. The diagonal line across the plot indicates where a 'useless' test would fall. Ideally, a perfect

ROC curve would be comprised of a vertical line along the x axis, reaching 0 on the x axis and 100 on the Y axis, and then being a horizontal line along the y axis, indicating a 100% true positive rate and a 0% false positive rate.

The area under the curve (AUC) is one possible measure of the overall accuracy of the test. A perfect test would show an overall accuracy of 100% i.e. this test has correctly identified 100% of those with MCI whilst also correctly identifying all of those who are healthy ageing. If the AUC is calculated as 50% or lower, this indicates a poor or 'useless' test which is the same or worse than chance.

As discussed, there is a trade-off between sensitivity and specificity. The threshold can be adjusted to increase sensitivity, but this then decreases specificity and vice versa. With this trade-off in mind, Youden's J is often used in conjunction with ROC analysis as it combines both sensitivity and specificity in order to try to capture the diagnostic success of a test in a single value (Youden's J = Sensitivity + Specificity minus 1). Therefore, Youden's J goes from -1 to +1 with +1 being a perfect test

The ROC curve analysis below (Figures 5.7, 5.8, 5.9 and 5.10) show that the 4MT and the SSEVT demonstrated better diagnostic accuracy at differentiating between MCI and HA participants (AUC= 0.707, p=0.016 and AUC= 0.792, p<0.001 respectively). This remained true when using older participants so that age did not differ across groups in the SSEVT (AUC= 0.768, p=0.012). Both presumptive hippocampal tasks showed better diagnostic ability than the ACE III (AUC= 0.629, p= 0.227).

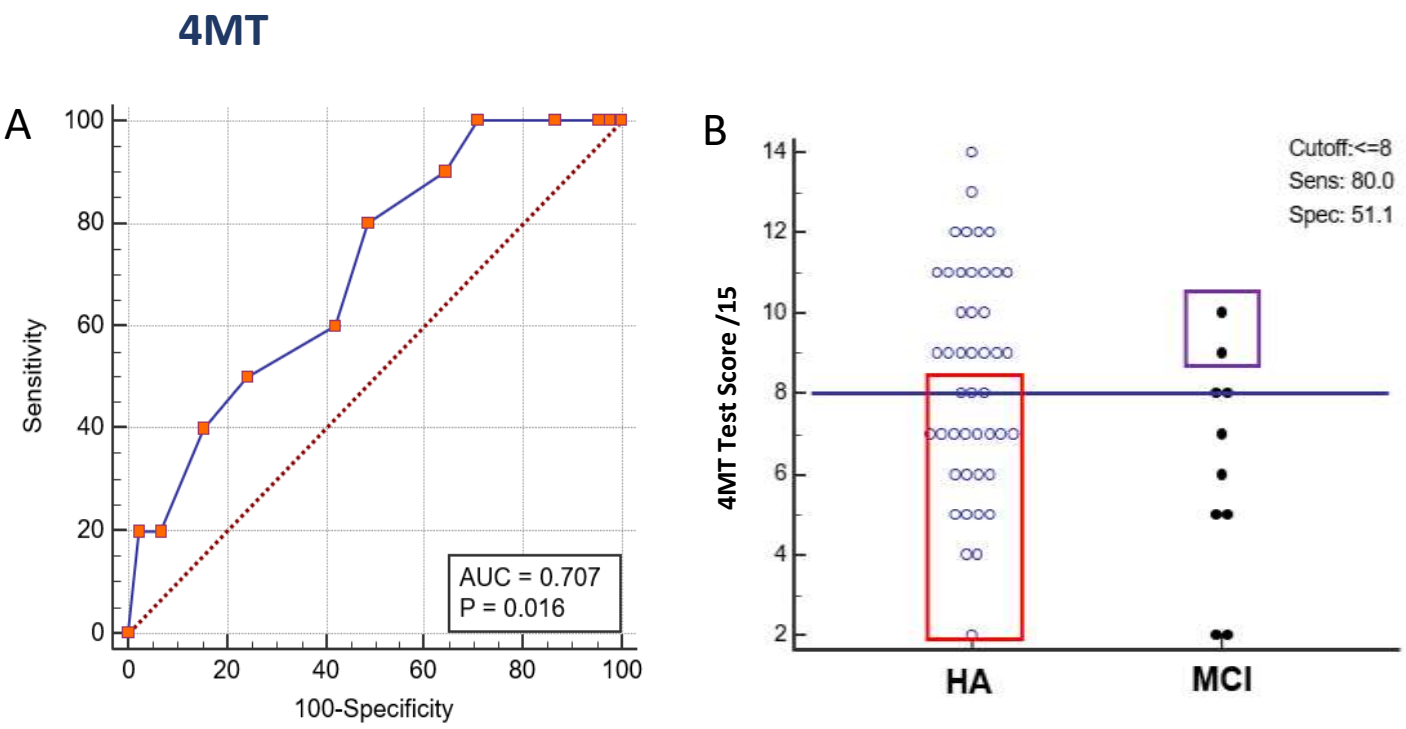

Figure 5. 3. **(A)** ROC curve to demonstrate the trade-off between sensitivity and specificity at various cut-offs of a diagnostic test and is also able to tell the reader the overall accuracy of a given test via the area under the curve (AUC). In this instance, the true positive rate or 'sensitivity' is the amount of people with MCI who are correctly identified whereas the false positive rate refers to the number of individuals inaccurately identified as MCI when they are not and is calculated as '1 minus specificity'. ROC curves can be used to determine a cut-off point which optimises the trade-off between sensitivity and specificity. Optimal cut-off for 4MT is shown as a score of 8/15. Sensitivity/ True positive rate is plotted on the Y axis. The false positive rate, 1 minus specificity, is plotted along the X axis. The diagonal line across the plot indicates where a 'useless' test would fall. Ideally, a perfect ROC curve would be comprised of a vertical line along the x axis, reaching 0 on the x axis and 100 on the Y axis, and then being a horizontal line along the y axis, indicating a 100% true positive rate and a 0% false positive rate. The area under the curve (AUC) is one possible measure of the overall accuracy of the test. A perfect test would show an overall accuracy of 100% i.e., this test has correctly identified 100% of those with MCI whilst also correctly identifying all of those who are healthy ageing. If the AUC is calculated as 50% or lower, this indicates a poor or 'useless' test which is the same or worse than chance. **(B)** Threshold plot illustrating the difference in 4MT scores between MCI and HA participants at the chosen cut-off point. Each point represents a participant. Red box= amount of HA scores below threshold (false positives), purple box= amount of MCI scores above threshold (false negatives). Cut-off <=8, Sensitivity= 80.0, Specificity= 51.1.

SSEVT

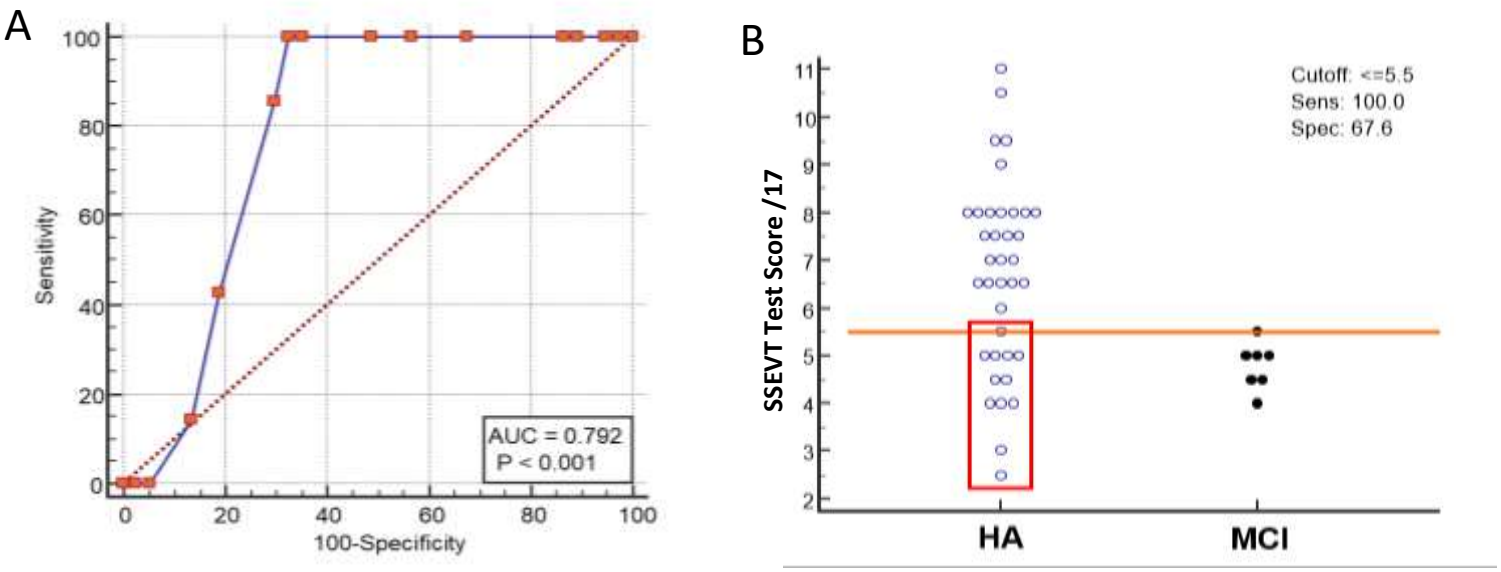

Figure 5. 4. **(A)** Accuracy of the SSEVT test performance for classifying MCI from HA participants (AUC= 0.792, P<0.001). **(B)** Threshold plot illustrating the difference in SSEVT scores between MCI and HA participants. Cut-off<= 5.5, Sensitivity= 100.0, Specificity= 67.6.

SSEVT OLDER AGE GROUP (72+)

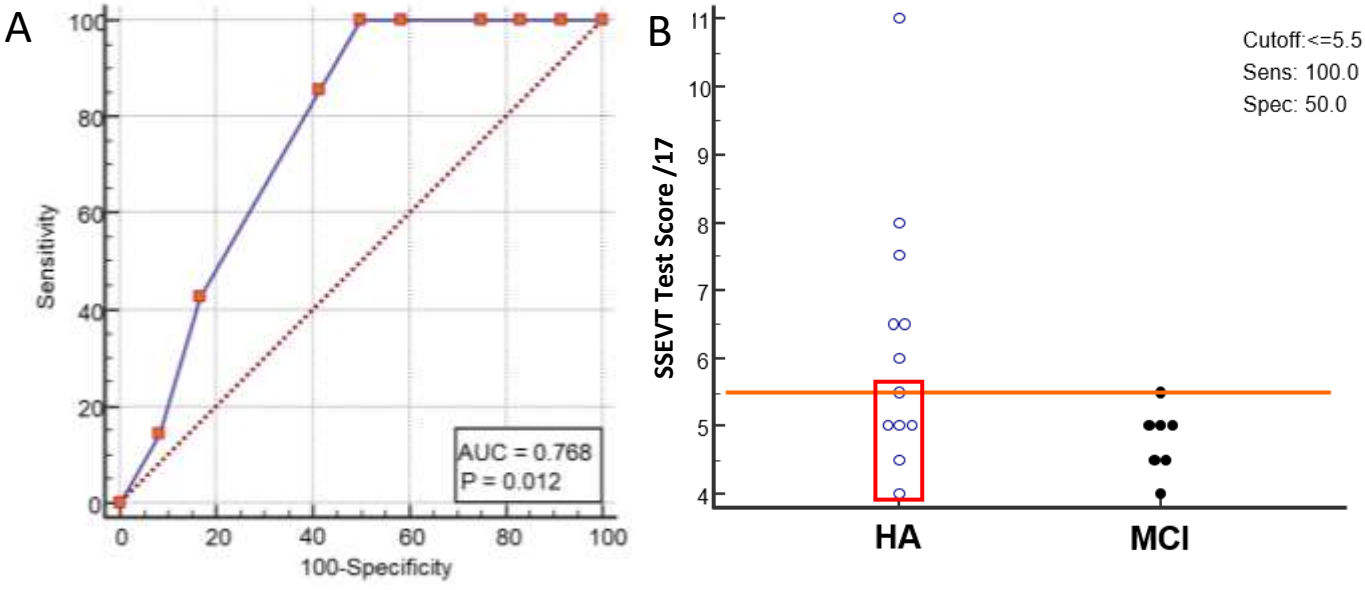

Figure 5. 5. **(A)** Accuracy of the SSEVT older age group test performance for classifying MCI from HA participants (AUC= 0.768, P=0.012). **(B)** Threshold plot illustrating the difference in SSEVT scores between MCI and HA in older participants over the age of 72. Cut-off= <=5.5, Sensitivity= 100.0, Specificity= 50.0.

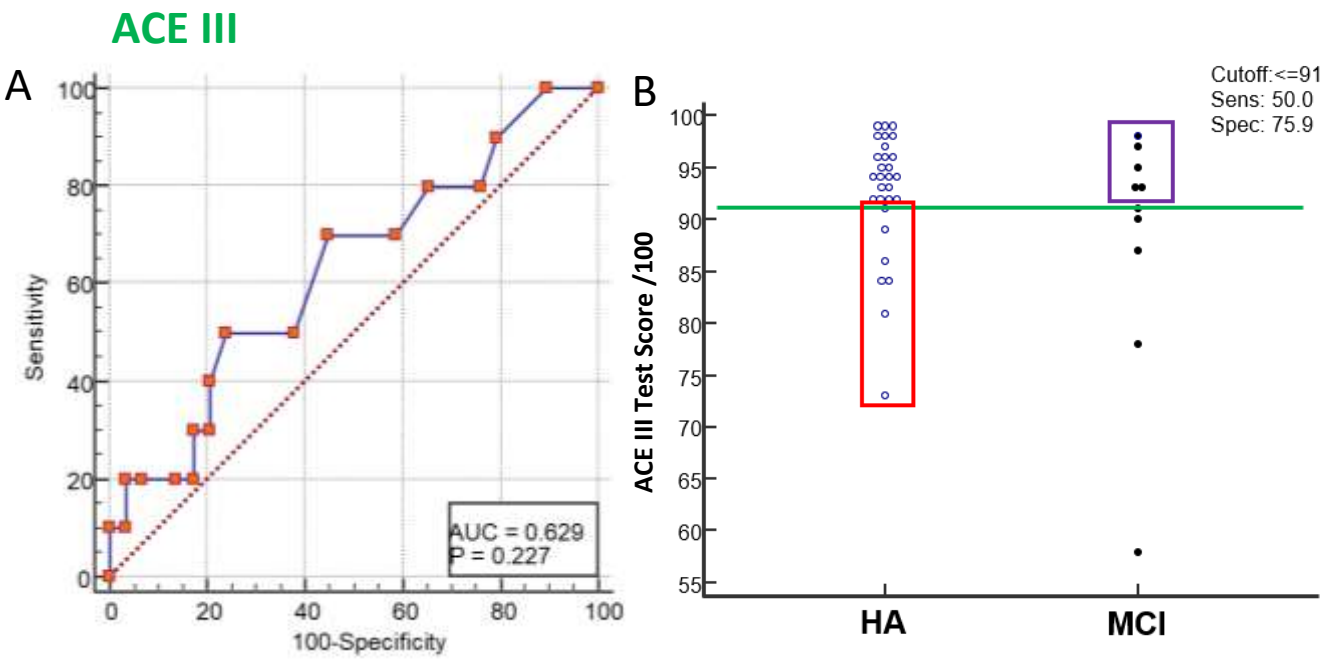

Figure 5. 6. **(A)** Accuracy of the ACE III test performance for classifying MCI from HA participants (AUC= 0.629, P= 0.227). **(B)** Threshold plot illustrating the difference in ACE III scores between MCI and HA participants. Cut-off<= 91, Sensitivity= 50.0, Specificity= 75.9.

5.4: The difference in HA and MCI scores on the 4MT and SSEVT remains significant when only looking at patients and controls who took all three tests (4MT, SSEVT and ACE III).

As discussed above, the patients and control samples greatly overlap but are not identical across the three tests. In principle then, especially with a small sample, a few non-overlapping participants could skew results in favour of one or tests. Accordingly, I then re-analysed the group differences across the three tests looking only at those MCI patients and healthy aged controls that underwent all three tests. Effect sizes are also shown in the table below (table 5.8). Hedges' g was chosen to measure effect size between group scores due to the small sample size (<20). Glass's delta was also analysed to control for any significant difference in standard deviation between group scores as it only uses the standard deviation

of the control group. A large effect size was found between MCI and HA scores on both the 4MT and the SSEVT when using either Hedges' g or Glass's delta whereas a small effect size was found between HA and MCI on ACE III scores using either Hedges' g or Glass's delta. A medium effect size was found between HA and MCI scores when using the SAPQ and the SNSEQ. A small effect size can be seen between HA and MCI education scores, which is advantageous as it suggests that the results obtained were not due to educational bias. The difference in effect size is illustrated in table 5.8.

Table 5. 8.

Baseline Comparisons between MCI and HA participants all of whom took the 4MT, SSEVT and ACE

	MCI (n=7)	HA (n=28)	Hedge's g	Glass's Delta	T-test comparison
Age	77.6 ± 5.9	70.4 ± 4.3	1.55	1.22	*t* (33)=3.660, *p*=0.001
Education	1.7 ± 1.3	2.0 ± 1.4	0.22	0.23	*t* (33)=0.562, *p*=0.578
Sex	4 F : 3 M	17 F : 11M	-	-	-
4MT	5.7 ± 3.0	8.5 ± 2.7	1.02	0.93	*t* (33)= 2.384, *p*=0.023
SSEVT	4.7 ± 0.5	6.7 ± 1.9	1.15	4.00	*t* (32.726)* = 5.053, *p*=0.000016
ACE III	92.3 ± 3.3	92.6 ± 6.1	0.05	0.09	*t* (33)= 0.118, *p*= 0.906.
SAPQ	47.3 ± 12.3	52.9 ± 8.4	0.61	0.46	*t* (33)=0.158, *p*=0.158
SNSEQ	53.7 ± 8.3	58.7 ± 9.3	0.55	0.60	*t* (33)=1.299, *p*=0.203

*Levene's correction applied.

Data represented as mean ± standard deviation except Sex which is the n of males (M) and females (F), n=7. MCI = Mild Cognitive Deviation, HC= Healthy Controls. 4MT- Four Mountains Test, SSEVT-Spaces and Sequence Episodic Video Task, ACE III- Addenbrookes Cognitive Examination III, SAPQ- Spatial Abilities and Practices Questionnaire, SNSEQ- Social Networks and Embeddedness Questionnaire. Hedges' *g* was chosen to measure effect size between group scores due to the small sample size (<20). Glass's delta was also analysed to control for any significant difference in standard deviation between group scores

As can be seen above no significant difference between groups was found when looking at sex or education level (details of education scoring in Table 5.2). Both the 4MT and the SSEVT were found to again effectively distinguish MCI patients from healthy controls whilst the ACE III did not. This is particularly interesting given the frequency with which the ACE III is used within clinical settings (Chapter 1, Section 1.6).

ROC curves can also be used to compare the diagnostic accuracy of different tests. This was useful in the present thesis, allowing for direct comparison between the accuracy of the SSEVT, 4MT and the ACE III (figure 5.7, which superimposes the three ROC curves in one diagram). The best test is shown as the SSEVT as the ROC curve is shown to more closely approach the left-hand corner (i.e. lower false negative rate, higher false positive rate), followed by the 4MT and then the ACE III. This is shown via the AUC results which offer a measure of overall diagnostic accuracy. The SSEVT and 4MT demonstrated higher diagnostic sensitivity and specificity for differentiating between MCI and HA participants (AUC= 0.832, $p<0.001$ and 0.753, $p= 0.016$ respectively), than the ACE III (AUC = 0.602, $p= 0.34$). Results are summarised in table 5.9.

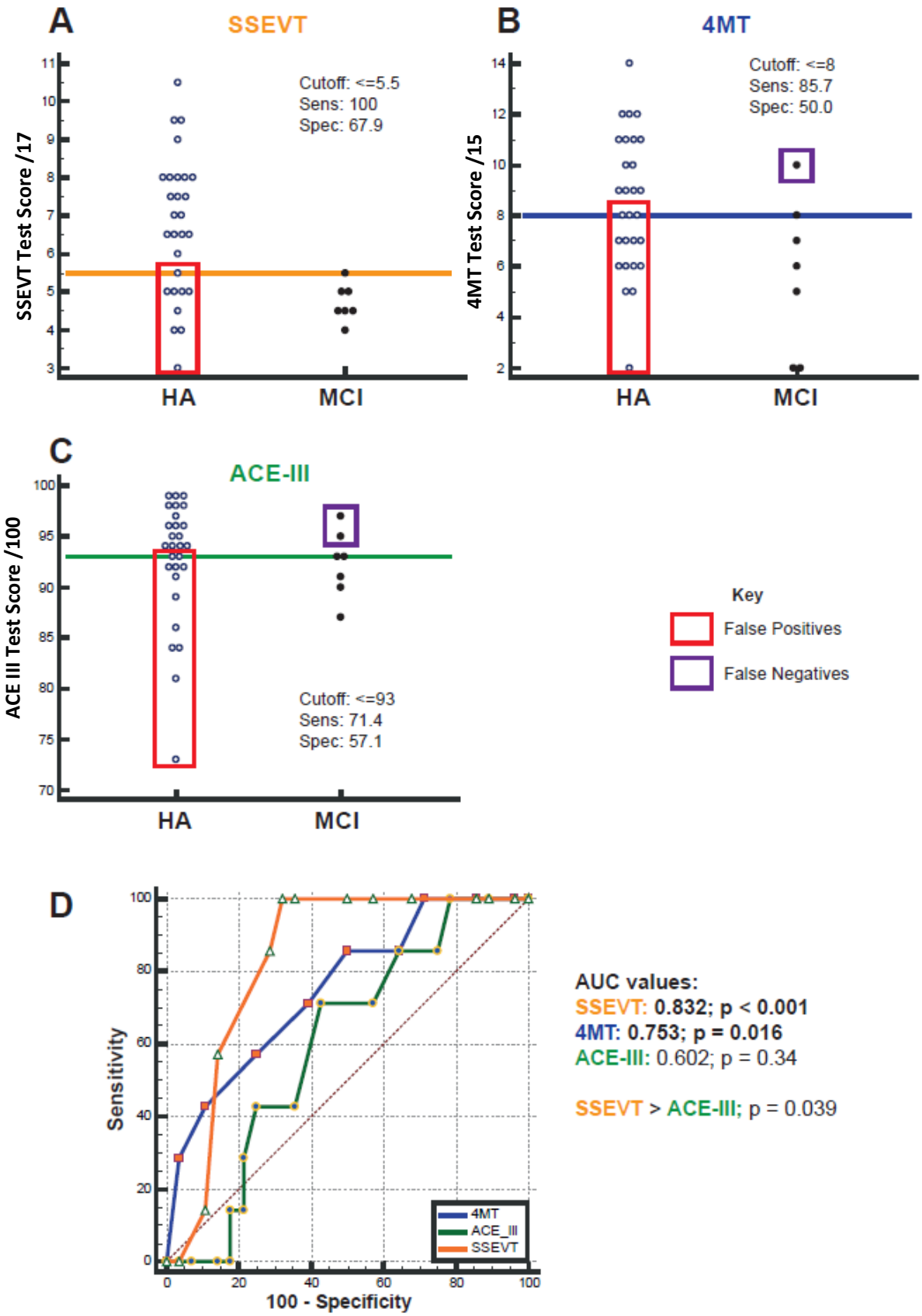

Figure 5. 7. (A-C) Threshold plots illustrating the difference in scores between MCI and HA participants. Red box indicates false positives. Purple box indicates false negatives. **(A)** Spaces and Sequence Episodic Video Task (SSEVT). **(B)** Four Mountains Test (4MT). **(C)** Addenbrooke's Cognitive Assessment (ACE III). (D) Accuracy of the 4MT, SSEVT and ACE III test performance for classifying MCI from HA participants. Test performance of the SSEVT is represented by the orange line, 4MT via the blue line and the ACE III via the green line.

Table 5. 9.

Accuracy of the SSEVT, 4MT and ACE III in identifying patients with MCI.

	Criterion for positive test	Sensitivity	Specificity	AUC	AUC P-value
SSEVT	<5.5	100.0	67.9	0.832	**<0.001**
4MT	<8	85.7	50.0	0.753	**0.016**
ACE III	<93	71.4	57.1	0.602	0.34

AUC, Area Under the Curve. Criterion for positive test, cut-off point as shown in Figure 5.8. Bold font signifies p-values that are statistically significant at the p<0.05 level.

5.5: MCI patients scored significantly lower than HA participants on the Social Networks and Social Embeddedness Questionnaire (ages 65+).

No difference was found between MCI and HA participants in terms of age or education. The scores achieved on the Social Networks and Embeddedness Questionnaire (SNSEQ) were also found to be able to differentiate between MCI (M=51.0, SD=8.1) and HA (M=57.9 SD=9.81) participants (t (47) =2.048, p=0.046), although this significance was relatively small it does indicate that MCI participants may have smaller social networks than HA adults of a similar age and level of education. There was also a medium effect size found between MCI and HA overall scores on the SNSEQ using both Glass's delta and Hedges' g (0.70 and 0.73 respectively). Interestingly certain SNSEQ questions alone showed a significant difference between HA and MCI scores. Scores on question 3 'There are people outside of my family that I can talk to about personal matters.' (MCI: M=2.4, SD=1.26; HA: M=3.47, SD=1.13), (t (46)= 2.605, p= 0.012), and question 15 'I am actively involved in my community' both

showed a significant difference between MCI (M=2.3, SD=1.06) and HA participants (M=3.29, SD=1.29), (t (46)=2.227, p=0.031). Both question 3 and question 15 showed large effect sizes between MCI and HA participant scores using both hedge's g and glass's delta (Q3: Hedge's g= 0.93, Glass's delta= 0.85. Q15: Hedge's *g*= 0.79, Glass's delta= 0.93). When analysing the SNSEQ questions alone, 1 participant was excluded due to a lack of information on individual questions.

5.6: The ability of the SAPQ to differentiate between groups.

No significant difference was found between MCI and HA scores on the SAPQ overall. However, a large effect was found using Glass's *delta* (0.821) and a medium effect size found when using hedges' *g* (0.658), so further research with larger samples could be of value. Question 4 on the SAPQ, 'I have difficulty visualising in my mind's eye the local walking routes (e.g. to shops, pubs and restaurants) to and from my home' was shown to significantly differ between groups (MCI: M=3.10, SD=1.52; HA: M=0.01, SD=0.09), *t*(9)= 6.433, *p*=0.00021), (Levene's correction applied), with a large effect size found between groups when using either Hedge's *g* (4.61) or Glass's delta (2.03) which may offer some interesting insight into difficulties those with MCI may have in the visualisation of routes.

5.7: Healthy ageing vs MCI: Summary of main results and discussion.

One of the present projects' main aims was to see whether the new and recently developed hippocampal tasks, the 4MT and SSEVT, could discriminate between MCI and HA participants and whether they performed at least as well as the ACE III. As early diagnosis is paramount, being able to detect cognitive degeneration at a prodromal stage would be hugely beneficial as MCI is often thought to indicate an increased risk of progressing to probable AD (Lopez et al, 2003; Plassman et al, 2008; Manly et al, 2008) as discussed in Chapter 1, Section 1.10.1, and therefore using an MCI cohort may prove particularly useful.

The above analyses found that test scores on both the SSEVT and the 4MT were significantly different between groups whilst scores on the ACE III were not, thus supporting the hypothesis that presumptive hippocampal dependent tasks are able to distinguish between healthy ageing individuals and those with impairment. The present thesis also aimed to analyse whether such tasks are at least as effective as the widely adopted ACE III and found both hippocampal tasks to surpass the ability of the ACE III in distinguishing between MCI and HA groups. The ACE III did not reliably distinguish MCI patients from HA participants.

Although no significant differences in age and education between the MCI group and the 65+ HA were found when analysing the ACE III or 4MT, there was a significant difference in age on the SSEVT as the mean age of the MCI group was significantly older than the 65+ HA group. The SSEVT remained able to distinguish between the MCI and AD groups when the age difference was no longer significant, and the HA group was raised to 72+, albeit creating a smaller HA sample. Furthermore, test scores on the SSEVT and the 4MT remained

significantly different between HA and MCI groups when the three tests were re-analysed looking only at patients and HA controls who underwent all three tests, as did the inability of the ACE III to distinguish between groups. This ensured that the previously seen group differences were not due to a lack of homogeneity in the sample. Although false positive results were found in the SSEVT group and false positives and false negative results were found in the 4MT, the AUC analysis found the ACE III to be more prone to both, a phenomenon which has been previously discussed in Chapter 1, Section 1.6.

The SNSEQ was shown to differentiate between HA and MCI participants, and a medium effect size was found between scores. Interestingly, the specific questions which showed a significant difference in scores between the MCI and HA participants pertain to socialising outside of the first ring of their social network (family, close friends). This reduction in social network may be worth further exploration in the future.

No significant difference was found between MCI and HA scores on the SAPQ overall. However, a large effect size when using *glass's delta* and medium effect size when using hedges' *g* was found which may indicate that the SAPQ may benefit from the use of a larger sample size in future research. Question 4 'I have difficulty visualising in my mind's eye the local walking routes (e.g. to shops, pubs and restaurants) to and from my home' was shown to significantly differ between groups, which may offer some interesting insight into difficulties those with MCI may have in the visualisation of routes.

5.7.1: ACE III scores were unable to distinguish between Healthy Controls and MCI patients.

In the present study the ACE III test scores were found to be unable to identify which participants included in the sample had an MCI diagnosis. There is much less literature which focuses upon the ACE III's ability to identify MCI patients, as most look at the test's efficacy in identifying dementia or AD specifically, however there is some comparable literature. Research such as Wang et al, 2019 contradicts the above findings, reporting that Healthy controls perform significantly better on the ACE III total and subdomain scores than those in the MCI group. The study by Wang et al also reported the AUC total score was to be 0.978 with a sensitivity of 97.3% and a specificity of 90.7%. However, there was a difference in ages of 7.63 years, with MCI participants being significantly older than healthy controls, which may have affected scores somewhat. Another difference between the 2019 study and the present project is the cut-off score, with Wang et al deeming the cut-off point to be a score of >=85. A higher level of accuracy than reported in the current project was also found in a recent study by Takenoshita et al (2019) (sensitivity 0.82, specificity 0.90). As is also the case with Wang et al, 2019, the ACE III cut off score in Takenoshita et al 2019 was also lower than the current study at >=88/89 as opposed to >=93 as shown above in Figure 5.8. When the cut-off point is changed to 88 within the current analysis the sensitivity changes to 14.3%, whilst the specificity changes to 82.1%. Takenoshita et al (2019) did have appreciably more participants than the present study (MCI=137, Controls=73), as did Wang et al (MCI=120, Healthy controls=136).

The Cochrane review 'Addenbrooke's Cognitive Examination III (ACE III) and mini-ACE for the detection of dementia and mild cognitive impairment (Review)' (Beishon et al, 2019) the ACE III's ability to differentiate between healthy controls and MCI patients to vary

between 64-95% in terms of sensitivity and between 64%-100% in specificity, indicating inconsistent findings with regards to the accuracy of the ACE III in identifying those with MCI specifically. The review summarised that when all included studies were considered, a definitive conclusion on whether the ACE III should be used to identify MCI patients could not be reached. Furthermore, it recommended that the findings could only be used in a hospital setting as no included studies investigated general populations or community. Ultimately the review concluded that the ACE III 'should only be used as part of a clinical assessment when making a diagnosis of dementia, and should not be relied upon alone..'. This further supports the current analysis which indicates that the ACE III is unsuitable for use as a screening tool, due to its inability to differentiate between MCI and HA participants. This is somewhat significant given how commonly the ACE III is used in primary care settings due to its time effective benefits, ease of use and relatively low cost (Mirza et al, 2017; Hodges et al, 2017).

5.7.2: Presumptive hippocampal tasks are better able to distinguish between healthy ageing and MCI patients than the ACE III.

As predicted, the 'hippocampal' tasks were able to clearly differentiate between the MCI and HA groups. This in turn supports the hypothesis that due to the early degeneration of the entorhinal cortex (the main interface between the hippocampus and neocortex) and the hippocampus in AD (Braak & Braak, 1996), tasks which tap hippocampal-dependent functions, such as episodic memory (SSEVT) and topographical memory (4MT), may be effective in highlighting early-stage AD.

5.7.3: The 4MT was able to distinguish between healthy ageing and MCI patients: focus upon spatial allocentric memory

As previously discussed in Chapter 1, Section 1.8, given that preclinical neurodegeneration is observed at an early stage within the hippocampus and MTL structures , the significant role these regions play in the processing of spatial information suggests that impaired performance on spatial tests may represent a behavioural marker of early AD related brain changes (Gomez- Isla et al, 2005). This is supported by longitudinal MRI studies which show that altered performance on visuospatial tasks predates medial temporal lobe atrophy in preclinical individuals (Ritchie et al, 2018; Laakso et al, 2000). Therefore a task such as the 4MT may prove beneficial in identifying early degeneration within the hippocampus. This relationship is explained in detail in Chapter 1, Section 1.8. The 4MT tests allocentric spatial memory specifically, which is dependent upon hippocampal integrity.

As discussed in detail in Chapter 2, Section 2.10), the Four Mountain Test (4MT) is a short test of spatial memory. The test consists of computer-generated landscapes, each featuring four mountains of varying shapes and sizes. The participants are asked to observe the landscape image for 8 seconds. After a 2 second delay participants are asked to identify the previously seen landscape but seen from a different viewpoint. Participants are offered four landscapes, of which 3 are foil images and participants are then given 30 seconds to choose. Non-spatial features such as the lighting, vegetation colour and cloud cover of all of the landscapes offered varied between presentation and testing, in order to avoid the possibility of non-spatial features being used to answer. This follows the same logic as the characters in the SSEVT standing against neutral backgrounds in the questions (discussed below in Section 5.7.4), to provide no hints which may prompt an answer of familiarity.

In the present study, as predicted, MCI participants were shown to perform significantly worse on the 4MT, thus indicating that the 4MT may be effective in identifying the early stages of AD, as MCI is often thought to indicate an increased risk of AD progression (Lopez et al, 2003; Plassman et al, 2008; Manly et al, 2008). Although there has not been extensive research into the ability of the 4MT to identify those with MCI, Moodley et al, 2015 also found that performance on the 4MT was able to distinguish between patients with MCI from age-matched controls. They also found the 4MT able to differentiate between HA and MCI groups with and without cerebrospinal fluid (CSF) biomarker evidence of underlying AD, further supporting the findings of the current project. Chan et al, 2016 assessed the ability of the 4MT to differentiate between MCI participants who were biomarker positive and MCI participants who were biomarker negative and found it to be successful. Those with MCI who were biomarker positive scored significantly worse than those who were biomarker negative. Interestingly, the cut-off score within this study was the same as the current project, with a score of <8/15 associated with 100% sensitivity and 78% specificity in identifying biomarker positive MCI participants vs negative ones (Chan et al, 2016).

Ritchie et al, 2018 examined allocentric and egocentric spatial processing in relation to future dementia risk in a middle-aged cohort. The CAIDE (Cardiovascular Risk Factors, Ageing, and Incidence of Dementia) Dementia Risk Score (DRS) was calculated for 188 people aged between 40-59 of whom 94 had a parent with dementia. Participants took the 4MT, which tests allocentric spatial processing and the Virtual Reality Supermarket Trolley Task (VRSTT), which tested egocentric spatial processing (described in Chapter 1, Section 1.8.1). They found a significant negative association between the DRS and 4MT scores (Spearman correlation -0.26, p=0.0006), however this was not found with the VRSTT. This

further supports the potential ability of the 4MT to identify early-onset dementia through tapping hippocampal dependent allocentric spatial ability specifically, an effect that was not found when assessing egocentric spatial ability through the VSRTT. Furthermore the 4MT was found to be a better predictor of DRS than tests of episodic memory, verbal fluency. or executive functioning, functions that many other neuropsychological tests aim to assess.

Further lending support to the efficacy of the 4MT's ability to identify those with AD related deficit, Bird et al (2010) found that performance on the 4MT was impaired in patients with diagnosed early AD dementia, with a similar observation being made by Pengas et al, 2010 in a study which compared several different tests of spatial memory.

If a diagnosis of MCI is indicative of an early stage of cognitive decline which could result in a future diagnosis of AD, there is value in looking at the predictive ability of the 4MT, should it be used within clinical practice. Wood et al, 2016 conducted a longitudinal study of 15 MCI patients who were followed up after 24 months and found the 4MT predicted conversion with a classification accuracy of 93%, outperforming tests such as the RAVLT (64%) and the TMT-B (79%). This further supports the potential benefits of the 4MT's use as a neuropsychological tool.

One criticism of much of the research into the 4MT is that most studies have relatively small sample sizes, possibly due to how recently developed it is, and larger scale studies would be beneficial in the future. Whilst there are limited studies which look at the same points as the current study (the 4MT's ability to differentiate between MCI and AD), the research into the 4MT does all generally support the idea that the 4MT is hippocampus dependent and appears effective in identifying the early stages of AD. The short duration, ease of application, and scoring and the seemingly favourable levels of accuracy may

indicate that the 4MT fulfils the need for a simple yet accurate screening tool or possibly a valuable component of a diagnostic battery in order to identify AD at an early stage.

5.7.4: The SSEVT was able to distinguish between healthy ageing and MCI patients: episodic recollection and sequence memory.

The consensus on recognition memory suggests that there are two separate processes which underlie recognition memory; familiarity and recollection (Yonelinas, 2001; Duarte et al, 2004; Wais et al, 2008). Although the exact nature of the hippocampus- episodic memory relationship remains unclear, episodic memory deficits are common in healthy ageing, particularly with respect to encoding new information (Small et al, 1999; Ezzati et al, 2016). More pertinent to the present project episodic memory decline has been associated with conversion to Alzheimer's disease (Small et al, 2000; Grober et al, 2008).

A large number of fMRI studies have found dissociable patterns of activity for measures of familiarity and recollection (Daselaar et al, 2006; Henson et al, 2005; Montaldi et al, 2006; Raganath et al, 2004), which support the idea that they are two distinct processes. Using the remember-know procedure an increase in hippocampal activity has been associated with the recollection of the learning episode but not with familiarity (Eldridge et al, 2000; Yonelinas et al, 2005). The remember-know procedure was first introduced by Tulving (1985). It requires that the participants introspect and offer their subjective response as to how. 'Remember' (i.e. recollection) refers to the ability of the individual to consciously recall a prior event, "mentally travelling" to the specific time and/or location of an event; they may able to recall associations, images or sensory

information from the event. 'Know' (i.e. familiarity) refers to the subjective feeling of prior occurrence: a stimulus feels familiar, but the participant fails to recall anything about the occurrence or what was experienced at the time of the event. The memory is not accompanied by specific details about the time, place, or associations with the event.

Neuroimaging studies have suggested that the hippocampus is critical for recollection whereas familiarity is dependent on the integrity of the perirhinal cortex (Ranganath et al, 2004; Daselaar et al, 2006; Eldridge et al, 2000; Haskins et al, 2008; Rolls et al, 2011). This has been further supported via a meta-analysis by Koen & Yonelinas (2014) who found recollection to be significantly more impaired than familiarity in aMCI patients whereas AD was associated with large decreases in both familiarity and recollection. This suggests that due to the effect AD has upon the hippocampus at an early stage, recollection is more hippocampal dependent than familiarity, which is affected much later. Therefore, a test which aims to identify early decline due to AD should focus upon recollective episodic memory.

An early task containing both familiarity- and recollection-based questions and which was created by Dr Colin Lever (Primary supervisor) and myself as part of an undergraduate project acted as a 'proof of concept' precursor task to the SSEVT. This earlier project found that MCI participants performed significantly worse than HA controls on recollection-based questions specifically. Accordingly, we intended that only questions tapping recollective memory should be included in the present SSEVT.

One of the key obstacles to avoid when creating a test of episodic memory that taps hippocampal function is the risk of participants answering questions based upon familiarity and not recollection. The use of familiarity-based techniques to answer forced choice

memory questions is always a risk that must be taken into consideration. Therefore, great care was taken in the SSEVT to ensure that the questions rely on recollective memory and cannot be answered due to familiarity.

Section 1 focused upon person associations in which the participant is required to recall an event that occurred and match the event to a character in the video e.g. 'Who missed the phone call?'. Should only one of the characters that are presented as a possible answer be present in the video, this could be answered based upon familiarity alone. To address this, all four of the characters presented appear within the video and therefore the participant must remember the specific event that occurred and the character that was associated with the event, meaning that the question is only answerable via recollection and not familiarity alone. In order to avoid contextual cues which may prompt familiarity, the pictures of the characters when presenting the possible answers to the question all appear against neutral backgrounds in order to provide no hints which may prompt an answer of familiarity. Section 2 focuses upon object-room associations in which an object which is present in the video is shown against a neutral background. A further four pictures of rooms are shown from a bird's-eye view and the participant is asked in which room the object was present e.g. 'In which room did you see this phone?'. The use of event-context associations in order to prompt recollection is deliberate. The BIC model (Eichenbaum et al, 2007) explains the hippocampus as binding an item (or event) to its context and intervening in the recollection process (Diana, Yonelinas & Ranganath, 2007). Within Sections 1 and 2 in particular participants are asked to view a person/object and associate it to an event/room, which requires hippocampal-dependent recollection in order to answer correctly.

Episodic memory also requires the binding of sequential experiences and memories are organised by the order of serial events (Tulving & Markowitsch, 1998). This memory of sequential events provides a structure for the flow of daily life and the ability to integrate occurrences across time is crucial for later retrieval of such experiences (Clayton & Dickinson, 1998; Eichenbaum, 2004). Memory for the sequence of events appears to decline even in healthy ageing adults (Allen et al, 2015), but perhaps unsurprisingly given its hippocampal dependency the recollection of event order appears to be further impaired in those with impaired hippocampal function (Grafman et al, 1991; Dede et al, 2016).

As discussed in Chapter 1, Section 1.8.1, Dede et al (2016) showed that amnesic patients were weak at remembering the sequence of events on an earlier walk. Based upon this rationale, Sections 3, 4 and 5 all focussed upon room and/or event order. Section 3 presented the participant with an event e.g. 'Recall the time you were in the room where you were asked if you liked the painting on the wall. What event occurred in the room immediately before this?' before presenting 4 possible answers 'A) Two people welcomed you to the house. B) You saw a person miss a phone call. C) You saw a person watching TV. D) You saw a person dancing.'. All of the possible events had happened within the video to avoid answers being answerable purely by familiarity rather than recollection. In this Section 3, the question required the participant to recall a particular event and to additionally remember a separate event that occurred directly before or afterwards, testing both event recollection and event order. Section 4 offered 4 questions which each list events in different sequences e.g. 'You were offered a drink; you were offered a snack; the phone rang'. Here the questions are explicitly requiring event order recollection. As with Section 3, all of the events included did occur at some point during the video. Section 5 showed pictures of two rooms along with either 'Which room did you visit first?' or 'Which room did

you visit most recently?'. This form of question required the participant to remember both rooms before establishing the order in which they were visited. It could be argued that familiarity may play some role in the answering of room order questions. For example, pictures of the room which prompt stronger feelings of familiarity may signal that that particular room was visited most recently. However this test was purposely designed to limit the scope of such techniques as 7 of the rooms appear twice, in a different order, and with different events taking place upon each visit.

The main aim of the SSEVT was to focus upon recollective memory in a way that was more true to real-life experiences than current clinical episodic memory tests, which mostly consist of list-learning (RAVLT, CVLT etc, see Chapter 1, Section 1.8.1). The test was designed to avoid answers of familiarity to ensure that recollective, hippocampal dependent memory was tested. The SSEVT was successful in differentiating between the MCI and HA groups within the current project which may be at least partly due to the hippocampal degeneration experienced at the early stages of Alzheimer's disease, as is expected to be present to a greater or lesser extent in the MCI group. Furthermore, Youden's J index was maximised with a sensitivity of 100% and a specificity of 67.9% according to the ROC analysis, suggesting highly promising sensitivity. In principle, if this task is sensitive to early AD, it could be combined with a task that is specific for early AD, to provide good overall diagnostic value. Although the sample size is small this makes for a promising first study into the efficacy of the SSEVT in detecting hippocampal degeneration and therefore AD at an early stage.

5.7.5: Sensitivity vs Specificity: Hippocampal tasks vs ACE III.

It may be argued that although displaying good sensitivity (4MT= 85.7%; SSEVT= 100%), the 4MT and SSEVT only achieve specificity of 50.0% and 67.9% respectively, which is insufficient for a diagnostic test. However the new and recently developed tests within this chapter are proposed to be used as primary care or screening and not diagnostic tools, which as defined by the 1998 UK National Screening Committee is 'The systematic application of a test, or inquiry, to identify individuals at sufficient risk of a specific disorder to warrant further investigation or direct preventative action….'. The main focus of many screening tests is that of sensitivity, in order to avoid missing cases at a crucial first stage. In terms of AD testing and diagnosis, this may be a screening tool used in a GP surgery. Sensitivity depends on the threshold applied, a threshold that maximises Youden's J (sensitivity + specificity-1), was used in the above analysis, to ensure high sensitivity, the trade-off is often a lower level of specificity (Florkowski et al, 2008; Morel et al, 2016). A sensitive test is good at identifying those who do have a particular disease (in this case MCI) but may also identify those who do not. This is not unusual during the screening process, Croswell et al, 2009 reported on the cumulative incidence of false-positive results in repeated multimodal cancer screening. The study revealed that for a woman, the cumulative risk of undergoing a diagnostic procedure due to a false-positive screening result was about 12.3% after 4 tests increasing to 22.1% after 14 tests. For men the corresponding percentages were 17.2% after 4 tests and 28.5% after 14 tests. Essentially the more screening tests an individual experiences, the more likely they are to experience a false-positive result. The screening process is often extremely sensitive, often at the expense of specificity with the understanding that more extensive testing will identify those who do not

have a particular disease or impairment whilst the sensitive nature of the screening test limits the amount of false negative results, risking those without a disease or impairment being undiagnosed.

The neuropsychological process following initial testing in a GP surgery is lengthy, with family history, interviews with both the patient and family/carers and longer neuropsychological testing required to lead to an eventual diagnosis. Put in this context, based upon the ROC curve analysis shown in Figure 5.8, At a primary care level, should only the tests included in this project be used, the SSEVT would highlight 100% of participants with MCI, the 4MT would identify 85.7% of those with MCI, whilst the ACE III would identify 71.4% of those with MCI. Currently in the UK many participants who do not show signs of cognitive deficit at the screening stage are discharged. To use a rather blunt hypothetical instance, based upon sensitivity alone, if this particular cohort had attended a GP surgery, 28.6% of participants would be discharged if the ACE III was the only screening tool used to assess cognitive deficit compared to 14.3% had the 4MT been used and 0 had the SSEVT been used. Diagnostic tools are naturally held to a much higher standard in terms of specificity. The efficacy of current AD diagnostic tests is addressed in the Chapter 3 meta-analysis, in which the ability for existing neuropsychological tests to predict conversion from MCI to AD is assessed. The hippocampal dependent tests included within this thesis certainly seem to hold some promise as potential screening tools however a larger sample size and further testing is required in order to further investigate this.

5.7.6: Does social embedding predict cognitive decline? patients with MCI were less socially embedded than Healthy Ageing individuals.

Social networks and social embeddedness are thought to play a crucial role in AD. As addressed in detail in Chapter 1, Section 1.3.2, evidence from longitudinal studies suggest that participation in social activity, the size of an individuals' social network, or social engagement level may all be potentially modifiable risk factors. Older adults who are more socially active experience less decline in cognitive abilities (Barnes et al, 2004; Ertel et al, 2008; Lovden et al, 2005; Fratiglioni et al, 2004; James et al, 2011) and have a reduced risk of dementia (Karp et al, 2005; Saczynski et al, 2006). Therefore, social network size and complexity may act as somewhat of a protective factor against AD.

The positive effects of social engagement have also been shown via the use of biomarkers. MRI studies have found an association between the size and complexity of social networks and the density of grey matter (Kanai et al, 2012) and amygdala volume (Bikart et al, 2011). This is supported by primate research which suggests that social network size could contribute to changes in brain structure and function (Sallet et al, 2011). More relevant to the present study, rodent studies have found mice to have improved hippocampal functioning when housed in large groups as opposed to mice housed in pairs, displaying better novel-object location memory (Smith et al, 2018). Inversely, social isolation can lead to cortisol dysregulation (Fujiwara et al, 1996; Payne & Nadal, 2004; Stark et al, 2006), which is a commonly observed in AD patients. This research, and the overall aim of developing time and cost-effective neuropsychological tests, was the basis upon which the Social Networks and Social Embeddedness Questionnaire (SNSEQ) was formed. It was reasoned that a questionnaire which evaluates the size and complexity of an individuals'

social network may prove valuable for highlighting those who may be at a greater risk of converting from MCI to AD. As hypothesised the SNSEQ was shown to differentiate between HA and MCI participants, and a medium effect size was found between scores. Those with MCI were shown to have smaller social networks, less social embeddedness, and engage in less social activity as compared to the HA sample. This implies that larger social networks and a degree of social embeddedness may protect against cognitive decline.

However, there other hypotheses which may explain the effect seen in the present study. This decrease in social network size and complexity may be due to possible reverse causations (Dodge, Ybarra & Kaye, 2014). For example, a lower level of social engagement may be a result of presymptomatic dementia, not a dementia cause or contributing factor and cannot then be a protective factor either. Indeed there are studies which have found a higher level of social activity or level of interaction to be associated with less cognitive decline (Aartsen et al, 2002; Hultsch et al,1999). The results obtained within the present study did not allow for more detailed testing into reverse causation and the subject has not been widely researched but some studies that tested for reverse causation found little evidence of this (Barnes et al, 2004; Ertel et al, 2008; Lovden et al, 2005; Amieva et al, 2010). It cannot however, be ruled out as a possible explanation. However, this alternative cause is interesting in itself. If the structural changes occurring within the brain due to AD cause a form of social withdrawal, this may compound the issue. Research has shown the detrimental effect that social isolation has upon the hippocampus (Scaccianoce et al, 2006; Shao et al, 2015; Chang et al, 2015; Khodaie et al, 2015), therefore if an individual were to socially withdraw from previously enjoyed activities and relationships, this may still lead to faster degeneration. This is somewhat taken into consideration due to the 'change' score included in the SNSEQ but the MCI sample size of 10 was insufficient to see any clear effect.

Scores on question 3 ‘There are people outside of my family that I can talk to about personal matters.’ (t (46)= 2.605, p= 0.012) and on question 15 ‘I am actively involved in my community’ both showed a significant difference between MCI and HA participants. This difference may indicate that individuals with MCI tend to interact more with the ‘first ring’ of their social network, i.e. close family such as spouse and do not tend to be involved within their community. This also supports the findings within Chapter 4, which suggest that as people age, their social networks consists of more familial and emotionally close connections. This may be an interesting point for further investigation in future research.

If an individual’s social network and level of social embeddedness does have a causal role in delaying or preventing cognitive decline or conversion from MCI to AD, the exact mechanisms remain unknown. However there are a few possibilities; one commonly referred to theory is that social encounters challenge older adults to participate in complex interactions which assist to maintain efficient neural networks (Hultsch et al, 1999) in a form of ‘use it or lose it’. This in turn may create a cognitive reserve capacity that assists to buffer the brain against the manifestation of impairment, even if there is underlying neuropathology (Stern, 2002; Valenzuela & Sachdev, 2006). Therefore, as discussed in Chapter 1, Section 1.3.3, having a large social network may provide a meaningful social role which could reduce stress response (Berkman, 2000; Fratiglioni et al, 2004).

Finally, there are other physical factors which may be considered. There are many physical ailments that may contribute to reduced social interaction and subsequently smaller social networks. For example, social interaction often requires some degree of physical activity which may be limited if an individual suffers from issues affecting mobility. Such disabilities may have affected the way MCI patients responded to SNSEQ questions

such as ‘I am actively involved in my community’ as an inability to independently move around may limit such interactions.

In addition to mobility issues, hearing loss is more common in people with dementia than expected by chance (Uhlmann et al, 1986; Lin et al, 2011; Livingston et al, 2017) and the use of hearing aids has been associated with a reduction in social isolation and depression (Chisolm et al, 2007). However, with up to 48% of men and 39% of women at or over the age of 65 reporting hearing difficulties and only 31% of adults aged 65 and over reporting good hearing, only 18% are reported to use hearing aids according to the 2014 health survey for England (Scholes et al, 2014).

An inability to hear can in turn result in an inability to engage in social situations, thus in turn heightening dementia risk. This was somewhat accounted for in the administration of the SNSEQ by requesting the use of hearing aids, should participants use them. However, hearing may still pose a problem both in social interaction and neuropsychological testing (Ciorba et al, 2012; Fritze et al 2016; Pye et al, 2017). Longitudinal studies into the relationship between hearing loss and social networks and embeddedness are limited but is an interesting issue to consider.

Living situations and physical health issues may have also affected answers on questions such as ‘I find it easy to meet new people’. Age remains the biggest risk factor in the development of Alzheimer’s disease and with age comes a higher chance of physical ailments which may adversely affect social interaction. The idea that physical disabilities or ailments may lead to enforced social isolation, and the extent to which this is a result of the cognitive decline MCI patients experience was beyond the scope of the current

questionnaire but is an interesting question to consider in future research or in the further development of the SNSEQ.

Another limitation of the SNSEQ was the use of a self-report questionnaire, which may have been subject to recall bias. This may be particularly important when completed by individuals with a cognitive impairment. There are issues surrounding how much insight patients may have into their current ability (Starkstein et al, 1996). However we attempted to mitigate this by asking that someone that knows them well be present. Only 2 out of 10 participants filled out the questionnaire with someone that knew them well, despite the examiners request of the presence of another person. Therefore, there was insufficient data to analyse how answering by someone who knew participants well affected scoring.

The purpose of the SNSEQ within this project was to see whether a quick questionnaire could identify a difference in social network size and overall social embeddedness between MCI participants and HA controls, in which the questionnaire proved successful. MCI participants within this particular sample were shown to have smaller social networks than HA controls. This is particularly interesting when considering that the SNSEQ was shown to not decline in healthily ageing participants in Chapter 4. This may indicate that there is a clear difference in social embeddedness and social networks as individuals begin to decline in a way that is abnormal to healthy ageing. The SNSEQ is recently developed and the above study was used primarily in order to validate its potential use, which has shown to be somewhat promising. However, a much larger sample size is necessary in order to further develop and validate the SNSEQ's use as a neuropsychological tool.

5.7.7: MCI participant's may have difficulty visualising routes in their 'mind's eye'.

No significant difference was found between MCI and HA scores on the SAPQ overall. However a large effect size when using Glass's *delta* and medium effect size when using hedges' *g* was found which may indicate that the SAPQ may benefit from the use of a larger sample size in future research. Question 4 'I have difficulty visualising in my mind's eye the local walking routes (e.g. to shops, pubs and restaurants) to and from my home' was shown to significantly differ between the 'Older' 65+ healthy older adults (M=0.01, SD=0.09) and MCI (M=3.10, SD=1.52) (t(9.01)=6.414,p=0.00012). In Chapter 4, this question was found to not significantly differ between age groups (Young, Middle, Old) and so this significant difference between groups can reliably be attributed to MCI participants. This difference in HC and MCI patients' ability to visualise routes is interesting and the two areas which may be involved in this process, the hippocampus and precuneus, are both part of what is known as the default mode network.

The default mode network (Raichle et al, 2001) refers to an interconnected group of brain structures that are hypothesised to be part of a functional system. Such brain regions seem to show lower levels of activity when humans are engaged in a specific task yet higher levels of activity when we are awake and not involved in any particular mental task. During these times people may be daydreaming, monitoring the environment, recalling memories etc, things that people may do when they are simply 'thinking', without any obvious thinking goal in mind.

Due to being a relatively recent concept, there is still on-going research and some debate around which brain structures should be included in the definition of the DMN.

However despite this, some structures that are generally included are the medial prefrontal cortex, posterior cingulate cortex and the inferior parietal lobule (see figure 5.8).

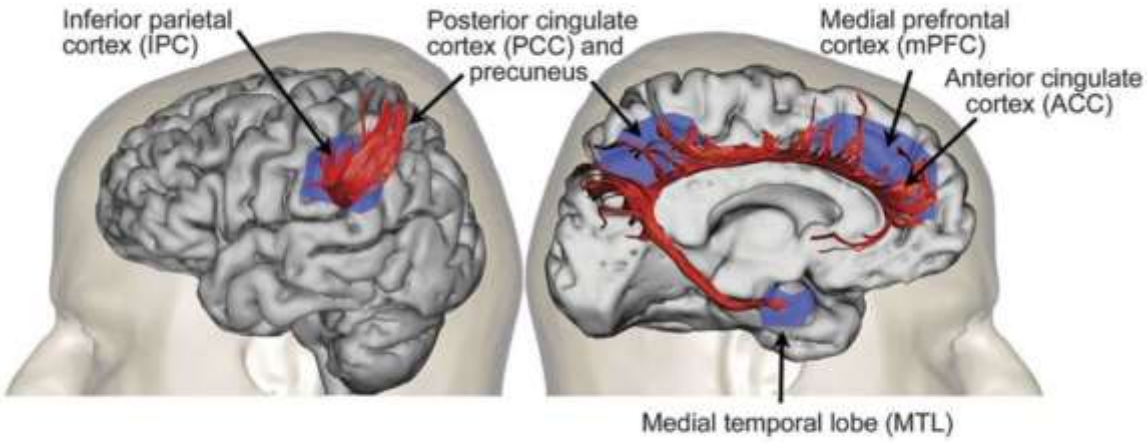

Figure 5. 8. **Lateral and medial view of the default-mode network of the left hemisphere.**

The medial regions of the default-mode network are connected through the cingulum, whereas the inferior parietal cortex is connected to the precuneus and posterior cingulate cortex through a short intraparietal tract. The tracts are reconstructed using diffusion tensor imaging tractography.
Source: Sandrone & Catani, Neurology 2013.

Other structures that are generally considered part of the network are the lateral temporal cortex, hippocampal formation, and the precuneus, of which the latter two are of particular relevance to the earliest stages of AD. The role of the hippocampus in relation to episodic memory and spatial navigation has already been discussed in detail within this thesis, but the precuneus has particular relevance when considering why there was a significant difference between MCI and healthy controls on Q4 of the SAPQ (‘‘I have difficulty visualising in my mind’s eye the local walking routes (e.g. to shops, pubs and restaurants) to and from my home’).

The precuneus has emerged in recent research as one of the main areas concerned in the global organisation of the brain, as the central node of the default mode network, and possibly the most connected hub in the cortex (Cavanna, 2007; Pereira-Pedro & Bruner, 2016; Tomasi & Volkow, 2011). The precuneus is thought to be a particularly dynamic area, involved in many perceptual, motor and cognitive functions such as episodic memory retrieval, metacognition, spatial mapping, integrating perceptions, self-awareness, consciousness and mental imagery (Andrews-Hanna et al, 2010; Cavanna & Trimble, 2006; Fletcher et al, 1995). Essentially the precuneus is involved in the self-related aspects of an individual's experience, an episodic memory-based self. Supporting this, a landmark PET study by Fletcher et al (1995) used a mnemonic strategy during retrieval to test the relationship between the precuneus activity and visual imagery. The results of this study led them to label the precuneus as the 'mind's eye'.

Question 4 asks specifically about visualising a route in the individual's 'mind's eye' and many imaging studies have found precuneus activation during tasks requiring spatial information about the direction of movement in an imaginary field (Bonda et al, 1995; Parsons et al, 1995). For example, the precuneus was found to be more active during motor imagery that during the use of a real joystick (Stephan et al, 1995). This role in motor imagery has also been confirmed by an electromagnetic study in which Magnetoencephalography (*MEG*) was applied to participants who were asked to imagine themselves hurdling through self-centred space (Ogiso et al, 2000).

Perhaps unsurprisingly given the precuneus' role in spatial and motor imagery, there are extensive connections that exist between posterior cortical regions including the precuneus and medial temporal regions affected early in AD pathology such as the

hippocampus (Dorfel et al, 2009; Kobayashi & Amaral, 2003; Teipal et al, 2010). A decreased resting state functional connectivity between the precuneus and the hippocampus (along with other regions of the default mode network) have been found in early AD patients and normal healthy APOE4 carriers (Sheline et al, 2010; Sheline et al, 2013).

The role of the hippocampus in conscious allocentric navigation has been discussed throughout this thesis in relation to the conscious navigation required in the 4MT. Interestingly, Chan et al (2016), study discussed above, also found that 4MT performance correlated with hippocampal volume and the cortical thickness of the precuneus. However, when navigational recollection is required, as is the case in question 4 within the SAPQ, we as experimenters are asking individuals to use their 'mind's eye', in this case literally. The hippocampus remembers in an allocentric fashion (Chapter 1, Section 1.9.2) but when we remember in our mind's eye, we inevitably use an egocentric perspective, and therefore the precuneus is thought to translate this hippocampal-spatial framework from allocentric to egocentric.

The significant difference between MCI and HC answers on Q4 therefore may further lend its support to the idea that there is decreased connectivity between the precuneus and the hippocampus in early AD patients and this affects the MCI patients ability to visualise routes in their mind's eye. Based upon this result, it may be beneficial to include more 'in my mind's eye' or route visualisation questions in further iterations of the SAPQ in order to investigate further.

It is possible to question the very use of MCI participants as a pre-clinical or early onset AD group as not all patients diagnosed with MCI go on to develop AD (Bruscoli & Lovestone, 2004; Shiri-Feshki, 2009; Koepsell & Monsell, 2012). Indeed, it is likely that not

all of the MCI participants included in this project will progress to AD and a screening tool that distinguishes well between MCI and HA in cross-sectional samples may not be accurate in the diagnosis of early-stage AD. However as stated in the present Chapter in Section 5.2, conversely, a tool which consistently fails to distinguish between MCI and HA groups is unlikely to be a useful tool for detecting early AD. Furthermore, a good screening tool should have the ability to identify those with cognitive deficit in order to open the gateway to further and more extensive neurological assessment. As both the hippocampal tasks (4MT and SSEVT) were both shown to identify MCI patients more effectively than the commonly used ACE III this may indicate that the new and recently developed tools may prove valuable.

Chapter 6: Thesis general discussion

This thesis aims to address the lack of neuropsychological tests which reliably diagnose the early stages of Alzheimer's Disease (AD). As outlined in Chapter 1, detecting AD in its earliest stages increases the likelihood that therapeutic agents and interventions can prolong quality independent living. An ideal test would have the sensitivity to detect everyone who has early-stage AD, whilst simultaneously not giving a 'false alarm' to anyone who shows some age-related impairments in cognition but who does not have early-stage AD. Secondly, an ideal test should be free and simple to administer on a national scale, without requiring extensive training on the part of the testers to set up, run, and interpret.

As the hippocampus is known to degenerate at an early stage in AD pathology (Bäckman, Small & Fratiglioni, 2001; Ghoshal et al, 2002) I saw value in assessing whether tests designed to specifically tap hippocampal function were better able to identify early-stage impairment better than existing neuropsychological tests commonly used in clinical practice, namely, the ACE III. More specifically, I proposed to examine whether the use of hippocampus dependent spatial and episodic memory tests can get us nearer to this ideal. I operationalised this by examining two new and recently developed tests, the Four Mountains Test (4MT) and Spaces and Sequences Episodic Video Task (SSEVT). I also examined whether questionnaires tapping spatial ability (Spatial Abilities and Practices Questionnaire) and social networks (Social Networks and Embeddedness Questionnaire) may prove beneficial in identifying decline.

Chapter 3 explored which existing neuropsychological measures provide the best predictive diagnosis of AD via meta-analysis of longitudinal studies which looked at the

predictive ability of neuropsychological tests in patients with MCI who did, and did not, convert to AD. The emphasis of the present thesis was to examine the efficacy of neuropsychological tests, for a variety of reasons including their feasibility for widespread use. However, there are many other kinds of tests and markers which are associated with high diagnostic accuracy. In order to provide a comparative benchmark, the best performing neuropsychological tests were also compared to CSF biomarkers in order to give a comparison of predictive ability.

Having established which *existing* neuropsychological tests may be sensitive to early AD-related decline, Chapter 4 focused upon a cognitively healthy sample and addressed four main research questions:

1) whether the two new and recently developed neuropsychological tests, The Spaces and Sequences Episodic Video Task (SSEVT) and the Four Mountains Test (4MT), were sensitive to healthy cognitive ageing;

2) whether participants' level of education influenced test scores;

3) whether an individual's social network size was associated with scores on the two hippocampal tasks via a newly developed questionnaire (the Social Networks and Social Embeddedness Questionnaire (SNSEQ))

4) whether a questionnaire probing spatial ability (The Spatial Abilities and Practices Questionnaire (SAPQ)) would prove to be a useful screen for spatial ability.

Chapter 5 compares the performance of an MCI patient group to a sample of healthy-ageing controls on three cognitive tasks, the 4MT, SSEVT and ACE III and the two project specific questionnaires (SAPQ and the SNSEQ). A key goal of the present thesis was

to examine whether the two hippocampal tasks, the 4MT and SSEVT, can discriminate between HA and MCI patients and if they can, could they make the distinction at least as well as the ACE-III.

Chapter-specific discussions offer an in-depth explanation and evaluation of the results, whereas this final Chapter aims to offer an overall summary of the present thesis' main findings.

6.1: Summary of findings

6.1.1: The best performing neuropsychological tests may not be currently used in clinical practice.

Before exploring the efficacy of new and recently developed hippocampal dependent neuropsychological tests, I first felt it necessary to explore which existing neuropsychological measures provide the best predictive diagnosis of AD. For any treatment to be effective, it is crucial that any therapeutic interventions occur early in the disease timeline, as currently envisaged treatments are unable to reverse disease progress (e.g. Laske, 2014; Laske et al, 2015) and therefore, early diagnosis is key. Chapter 3 explores this via the use of meta-analysis. I used the common approach to assess predictive diagnostics for AD by including longitudinal studies which examined which tests best predicted which patients with Mild Cognitive Impairment (Petersen et al, 1999) did or did not 'convert' to AD.

The analysis found the best 5 performing neuropsychological tests to be the Free and Cued Selective Reminding Test, The California Verbal Learning Test: Short Delay Free Recall, The California Verbal Leaning Test; Long Delay Free Recall, Rey Osterrieth Complex Figure Recall: Immediate Recall, RAVLT: Delayed Recall and the Alzheimer's Disease Assessment Scale: Cognitive Subscale.

I also evaluated the ability of cerebrospinal fluid markers, often considered a gold standard in AD diagnostics (e.g. Diniz et al, 2008; Alberts et al, 2011; Sperling et al, 2011; Dubois et al, 2007; 2014; Herruka et al, 2016; Jack et al, 2018) to predict conversion from MCI to Alzheimer's disease. Perhaps surprisingly, when comparing Hedge's g, I found that there was no evidence from these weighted average effect sizes that the best CSF biomarker ($A\beta_{1-42}$) was superior to that of the best six neuropsychological tests, all of which produced average effect sizes greater than 0.90.

Based upon these results, it may be tempting to suggest that the diagnostic performance of the best six neuropsychological tests rivals that of the CSF biomarkers, however these results must be treated with a degree of caution as there are some limitations of these findings which must be acknowledged. A detailed discussion of the strengths and limitations of the meta-analysis is included in Chapter 3 and mostly surround the difference in study size as CSF studies tended to have large sample sizes and larger studies than the neuropsychological tests. However, concluding that the top performing neuropsychological tests are at least as diagnostic and robust as the p-tau and $A\beta_{1-42}$ CSF biomarkers seems plausible for the following reasons: 1) the three tests produced higher effect sizes than the three CSF biomarkers; 2) no single conversion study using any of the three top-ranking neuropsychological tests obtained a lower effect size than 0.956 (CVLT Free Recall Long Delay: 0.956; CVLT Free Recall Long Delay: 0.968; SRT: 0.961), i.e. the lowest-obtained single-study

effect size was higher than that obtained from the average of any of the CSF biomarkers, including the highest performing one ($A\beta_{1-42}$: 0.88); 3) the RAVLT: Delayed Recall and ADAS-COG, producing an effect sizes of 0.95 and 0.90 respectively, had sample sizes larger than all three CSF tests. These considerations suggest that sample size alone cannot discredit the apparent efficacy of the six best-performing neuropsychological testing.

One of the interesting results to arise from the meta-analysis were the kinds of neuropsychological tests which yielded a higher hedge's g between converters and non-converters. The top five performing neuropsychological tests within the meta-analysis were tests of episodic memory (FCSRT, CVLT: Short Delay Free Recall, CVLT: Long Delay Free Recall and RAVLT: Delayed Recall) and Spatial Ability (Rey's Complex Figure Recall: Immediate Recall). It seems possible that these results are due to a superior ability of hippocampal dependent tests to identify impairment before an AD diagnosis, due to the hippocampal degeneration which occurs at an early stage in AD pathology, a key theme throughout this thesis.

Considering the rest of the thesis' focus, one of the clear limitation of the meta-analysis is the exclusion of the ACE III, which is commonly used within the UK. It's widespread use can be seen even within the MCI patients included within the current project, all but one of the NHS patients recruited from memory clinics with a diagnosis of MCI include in Chapter 5 had already taken the ACE III within the last few months as part of their regular NHS work-up. If we are to test the efficacy of existing neuropsychological tests, it may be suggested that the meta-analysis cannot be fully comprehensive without the ACE III. Unfortunately, the ACE III was excluded as there were insufficient longitudinal studies which used the ACE III to look at conversion from MCI to AD. Moreover, 2 of the 3 studies were conducted in Cambridge, which might conceivably entail some degree of bias.

However, this lack of research is interesting in itself. A 2019 Cochrane Review concluded 'There is insufficient information in terms of both quality and quantity to recommend the use of either the ACE-III or mini-ACE for the screening of dementia or MCI in patients presenting with, or at high risk of, cognitive decline. No studies were conducted in a primary care setting so the accuracy of the ACE-III and mini-ACE in this setting are not known.' (Beishon et al, 2019). The absence of sufficient MCI to AD conversion studies may further call into question the basis upon which the ACE III is so commonly used by GPs and memory clinics, certainly its ability as a neuropsychological tool to identify early-stage AD.

There were three main conclusions which arose from the meta-analysis: 1) The results suggest that even with the development of expensive and well-researched CSF tests, neuropsychological testing remains an important tool in a clinicians armoury whilst also being non-invasive and cost-effective, 2) The best tests that predict conversion from MCI to AD may not be currently used in clinical practice and 3) The best performing tests all focused upon episodic and spatial memory, which further reinforces the value of tapping such functions when developing tests which identify early or pre-AD impairment.

6.1.2: Education did not influence SSEVT scores.

When analysing the healthy ageing sample included in Chapter 4, education level was found to not correlate with or predict SSEVT test scores. When discussing ideal characteristics of a task diagnosing early AD in Chapter 1 (Sections 1.8 and 1.3.4), I stated that one of these characteristics was that education should not be an overly influential asset in successful task performance. If education does affect score, such a task may become vulnerable to false

positives whereby the less-educated perform worse than expected, and to false negatives whereby highly educated individuals are able to mask their neurological deficits, commonly referred to as 'cognitive reserve' (Katzman, 1993; Stern, 2002,2006; Valenzuela et al, 2007). Therefore, the lack of educational influence over SSEVT scores as seen in Chapter 4, may further lend its support to the suitability of the newly developed SSEVT as a neuropsychological test.

Unlike the SSEVT, a positive correlation was found between the participants' level of education and the number of correct answers they acquired on the 4MT. Furthermore, education appeared to be positively predictive of scores in that those with a higher level of education tended to score higher on the 4MT. It is difficult to say if these findings are reflective of other research as the other studies that examine the 4MT are few, due to the recent development of the tool. Previously published studies often say that there was no significant difference in education between participants (e.g. Chan et al, 2016; Moodley et al, 2015; Wood et al, 2016). There are several possible explanations for this result, for example, 'Older' adults did have a lower education score (M=2.0, SD= 1.4) as compared to the Middle (M=2.8, SD=0.8) and 'Younger' group (M=2.4, SD=0.7). Therefore, the perceived lower scores due to education may be due to older individuals having an average lower level of education and is therefore a reflection of age-related lower scores, not education. However, this effect is not seen in the SSEVT.

It has been suggested in previous research by Chan et al (2016) that performance on the 4MT can be limited by participant co-operation, motivation and attention and by their understanding of the instructions. It is important that researcher ensures that the participant fully understands the test requirements and are motivated and attentive. All

student testers were trained in how to administer the 4MT but it is conceivable that there may have been some unavoidable inconsistency in the way it was administered, which may have affected participant understanding and therefore, results.

It may be the case that those with a higher level of education are simply more practiced in taking tests which appear somewhat abstract and can utilise appropriate, learnt skills more easily, prior knowledge in mathematics and shapes may also assist in accuracy during the task. For example, when surveying the 4 mountains some individuals may remember their location in relation to each other by shape e.g. 'The conical mountain is placed next to gaussian shaped mountain'.

6.1.3: Ageing is associated with lower scores on the two hippocampal tasks, but not the ACE III.

Chapter 4 focussed upon how sensitive the new and recently developed tests were to healthy ageing. Specifically, I aimed to determine whether the hippocampal dependent 4MT and SSEVT were sensitive to the comparatively subtle hippocampal changes experienced as humans age.

Although a test which is sensitive to ageing may not guarantee that such a test will also be sensitive to AD, episodic detail has been found to become increasingly impaired as people age, whilst semantic detail is spared (Levine et al, 2002). As episodic memory is hippocampus dependent it follows that a test which aims to detect cognitive decline in those with early-stage AD should also be sensitive to the comparatively subtle hippocampal decline which occurs as people age.

As predicted, performance on both of the new and recently developed hippocampal dependent tasks, SSEVT and to a lesser extent the 4MT were shown to be sensitive to the changes that occur in healthy ageing which could reflect a decline in the integrity and functioning of hippocampal tissue.

Aside from looking at correlations between test score and age, the data was divided into 3 groups: Young (18-34), Middle (45-64) and Older (65+). The younger group 18-34 group ages were chosen to reflect the youngest age tested up to adulthood. Middle (45-64) was chosen to reflect slightly older people. It is thought that relatively little decline occurs until individuals are around 50 years old (Albert & Heaton, 1988), and this group was created to capture this. The older group of 65+ was chosen to encapsulate older individuals who possibly may be at retirement age. Perhaps unsurprisingly, scores significantly differed between groups, finding lower scores between the 'Young' to 'Middle' and 'Middle' to 'Older' groups. This finding is consistent with other research such as a longitudinal study by Salami, Eriksson & Nyberg (2012) who showed a decline in hippocampal function during the course of an adult's lifespan, with a more significant reduction after the age of 65, the same age as the 'Older group' included in Chapter 4.

Such findings on the two hippocampal tasks are consistent with research which shows that hippocampal tissue and volume naturally declines in healthy ageing (e.g. ageing (e.g. Zimmerman et al, 2008; Barnes et al, 2009; Fotuhi et al 2012; Kurth et al 2015; Ezzatti et al, 2016), and appreciably faster than other brain regions (Raz et al, 2004; Raz et al, 2005; Raz et al, 2010). Such results appear promising of the ability of the newly developed SSEVT to detect hippocampal degeneration, although more research is necessary to fully establish the efficacy of the SSEVT as it was developed purely for the current project.

The decline in 4MT scores as individuals age supports existing research which also finds the 4MT to be a robust measure and indicator of hippocampal health in ageing individuals (Wood et al, 2016; Moodley et al, 2015). However, the real test of efficacy for the two hippocampal tasks' ability to identify early-stage AD required testing their ability to detect when healthy hippocampal decline becomes abnormal i.e. AD pathology begins. Accordingly, Chapter 5 explored whether the 4MT and SSEVT could distinguish between MCI and HA participants.

Somewhat surprisingly, there was no significant difference found between age group when using the ACE III. No significant difference was found in the group scores on the ACE III and this remained the case when the ACE III 'memory' section was tested alone. However, it could be reasoned that the ACE III is designed to highlight distinct cognitive impairment (Hsieh et al, 2013; Beishon et al, 2019), not to identify the more subtle decline that occurs as a consequence of the healthy ageing process and so critiquing the test against such standards is somewhat inequitable. But it does pose the question- How effective can a neuropsychological test be at detecting AD in its early stages if it is insensitive to healthy ageing decline? In conclusion, the age-related decline in scores on the hippocampal-dependent tasks further confirm the association between not just hippocampal function, spatial memory and episodic memory, but also the degeneration of the hippocampus itself as we age. Importantly, it also demonstrated the ability of the new and recently developed tests to detect subtle age-related hippocampal decline better than the established ACE III.

6.1.4: The two hippocampal tasks were able to distinguish between healthy ageing and MCI participants, whilst the ACE III could not.

Chapter 4 demonstrated how performance on the SSEVT, a hippocampal dependent test of episodic recollection, decreased with age. Predictably, given its hippocampal dependency the recollection of events within the SSEVT appears to be further impaired in those with a diagnosed MCI. Furthermore, SSEVT test scores were able to detect MCI patients amongst similarly aged healthy controls with a medium effect size. The main aim of the SSEVT was to focus upon episodic memory, more specifically recollective memory and the test was designed to test recollection of events, that could not be answered via familiarity alone. The ability of the SSEVT to identify those with MCI supports research such as that by Koen & Yonelinas (2014) who conducted a meta-analysis which found recollection to be significantly more impaired than familiarity in MCI patients whereas AD patients experienced large decreases in both familiarity and recollection.

Another aim of the SSEVT was to test recollective memory in a way that was more true to real-life experiences than current clinical episodic memory tests, such as the list-learning tests which were analysed in Chapter 3 (CVLT, RAVLT etc). Within the SSEVT, Sections 1-3 specifically ask about the characters that appeared and the association between spatial context and its contents i.e. object-room associations. Sections 3-5 examine sequence memory. While it would be expected that spatial sequences depend upon the hippocampus, it was considered important to tap sequence memory that was not necessarily spatially mediated. Evidence from both animals and humans strongly implicate the hippocampus in supporting memories for sequences of events, which are not

necessarily reliant on spatial context (e.g. Fortin et al, 2002; Gilbert et al, 2002; Kumaran and Maguire, 2006)

The test is relatively quick and easy to administer and was shown to be sensitive to those who had been diagnosed with MCI as diagnostic sensitivity which was calculated using Youden's J index and found to be 100% whilst specificity was 67.9%. Such results do indicate that the SSEVT may prove to be an accurate neuropsychological tool with which to detect early-stage AD pathology.

Chapter 4 appears to show the hippocampal decline that occurs due to typical ageing, Chapter 5 demonstrates how the 4MT is also able to identify a-typical ageing (i.e. mild cognitive impairment) within a group of 10 MCI patients and 45 HA participants aged 65 and over. As predicted, MCI patients were shown to perform significantly worse than HA controls. These findings are in agreement with those obtained by Moodley et al (2015), who found also a significant difference in scores between healthy controls and AD groups ($P<0.001$) performance. The ability of the 4MT to distinguish between HA and MCI also supports research which shows that hippocampal degeneration, such as occurs in early-stage AD, significantly affects the ability to maintain an allocentric representation of their surrounding environment (Maguire & Cipolotti, 1998; Chan et al, 2001; Galton et al, 2001; Kalova et al, 2005; Burgess, 2006).

ACE III scores were found to be unable to differentiate between MCI patients and HA. This blunt insensitivity was somewhat surprising and do not match those seen in previous studies who found the ACE III to be a useful cognitive instrument to detect MCI (Wang et al, 2019; Takenoshita et al, 2019; Senda et al 2020). The reason for this is not clear and a study with a larger MCI sample whereby MCI patients take the 4MT, SSEVT and the

ACE III is necessary to further explore whether this insensitivity is still present. However, the result within this admittedly small sample remains notable, 10 participants with a diagnosis of MCI took all three neuropsychological tests of which only two, the hippocampal dependent new and recently developed tests, identified them as MCI patients. Regardless of sample size, this is an interesting result which lends its support to the benefit of neuropsychological tests which tap hippocampal function as a way to potentially identify early-stage AD pathology.

The ability of the two hippocampal tasks to distinguish between the two groups, MCI and AD, therefore appear to meet the two ideals set out in the introduction. Firstly, a good neuropsychological test should have the sensitivity to detect everyone who has early-stage AD. Secondly, such test must also not give a 'false alarm' to anyone who shows some age-related impairments in cognition but who does not have early-stage AD.

6.1.5: Overall analysis and interpretation of the SNSEQ.

Overall SNSEQ scores were found not to predict age in HA participants, this is particularly important as it is fairly well established that larger social networks can reduce the risk of cognitive impairment and AD in old age (Bennett et al, 2006; Crooks et al, 2008). Whilst these results suggest that social networks and embeddedness did not decrease with the sample as people age, this explanation may be too simplistic. Questions such as 'On an average week, I will only interact with my spouse and /or children' and 'I would avoid going to a new place if there were a lot of people I didn't know there' were found to correlate with the hippocampus-dependent SSEVT, the scores on which were shown to decrease with

age. Such questions all seem to suggest a preference for closer, more established relationships and networks in older adults. This is supported by previous research which finds age to be positively correlated with higher-quality relationships (Marsden, 1987; Schnittiker, 2007; Shaw et al, 2007), and findings that people shed less meaningful connections in favour of close, high quality contact as they age (Fredrickson & Carstensen, 1990).

It is thought to be a deficit of close, high quality relationships specifically which increases dementia risk (Fratiglioni et al, 2000; Rafnsson et al, 2017). When developing future iterations of the SNSEQ, it may be beneficial to focus upon the distinction between close (i.e. familial, established friendships) and peripheral connections in order to further explore how social networks change as individuals age, rather that simply looking at change in terms of size.

Promisingly, the SNSEQ was found to differentiate between HA and MCI participants in Chapter 5. Those with diagnosed MCI were found to score lower and such findings confirm the association between smaller social networks and embeddedness and cognitive decline, and are in line with those of previous studies (Bennett et al, 2006; Rafnsson et al, 2017)

Taken together, the results of Chapters 4 and 5 suggest that individuals may show a preference for a smaller, higher quality social network as people age which then becomes dramatically smaller should abnormal pathology occur, at which point smaller networks become apparent on the SNSEQ questionnaire. However, further research with a larger MCI sample is necessary to further validate the ability of the SNSEQ to differentiate between HA and MCI groups, as the questionnaire was recently developed, and the study acts more as a

'proof of concept'. The results are somewhat promising as a first step towards validating the use of the SNSEQ to evaluate the size and complexity of an individuals' social network to potentially highlight those at risk of AD. However, there still remain some answered questions, Does the decrease in social networks occur before abnormal pathology and contributes to MCI and AD? Or is a lower level of social engagement a result of pre-symptomatic dementia? there clearly remains abundant room for further progress in determining why social networks decrease in those with MCI.

6.1.6: Overall analysis and interpretation of the SAPQ.

The Spatial Navigation and Practices Questionnaire (SAPQ) was found to not predict level of education, age or 4MT score in healthy ageing participants. It was initially expected that a self-report questionnaire of spatial ability such as the SAPQ would correlate with the 4MT however there may several reasons for this not being the case. Self-report questionnaires can be vulnerable to desirability bias or an inflated sense of ability. Interestingly, some individual questions on the SAPQ were found to be predictive of 4MT score, all of which seemed to relate the participants ability to adjust to spatial change and their flexibility in navigational ability e.g. Q6 'When a walking route I usually take is completely blocked off (e.g. for maintenance, treefalls). I find it difficult to work out a new route.' and Q10 ''It is difficult for me to find my bearings in a new town/city'. This finding is in agreement with other survey research which indicates that that over time elderly individuals develop behavioural patterns in order to avoid unfamiliar routes (Burns, 1999) and may be due to hippocampal change affecting the way in which older adults navigate their environment, especially unfamiliar places (Adrienne, Li & King, 2019). These results

may suggest that a questionnaire which places more focus upon navigational flexibility may be better able to pick up upon changes that occur in spatial ability as people age.

No significant difference was found between MCI and HA scores on the SAPQ overall. However, question 4 ‘, ‘I have difficulty visualising in my mind’s eye the local walking routes (e.g. to shops, pubs and restaurants) to and from my home’ was shown to significantly differ between groups. This may suggest that those with MCI have particular difficulty visualising routes. Imaging studies have found precuneus activation during tasks requiring spatial information about the direction of movement in an imaginary field (Bonda et al, 1995; Parsons et al, 1995) and Moodley et al (2015) found 4MT performance to be correlated with hippocampal volume and the cortical thickness of the precuneus. Further versions of the SAPQ may also benefit from more questions regarding imagined navigation in the participants ‘mind’s eye’.

6.2: Study strengths, limitations, and future research.

Only 10 MCI patients were included in the current project. The results therefore must be treated with a degree of caution and it is important to acknowledge that a sample size this small certainly does not permit any definitive conclusions to be drawn. However, as a small ‘proof of concept’ study, the above findings do offer some important insights into the potential use of the two new and recently developed hippocampal tasks, which warrant further investigation, with a larger sample.

Studying patients with MCI may be considered an unsatisfactory approach as most do not progress to dementia (Schneider, 2008) and so research that include patients with MCI, including the current project, inevitably include unknown proportions of patients with and without the neuropathology of AD. However, MCI patients still remain a valuable cohort when analysing the efficacy of neuropsychological tests. As discussed in Chapter 5, Section 5.2, whilst a task or questionnaire that distinguishes well between MCI and matched healthy control cross-sectional samples may not necessarily be accurate at diagnosing earlier stages of AD, one can be confident of the converse: that a task or questionnaire that consistently fails to distinguish MCI and HA groups is unlikely to be a useful diagnostic for early AD.

Another potential limitation of the present study is that only healthy and MCI patients are tested. Whilst this is a useful first step in further establishing the hippocampal nature of the two new and recently developed tasks, and how sensitive they are to Mild Cognitive Impairment, which is often thought to be a precursor to AD, it would be beneficial to see the predictive ability of the tasks in relation to AD conversion. The development of different versions of the SSEVT (different versions of the 4MT already exist) would also be beneficial for the repeat testing of healthy individuals to establish whether the new and recently developed tasks predicted healthy-MCI and MCI to AD progression. However, it must be noted that practical limitations lie in the fact that successful application of the SSEVT and the 4MT require visual function that is sufficiently intact to perceive the test stimuli, which may exclude some older individuals.

The two hippocampal tasks' potential for at-home testing may be considered one of their biggest strengths. Due to the Covid-19 pandemic, the landscape of clinical practice has seen a seismic shift towards the adoption of technology for remote consultations and

testing due to intermittent restrictions on movement and the shielding of many in the older population. Martin Marshall, chairman of the Royal College of General Practitioners, said in a recent article that it has taken **"**two and bit weeks to achieve more than we have achieved in 20 years" in adopting new technology (Brown, 2020). Most neuropsychological measures currently used within primary care and memory clinics are traditional pen and paper tests which are unsuitable for remote use.

A recent update on the Alzheimer's Society website on the 10th August 2020 states 'recent data shows a sharp drop in the number of referrals to memory services. There are usually on average 2,600 referrals from primary care to memory clinics per month, yet data from April showed only 84, May 435 and June 994.'. Furthermore, the Cochrane library has just released a research protocol which aims to assess the 'diagnostic test accuracy of remote, multidomain cognitive assessment (telephone and video call) for dementia.' (Elliot et al, 2020). More than ever, there seems to be a need for accurate, easy to use neuropsychological tools which can be administered remotely. In this regard, one of the main strengths of the present study is the practical nature of the two hippocampal dependent tasks, especially the 4MT.

Since the current project began, an 'app' version of the 4MT has been developed which includes instructions and automatically scores results. This offers many benefits such as automatic scoring and its ability to provide accurate time control of stimuli presentation and measurement of motor response accuracy. In addition to this, alternative difficulty-matched 15-item alternate-version tests have also been developed, a process in which I assisted, in order to facilitate repeat testing. The creation of a similar fully computerised

version of the SSEVT, along with different difficulty matched versions may prove beneficial and should be considered in further research.

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Appendix A

Diagnosing Dementia Earlier Project - Spatial Questionnaire

Version 1

28th September 2016

Spatial Abilities and Practices Questionnaire

This questionnaire asks about your spatial abilities and practices in everyday life. There is no time limit so please feel free to take your time. We would advise that, if possible, you fill out this questionnaire together with someone who knows you well.

Have you filled out this questionnaire with someone who knows you well?

YES NO

Read each statement carefully. Answer to what extent you agree with each statement by choosing the answer that most applies to you.

After each statement, we also ask if you think that there has been a change in your spatial ability in the last 12 months.

1) I am good at recognising a place (eg. town square, building) even when I approach it from a new direction.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

2) When leaving or returning home, I generally have a good idea of the direction between my home and destination.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

3) When I walk out of a large shop or shopping centre, I sometimes find I am taking the wrong direction from the one I intended.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

4) I have difficulty accurately visualizing in my mind's eye the local walking routes (e.g. to shops, pubs, parks, restaurants) to and from my home.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

5) I find it easy to visualize in my mind's eye the routes to places further afield (e.g. to nearby towns).

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

6) When a walking route I usually take is completely blocked off (e.g. for maintenance, treefalls), I find it difficult to work out a new route.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

7) I find it easy to remember precisely where the car is parked.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

8) I stick to major walking routes, and avoid minor paths and shortcuts, to avoid getting lost.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

9) When visiting new places, I prefer to be with people I know and follow them, rather than find my way myself as I feel that if I am alone, I may become lost.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

10) It is difficult for me to find my bearings in a new town/city.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

11) As a passenger in a car, I usually have to take the same route many times to remember it.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

12) Before I go somewhere, I tend to visualise the different points along the journey where I need to make a decision (e.g. where I will need to go straight, left or right).

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

13) I can tell quite quickly that I am approaching a place I have been to before, even if I have only been there once or twice.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

14) On an outing or holiday, having walked around visiting several locations (e.g. coffee shop, museum) I can generally calculate a shortcut route back to my starting point without consulting signs and maps.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

15) I can find my way around places when travelling in the dark.

STRONGLY AGREE AGREE UNDECIDED DISAGREE STRONGLY DISAGREE

Has your spatial ability in this respect changed over the last 12 months? Has it got better, is it the same as before, or is it worse?

BETTER SAME WORSE

Appendix B

Diagnosing Dementia Earlier Project - Social Questionnaire

VERSION 1

28th September 2016

Social Situation Questionnaire

This questionnaire asks questions about your social circle. There is no time limit so feel free to take your time. We would advise that, if possible, you fill out this questionnaire together with someone who knows you well. Have you filled out this questionnaire with someone who knows you well?

YES NO

Read each statement carefully. Answer to what extent you agree with each statement by choosing the answer that most applies to you.

After each statement, we also ask if you think that there has been a change in your social situation in the last 12 months.

	Strongly Disagree	*Disagree*	*Neither agree nor disagree*	*Agree*	*Strongly Agree*
1. I would describe myself as very sociable.	☐	☐	☐	☐	☐
This statement has become less applicable to me in the last 12 months.	☐	☐	☐	☐	☐
2. I find it easy to meet new people.	☐	☐	☐	☐	☐
This statement has become less applicable to me in the last 12 months.	☐	☐	☐	☐	☐
3. There are people outside of my family that I can talk to about personal matters.	☐	☐	☐	☐	☐
This statement has become less applicable to me in the last 12 months.	☐	☐	☐	☐	☐
4. On an average week, I will only interact with my spouse and/or children.	☐	☐	☐	☐	☐
This has become more applicable to me in the last 12 months.	☐	☐	☐	☐	☐
5. I have friends outside of family members that I see on at least a fortnightly basis.	☐	☐	☐	☐	☐
This statement has become less applicable to me in the last 12 months.	☐	☐	☐	☐	☐
6. I can sometimes feel lonely.	☐	☐	☐	☐	☐
This statement has become more applicable to me in the last 12 months.	☐	☐	☐	☐	☐
7. I have less desire to meet new people than I used to.	☐	☐	☐	☐	☐
This statement has become even more applicable to me in the last 12 months.	☐	☐	☐	☐	☐
8. If I were to have a party, I can think of more than 5 people aside from family members that would attend.	☐	☐	☐	☐	☐
This statement has become less applicable to me in the last 12 months.	☐	☐	☐	☐	☐

9. I tend to avoid social situations unless they are with my immediate family.	☐	☐	☐	☐	☐
This statement has become more applicable to me in the last 12 months.	☐	☐	☐	☐	☐
10. I'd rather stay at home than have day trips out.	☐	☐	☐	☐	☐
This statement has become more applicable to me in the last 12 months.	☐	☐	☐	☐	☐
11. I've fallen out of touch with many of my closest friends.	☐	☐	☐	☐	☐
This statement has become more applicable to me in the last 12 months.	☐	☐	☐	☐	☐
12. I enjoy socialising outside of my home environment.	☐	☐	☐	☐	☐
This statement has become less applicable to me in the last 12 months.	☐	☐	☐	☐	☐
13. I would avoid going to a new place if there were a lot of people I didn't know there.	☐	☐	☐	☐	☐
This statement has become more applicable to me in the last 12 months.	☐	☐	☐	☐	☐
14. If a situation arises where I need to speak to someone new, e.g. a new neighbour, I prefer my partner/family member to lead the conversation.	☐	☐	☐	☐	☐
This statement has become more applicable to me in the last 12 months.	☐	☐	☐	☐	☐
15. I am actively involved in my community.	☐	☐	☐	☐	☐
This statement has become less applicable to me in the last 12 months.	☐	☐	☐	☐	☐
16. I think I would find things less stressful if I had more social contact with people.	☐	☐	☐	☐	☐
This statement has become more applicable to me in the last 12 months.	☐	☐	☐	☐	☐