Examining the Use of Cognitive Assessments in Clinical and Healthy Populations: A Focus on Spatial Cognition

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Abstract

Spatial navigation and orientation deficits are often presented in early stages of Alzheimer's disease (AD) and can even be recognised in the predementia stage of Mild Cognitive Impairment (MCI). Despite this, specialized tests of spatial cognition are not used in clinical settings as part of MCI/AD screening procedures. Currently, the most widely used cognitive marker for AD diagnosis is episodic memory. Episodic memory decline is evident not only in other forms of dementia but also during healthy ageing. This complicates the early detection of AD which is essential in allowing for early intervention and treatment of the disease. Recent research has focused on spatial navigation/orientation as a potential cognitive marker for MCI and AD and has shown greater specificity in detecting preclinical AD compared to episodic memory. Two widely used clinical screening tools for MCI/AD detection are the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA). In Chapter 2, the usefulness of these tests in MCI/AD detection was examined, as well as utility of spatial subscales in predicting AD conversion from MCI. MoCA subscales relating to spatial ability predicted MCI progression to AD and reversion to cognitively normal, highlighting the importance of assessing spatial cognition in these clinical populations. Tests of spatial cognition were used in Chapter 3 with a healthy population to determine their use in a clinical setting as possible follow-up assessments with MCI/AD patients. These tests were deemed useful for examining spatial cognition in a healthy population, although further research would be required in order to inform clinical practice. This thesis displays promising early findings for the use of spatial cognition tests as screening tools for MCI/AD.

Chapter 1

General Introduction

1.1 Ageing

1.1.1 Population Ageing

Population ageing refers to changes of the age of a population whereby the proportion of older people is increasing (Beard & Bloom, 2016). The World Health Organisation has estimated that by 2050 the proportion of adults in the world's population aged over 60 years will have nearly doubled from what it was in 2015 (World Health Organisation [WHO], 2021). People are living longer worldwide, and this increased proportion of older adults is also evident within the Irish population (Sheehan & O'Sullivan, 2020). For example, the life expectancy in Ireland increased by nearly 6 years in 2017 (from 76.6 years to 82.2 years) since the year 2000, which has been identified as one of the fastest growing life expectancy rates across the EU (OECD, 2019). Although the proportion of adults over 65 years in Ireland is relatively low (13%) compared to other European countries, this is predicted to double to 26% in Ireland by 2050 (OECD, 2019). While population ageing demonstrates the success of modern medicine and public health generally, it also comes with challenges (Bishop et al., 2010; May, et al., 2019; Sheehan & O'Sullivan, 2020). The increased age of the global population has been identified as a threat by many, as the need for adequate health measures to deal with this population change becomes a focus of concern for countries across the world (WHO, 2021). Ensuring the needs of the ageing population are met is vital as healthcare demands are rising (Beard & Bloom, 2016). People are living longer but this is not necessarily healthy living, as our population's age increases so too are age-related health issues such as physical and cognitive decline (Lim et al., 2017).

1.1.2 Physical Decline during Ageing

Physical frailty refers to a deterioration of physical abilities such as strength, balance, gait, muscle coordination and fatigue and is common among elderly populations (Brown et al., 2000; Liu et al., 2020). Physical frailty often follows a seemingly minor health-related stressor but can lead to a major change in health state (Clegg et al., 2013). Many health-related issues can result from frailty including hospitalisation, disability, and mortality (Ferrucci et al., 2004; Hubbard et al., 2017; Liu et al., 2020; Ringer et al., 2017). Keeble et al. (2019) reported that physically frail older adults spend longer in hospital compared to those who are not frail. In addition, this study also found that individuals who were frail at the start of their study had a significantly increased risk of mortality (Keeble et al., 2019). Frailty increases with age, for example, Bandeen-Roche et al. (2015) estimated that 9% of US adults aged between 65-69 years old experience frailty, but this figure increased to 38% in older adults aged over 90 years. Similar findings have been reported by Clegg et al. (2013) who stated between 25-50% of older adults over the age of 85 are physically frail. Understanding this physical decline in older adults has become of particular interest to researchers as a result of global population ageing (Clegg et al., 2013; Liu et al., 2020). Individuals are living longer and the number of older adults suffering from physical frailty is increasing as a result. Researchers have emphasised the importance of understanding the impact frailty has on the health status of the elderly population as well as the need for preparing targeted health care services to deal with increasing numbers of frail older adults within the population (Keeble et al., 2019; Lim et al., 2017; Woo, 2018). Frailty has also been associated with cognitive decline and Alzheimer's disease (AD; Buchman et al., 2008; Clegg et al., 2013; Lee et al., 2010). Being physically frail leads to a more rapid decrease in cognitive ability, which is another major age-related health issue (Clegg et al., 2013).

1.1.2 Cognitive Decline during Ageing

Cognitive decline has become one of the main concerns associated with ageing (Bishop et al., 2010). Understanding this decline is paramount to ensure appropriate precaution is taken. As stated by WHO (2021), not all older adults experience age-related decline in the same way or at the same pace. Some cognitive processes are better maintained than others during the ageing process. These processes are commonly categorised into fluid cognitive abilities and crystallised cognitive abilities (McDonough et al., 2017). Crystallised cognitive abilities involve using previously acquired knowledge and information gained through past experiences and are often assessed using vocabulary or general knowledge tests (Murman, 2015; Tucker-Drob et al., 2022). Fluid cognitive abilities require the use of currently available information and the ability to process, manipulate and interact with this information to help problem solving (Murman, 2015). Fluid abilities include processes relating to visuospatial skill, working memory, reasoning and processing speed (Murman, 2015; Tucker-Drob et al., 2022). While crystallised abilities have been shown to increase with age up until about 60-70 years onwards, fluid abilities decrease from around 20 years, and this decline continues steadily into older age (Murman, 2015; Tucker-Drob et al., 2022). In healthy ageing adults, fluid cognitive abilities have a high correlation with crystallised cognitive abilities, they tend to depreciate at a similar rate (McDonough et al., 2017). Although, this is not the case for those with dementia, fluid abilities have been shown to depreciate quicker than crystallised abilities in early stages of AD (McDonough et al., 2017).

1.2 Neurodegenerative Diseases

1.2.1 Dementia and Alzheimer's Disease

Cognitive decline is part of the normal ageing process. Dementia involves a deterioration of cognitive abilities beyond what is typically expected from a healthy ageing process. Dementia is a progressive and chronic syndrome which affects cognitive abilities including memory, orientation, attention, language, problem solving and communication (WHO, 2021). The WHO have estimated that by 2050 there will be 139 million cases of dementia globally. Dementia cases are rising as a result of an increased proportion of older adults in the population. Alzheimer Europe (2019) released a report providing estimations regarding prevalence rates of dementia across countries in Europe. It was projected that the number of dementia cases in Ireland are set to more than double between 2018 and 2050 (from 52,736 to 141,200 cases of dementia). This increase in case numbers comes as a result of population ageing within Ireland, with the number of adults aged over 60 years also set to rise substantially by the year 2050 (Alzheimer Europe, 2019).

There are several different forms of dementia, including AD, vascular dementia, dementia with Lewy bodies, and frontotemporal dementia (WHO, 2021). AD is the most common form of dementia, it has been estimated to make up between 60-70% of all cases (WHO, 2021). Brookmyer and colleagues (2018) reported that in 2017, 6.08 million Americans had been diagnosed with AD or Mild Cognitive Impairment due to AD. This was predicted to rise to approximately 15 million in the United States alone by 2060 (Brookmyer et al., 2018). In addition, AD has been recognized as the sixth leading cause of death in the United States (Alzheimer's Association, 2019). Death due to AD is also increasing in European Countries, indeed, Niu et al. (2017) reported AD mortality trends from 28 European Union countries and found AD related deaths more than doubled from 1994 to 2013 (41,255 to 86,822). In the last 20 years there has been a large increase

in the number of deaths from AD in Ireland with population ageing as well as improved diagnostics were noted as contributing factors for these increased AD related deaths (OECD, 2019). In 2019 there were over 2,300 deaths due to AD and other forms of dementia in Ireland alone (CSO, 2021). These figures highlight the importance of early diagnosis and the need for early intervention to possibly slow the progression of the disease, especially given the suggested effectiveness of intervention before at-risk individuals are symptomatic (Dubois, 2016; Giau et al., 2019; Horgan et al., 2020).

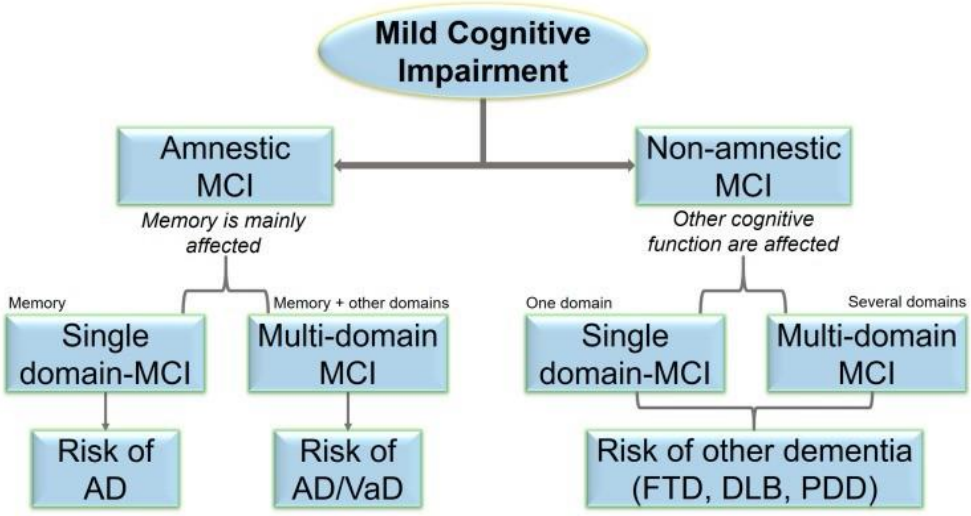
1.2.2 Mild Cognitive Impairment and Progression to Dementia

Mild cognitive impairment (MCI) refers to an intermediatory stage between the cognitive decline experienced as a result of normal ageing and that experienced by those with AD (Petersen, 2004). People with MCI experience a deterioration of cognitive abilities which exceeds that expected from normal ageing but does not reach the severity of AD. The daily activities of those with MCI are largely unaffected and individuals are capable of living their lives as normal with little disruption. However, those who develop MCI are at high risk of progressing to AD (Petersen et al., 1999), although many do remain stable or revert to a cognitively normal state (Julayanont et al., 2014). Different subtypes of MCI include amnestic MCI and non-amnestic MCI (Petersen, 2004). Those who have amnestic MCI (aMCI) experience memory impairments, whereas those with non-amnestic MCI (naMCI) do not have memory impairments but suffer deficits in other cognitive domains (Petersen, 2004). Figure 1.1 (from Giau et al., 2019) shows various subtypes of MCI and their progression to various neurodegenerative diseases. Conversion rates to AD are higher in aMCI than in naMCI, although naMCI tends to result in higher risk of progression to other forms of dementia such as frontotemporal dementia (FTD), vascular dementia (VaD),

Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB; Petersen, 2004; Vos et al., 2013). There is an approximate 10-15% conversion rate from aMCI to AD every year (Petersen et al., 1999), although some have found annual progression rates as high as 30% (Schmidtke & Hermeneit, 2008). Early identification of MCI has become of interest in recent years due to the risk of developing AD as soon as 5 years after diagnosis with MCI. Research interest in MCI has grown in recent years, since a state of mild cognitive impairment usually precedes an eventual AD diagnosis, understanding this stage and identifying it early is of utmost importance (Giau et al., 2019; Julayanont et al., 2014).

Figure 1.1

MCI subtypes and their risk of progression to various forms of dementia. Figure adapted from Giau et al. (2019).



1.3 Predicting Alzheimer's Disease

1.3.1 Biomarkers of AD

The difficulty in diagnosing AD early can be attributed to the fact that initial symptoms of the disease are not easily distinguishable from other conditions, namely other forms of dementia (Humpel, 2011). Symptoms which are common in early stages of AD such as memory deficits are also presented in other conditions. For example, memory issues are also experienced by those with frontotemporal dementia (FTD; Flanagan et al., 2016; Hornberger et al., 2010), yet memory deficits are still widely considered as the current benchmark for AD diagnosis (Coughlan et al., 2018). One way of attempting to distinguish AD from other conditions has been to identify biomarkers which are specific to the disease. As stated by Humpel (2011), a biomarker which can differentiate AD from other forms of dementia would be the best possible outcome for aiding diagnosis and treatment. Hippocampal atrophy is a well-established biomarker for AD, the volume of the hippocampus, which is involved in memory and navigation, has been shown to reduce in AD patients as well as those with MCI (Pini et al., 2016). Additionally, Weniger et al. (2011) found that MCI patients who converted to an AD diagnosis had reduced hippocampal volume in comparison to those who did not progress to AD. Decreased hippocampal volume in an AD patient's brain compared to a control can be seen in Figure 1.2, an increase in the lateral ventricle can also be observed here. Research suggests that the most widely used cerebrospinal fluid (CSF) biomarkers for AD diagnosis are beta-amyloid 42 (Aβ), total tau (t-tau) and phospho-tau (p-tau) which have been shown to be well-established hallmarks of AD (Blennow & Zetterberg, 2018; Humpel, 2011; Sengoku, 2020) and can be seen in Figure 1.3.

Figure 1.2

Comparison of (A) an Alzheimer's Disease Brain and (B) a Control Brain Matched for Age and Sex. Figure adapted from Sengoku (2020)

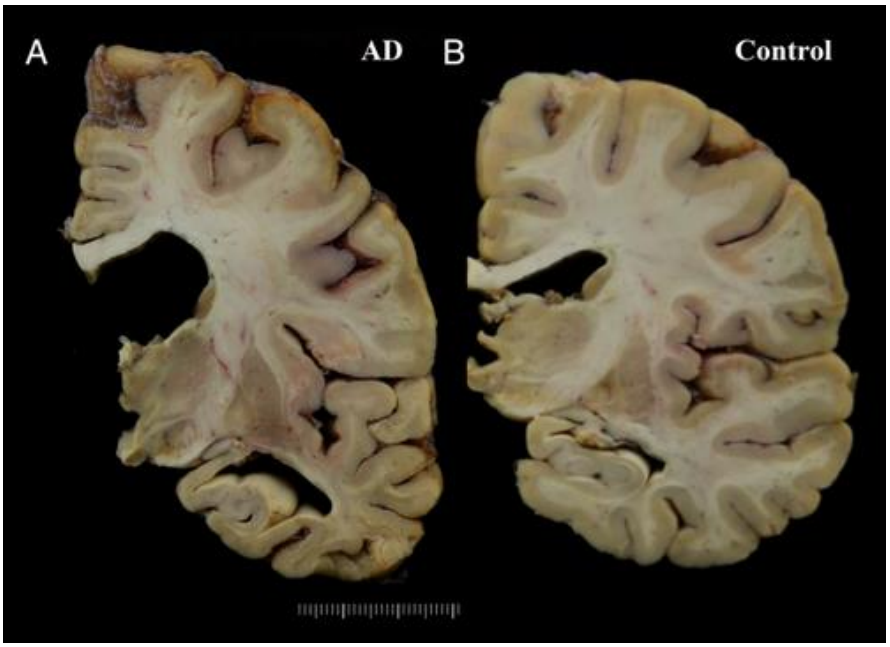
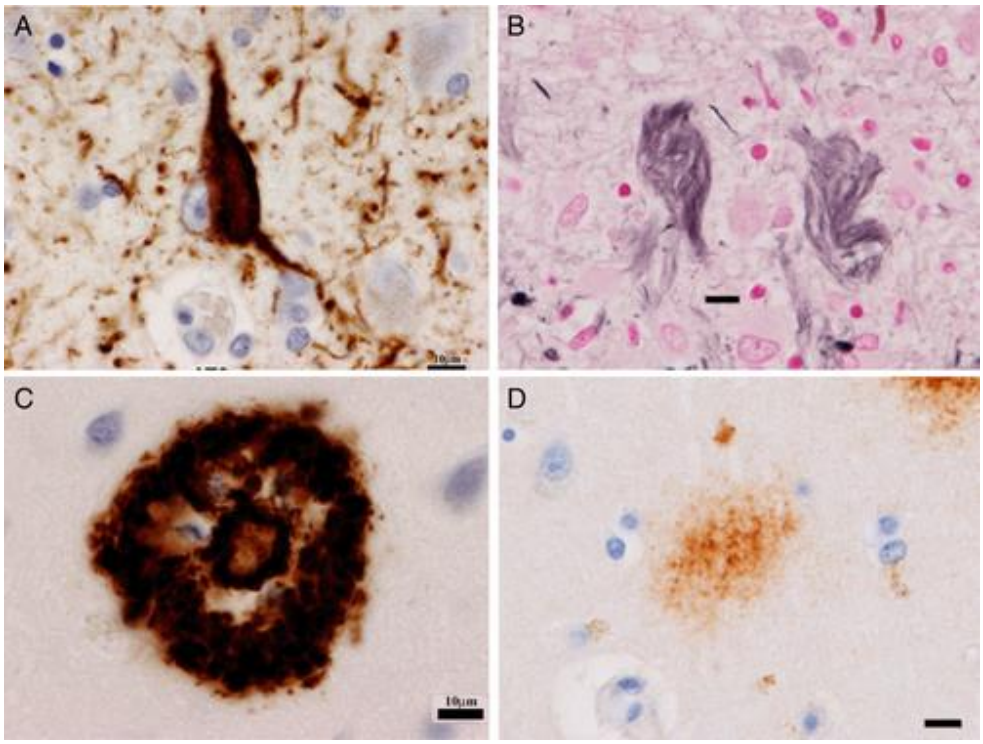


Figure 1.3

Histological Image of (A) Intracellular and (B) Extracellular Neurofibrillary Tangles and (C,D) Aβ Plaques in a Brain with Alzheimer's Disease. Figure adapted from Sengoku (2020)

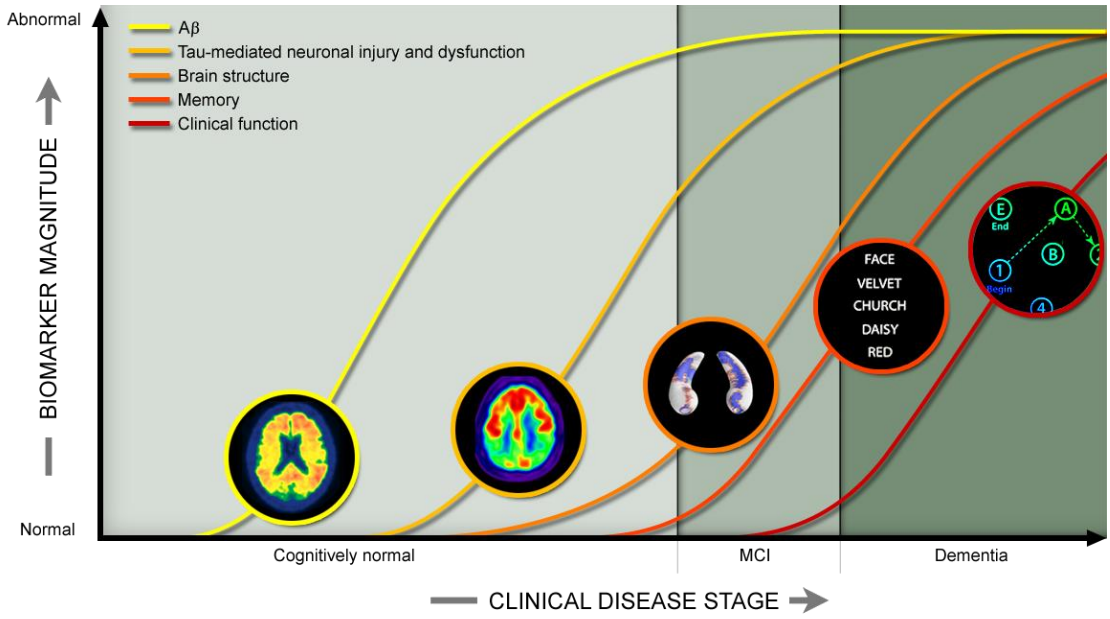


Amyloid-β is an amino acid which is recognized as playing a central role in AD pathology (Gabelle et al., 2013; Humpel, 2011). Extracellular plaques of Aβ form (as seen in Figure 1.3) as a result of the irregular break down of amyloid precursor protein (APP) by the β- and γ-secretases (Sadigh-Eteghad, 2015). These plaques interfere with neuron connectivity. Low Aβ levels are found in patients with AD, with higher levels evident in healthy controls (Humpel, 2011). These lower levels of Aβ are also indicative AD progression, as lower levels of the amino acid have been found in MCI patients who progress to AD compared to those who do not (Gabelle et al., 2013). Depositions of Aβ plaques initiates the formation of neurofibrillary tangles (seen in Figure 1.3) from phosphorylated tau protein (Hardy & Higgins, 1992). These tangles form within the cell, as

a result microtubules become unstable and this in turn disrupts cell signals, including those to the hippocampus (Pini et al., 2016). Patients with AD have higher levels of tau compared to healthy controls (Humpel, 2011; Wattmo et al., 2020). Neurofibrillary tau tangles have been shown to gather in the entorhinal cortex of AD patients (Pini et al., 2016). Increased tau levels have also been shown to predict progression to AD among MCI patients (Blennow, 2004; Humpel; 2011). The combination of extracellular Aβ plaques and intracellular tau tangles leads to cell apoptosis which results in the manifestation of AD symptoms (Coughlan et al., 2018). Pini et al. (2016) notes that disruption to the entorhinal cortex and hippocampus, which are both comprise the medial temporal lobe memory system, leads to a decline in memory which is one of the earliest cognitive declines evident in AD. Humpel (2011) stated that a combination of these biomarkers results in high sensitivity and high specificity for AD detection. Additionally, these biomarkers may be present years before disease onset and hence have been found useful for predicting AD before the onset of symptoms (Sadigh-Eteghad, 2015). The magnitude of these biomarkers during a cognitively normal state before MCI or dementia diagnosis can be seen in Figure 1.4 below.

Figure 1.4

Graph Illustrating the Changes in Biomarker Magnitude during AD Progression. Figure adapted from Alzheimer's Disease Neuroimaging Initiative (ADNI)



1.3.2 Cognitive Markers of AD – Episodic Memory

Cognitive markers may be a useful accompaniment to biomarkers for early diagnosis of AD since the presence of biomarkers is not always manifested through symptoms (Coughlan et al., 2018). Biomarker sampling can be intrusive, time-consuming and expensive compared to cognitive testing and is not always feasible as a clinical screening tool (Gomar et al., 2011; Gabelle et al., 2013; Julayanont et al., 2014; Laske et al., 2014). In addition, some have found cognitive markers to be more useful than biomarkers in predicting MCI to AD conversion (Gomar et al., 2011). Episodic memory decline is currently the most prevalent cognitive marker used for AD diagnosis (Coughlan et al., 2018). This type of memory involves retrieval of information relating to past personal experiences and includes detail around what happened, as well as where and when such events took place (Pause et al., 2013; Tulving, 1993). Recall ability is typically used as an

indication of episodic memory function in neuropsychological testing, but the ability to recall items after a delay tends to decline with age and is not unique to AD (Spaan et al., 2003). Tests such as the Rey Auditory Verbal Learning Test (Rey, 1964) are widely used in a clinical setting, although some have suggested that such tests are not appropriate as they were designed for use with healthy populations as opposed to clinical ones (Boelaarts et al., 2019; Spaan et al., 2003). Boelaarts et al. (2019) suggested the need for episodic memory tests to be developed specifically for patient groups such as MCI and AD. More general tests of cognitive ability which were developed for clinical use include the Mini Mental State Examination (MMSE) and the Montreal Cognitive Assessment (MoCA), both of which include memory items which assess delayed recall ability and are often used as clinical screening tools for MCI and AD (Pinto et al., 2019). However, early diagnosis of AD based solely on memory impairment is complicated by the fact memory deficits are often present during healthy ageing (Hedden & Gabrieli, 2004), as well as in various other conditions (e.g., Parkinson's Disease, Huntington's Disease, Major Depressive Disorder), including other forms of dementia, such as FTD (Coughlan et al., 2018; Julayanont et al., 2012; Pause et al., 2013).

1.3.3 Cognitive Markers of AD – Spatial Navigation/Orientation

Given the lack of specificity of episodic memory in diagnosing AD, Coughlan et al. (2018) suggests the usefulness of spatial navigation/orientation as a cognitive marker in AD diagnosis. Spatial navigation and orientation deficits are often observed in individuals who have been diagnosed with AD (Coughlan et al., 2018; Hort et al., 2007). Difficulties in navigating new settings are evident in initial stages of the disease, but as the disease progresses individuals can experience disorientation in even the most familiar environments (Hort et al., 2007). Such deficits

are not usually evident in other forms of dementia and tests assessing spatial ability have distinguished between those with AD and FTD, and also healthy controls (Hornberger et al., 2010; Tu et al., 2017). Spatial navigation and orientation appear to be useful cognitive markers for AD diagnosis which are unique to the disease (Coughlan et al., 2018). This is important since MCI usually precedes AD diagnosis and indicates that spatial deficits are present in early forms of AD which could aid early detection (Gazova et al., 2012). As discussed above, Aβ plaques and neurofibrillary tangles typically accumulate first in the entorhinal cortex and hippocampus during MCI and AD. These structures play a pivotal role in spatial navigation ability, and so impairment in these areas leads to the manifestation of spatial deficits AD (Coughlan et al., 2018). Additionally, deficits in spatial navigation and orientation have been found in individuals with MCI, who have also been shown to display a reduction in hippocampal volume (Coughlan et al., 2018; Hort et al., 2007).

1.3.4 Testing Spatial Cognition

Large-scale real-world environments are commonly used to assess spatial navigation and orientation ability, or more recently, virtual reality environments have also shown to be good measures of spatial ability since testing in large-scale environments is not always possible (Cogné et al., 2017; Gazova et al., 2012). For example, computerised versions of the Morris water maze are often used to test spatial navigation ability in humans (Commins et al., 2020; Thornberry et al., 2021), including MCI and AD patients (Laczó et al., 2010). When testing MCI and AD patients using a virtual water maze, Laczo et al. (2010) found that MCI and AD participants had impaired spatial ability. Additionally, the importance of the hippocampus in navigation was reiterated and the virtual water maze was concluded to be an effective diagnostic tool for MCI (Laczo et al.,

2010). While real-world or virtual reality spatial tasks would be the ideal assessment of spatial ability, such tests may not always be feasible in a clinical setting. Having easy to administer clinical based assessments which accurately measure spatial cognition would be beneficial in these cases. Performance-based pen-and-paper screening tools are already commonly used in clinical settings such as MMSE and the MoCA. Both tests are widely used by clinicians to assess cognitive performance and are often used to aid diagnosis of AD and MCI (Mateos-Alvarez et al., 2017; Nasreddine et al., 2005; Pinto et al., 2019). Even though spatial navigation deficits are evident early in AD and have even been reported as one of the first symptoms experienced by AD patients (Gazova et al., 2012), these tests have limited focus on spatial ability. Indeed, Choe et al. (2020) found that MMSE subscales relating to orientation and visuospatial ability could predict MCI conversion to AD. The lack of complex items relating to spatial ability on the MMSE has been reported as a limitation of the test (Nasreddine et al., 2005). Whereas the MoCA contains more items relating to spatial ability which are also of greater difficulty (Nasreddine et al., 2005). It is likely that these MoCA subscales relating to spatial ability would also be helpful in predicting MCI to AD conversion. Overall, both tests have little focus on spatial ability and yet related subscales are proving useful for AD prediction, as shown by Choe et al. (2020). Including direct tests of spatial ability in test batteries for at-risk individuals seems promising for early diagnosis of AD and identifying predementia stages such as MCI (Gazova et al., 2012).

1.4 Aims of Thesis

Episodic memory is still widely regarded as the most useful cognitive marker of AD. However, there has been a recent move towards understanding the utility of spatial navigation/orientation deficits for AD detection (Coughlan et al., 2018). Recent research suggests spatial navigation/orientation ability could be a more sensitive tool for early AD diagnosis compared to episodic memory. This is due to the fact spatial navigation deficits are rarely reported in other forms of dementia, while episodic memory deficits can be recognised in various other conditions (Humpel, 2011). Indeed, a decline in spatial navigation ability has been shown to manifest earlier in MCI/AD symptomology than episodic memory decline (Gazova et al., 2012) and so could be a unique cognitive marker for the disease. The MMSE and MoCA tests are often used as MCI and AD screening tools. An aim of the current project is to investigate whether these tests can predict MCI to AD conversion. Following on from the findings of Choe et al. (2020), who showed the usefulness of MMSE spatial/orientation subscales in predicting MCI to AD conversion, the current project aims to investigate the utility of MoCA subscales in predicting this conversion in addition to MMSE subscales. While memory scales of the MoCA have shown to predict MCI to AD conversion (Julayanont et al., 2014), we wish to understand the usefulness of the MoCA spatial subscales in predicting MCI patients at risk of AD progression, as Choe et al. (2020) showed with the MMSE. Using the Alzheimer's Disease Neuroimaging (ADNI) database, **Chapter 2** aims to investigate whether the MMSE and MoCA and their subscales can predict MCI outcomes, including conversion to AD.

Although, tests such as the MMSE and the MoCA have some spatial items, these are quite limited. Comprehensive measures of spatial ability are not generally used for MCI/AD diagnosis, but the inclusion of pen and paper spatial tasks could be useful for clinicians (Gazova et al., 2012),

especially given that large-scale testing may not always be possible in a clinical setting. There are several possible pen and paper tests which assess spatial cognition that could be used as follow-up tests to the MMSE and MoCA in clinical settings. Including specialised tests of spatial cognition could allow for earlier identification of AD and may also be useful in determining a conversion from MCI to AD. Before testing of patient populations can take place, normative values should be gathered to allow for direct comparisons between patient groups and healthy controls. Testing a healthy population will allow us to determine which pen and paper tasks might be useful in a clinical setting, this will be done in **Chapter 3**. Such spatial tests include the Spatial Orientation Test (SOT; Hegarty & Waller, 2004), Santa Barbara Sense of Direction scale (SBSOD; Hegarty et al., 2002) and the Subjective Spatial Navigation Complaints questionnaire (SSNC; Cerman et al., 2018). A goal of the current project is to contribute to the current knowledge which is held in regard to the spatial ability of the Irish population, while investigating the possible usefulness of pen and paper spatial tasks as tools to be used in a clinical setting for AD detection.

Chapter 2

Examining the Use of MMSE and MoCA Tests (and their subscales) as Predictors of MCI and AD

2.1 Introduction

Mild cognitive impairment (MCI) describes an intermediate stage between normal ageing and dementia (Grundman et al., 2004; Petersen et al., 1999). Individuals with MCI experience cognitive deficits which are more severe than that expected from normal ageing, but not severe enough for a dementia diagnosis. There are different types of mild cognitive impairment including amnestic (memory impairment present) and non-amnestic (no memory impairment present) variations (Csukly et al., 2016). Amnestic MCI can be further divided into single domain MCI (aMCI) where only memory deficits are evident, or multidomain MCI (aMCImd) where memory has been affected, as well as deficits in other domains (Csukly et al., 2016; Giau et al., 2019). Amnestic MCI almost always precedes a dementia diagnosis, with an annual conversion rate of amnestic MCI to dementia reported to lie between 10-15% (Petersen et al., 1999). As such, it is an important goal to be able to identify which individuals might convert from MCI to AD and why. If at-risk individuals can be identified, early diagnosis becomes possible, as well as the ability to develop suitable interventions and treatments.

The MMSE is a pen and paper performance-based screening tool, and since its publication in 1975 (Folstein et al., 1975) has been widely used to assess cognitive ability in clinical settings (Mossello & Boncinelli, 2006). The test consists of 11 items divided into 6 subscales with a maximum overall score of 30. The subscales included in the test are orientation, registration, attention and calculation, recall, language and copying/construction. This test has been reported as the most widely used cognitive test in healthcare settings, with many healthcare professionals using the tool for dementia diagnosis (Mateos-Álvarez, et al., 2017; Mitchell, 2009). However, the usefulness of the test as a standalone tool for diagnosing AD has been questioned more recently

and its limited use in primary care settings has also been highlighted (Creavin et al., 2016; Wind et al., 1997). As such, the MMSE has been recommended as a tool not be used in isolation in diagnosing dementia, but instead should be used alongside other screening measures to form an overall understanding of an individual's clinical profile (Creavin et al., 2016; Wind et al., 1997). More critically, the MMSE is often criticized for its poor ability in distinguishing those with mild cognitive impairment from normal controls, with MCI participants often scoring within the normal range for MMSE scores (Nasreddine et al., 2005; Tombaugh & McIntyre, 1992). For example, Nasreddine et al. (2005) reported that those who have been diagnosed with MCI usually score 26 or above on the MMSE, a score which is classed as being within the normal range. A possible explanation for this insensitivity to MCI could be the lack of complexity presented in examination items (Trzepacz et al., 2015). The MMSE has been reported as being too simple for both individuals without cognitive impairment and also those with MCI resulting in an observed ceiling effect and inability to distinguish MCI patients from normal controls (Nasreddine, et al., 2005; Philipps et al., 2014).

MCI diagnosis has become an important goal in research since it has been considered as both a risk-factor for AD and also a state of predementia (Giau et al., 2019). Given the limitations associated with the MMSE an alternative test was needed, especially one which could help in the detection of mild cases of cognitive decline. The Montreal Cognitive Assessment (MoCA) was developed as an alternative screening tool with improved sensitivity (Galvin & Sadowsky, 2012; Nasreddine et al., 2005) and since has become a widely used cognitive assessment which has been translated into 56 languages. The MoCA takes 10 minutes to administer and consists of 30 items divided among 8 subcategories which include: visuospatial/executive function, naming, memory, attention, language, abstraction, delayed recall and orientation (Julayanont & Nasreddine, 2017).

Several studies have found the MoCA to be a more credible test to determine MCI compared to the MMSE (Ciesielska, et al., 2016; Damian, 2011; Hoops et al., 2009; Nasreddine et al., 2005). Nasreddine et al. (2005) stated that the MoCA is more sensitive to MCI because it was designed to assess deficits known to be present in MCI. The lack of executive function items on the MMSE (Mai et al., 2016; Trzepacz et al., 2015) was considered while developing the MoCA. This led to the inclusion of executive function items as well as more complex items relating to language and visuospatial processing, all of which are known deficits related to MCI (Nasreddine et al., 2005). Detection of milder cognitive deficits has been improved on the MoCA and as a result of these more complex items, deficits outside of memory can be detected earlier (Farias et al., 2011). Although, researchers tend to regard the MoCA as the superior assessment when it comes to identifying mild cases of cognitive impairment (Farias et al., 2011; Freitas et al. 2013; Larner, 2012; Tsoi et al., 2015), the MMSE has still been regarded as the better tool in more severe and later stages of AD (Nasreddine, et al., 2005) and both are widely used in the clinic (Damian, 2011; Pinto et al., 2019).

Busy healthcare settings and increased demand for care has led to challenges in dementia diagnosis (Farias et al., 2011). Indeed, primary care workers have expressed concerns that tests such as the MMSE which are used for AD screening are too time-consuming to administer in a clinical setting and have suggested they be narrowed down further (Borson et al., 2005; Laske et al., 2014; Mitchell, 2009), this has led to an increased focus on various subcategories relating to specific cognitive domains. Indeed, recently Choe et al. (2020) showed the usefulness of MMSE subscale scores in predicting MCI conversion to AD, emphasizing orientation and construction as the most informative domains. Additionally, Damian et al. (2011) found that subscale MoCA items relating to orientation, visuospatial and language could discriminate controls, MCI and AD

patients. Since subcategory scores on the MMSE have shown to provide valuable information about MCI conversion to AD, and given the specificity of MoCA subcategories to MCI, it is likely that MoCA subscale scores would also be very useful in predicting AD conversion from MCI. Understanding the usefulness of the subcategories of these tests could also help aforementioned limitations based around tests taking too long to administer. As suggested by Choe et al. (2020), investigating these specific subscale scores would allow for quick, simple and effective administration and interpretation.

The Alzheimer's Disease Neuroimaging Initiative (ADNI) is a longitudinal study which was first launched in 2004. Since then, the ADNI has had several phases, including ADNI1, ADNI-GO, ADNI2, and the most recent and ongoing ADNI3. Each phase has slightly varied objectives and often includes participants from the preceding phase as well as new participants. Overall, the main aim of the initiative is to contribute to AD research by tracking the progression of the disease over time and identify possible biomarkers for its early detection (Weiner et al., 2010). The ADNI has been recognized as having a positive influence on clinical AD trials in the field by successfully contributing to what is known about AD and its progression. ADNI has already had a great impact on AD research as evidenced by the 600+ publications (as of February 2015) which have used its data, leading to an increase in research both in the field of AD and others (Weiner et al., 2015). Large sample sizes, easily accessible data and the extensive range of cognitive and biological makers which are assessed all make the ADNI an ideal tool for AD research (Gomar et al., 2011).

Participants involved in the ADNI are initially classified as being cognitively healthy, having mild cognitive impairment (MCI) or Alzheimer's disease (AD). In order to be included in the study as a participant with MCI, it is necessary for individuals to have abnormal memory function, as defined by a combination of objective memory tests used during screening (Logical

Memory II subscale from the Wechsler Memory Scale, Memory box score from the Clinical Dementia Rating) and subjective memory concern as reported by the subject themselves, their study partner or their clinician. Additionally, any significant deficits in other cognitive domains must not be evident, general cognition should be intact and patients should show sufficient performance in daily tasks. As a result, all MCI participants involved in the ADNI are considered amnestic MCI. This has been noted as a limitation of the initiative, as having a participant population which is primarily amnestic results in a group which is not representative of a real-life population (Weiner et al., 2015). However, it is understandable why this group has been chosen - amnestic MCI is the form of MCI which often precedes AD, while non-amnestic MCI patients are more likely to develop other forms of dementia (Csukly et al., 2016). Furthermore, research into aMCI is becoming increasingly prevalent as it is now recognized as a prodromal stage of AD (Risacher et al., 2009).

The current study focuses on the third phase of the Alzheimer's Disease Neuroimaging Initiative (ADNI2). This phase includes approximately 1300 individuals and is made up of participants who rolled over from previous phases of the ADNI and new participants. We focus on new entrants to ADNI2 only here. The aim of this chapter is to (i) compare performance of healthy controls, MCI and AD patients on two of the most common cognitive assessments: the MMSE and MoCA and (ii) to examine whether baseline scores on both cognitive assessments (the MMSE and the MoCA) can successfully predict later diagnosis. Specifically, we hope to gain an insight into the conversion that takes place from patients with MCI to AD, as well as the conversion from healthy control to both MCI and AD.

It is hypothesized that patients with AD will perform significantly worse on both the MMSE and MoCA compared to patients with MCI and healthy controls. However, it is predicted that the

MoCA will be more sensitive than the MMSE in detecting individuals who convert from MCI to AD. Additionally, the subcategories from both the MMSE and the MoCA will be investigated. Given the specificity of the MoCA and its reported usefulness in MCI detection, it is predicted that some subcategories of cognitive function will lead to better prediction rates compared to others, and that the subcategories of the MoCA will be better detectors of possible AD conversion compared to the subcategories of the MMSE.

2.2 Methods

2.2.1 Participants

The ADNI2 was the third phase of the ADNI (http://adni.loni.usc.edu), this phase began in September 2011 and continued for 5 years. While this phase was 5 years, the current study follows participants up to year 4, due to a lack of participants with follow up assessments for year 5. Participants involved in the ADNI2 were adults between 55 and 90 years of age. Individuals went through an initial series of screening procedures to determine their eligibility to take part in the study. Participants involved in the study take part in various imaging and cognitive assessments at visits which are 3, 6 or 12 months apart for up to 5 years. Brain imaging techniques are used as part of participant assessment, these include magnetic resonance imaging (MRI), positron emission tomography (PET) as well as other biological markers. Neuropsychological tests are also administered to participants, including the MMSE and the MoCA. One of the main objectives of the ADNI is to understand how imaging techniques, biomarkers and neuropsychological assessments can be used together to help determine a framework for the progression of AD. The ADNI also used a set of exclusion and inclusion criteria to help determine whether participants were healthy controls, MCI and AD.

Inclusion Criteria. Different inclusion criteria applied depending on the diagnosis of the individual. The criteria below were outlined by the Alzheimer's Disease Neuroimaging Initiative. For an extensive list of both inclusive and exclusive criteria, see Appendices I and II.

General Inclusion Criteria. Participants were required to be between 55 and 90 years of age at the time of the initial screening. It was necessary for subjects to be of good health generally, and not have any health-related issues which might interfere with the study or their ability to participate. For tests to be completed, sufficient visual and auditory acuity was also required of individuals.

Cognitively Normal. Individuals must be free from any memory complaints and should be cognitively normal based on the ability to carry out daily tasks with the absence of impairment of cognitive function. Subjects must have scored above a cutoff score (determined by their years in education) in the Logical Memory II subscale from the Wechsler Memory Scale – Revised (Wechsler, 1987). A score of 24 or above was required on the MMSE, as well as a Clinical Dementia Rating (Morris, 1993) of 0.

Mild Cognitive Impairment. Subjects must have had subjective memory concerns to be included in the study. Scores on the Logical Memory II subscale from the Wechsler Memory Scale needed to be above a designated cutoff score which was dependent on their years in education. Subjects needed a score of 24 or above on the MMSE (note this is similar to the healthy patients above), as well as a Clinical Dementia Rating score of 0.5. General cognition and interference with everyday life must have been intact to a degree whereby a diagnosis of AD could not be made at screening.

Alzheimer's Disease. Individuals must have had subjective memory concerns. Scores on the Logical Memory II subscale from the Wechsler Memory Scale needed to be above a designated cutoff score which was dependent on their years in education. A score between 20 and 26 was required on the MMSE. A score of 0.5-1 on the Clinical Dementia Rating scale was necessary of individuals, as well as meeting the criteria for probable AD as defined by the National Institute of

Neurological and Communicative Diseases and Stroke/AD and Related Disorders Association (NINCDS/ADRDA).

Exclusion Criteria. The presence of any significant neurological disease (e.g., Parkinson's Disease, Huntington's disease or multi-infarct dementia) was exclusionary, except for suspected AD in subjects with Mild Cognitive Impairment. Subjects with AD should not have had any other neurological diseases other than AD. Major depression or bipolar disease in the last year were also exclusionary, as well as a history of schizophrenia. Subjects with a history of alcohol or substance abuse within the last 2 years were also excluded from the study. Further details of diseases which were deemed as exclusionary can be found in Appendix II.

Additional Exclusion Criteria. We also generated a number of our own exclusion criteria for the purpose of the analysis. (1) Multiple conversions were removed from the data set. For example, if an individual was cognitively normal at baseline, and was diagnosed with MCI and then reverted to a cognitively normal diagnosis (CN-MCI-CN), they were excluded from the analysis. This was the case for all other participants who experienced multiple conversions; only single conversions were included. An exception to this was those that converted from cognitively normal to MCI and onto AD during the 4-year period. These individuals were not excluded as MCI is known to be a prodromal stage of AD. For the purpose of this study, this progression was labelled as CN-AD. This ensured only single conversions remained to be analyzed (i.e., CN-CN, CN-MCI, CN-AD, MCI-CN, MCI-MCI and MCI-AD).

(2) As we were interested in understanding the ability of baseline MMSE and MoCA test scores to predict later diagnosis, it was important for participants to have baseline scores for each of these tests. In cases where baseline scores were missing for a particular test, the individual was excluded. All participants had baseline test scores for the MMSE, and so no individuals were excluded. However, 5 participants were excluded as result of missing baseline scores pertaining to the MoCA.

Following this, data was analyzed using 764 participants from the third phase of the Alzheimer's Diseases Neuroimaging Initiative database (ADNI2). At baseline, 290 of these participants were classified as being cognitively normal, 325 had been diagnosed with Mild Cognitive Impairment (either early MCI or late MCI) and 149 with Alzheimer's Disease (see Table 2.1 for breakdown by sex). For the purpose of the present analysis, EMCI (early MCI) and LMCI (late MCI) participants were grouped together under MCI. Previous studies which utilized the ADNI database were used to establish if the sample size for the current study was appropriate. This showed that the sample size used here was often similar to other studies which also used ADNI data and compared healthy controls, MCI and AD patients. For example, a study conducted by Trzepacz et al. (2015) had a total sample size of 618 and consisted of 219 healthy controls, 299 MCI and 100 AD patients from the ADNI database. Similarly, Risacher et al. (2009) examined a sample of 693 ADNI participants, which was made up of 206 healthy controls, 339 MCI and 148 AD patients. In particular, studies which used data exclusively from the ADNI2 cohort (as used here) also had similar sample sizes. For example, Ben-Bouallègue et al. (2017) had a total sample of 677 participants, consisting of 252 healthy controls, 301 MCI and 124 AD and a study conducted by Edmonds et al. (2019) used data from 294 healthy controls and 336 MCI patients. These studies indicate that the sample gathered here was of an appropriate size to use for the current study.

Table 2.1

Participant demographics broken down by baseline diagnosis

Diagnosis	Cognitively Normal	Mild Cognitive Impairment	Alzheimer's Disease
N	290	325	149
Sex (m/f)	132/158	175/150	88/61

2.2.2: Conversion of participants across the 4 years

Over the course of the ADNI2 (2011 –2016) a number of participants changed status from the original diagnosis. Of the 290 participants who were cognitively normal (**CN**) at baseline, 258 (89%) remained cognitively normal for the remainder of their time in the study (CN-CN), 27 (9%) received a diagnosis for Mild Cognitive Impairment (CN-MCI), and 5 (2%) developed Alzheimer's disease (CN-AD). Table 2.2 displays the sex breakdown for these individuals. To test whether this number has sufficient power, we performed a power calculation. Using G*Power (Faul et al., 2007), indicating high power (0.9), moderate effect size (0.3), and probability of 0.05, across three separate groups (CN-CN, etc.) a total sample size of 144 was calculated. From this, we are confident the size of this current sample (n = 290) has sufficient power, especially when compared to similar studies as described above.

Table 2.2

Participant demographics of cognitively normal participants at baseline

Conversion	CN-CN	CN-MCI	CN-AD	Total
N	258	27	5	290
Sex (m/f)	113/115	17/10	2/3	132/158

Of the 325 participants that were diagnosed with **MCI** at baseline, 222 (68%) continued with a diagnosis of MCI (MCI-MCI) for the remainder of the study, 83 (26%) converted to Alzheimer's Disease (MCI-AD), and the final 20 (6%) reverted to being cognitively normal after an initial diagnosis of MCI (MCI-CN). Table 2.3 details the demographics for these participants with an MCI diagnosis at baseline. Once again, power statistics were calculated to ensure confidence in this sample size using G*Power (Faul et al., 2007). A power of 0.9, an effect size of 0.3, and probability of 0.05 for these three groups (MCI-CN, etc.) yielded a total sample size of 144. This calculation gives us confidence in the current sample size (n = 325) and suggests sufficient power.

Table 2.3

Participant demographics of conversions within 4 years for those with a baseline diagnosis of MCI

Conversion	MCI-MCI	MCI-AD	MCI-CN	Total
N	222	83	20	325
Sex (m/f)	126/96	41/42	8/12	175/150

2.2.2 Materials

Participant's MMSE and MoCA scores were obtained from the ADNI database and used for the present analysis. The MMSE is a 30-point cognitive based assessment which takes 10-15 minutes to administer. The test is made up of 6 subscales, each relating to a different cognitive domain. The subscales of the test are orientation, registration, attention and calculation, recall/memory, language and copying/visuospatial. The MoCA (available at mocatest.org) takes 10 minutes to administer and is also scored out of 30. Subscales included on the MoCA assess visuospatial ability, executive functions, attention, concentration, memory, language and orientation. See Appendices III and IV for MMSE and MoCA tests.

2.2.3: Ethics

Informed written consent was obtained at each site by the ADNI from all participants before any screening procedures or data collection began, as outlined in the ADNI2 procedure manual (https://adni.loni.usc.edu/wp-content/uploads/2008/07/adni2-procedures-manual.pdf). The study was also approved by the institutional review board of each site.

2.2.4 Statistics

Data from the ADNI database (http://adni.loni.usc.edu) were exported to Microsoft Excel which was used to organize data for analysis. Participants from the ADNI2 cohort were extracted and divided into groups depending on their baseline diagnosis and their conversion/non-conversion to any other diagnosis. At this stage, participants without baseline scores on the MMSE or the MoCA were excluded, as well as those who experienced multiple conversions within the 4-year period (as described above). G*Power (Faul et al., 2007) was used to ensure sufficient statistical power and appropriate sample size. These data were then exported to IBM SPSS (version 28) for statistical analysis. One-way Analysis of Variances (ANOVA) or Kruskal Wallis H tests (nonparametric alternative) were conducted using SPSS to compare age, education, MMSE and MoCA scores between groups. Multivariate Analysis of Variances (MANOVAs) were also conducted using SPSS to compare groups performance in the subscales of each test. *Post hoc* tests were conducted using Tukey's honestly significant difference (HSD), pairwise comparisons are reported where a nonparametric analysis was conducted. Statistical significance was indicated at the $p < 0.05$ level for all analyses. Effect sizes are reported throughout the results section as eta squared (η^2) and partial eta squared values (η_p^2). Raincloud plots were constructed using the website https://gabrifc.shinyapps.io/raincloudplots/ and described by Allen et al. (2019).

2.3 Results

2.3.1: General demographics at baseline

Initial tests were conducted on groups who were categorized according to their baseline diagnosis (i.e., cognitively normal, mild cognitive impairment or Alzheimer's disease). Shapiro-Wilk test of normality indicated that age was normally distributed (p = .06) and so, a one-way analysis of variance (ANOVA) was conducted to compare age between the three baseline groups. There was a statistical difference found between groups based on age, F (2, 761) = 9.63, p < .001, η^2 = .03). A Tukey HSD *post hoc* test revealed that age was significantly lower in the cognitively normal (Mean = 73.0, SEM = +/- 0.3, p = .046) and mild cognitive impairment groups (71. +/- 0.4, p < .001) compared to the AD group (74.7 +/- 0.7). There was no significant difference in age when comparing the cognitively normal group and the mild cognitive impairment group (p = .52). The number of years spent in education was also compared between these 3 groups, but education was not normally distributed, as indicated by Shapiro Wilk test of normality (p < .001). The nonparametric Kruskal-Wallis H Test was employed and revealed that the groups differed significantly on their years spent in education, χ^2 (2, n = 764) = 10.91, p = .004. Pairwise comparisons revealed the number of years spent in education was significantly lower for the AD group (15.7 +/- 0.2) compared to the cognitively normal group (16.6 +/- 0.2, p = .003). No significant difference was found between the cognitively normal group (p = .66), or the AD group (p = .06) compared to the MCI group (16.3 +/- 0.2).

MMSE scores were not normally distributed as indicated by Shapiro-Wilk test (p < .001). As a result, the nonparametric Kruskal-Wallis H Test was conducted to compare baseline scores on the MMSE. This also showed a statistically significant difference between groups based on

MMSE scores, χ^2 (2, n = 764) = 379.64, p < .001. Pairwise comparisons revealed that all groups were statistically different from each other. The cognitively normal group scored significantly higher in the MMSE (29.0 +/- 0.1) compared to the MCI (27.9 +/- 0.1, p < .001) and AD (23.1 +/- 0.2, p < .001) groups. The AD group's MMSE score was also significantly lower than the MCI mean score (p < .001). MoCA scores also varied from the normal distribution (p < .001). Differences in MoCA scores were analyzed using a Kruskal-Wallis H Test. A statistically significant difference was found between groups based on MoCA scores, χ^2 (2, n = 754) = 324.17, p < .001. Pairwise comparisons showed that all groups scored differently on the MoCA. The cognitively normal group scored significantly higher in the MoCA (25.7 +/- 0.1) compared to both the MCI group (23.1 +/- 0.2, p < .001) and the AD group (17.2 +/- 0.4, p < .001). The AD group scored significantly lower in the MoCA compared to the MCI group (p < .001). See Table 2.4 for a summary. The individual scores showing the range and boxplots of the baseline groups on the MMSE and the MoCA are illustrated in Figures 2.1 (a) and (b) below.

Figure 2.1

Raincloud plots illustrating the range of baseline (a) MMSE scores and (b) MoCA scores of cognitively normal (CN), MCI and AD participants

2.1(a) **2.1(b)**

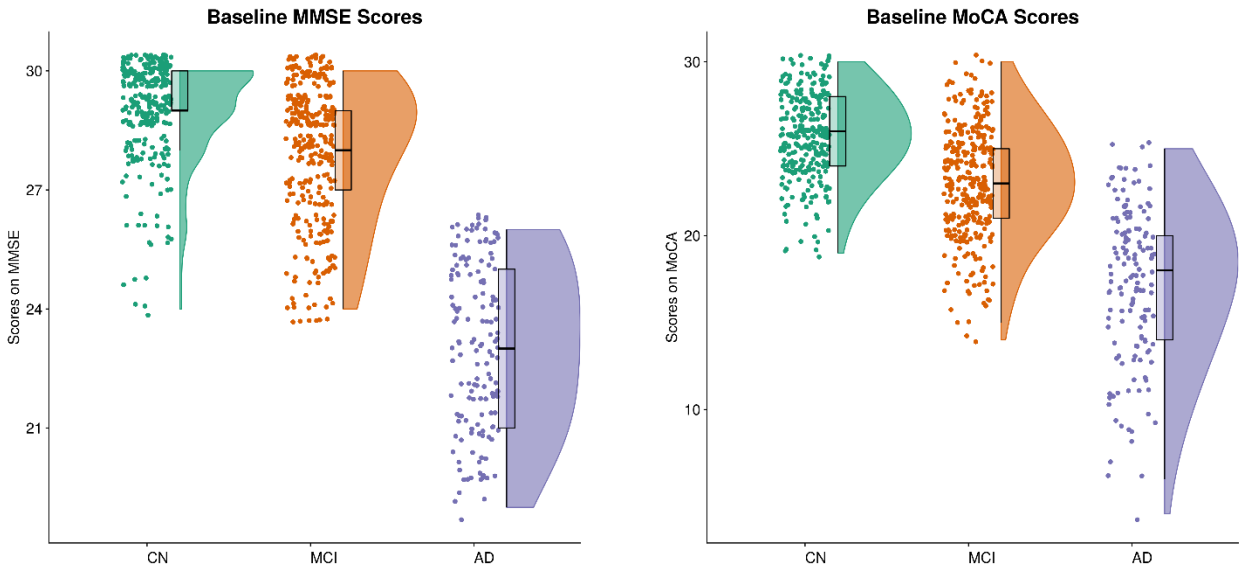


Table 2.4

Participant demographics, MMSE and MoCA mean (SEM) baseline scores arranged by baseline diagnosis

Baseline Diagnosis	Cognitively Normal	Mild Cognitive Impairment	Alzheimer's Disease
N	290	325	149
Sex (m/f)	132/158	175/150	88/61
Age	73 (0.4)	71.7 (0.4)	74.7 (0.7)
Education	16.6 (0.2)	16.3 (0.2)	15.7 (0.2)
MMSE	29.0 (0.1)	27.9 (0.1)	23.1 (0.2)
MoCA	25.7 (0.1)	23.1 (0.2)	17.2 (0.4)

2.3.2 Breakdown of baseline measures of those that converted (or not) during the study.

Table 2.4 shows the baseline measures of individuals who were classified as **cognitively normal** at baseline (n = 290), some of which then later converted to MCI or AD. The majority of the cognitively normal group remained healthy for the 4 years (CN-CN, n = 258), some converted to MCI (CN-MCI, n = 27), while others developed AD (CN-AD, n = 5). Shapiro-Wilk test of normality revealed that neither age ($p < .001$) or education ($p < .001$) were normally distributed in this sample of cognitively normal participants. Kruskal-Wallis H tests were conducted to compare these groups based on age and education. The groups were statistically different from one another in age, χ^2 (2, n = 290) = 12.75, p = .002. Pairwise comparisons revealed that the CN-MCI group (77.5, +/- 1.3) was significantly older in age compared to the CN-CN group (72.5, +/- 0.4, $p <$

.001). The CN-AD group (73.4, +/- 1.8) was not statistically different to either the CN-CN group (p = .61) or the CN-MCI group (p = .94) based on age. The groups were not statistically different from one another based on years spent in education, χ^2 (2, n = 290) = 1.69, p = .43. See Table 2.5.

Shapiro-Wilk tests indicated that scores were not normally distributed for CN groups in either the MMSE (p < .001) or the MoCA (p < .001) and so nonparametric tests were employed. A Kruskal-Wallis H Test was conducted to compare the three groups based on MMSE scores at baseline. The groups were found to have statistically different MMSE scores at baseline χ^2 (2, n = 290) = 10.51, p = .005. A *post hoc* pairwise comparison revealed that the MMSE scores for the CN-MCI group (28.4 +/- 0.3) were significantly lower than both the CN-CN group (29.1, +/- 0.1, p = .016) and the CN-AD group (29.8 +/- 0.2, p = .03). No differences were found between the CN-CN and the CN-AD group (p = 0.38). Scores on the MoCA were also compared between these groups using a Kruskal-Wallis H Test. A statistical difference was found between the baseline MoCA scores χ^2 (2, n = 285) = 16.56, p < .001. A *post hoc* pairwise comparison revealed that the CN-MCI group scored significantly lower in the MoCA (23.9 +/- 0.5) compared to the CN-CN group (25.9 +/- 0.15, p < .001). No statistical difference was found when comparing the CN-AD group (24.0, +/- 0.7) to the CN-CN group (p = .19) or the CN-MCI group (p = .75). The individual baseline scores showing the range and boxplots of the cognitively normal participants on the MMSE and the MoCA are illustrated in Figures 2.2a & Figures 2.2b below.

Table 2.5

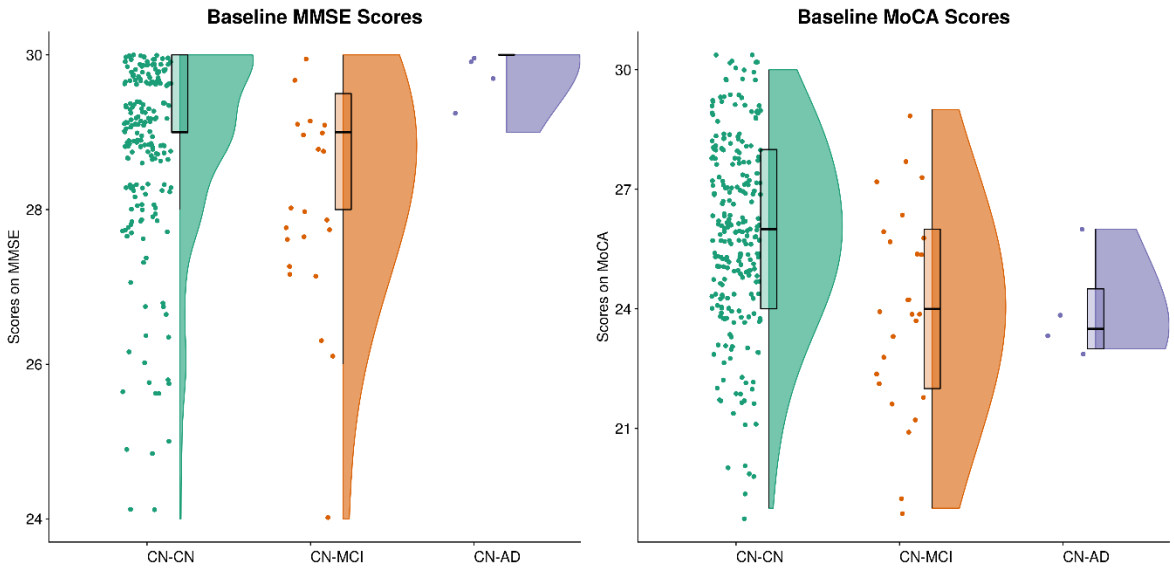
Participant demographics, MMSE and MoCA baseline scores of conversions within 4 years for those deemed cognitively normal at baseline

Conversion	CN-CN	CN-MCI	CN-AD	Total
N	258	27	5	290
Sex (m/f)	113/115	17/10	2/3	132/158
Age	72.5 (0.4)	77.5 (1.3)	73.4 (1.8)	73.0 (0.4)
Education	16.7 (0.2)	16.0 (0.5)	16.2 (1.2)	16.6 (0.2)
MMSE	29.1 (0.1)	28.4 (0.3)	29.8 (0.2)	29.0 (0.7)
MoCA	25.9 (0.2)	23.9 (0.5)	24.0 (0.7)	25.7 (0.1)

Figure 2.2

Raincloud plots illustrating the range of baseline (a) MMSE scores and (b) MoCA scores of cognitively normal (CN) conversion/non-conversion groups

2.2(a) **2.2(b)**



We then examined the scores and demographics of those that were initially classified as **MCI** patients at the start of the study (n = 325); some of which remained with MCI throughout the 4 years (n = 222) while others progressed onto AD (n = 83) and a few reverted to normal (n = 20). Shapiro-Wilk test of normality revealed that age (p = .026) and education (p < .001) were not normally distributed for MCI patients. Kruskal-Wallis H tests were conducted to see if there were any difference across the three groups in terms of age and years in education. The groups were not statistically different from one another in age χ^2 (2, n = 325) = 5.67, p = .059, or in years spent in education, χ^2 (2, n = 325) = 5.34, p = .069. Means and Standard Error of the Mean (SEM) for age and education can be seen in Table 2.6.

Scores on both the MMSE and MoCA were also compared for MCI groups, Shapiro-Wilk test revealed that both these test scores violated the assumption of normality ($p < .001$), which indicated the need for nonparametric tests to be employed. A Kruskal-Wallis H Test was conducted to compare the baseline MMSE scores of the groups who had mild cognitive impairment. There was a statistical difference found between the three groups based on baseline MMSE scores, χ^2 (2, $n = 325$) = 27.66, $p < .001$. A pairwise comparisons of the groups showed that the MCI-AD group (27.2, +/- 0.2) had significantly lower MMSE scores than both the MCI-CN group (29, +/- 0.3, $p < 0.001$) and the MCI-MCI group (28.1, +/- 0.1, $p < 0.001$). No significant difference was found between the MCI-CN group and the MCI-MCI group ($p = .07$). Baseline scores in the MoCA were also analyzed using a Kruskal-Wallis H Test. The groups baseline MoCA scores were found to be different between the three groups, χ^2 (2, $n = 322$) = 47.23, $p < .001$. Pairwise comparisons of the three groups showed that all groups differed from one another in their MoCA scores. The MCI-CN (25.6, +/- 0.5) group had significantly higher MoCA scores compared to both the MCI-MCI group (23.5, +/- 0.2, $p = .01$) and the MCI-AD group (21.3, +/- 0.3, $p < .001$). The MCI-AD group was also significantly lower than the MCI-MCI group ($p < .001$). See Table 2.6 and Figures 2.3a and 2.3b for summary details.

Table 2.6

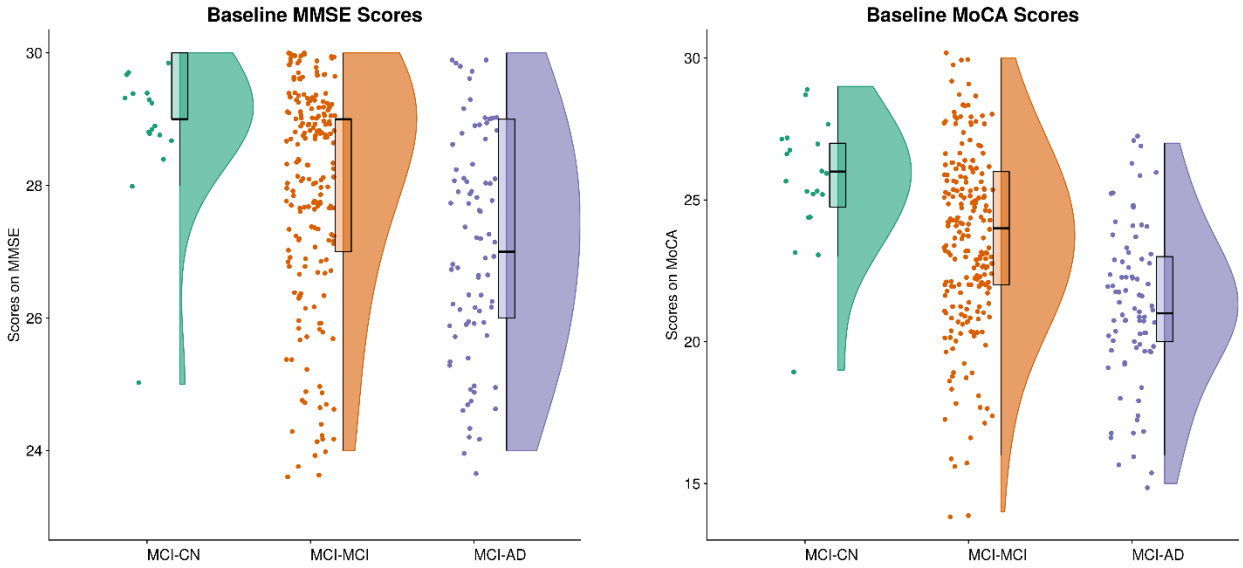
Participant demographics, MMSE and MoCA baseline scores of conversions within 4 years for those with a baseline diagnosis of MCI

Conversion	MCI-CN	MCI-MCI	MCI-AD	Total
N	20	222	83	325
Sex (m/f)	8/12	126/96	41/42	175/150
Age	68.8 (1.6)	71.6 (0.5)	72.6 (0.8)	71.7 (0.4)
Education	17.6 (0.5)	16.1 (0.2)	16.5 (0.3)	16.3 (0.1)
MMSE	29.0 (0.3)	28.1 (0.1)	27.2 (0.2)	27.9 (0.1)
MoCA	25.6 (0.5)	23.5 (0.2)	21.3 (0.3)	23.07 (0.2)

Figure 2.3

Raincloud plots illustrating the range of baseline (a) MMSE scores and (b) MoCA scores of MCI conversion/non-conversion groups

2.3(a) **2.3(b)**



2.3.3. Examination of baseline scores on each subcategory of MMSE & MoCA for those initially classified as being cognitively normal.

MMSE and the MoCA are each comprised of subscales which relate to various cognitive domains. These subscales were also analyzed to distinguish any cognitive deficits which may have been apparent between groups at baseline. A one-way multivariate analysis of variance (MANOVA) was conducted for those initially classified as being **cognitively normal** to determine any differences between groups on subcategories of the MMSE. There was a significant difference found between groups based on these subcategories, F (10, 566) = 2.246, p = .014, Wilk's Lambda

= 0.925, η_p^2 = 0.038. Table 2.7 shows that participants in the three subgroups differed significantly in a number of subcategories of the MMSE. These subcategories included recall (p = .037), language (p = .049) and copying (p = .038) tests. Tukey's HSD *post-hoc* test revealed no significant difference between the 3 groups in the recall category. The CN-MCI conversion group differed from the CN-CN group in both language (p = .038) and copying (p = .035). No significant difference was found between the CN-AD group and the CN-MCI or the CN-CN groups in either language or copying subscales (see Table 2.7 for full statistical analysis for each group).

Table 2.7

*Mean (SEM) scores for each of MMSE subscales for **Cognitively Normal** participants at baseline*

	CN-CN	**CN-MCI**	**CN-AD**	***F* (2,287)**	***p***	**η_p^2**	**Tukey post-hoc ($p < 0.05$)**
Recall	2.8 (0.0)	2.5 (0.1)	3.0 (0.2)	3.334	.037*	0.023	
Orientation	9.7 (0.0)	9.6 (0.1)	10.0 (0.2)	1.794	.168	0.012	
Copying	0.9 (0.0)	0.8 (0.1)	1.0 (0.1)	3.301	.038*	0.022	CN vs MCI
Language	7.8 (0.0)	7.6 (0.1)	7.8 (0.2)	3.047	.049*	0.021	CN vs MCI
Attention/ Calculation	4.8 (0.0)	4.8 (0.1)	5.0 (0.3)	0.255	.775	0.002	
Registration	3.0 (0.0)	3.0 (0.0)	3.0 (0.0)	.	.	.	

*$p < .05$

Subscales of the MoCA were also compared between three groups by conducting a one-way MANOVA and an overall significant difference was found, F (14, 552) = 2.276, p = .005, Wilk's Lambda = 0.894, η_p^2 = 0.055. Significant differences were found between groups in the visual spatial subscale (p = .004) and in the delayed recall subscale (p = .001). Tukey's HSD *post-hoc* test revealed significant differences between the CN-CN group and the CN-MCI group in the visual spatial subscale (p = .004). This post-hoc analysis also showed that the CN-CN group were

significantly different from both the CN-MCI (p = .006) and the CN-AD group (p = .028) in delayed recall (see Table 2.8 for full statistical analysis for each group).

Table 2.8

Mean scores (and SEM) for each of the MoCA subscales for ***Cognitively Normal*** *at baseline*

	CN-CN	**CN-MCI**	**CN-AD**	***F* (2,282)**	***p***	**η_p^2**	**Tukey post-hoc ($p < 0.05$)**
Recall	2.5 (0.1)	1.4 (0.3)	0.3 (0.9)	7.835	.001**	0.053	CN vs MCI CN vs AD
Orientation	5.9 (0.0)	5.9 (0.1)	6.0 (0.1)	0.794	.453	0.006	
Visual Spatial	4.4 (0.1)	3.8 (0.2)	4.8 (0.4)	5.761	.004**	0.039	CN vs MCI
Language	2.6 (0.0)	2.4 (0.1)	2.5 (0.3)	1.004	.368	0.007	
Naming	2.9 (0.0)	2.9 (0.1)	3.0 (0.2)	0.628	.534	0.004	
Attention	5.7 (0.0)	5.7 (0.1)	5.5 (0.2)	0.328	.721	0.002	
Abstraction	1.9 (0.0)	1.7 (0.1)	1.8 (0.2)	0.970	.380	0.007	

**$p < .01$

2.3.4. Examination of baseline scores on each subcategory of MMSE & MoCA for those initially classified as being with MCI.

A one-way MANOVA was then conducted to compare MMSE subcategory scores between the 3 groups who were initially diagnosed with **MCI**. A statistical difference was found between groups based on subcategory scores, F (12, 634) = 3.928, $p < .001$, Wilk's Lambda = 0.866, $\eta_p^2 = 0.069$. Participants differed significantly in two subcategories of the MMSE, orientation ($p < .001$) and recall ($p < .001$). Tukey's HSD *post-hoc* test revealed that the group who converted to Alzheimer's disease (MCI-AD), differed significantly from the other two groups in both subcategories. Orientation scores differed between the MCI-AD group and the MCI-CN group ($p = .049$) and also from the MCI-MCI group ($p = .001$). The MCI-AD group was significantly different in recall scores compared to both the MCI-CN group ($p < .001$) and the MCI-MCI group ($p < .001$). The MCI-CN and MCI-MCI groups were not statistically different in relation to orientation score ($p = .983$) or recall score ($p = .078$). See Table 2.9 for the full statistical analysis of groups.

Table 2.9

*Mean scores (and SEM) for each of the MMSE subscales for **MCI** at baseline*

	MCI-CN	**MCI-MCI**	**MCI-AD**	***F* (2,322)**	***p***	**η_p^2**	**Tukey post-hoc ($p < 0.05$)**
Recall	2.8 (0.2)	2.3 (0.1)	1.8 (0.1)	13.766	.001**	0.079	MCI vs AD CN vs AD
Orientation	9.6 (0.2)	9.5 (0.1)	9.1 (0.9)	9.364	.001**	0.055	MCI vs AD CN vs AD
Copying	0.9 (0.1)	0.9 (0.0)	0.8 (0.0)	0.461	.631	0.003	
Language	7.7 (0.1)	7.7 (0.0)	7.7 (0.1)	0.430	.651	0.003	
Attention/ Calculation	5.0 (0.2)	4.7 (0.1)	4.8 (0.1)	2.279	.104	0.014	
Registration	3.0 (0.0)	3.0 (0.0)	2.9 (0.0)	1.462	.233	0.009	

**$p < .01$

Finally, MoCA subscale scores were compared between groups who were diagnosed with MCI at baseline. A one-way MANOVA was conducted to compare groups. MCI groups were found to be different from one another based on MoCA subscale scores, F (14, 626) = 4.093, p = .001, Wilk's Lambda = 0.839, $\eta_p^2 = 0.084$. Groups were significantly different in 6 out of 7 MoCA

subscales, these included: visual spatial ($p < .001$), naming ($p = .007$), attention ($p = .013$), language ($p = .004$), delayed recall ($p < .001$) and orientation ($p < .001$). Tukey's HSD post-hoc test revealed that the MCI-AD group had significantly lower scores than both the MCI-MCI group and the MCI-CN group in the following subscales: visual spatial, naming, delayed recall and orientation. In addition, the MCI-AD group were also significantly lower than the MCI-CN in the attention and language subscales. Table 2.10 below shows *p* values supporting these differences.

Table 2.10

*Mean scores (and SEM) for each of the MoCA subscales for **MCI** at baseline*

	MCI-CN	**MCI-MCI**	**MCI-AD**	***F* (2,319**	***p***	**η_p^2**	**Tukey post-hoc (*p* < 0.05)**
Recall	1.9 (0.3)	1.3 (0.1)	0.5 (0.2)	12.660	.001 **	0.072	MCI vs AD CN vs AD
Orientation	5.9 (0.2)	5.7 (0.0)	5.3 (0.1)	9.701	.001 **	0.057	MCI vs AD CN vs AD
Visual Spatial	4.4 (0.2)	4.1 (0.1)	3.7 (0.1)	9.00	.001 **	0.053	MCI vs AD CN vs AD
Language	2.9 (0.2)	2.4 (0.1)	2.2 (0.1)	5.722	.004 **	0.035	CN vs MCI CN vs AD
Naming	2.9 (0.1)	2.8 (0.0)	2.7 (0.1)	5.103	.007 **	0.031	MCI vs AD CN vs AD
Attention	5.9 (0.2)	5.4 (0.1)	5.2 (0.1)	4.371	.013 *	0.027	CN vs AD
Abstraction	1.8 (0.1)	1.7 (0.0)	1.6 (0.1)	0.683	.506	0.004	No significant differences

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

2.4 Discussion

The present study compared performance of cognitively normal, MCI and AD participants in two widely used cognitive assessments, the MMSE and the MoCA. Results from this comparison indicated that the three groups differed significantly from each other in their performance on both tests. The AD group scored significantly lower on the MMSE and the MoCA compared to both the MCI and CN groups, while the MCI group also scored significantly lower than the CN group in both tests. It was expected that the AD group would score significantly lower than both other groups on the MMSE and the MoCA, given the reported usefulness of both tests in detecting AD (Nasreddine et al., 2005). Although, it should be noted that a lower MMSE score (between 20 and 26 inclusive) made up part of the inclusion criteria for AD outlined by the ADNI. In addition, both cognitively normal and MCI participants were required to score within the normal range for the MMSE (between 24 and 30 inclusive) to meet inclusion criteria.

MCI participants scoring within the normal range of the MMSE has been a widely reported limitation of the test and this has been attributed to its ceiling effect (Trzepacz et al., 2015). MCI patients tend to score within the normal range of MMSE scores and it is easy for individuals without cognitive impairment to achieve the maximum score (Philipps et al., 2014). The MMSE lacks complexity for cognitively normal individuals, while the test has also been reported as too simple for those with MCI (Nasreddine, et al., 2005; Philipps et al., 2014). As a result, the MMSE is usually poor at distinguishing MCI from normal controls. However, there was a difference found between the MMSE scores of cognitively normal and MCI participants in this study. This is likely due to the amount of cognitively normal participants who scored maximum scores. It is clear from the raincloud plots provided (Figure 2.1a) that the maximum score of 30 was achieved more often

by the cognitively normal group than the MCI group. The lack of dynamic performance range of cognitively normal and MCI participants on the MMSE can be seen in the raincloud plots of MMSE scores. Differences between groups are more evident in the raincloud plots of MoCA test scores compared to the MMSE. The MoCA has been noted as having less of a ceiling effect than the MMSE (Damian, 2011; Trzepacz et al., 2015) and this has been shown in this study (see Figure 2.1b). The MMSE cut off scores employed by the ADNI don't seem to have attributed to the observed ceiling effect. While these cut off scores clearly define groups on the MMSE raincloud plots, it is also clear that the majority of cognitively normal and MCI individuals scored highly within the normal range, with a defined cluster of cognitively normal participants achieving the maximum score. A more dynamic performance range and distinct group differences are evident on the MoCA scores presented here, while the ceiling effect of the MMSE remains clear.

The MoCA was developed as a test which was more sensitive to MCI and could identify MCI patients who would usually be classed as cognitively normal based on their MMSE score (Nasreddine et al., 2005). MoCA test scores distinguished normal individuals from MCI patients in the present study, a finding which supports the MoCA as a sensitive measure for MCI detection (Galvin & Sadowsky, 2012). Although the MMSE is usually poor at detecting MCI, it can still distinguish AD patients from others and Nasreddine et al. (2005) suggest the sequential use of the MMSE and the MoCA in assessing varied levels of cognitive decline. It was suggested that if an individual presents cognitive deficit as well as difficulties in functional performance of daily activities, then the MMSE should be administered due to probable AD. If this score is within the normal range, then the MoCA can be used as a follow-up assessment. Alternatively, if an individual presents cognitive deficit but functional performance is preserved, then they are likely to be either normal or have MCI, so the MoCA should be administered (Nasreddine et al., 2005).

Trzepacz et al. (2015) suggests the use of a functional assessment (such as the Functional Activities Questionnaire, Pfeffer et al., 1982) to distinguish AD from normal and MCI individuals, this could be initially administered to help determine which test would suit best. Given that the MMSE is poor at distinguishing MCI, but is useful in cases of more severe cognitive impairment, this suggestion seems reasonable and could help to assess various levels of cognitive function, including normal, MCI and AD. Although this might not be the preferred approach for clinicians as many seek a time-effective solution for assessing their patients (Mitchell, 2009). This is where the use of subscales from the MMSE and the MoCA, which we discuss later, might be a useful tool for clinicians.

We also examined whether initial scores on the MMSE and the MoCA could predict later diagnosis. Firstly, scores of individuals who were cognitively normal at baseline were investigated. Those who converted from being cognitively normal to MCI had significantly lower MMSE scores than those who remained cognitively normal and those who converted to AD. Individuals who remained cognitively normal were not significantly different from those who converted to AD. Total MMSE scores could differentiate individuals who were cognitively normal at baseline and converted to MCI during the 4-years. Although it was expected that scores of individuals who remained cognitively normal would be different to that of those who converted to AD, this difference was likely not detected due to low conversion to AD among cognitively normal participants in the sample – a noted limitation of the present study. The group who converted from cognitively normal to MCI differed from those who remained cognitively normal, but no other differences were found between groups. MoCA scores were capable of detecting those who eventually converted to MCI but not those who converted to AD. Again, this is possibly due to the very few conversions to AD from the cognitively normal sample.

Following this, baseline MCI groups were then compared. Those who converted from MCI to AD had significantly lower MMSE scores compared to those who remained with MCI and those who reverted to cognitively normal. Hence, baseline MMSE scores could distinguish MCI individuals who went on to be diagnosed with AD from others during the 4-years. This finding is consistent with previous research which suggested the MMSE as a possibly useful tool in detecting AD conversion (Choe, et al., 2020). MMSE baseline scores were not useful in distinguishing between the group who remained MCI and those who reverted to cognitively normal. This finding could be explained by the widely reported inability of the MMSE to distinguish between healthy controls and those with mild cognitive impairment (Nasreddine et al., 2005). The MMSE seems to lack not only the sensitivity to distinguish MCI patients from healthy controls but also the ability to detect MCI outcomes (reversion/stable MCI) other than AD. It appears the insensitivity of the MMSE towards healthy control and MCI distinction is evident when attempting to predict subsequent diagnosis using only baseline values.

On the MoCA, all MCI groups were different from one another in their baseline scores. The MCI group who converted to AD were significantly lower in baseline MoCA scores compared to both the group who reverted to a cognitively normal state and the group who remained MCI for the rest of the study. The group who remained MCI were also significantly lower in MoCA scores compared to the reversion group. These findings suggest that baseline MoCA scores may be a very useful tool for predicting MCI outcomes, whether that be a continued MCI diagnosis, a conversion to AD, or a reversion to cognitively normal. When compared to baseline MMSE scores, which could distinguish those who converted to AD from those who did not, baseline MoCA scores could distinguish between not only those who converted to AD, but those who reverted to a cognitively normal state and those who remained with MCI. This is likely due to the improved sensitivity of

the MoCA compared to the MMSE (Nasreddine et al., 2005). While the MoCA improved upon the MMSE in MCI detection, this increased sensitivity and complexity seems to have also impacted the ability of the MoCA to predict MCI outcomes.

The usefulness of the MMSE and MoCA subcategories in detecting possible AD was also investigated here. When comparing the subcategories of the MMSE, two subscales distinguished MCI participants who converted to AD from both MCI non-convertors and MCI who reverted to cognitively normal. Both the orientation and delayed recall subscales detected AD conversion from MCI patient baseline scores on the MMSE. This finding is in line with research published by Choe et al. (2020) who found orientation and recall subscales to be useful predictors in AD conversion from MCI. Memory decline is a well-known deficit in AD (Coughlan et al., 2018) and the results presented here support the evidence which suggest episodic memory decline as a predictor of AD. Although episodic memory is currently the most widely used diagnostic marker for AD, early diagnosis of AD can be delayed due to difficulties in distinguishing normal memory decline of older adults from early AD (Coughlan et al., 2018). Additionally, memory decline is not unique to AD (Hornberger et al., 2010), and researchers have suggested the need for a different approach to help detect early AD (Coughlan et al., 2018). Spatial ability and orientation have been suggested as a potentially useful cognitive marker for early AD. Deficits in spatial ability and orientation are rarely seen in normal individuals or other forms of dementia, and so are advantageous as an early indicator of AD compared to episodic memory (Coughlan et al., 2018; Hornberger et al., 2010). The findings presented here support orientation deficits as an early indicator of AD, as scores on the orientation subscale of the MMSE differentiated AD converters from those who remained MCI and those who reverted to cognitively normal. Both orientation and memory are useful cognitive domains to help predict AD conversion in MCI patients.

The subscales of the MoCA were useful in predicting AD conversion. Several of the subscales from the MoCA were able to predict conversion from MCI to AD including orientation, recall, visuospatial and naming/language subscales. Those who converted from MCI to AD were significantly different in these subscales from those who remained MCI and those who reverted. In addition to these four categories, the MCI group who converted to AD were also significantly different from the group who reverted to cognitively normal, but not those who remained MCI, in the attention and language subscales. Again, in accordance with results presented by Choe et al. (2020), this study has shown orientation, visuospatial, language and memory as being important subscales in predicting AD progression from MCI. The importance of these items is supported by findings from Damian (2011) who found MoCA items relating to orientation, visuospatial and language have the best predictive value of all MoCA subscales. Several cognitive domains were increased in complexity for the MoCA to help MCI detection and these included visuospatial, language and executive function items. The addition of more complex items relating to these domains has not only led to increased sensitivity to MCI (Nasreddine et al., 2005) but has also improved AD prediction compared to the MMSE. As shown by the present findings, the subscales of the MoCA are better predictors of AD conversion from MCI than the MMSE.

It is likely that no differences were found between groups in the visual spatial subscale of the MMSE due to the lack of complexity of the item relating to this domain (Nasreddine et al. 2005). Choe et al. (2020) recommended using other methods to test visuospatial processing, as the item included on the MMSE accounts for only 1 point (out of 30) and subtle differences in visuospatial ability can be hard to detect because of this. More complex visuospatial items are included on the MoCA (Nasreddine et al., 2005) and are assessed by several items, accounting for 4 points (out of 30). The MMSE visuospatial item was not found to be a predictor of AD in our

study. However, differences were found between the 3 MCI groups visuospatial scores on the MoCA. This is likely because the MoCA is more capable of detecting deficits in this domain compared to the MMSE (Lim et al., 2018). The visual spatial domain of the MoCA, but not the MMSE, could be used to predict MCI outcomes including conversion to AD from MCI.

It was the aim of this chapter to understand the effectiveness of the MMSE and the MoCA in predicting subsequent diagnosis of individuals who were cognitively normal or had been diagnosed with MCI. Furthermore, we hoped to gain an insight into the usefulness of the subscales of these cognitive assessments in predicting conversion to AD. While the MMSE was useful in detecting AD conversion from MCI, the MoCA was the better predictor of MCI outcomes compared to the MMSE. All groups could be distinguished from one another based on initial MoCA scores alone. Additionally, the subscales of the MoCA were shown to be more effective than the MMSE in predicting AD conversion and overall MCI outcomes. Both the MMSE and MoCA subscales for orientation and recall were useful in predicting a conversion from AD from MCI. Additional MoCA subscales could predict this conversion including those relating to visuospatial processing and language. This is likely due to more complex items relating to these domains on the MoCA compared to the MMSE. Episodic memory is a widely used cognitive marker for AD but here we have shown the usefulness of looking at various other cognitive domains and how these can be helpful in predicting AD. Using test subscales could be advantageous for clinicians who find administering entire cognitive assessments too time-consuming. In particular, the subscales of orientation, recall, visuospatial processing, and language from the MoCA can all be quickly administered and used to identify possible progression to AD from MCI. Alternatively, these test subscales could be used as an initial assessment of spatial

ability for at-risk individuals. This could then be followed up with more comprehensive tests of spatial cognition, this idea will be expanded upon in subsequent chapters.

Chapter 3

Examining Spatial Cognition in Healthy Adults from the Irish Population

3.1 Introduction

Spatial cognition is a complex process which consists of many different spatial abilities and is vital for everyday functioning (Colby, 2009). It allows living animals to navigate their environment and to perform spatial transformations among objects (Vasilyeva, 2005). A decline in these skills can lead to becoming lost in familiar environments, feeling disorientated or an inability to recall locations. This depreciation can come as a result of certain neurodegenerative diseases, including Alzheimer's disease (AD; Coughlan et al., 2018). Spatial ability is comprised of large-scale and small-scale spatial ability (Yuan et al., 2019). Specifically, large-scale abilities relate to spatial navigation and spatial orientation and small-scale abilities refer to spatial visualization (Hegarty & Waller, 2004; Yuan et al., 2019). Spatial navigation can be defined as the ability to successfully plan and execute a route from one point to another in a large-scale environment (Brodbeck & Tanninen, 2012). Spatial orientation refers to an individual's ability to imagine objects from different perspectives (Hegarty & Waller, 2004). The large-scale measures of spatial navigation and orientation have been shown to be particularly useful in detecting preclinical AD (Coughlan et al., 2018). Whereas spatial visualization, as a small-scale ability, requires performing spatial transformations of an object itself, without changing the perspective from which it is viewed (Yuan et al., 2019). Deficits in visual spatial ability have also been shown in early stages of AD (Adduri & Marotta, 2009; Possin, 2010) and as seen previously Chapter 2, visual spatial deficits and orientation in time and place are key predictors of the conversion of MCI to AD.

Based on these distinctions, two spatial skills are commonly differentiated in the literature: perspective-taking (spatial orientation) and mental rotation (spatial visualization) (Hegarty & Waller, 2004; Kozhevnikov et al., 2006; Wang, Cohen & Carr, 2014). Perspective-taking tasks

rely on making egocentric spatial transformations where one attempts to imagine an environment from different perspectives while trying to identify the location of a target object (Friedman et al., 2020; Hegarty & Waller, 2004). One must alter their own frame of reference within an environment and attempt to imagine where objects in this environment would be given this new, imagined perspective. Such tasks have been shown to be useful tools for predicting large-scale navigation (Kozhevnikov et al., 2006). Conversely, mental rotation tasks involve making spatial transformations of either 2D or 3D objects, where one must try to imagine what the given object would look like in a different position to the one originally presented (Harle & Towns, 2011; Yuan et al., 2019). In this case, the egocentric perspective of the individual does not change only the object itself changes within the environment. This is commonly assessed using the Mental Rotations Test developed by Vandenberg and Kuse (1978). Hegarty and Waller (2004) supported the notion of perspective-taking and mental rotation as being two distinct spatial skills. Christoforou, et al. (2018) have also found that these two abilities rely on different cognitive processes by showing that the two rely on distinct neural mechanisms. Perspective-taking ability has been shown to better predict performance in large-scale spatial navigation tasks compared to mental rotation (Allen et al., 1996; Friedman et al., 2020; Kozhevnikov et al., 2006).

An example of a perspective-taking task is the Spatial Orientation Test (SOT), which was originally developed by Kozhevnikov and Hegarty (2001) and subsequently revised by Hegarty and Waller (2004). In this pen and paper task, participants are presented with an array of objects, they must imagine standing at one object and while facing another object in the given array. Participants are then tasked with indicating the direction of a third object by drawing a line from this newly imagined perspective to the object. In Hegarty and Waller's (2004) revised version of the spatial orientation test, each item requires one's perspective to be changed by at least 90°, this

was implemented to ensure a perspective-taking strategy was employed and hence increase difficulty. It has been found that when less than a 90° perspective change is required, people tend to opt for strategies which do not involve using perspective-taking skills (Hegarty & Waller, 2004; Kozhevnikov & Hegarty, 2001; Kozhevnikov et al., 2006). The Spatial Orientation test is deemed a valid test of spatial orientation ability and is widely used to assess the ability of individuals to use perspective-taking strategies while performing spatial tasks (Friedman et al., 2020; Hegarty & Waller, 2004). Hegarty and Waller (2004) found that performance on the SOT was related to performance in a real-world perspective-taking task in a memorized environment. Others have also found perspective-taking skills (as measured by the SOT) can predict performance in navigational tasks (Galati et al., 2015; Kozhevnikov et al., 2006). Friedman et al. (2020) recently developed a computerized version of the SOT which yielded similar results to the original and seems to be a suitable alternative for the pen and paper version of the task (Gunalp, et al., 2021). This computerized version eliminates the issue of human error that can arise when hand-scoring angular errors and in turn makes the test both quicker and easier to administer (Friedman et al., 2020).

One's subjective sense of direction has also been found to predict performance in large-scale spatial tasks (Hegarty et al., 2002; Hegarty & Waller, 2004). Following previous concerns over the ability of perspective-taking and mental rotation tasks to predict real-world spatial skills (Dunn & D'Amelio, 2020; Hegarty et al., 2002), Hegarty et al. (2002) developed a subjective measure of spatial ability, called the Santa Barbara Sense of Direction scale (SBSOD). This test requires individuals to indicate their level of agreement with statements related to sense of direction. The reliability of self-report measures to predict performance in tasks relating to spatial ability is widely recognized (Mitolo et al., 2015). The SBSOD has been widely used since its development (Dunn & D'Amelio, 2020) and has shown to be a valuable tool which correlates with

measures of real-world spatial ability, and specifically relates to navigation and orientation skills (Hegarty et al., 2002). Friedman et al. (2020) and Hegarty and Waller (2004) found that SBSOD scores correlated with scores from both the revised and computerized version of the SOT, providing evidence for the relationship between one's subjective sense of direction and performance in an objective spatial task.

Individual differences in spatial ability are widely reported across the literature and consist of sex and age-related differences, as well as differences based on location (urban versus rural environments). For example, Coutrot et al. (2018) recently found that being raised in a city environment negatively impacts navigation ability compared to growing up in a rural area. Regarding sex differences, males tend to outperform females in tasks relating to spatial ability, this male advantage has been observed in both large-scale and small-scale spatial tasks (Hoffmann, et al., 2011; Jansen & Heil, 2009; Reilly et al., 2017; Yuan et al., 2019; Zancada-Menendez et al., 2016). Although there is debate around the extent of this sex difference, Reilly, Neumann and Andrews (2016) argue that this is one of the largest sex differences seen across all cognitive domains. These sex differences have been shown in the spatial orientation task developed by Hegarty and Waller (2004), with males tending to have lower angular errors than females in the task (Zancada-Menendez et al., 2016; Tarampi, Heydari & Hegarty, 2016). This male advantage is evident in other well-known perspective taking spatial tasks, such as the Money road-map task (Money, Alexander, & Walker, 1965; Tarampi, Heydari & Hegarty, 2016) as well as in large-scale spatial tasks (Yuan et al., 2019). This sex difference has also been reported in subjective measures of spatial ability. Males have been shown to score higher in self-report sense of direction scales compared to females (Cornell, Sorenson & Mio, 2003; Kozlowski & Bryant, 1977) including the

SBSOD scale (Turano et al., 2009) and have shown greater confidence in their own spatial abilities generally (Hoffmann, Gneezy & List, 2011; Reilly et al., 2016).

Several researchers have attempted to understand this observed male advantage in spatial tasks. Firstly, spatial skills can be improved with training, Hoffmann, et al. (2011) state that such experience is usually held by males more so than females. In addition, the possible role of expectation in this sex difference has been highlighted (Hoffmann et al.; Reilly et al., 2016; Tarampi et al., 2016). Females are generally regarded as having poorer spatial ability compared to males, while males are aware of their own advantage (Hoffmann et al., 2011; Reilly et al., 2016). It has been questioned whether low performance expectations in spatial tasks could lead to decreased performance in females. The lack of direct supporting evidence for such a cause was highlighted by Hoffmann, et al. (2011). Tarampi, et al. (2016) attempted to understand this relationship between expectation and perspective taking task performance. It was found that females performed worse than males during the spatial condition and this was partially influenced by expectation (being told men had an advantage), which supports claims made by Reilly, et al. (2016) and Hoffmann, et al. (2011). However, when a social element (inclusion of human figures) was introduced in perspective taking tasks, females outperformed males (Tarampi, et al., 2016). Tarampi, et al. (2016) suggest that the observed performance difference between males and females in perspective-taking tasks might come as a result of the way tasks are presented (i.e., as spatial tasks or social/empathic tasks), as opposed to a difference in spatial ability. Others have suggested that this sex difference may come from greater spatial anxiety/stress of females compared to males, or as a result of employing different strategies while completing tasks (Alvarez-Vargas, et al., 2020; Gabriel et al., 2011).

Age differences in spatial abilities have also been highlighted throughout the literature, older people tend to underperform compared to younger individuals in spatial tasks (Borella et al., 2014; Jansen & Heil, 2009). Zancada-Menendez et al. (2016) found that older adults were more prone to errors than younger age groups in the original version of the spatial orientation test developed by Kozhevnikov and Hegarty (2001). The items in this version of the test can be categorized as requiring either perspective shifts of less than 90° or perspective shifts greater than 90°, while revised version items require perspective shifts greater than 90° only. Perspective shifts greater than 90° have been shown to have increased difficulty, resulting in poorer performance (Kozhevnikov & Hegarty, 2001; Zancada-Menendez et al., 2016). Younger age groups have been shown to outperform older groups in perspective-taking tasks, but performance in younger groups has shown to decrease as difficulty increases (Zancada-Menendez et al., 2016). This age-related decline is also evident in mental rotation tasks, as reported by Jansen and Heil (2009) who found that sex differences decrease with age in this task. Few have attempted to understand the relationship between sex and age in spatial tasks, according to Jansen and Heil (2009) and Zancada-Menendez et al. (2016). In attempting to understand this relationship, Zancada-Menendez et al. (2016) found no interaction effect between age and sex in their study using the perspective-taking spatial orientation task.

Age-related differences have also been reported in various other pen and paper spatial tasks (Taillade, et al., 2016), but this poorer performance of older adults is not always consistent with how they judge their own sense of direction. Taillade et al. (2016) found that despite performing significantly worse in psychometric spatial tasks, older adults were not different in their SBSOD scores compared to younger adults, suggesting a possible overestimation of their own spatial ability. Older individuals have often reported having similar spatial ability compared to younger

individuals in self-report measures but have still shown poorer performance in more objective spatial tests (Borella et al., 2014; Taillade, et al., 2016; Taillade et al., 2012). Navigation complaints are also rarely reported by older adults, despite poorer performance compared to younger adults in navigational tasks (Taillade, et al., 2016). This inconsistency between self-reported sense of direction and performance in navigation tasks in older adults might be lessened with the use of spatial tasks which closer resemble real-world navigation as opposed to abstract tasks such as perspective-taking tasks, as suggested by Taillade, et al. (2016). Older adults have been shown to perform significantly worse compared to younger adults in environments which are unfamiliar and in tasks which are abstract (De Beni et al., 2006; Devlin, 2001).

Understanding spatial cognition in healthy individuals is becoming as important as ever, due to evidence suggesting that navigation and spatial skills could potentially be used as an early indicator of onset dementia (Coughlan, et al., 2018; Hort et al., 2007). Indeed, spatial navigation and orientation have been suggested as important biomarkers in enabling the detection of preclinical AD and with greater specificity than episodic memory (Coughlan et al., 2018). While we are aware that Irish navigational and large-scale abilities are comparable to other European countries (Coutrot et al., 2018), we know very little about the population's general spatial skill level. As such, it is important to collect this information to try and understand the issues around spatial abilities in healthy participants before comparison with different patient groups can be made. As our results indicated in the previous chapter, individuals who had MCI and subsequently received a diagnosis of AD performed worse than those who did not in subcategories of MMSE/MoCA tests relating to memory, orientation and visuospatial skills often years before converting to an AD diagnosis. This supports the notion that in addition to memory, orientation and spatial skills are also important skills which should be assessed to help with the early detection

of AD, as suggested by Coughlan et al. (2018). Therefore, having normative values for spatial skills would allow direct comparisons to be made between age-matched healthy controls and patient groups. Particularly, those who are at risk of developing AD, such as those with MCI should be considered. The current chapter aims to investigate spatial skills of healthy Irish adults as well as gain an insight into how individuals subjectively report their own spatial abilities, and how these two measures might compare. This will be done with the hope of contributing to the current knowledge held around spatial abilities of the Irish population.

The current study uses an online questionnaire which is made up of tests/tasks relating to spatial ability. The questionnaire was distributed to Irish adults and included the Santa Barbara Sense of Direction (SBSOD) task, the Spatial Orientation Test (SOT), the Subjective Navigation Complaints Questionnaire (SSNC) and the Cognitive Failures Questionnaire (CFQ). As outlined above these tasks were deemed the most appropriate as they are simple to use, well established in the research literature and could potentially be used as a follow-up clinical tool (in addition to the MMSE and MoCA sub-scales) to examine spatial and orientation deficits further in at-risk individuals or patient groups. Demographic information including sex, age and location in Ireland was also collected. It is the aim of this study to assess both age and sex differences in spatial orientation skill and in subjective spatial ability. The relationship between age and sex for these tasks will also be investigated as Jansen and Heil (2009) and Zancada-Menendez et al. (2016) reported contrasting results, and both highlighted a lack of consideration for this relationship in the literature. It is hypothesized that there will be a significant difference between males and females in their self-reported sense of direction (SBSOD) scores, but that there will be no differences in these scores across age groups. It is expected that males will have lower angular error averages on the SOT compared to females and younger participants will outperform older

participants on the SOT, irrespective of sex. We expect to find correlations between the direct measure of spatial ability (SOT errors) and both self-report measures of spatial ability (SBSOD scores and SSNC scores), as well as correlations between the two self-report measures (SBSOD and SSNC).

3.2 Methods

3.2.1 Participants

Participants involved in the study were recruited through convenience sampling. Participants consisted of students of Maynooth University, friends and family members and were required to be 18 years or older. Individuals who expressed interest in participating were sent an anonymous link to the survey and were advised to read about the study, what it would entail and to consider their own eligibility by reading the study information and eligibility criteria (see Appendix V). Demographic information including age, sex and location within Ireland was collected at the beginning of the survey. The survey consisted of 4 different tests/tasks relating to spatial navigation. A total of 218 responses were collected, 25 of these did not complete any one of the tests in full and were excluded from the analysis. Any fully completed sections were included for analysis, even if the full survey was not completed by the participant. The full survey was completed by 163 participants and at least one test was completed by an additional 30 participants, so 193 participants (male = 62, female = 131) were included in the analysis. Participants were organized into three different age groups which can be seen in Table 3.1 below. A statistical power analysis conducted using G*Power (Faul et al., 2007) indicated a total sample size of 93 would be appropriate across the 3 age groups (18-24 years, 25-44 years, and 45+ years), with power of 0.9, an effect size of 0.3 and a probability of .05. Given this calculation, we can be confident that the current sample size (n = 193) yields sufficient power.

Table 3.1

Breakdown of each of the three age groups showing the number of participants and the breakdown of males and females in each group as well as mean (SEM) CFQ scores

Age Group	N	M/F	Mean CFQ
18-24 years	139	46/93	44.95 (1.21)
25-44 years	21	4/17	45.43 (3.92)
45+ years	33	12/21	32.59 (2.11)

Inclusion Criteria:

Participants were required to be at least 18 years of age at the time of data collection. It was necessary that participants did not have any health-related issues which might impact on their participation or the study itself. Sufficient visual acuity was also necessary in order to participate.

Exclusion Criteria:

Participants were informed that some health-related issues were exclusionary, including history of psychological/neurological impairment, epilepsy or memory issues, drug or alcohol abuse or if they were currently taking psychoactive medication. Participants were advised that if they have suffered from any of these, they may not be eligible to take part in the study. If 'yes' was answered to any of the aforementioned health issues, then participants were automatically brought to the end of the survey. As stated above, if any participant did not fully complete at least one section of the survey then they were excluded from analysis.

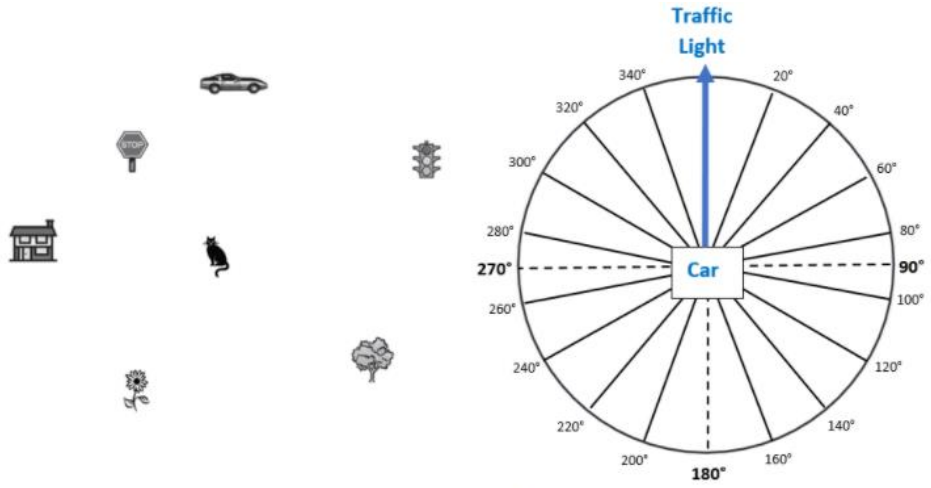
3.2.2 Materials

The spatial navigation survey was developed using the online survey tool Qualtrics (https://www.qualtrics.com/uk/core-xm/survey-software/). The survey comprised of a number of tests/tasks related to spatial and cognitive abilities, all of which were adapted for use in an online survey. The first test was the **Santa Barbara Sense of Direction Scale (SBSOD**; Hegarty et al., 2002). This is a 15-item test which requires respondents to report subjectively on their own spatial abilities (see Appendix VI). Each item includes a statement which the respondent must decide their level of agreement with (from "strongly agree" to "strongly disagree"). The average score is then calculated across items, so each respondent scores between 1 (poor sense of direction) and 7 (good sense of direction). The next test included in the survey was the **Subjective Spatial Navigation Complaints (SSNC)** survey developed by Cerman et al. (2018). This test also consisted of 15 items, and these were further divided into 7 sections. Each of these sections investigates the severity of decline (from "same or better" to "significantly worse") or frequency (from "never" to "everyday") of self-perceived navigation complaints in everyday living. The impact of this perceived decline on everyday living is also assessed using dichotomous "yes" or "no" questions. The maximum possible score for this test is 49, with higher scores representing more frequent navigational complaints (See Appendix VII). The **Perspective Taking/Spatial Orientation Test (SOT**; Hegarty & Waller, 2004) was also used in this survey. This is a 12-item test which aims to test the ability of individuals to imagine different perspectives. Respondents are shown an array of objects and each item requires them to imagine they are at one object, while facing a second object and from this perspective they must indicate the direction of a third object. In this online version we have provided each scenario with labelled angles so that participants could indicate the direction of the target item to the nearest degree. An example of one of these items can be seen in

Figure 3.1, task instructions can be found in Appendix VIII. Finally, we also included the **Cognitive Failures Questionnaire (CFQ)**, developed by Broadbent et al. (1982), which assesses how often respondents experience cognitive failures in daily life (See Appendix IX). This test consists of 25 questions with a response scale ranging from "never" to "very often" (0-5) for each item, respondent's total scores can range from 0-100 with higher scores predicting more frequent occasions of absent-mindedness. We included this cognitive assessment in order to compare levels of spatial cognition to levels of general cognitive ability, and to compare group performance based on cognitive ability.

Figure 3.1

Example of an item used in our computerized version of the Spatial Orientation Test



Imagine you are standing at the **car** and facing the **traffic light**. Please indicate to the nearest degree where the **stop sign** is.

3.2.3 Ethical Considerations

This study was approved by the Maynooth University Ethics Committee (Ethics Review ID: 2409892). Informed consent was received from each participant before testing began. An information sheet was provided to all participants to allow them to become familiar with the study before deciding to proceed.

3.2.4 Statistics

The online survey tool Qualtrics (https://www.qualtrics.com/uk/core-xm/survey-software/) was used to create the survey used for the current study. Following data collection, data were exported to Microsoft Excel and were organized for analysis. Any incomplete responses were removed at this stage. G*Power (Faul et al., 2007) was used to ensure sufficient statistical power and appropriate sample size. These data were then exported to IBM SPSS (version 28) for statistical analysis. Pearson product-moment correlation coefficient was used to determine relationships between tests. Two-way analysis of variances (ANOVAs) were used to examine the impact of sex and age on SBSOD, SSNC, SOT and CFQ scores. Tukey's honestly significant difference (HSD) was the *post-hoc* test used to help further understand any detected differences. Where a significant interaction between sex and age was found, independent samples t-tests and one-way ANOVAs were conducted to fully understand this interaction. Statistical significance was indicated at the $p < 0.05$ level for all analyses. Effect sizes are presented throughout the results section as eta squared (η^2) and partial eta squared values (η_p^2).

3.3 Results

3.3.1 Relationships between tests

The relationship between each of the tests used in the survey was initially investigated using Pearson product-moment correlation coefficient. The relationship between each test can be seen in Table 3.2 below. The subjective measures of spatial abilities (SBSOD and SSNC) had a significant medium negative correlation, with high levels of sense of direction associated with low spatial navigation complaints. These two subjective measures had small but significant correlations with the SOT, with fewer SOT errors associated with greater sense of direction (negative relationship) and with fewer spatial navigation complaints (positive relationship). The CFQ had a medium negative correlation with the SBSOD, with fewer cognitive failures associated with greater sense of direction. There was a positive correlation found between the CFQ and the SSNC, where higher levels of cognitive failure were associated with higher levels of spatial navigation complaints. The only relationship which was not statistically significant was between the CFQ and the SOT, which had a very small negative correlation.

Table 3.2: Pearson product-moment correlations between tests of spatial ability and cognition.

	1	2	3	4
1. SBSOD	-			
2. SSNC	-.43**	-		
3. SOT	-.20*	.18*	-	
4. CFQ	-.35**	.39**	-.06	-

**$p < .01$, *$p < .05$ (2-tailed)

3.3.2 Examination of the effect of sex and age on test scores

SBSOD

A two-way between groups ANOVA was conducted to examine the impact of sex and age on self-reported sense of direction, measured by the SBSOD. There was an overall statistically significant main effect for sex, F (1, 187) = 4.89, p = .03, but with a small effect size; $\eta_p^2 = 0.03$. Males (Mean = 4.7, SEM = +/- 0.1) reported a better sense of direction compared to females (4.1 +/- 0.9). A main effect for age was also found, F (2, 187) = 5.97, p = .003, $\eta_p^2 = 0.06$. A *post-hoc* test using Tukey's HSD revealed that the older group (45+; 4.8 +/- 0.2) was significantly higher in SBSOD scores than the 18-24 group (4.2 +/- 0.1, p = .003) and also the 25-44 group (4.1 +/- 0.3, p = .017). No statistical differences were found between the 18-24 age group and the 25-44 age group (p = .85). Finally, the interaction effect between sex and age group was not statistically significant, F (2, 187) = 0.60, p = .55. The bar chart in figure 3.2 below shows the average SBSOD scores of males and females across each age group.

Figure 3.2

Bar chart illustrating SBSOD scores for males and females across the three age groups

SSNC

The impact of sex and age on SSNC scores was also investigated using a two-way between groups ANOVA. There was no overall statistical difference between males (3.7 +/- 0.5) and females (4.4 +/- 0.4) based on SSNC scores F (1, 184) = 1.26, p = .264, η_p^2 = 0.01.

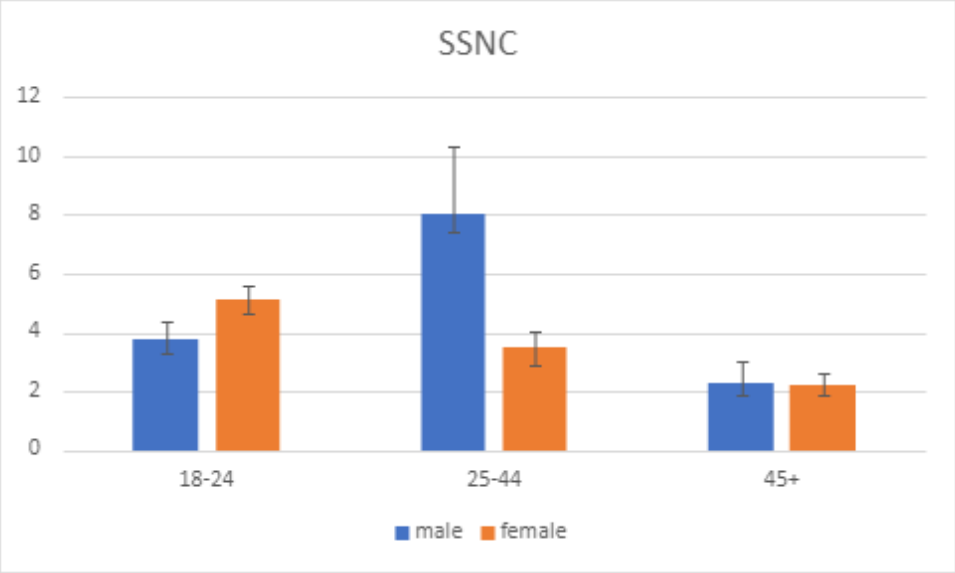
There was a significant difference found between age groups in SSNC scores, F (2, 184) = 5.35, p = .006, η_p^2 = 0.06. Tukey's HSD *post hoc* test revealed a significantly higher score for the 18-24 group (4.7 +/- 0.4) compared to the 45+ group (2.2 +/- 1.9, p = .004). No differences were found between the 25-44 group (4.3 +/- 3.4) and the 18-24 group (p = .93) or the 45+ group (p = .12). A significant interaction effect between sex and age was found, F (2, 184) = 3.41, p = .035, η_p^2 = 0.04. Further analyses were carried out to understand this interaction. Three independent samples

t-tests were conducted to compare males and females of each age group. These tests showed that males (3.8 +/- 0.6) were not significantly different from females (5.1 +/- 0.8) in the 18-24 group, t (134) = -1.73, p = .086, two-tailed; but in the 25-44 group, males (8.0 +/- 2.6) did score significantly higher on the SSNC compared to females (3.47 +/- 0.60), t (19) = 2.79, p = .012, two-tailed. Males (2.1 +/- 0.7) did not differ from females (2.2 +/- 0.4) in the 45+ age group, t (31) = -.21, p = .83, two-tailed.

Two further one-way ANOVAs were conducted to separately compare males and females based on age group. Males were statistically different from one another in SSNC scores based on age, F (2, 59) = 3.48, p = .04, η^2 = .11. Tukey's HSD revealed that 18–24-year-old males (3.8 +/- 0.6) were not statistically different from 25–44-year-old males (8.0 +/- 2.4; p = .10) or 45+ males (2.1 +/- 0.7; p = .40). But 45+ males did score significantly lower than 25–44-year-old males (p = .03). Females were also found to be statistically different from one another based on age, F (2, 125) = 5.20, p = .007, η^2 = .08. Tukey's HSD showed that females in the 18-24 group (5.1 +/- 0.5) scored significantly higher than females in the 45+ group (2.2 +/- 0.4; p = .008) but did not differ from females in the 25-44 group (3.5 +/- 2.5; p = .25). No differences were found between females in the 25-44 group and the 45+ group (p = .60).

Figure 3.3

Bar chart illustrating SSNC scores for males and females across the three age groups



SOT

There was no overall significant effect for sex, F (1, 158), p = .84, η_p^2 = 0.0, (males (35. +/- 3.9) and females (40.7 +/- 2.7). There was however an overall statistically significant effect for age, F (2, 158) = 6.89, p = .001, η_p^2 = 0.08. Tukey's HSD *post hoc* test revealed that the 18-24 group (33.6 +/- 2.2) scored lower than both the 25-44 group (52.4 +/- 7.4 p = .018) and the 45+ group (50.3 +/- 6.7, p = .01). The 25-44 and 45+ groups were not statistically different from one another (p = .965) in SOT scores. A significant interaction effect between sex and age was not found for SOT scores F (2, 158) = 0.35, p = .71, η_p^2 = 0.004.

Figure 3.4

Bar chart illustrating average SOT errors for males and females across the three age groups

Further investigation was carried out on SOT scores to determine whether error increased with angle size among males and females. To do this, we grouped angles together based on location within the 360° response circle. For example, items which had a correct answer between 0-90° would be in the first quadrant, between 90-180° would be in the second quadrant and so on (see Table 3.3). Based on the response required for each item, items were categorized as being in either quadrant 1, 2, 3 or 4. This was done to investigate whether items which required larger angle estimations were more difficult. A mixed between-within subjects ANOVA was conducted to assess the impact of sex (male/female) on participant's average error for the answers belonging to each quadrant on the SOT. There was no significant interaction between quadrant and sex, Wilk's Lambda = 0.98, F (3, 160) = 1.08, p = .361, η_p^2 = 0.02. There was a moderate main effect for quadrant, Wilk's Lambda = 0.91, F (3, 160) = 5.56, p = .001, η_p^2 = 0.094, with error increasing as angle size increased (see Table 3.3). The main effect comparing males and females was not

significant, F (1, 162) = 1.39, p = .24, η_p^2 = 0.008, suggesting no difference in performance between the two groups.

Table 3.3

Mean SOT scores (error) for males and females across each quadrant.

	Males			**Females**		
Quadrant (angles)	n	M	SEM	n	M	SEM
1 (0°-90°)	56	28.7	4.4	108	35.3	3.3
2 (90°-180°)	56	33.3	5.0	108	37.5	3.6
3 (180°-270°)	56	37.3	4.2	108	46.2	3.4
4 (270°-360°)	56	41.4	4.9	108	43.8	3.1

Table 3.4

Mean SOT scores (error) for all participants across each quadrant

	Total		
Quadrant (angles)	n	M	SEM
1 (0°-90°)	164	33.1	2.6
2 (90°-180°)	164	36.1	2.9
3 (180°-270°)	164	43.2	2.7
4 (270°-360°)	164	43.0	2.6

CFQ

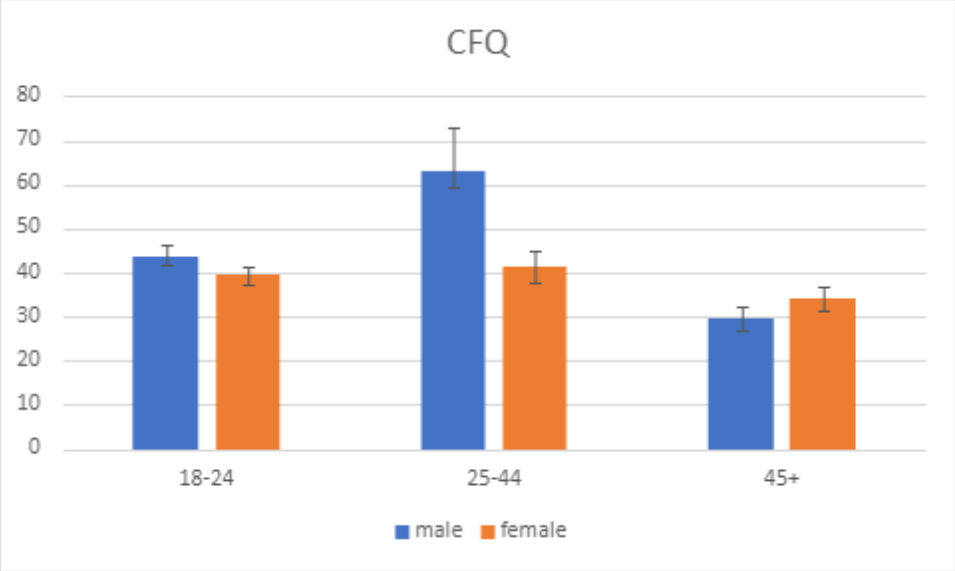
Finally, the impact of sex and age on CFQ scores was again examined using a two-way between groups ANOVA. There was no statistical difference between males (42.9 +/- 2.2) and females (42.7 +/- 1.2) in CFQ scores, F (1, 173) = 2.18, p = .14, η_p^2 = 0.012. However, there was a significant main effect for age, F (2, 173) = 14.96, $p < 0.001$, η_p^2 = 0.15. *Post hoc* analysis using Tukey's HSD revealed that the older group (45+; 32.6 +/- 2.1) was significantly lower in CFQ scores than both other groups: 18-24 group (44.9 +/-1.2, $p < 0.001$) and 25-44 group (45.4 +/- 3.9, p = .003). The 18-24 group and the 25-44 group were not significantly different from one another in CFQ scores (p = .988). A significant interaction effect between sex and age was also found F (2, 173) = 5.61, p = .004, η_p^2 = 0.06. Three independent samples t tests were conducted to examine this interaction between sex and age in CFQ scores further. These tests revealed that there was no difference between males (45.4 +/- 2.2) and females (44.7 +/- 1.5) in the 18-24 group, t (124) = 0.28, p = .78, two-tailed, or between males (27.3 +/- 3.5) and females (35.8 +/- 2.5) in the 45+ group, t (30) = -2.06, p = .05, two-tailed. Males (63.0 +/- 10.0) and females (41.3 +/- 3.7) only differed in CFQ scores in the 25–44-year-old age group, t (19) = 2.43, p = .03, two-tailed.

Two one-way ANOVAs were then conducted to examine scores of males and females on the CFQ based on age. A significant difference was found among males based on age F (1, 57) = 11.71, $p < 0.001$, η^2 = .29. *Post hoc* analysis using Tukey's HSD revealed that males in the 45+ age group (27.3 +/- 3.5) scored significantly lower than both other groups; 18–24-year-old males (45.4 +/- 2.2, $p < 0.001$) and 25–44-year-old males (63.0 +/- 10.0, $p < .001$). No difference was found between males who were 18-24 years old and males who were 25-44 years old (p = .06). A significant difference was also found between females based on age F (2, 116) = 3.79, p = .03, η^2 = .06. Tukey's HSD showed that females in the 45+ group (35.8 +/- 2.5) scored significantly lower

than the 18-24 group (44.7 +/- 1.5, p = 0.021) but not the 25-44 group (41.3 +/- 3.7, p = 0.418). Females in the 18-24 group did not differ in CFQ scores compared to females in the 25-44 group, p = .60.

Figure 3.5

Bar chart illustrating CFQ scores of males and females across the three age groups



3.3.3 Geographical spread of test scores across Irish counties

As part of the survey, participants were asked to indicate their location in Ireland and scores from each county were then averaged and used to create a map showing the geographical spread of test results across the country. Figure 3.5 shows the counties of the Republic of Ireland and the average scores for each county across the four tests used in this study. In the figure below, darker shades of blue indicate higher test scores. Figure 3.6 shows the urban/rural classification of Ireland by the

Central Statistics Office (CSO) for the 2016 national census (CSO, 2019) and can be used to help understand the results of the present study. Firstly, for SBSOD scores we can see that counties which had high self-reported sense of direction (darker shades of blue) seem to roughly resemble geographical areas which have been classified as cities or rural areas with high urban influence. This shows that counties which had a higher self-rated sense of direction were counties with urban areas or areas with high urban influence (as shown by the CSO). Additionally, we can also see that counties that scored higher on the SSNC were counties which consist of rural areas with moderate/no urban influence. This indicates that those living in more rural areas of Ireland expressed more navigational complaints than others. Location in Ireland did not seem to affect SOT scores generally, although the two counties with the highest error seem to have highly remote areas or areas with only moderate urban influence. CFQ scores do not seem to have been affected by location in Ireland.

Figure 3.6

Map of counties in the Republic of Ireland showing the spread of test scores

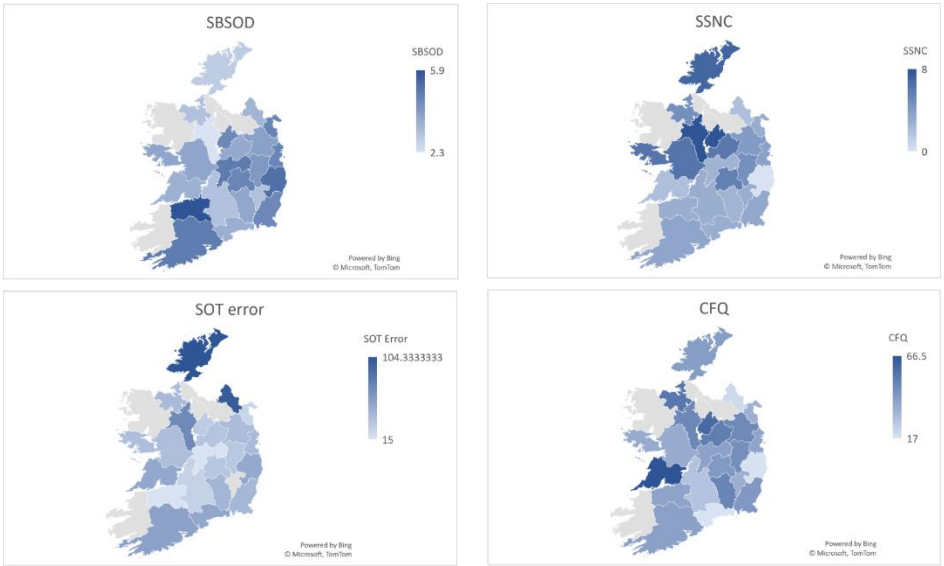
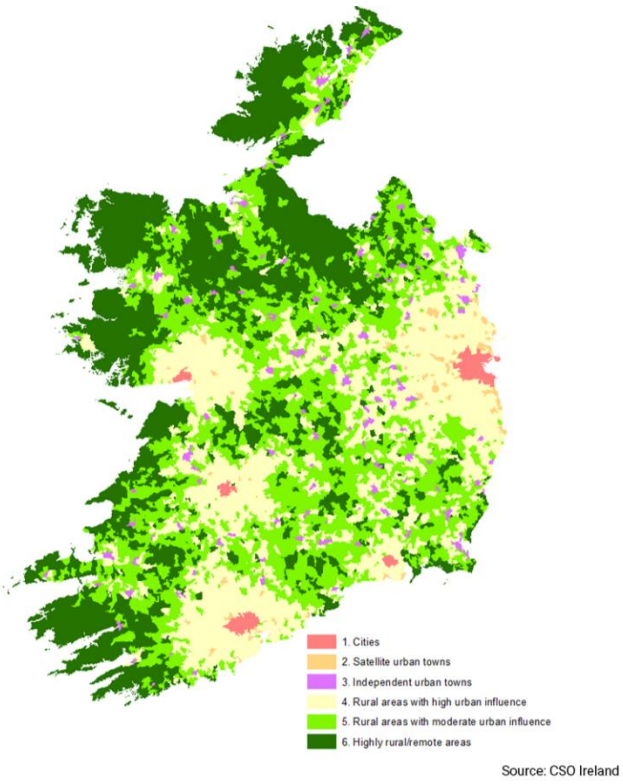


Figure 3.7

Map developed by the Central Statistics Office (CSO) using data from the 2016 Census illustrating the urban/rural classification of Ireland (CSO, 2019)



The average scores for each county across all tests were then compared to investigate whether scores were correlated. For example, if a county scored high on the SBSOD, did it also score high on the SOT. Table 3.5 below shows the correlations between counties in each test. From the maps above, it seemed that SBSOD and SSNC scores were the two tests which were most impacted by location in Ireland. Scores on the SBSOD and SSNC had a medium negative correlation, but this was not statistically significant (see Table 3.5). The SBSOD had a strong negative correlation with SOT error which was significant, indicating that counties that had poorer sense of direction had higher SOT errors, and vice versa.

Table 3.5

Pearson product-moment correlations between tests by county

	1	2	3	4
1. SBSOD	-			
2. SSNC	-.37	-		
3. SOT	-.55*	.12	-	
4. CFQ	-.12	.48*	-.19	-

*$p < .05$ (2-tailed)

3.4 Discussion

The current study aimed to examine spatial abilities in the general Irish population using measures which capture perspective-taking ability, sense of direction and subjective sense of spatial skill. Firstly, the relationship between each of the tests used in the questionnaire was examined. Individual scores from the SOT, SBSOD and SSNC were analyzed to determine if any correlations between the tests existed. As expected, the two subjective measures of spatial ability (SBSOD and SSNC) were correlated with one another, results indicated that a medium negative correlation existed between the two tests. A negative relationship was expected here as higher scores on the SBSOD scale indicate better sense of direction, while lower scores on the SSNC signify less navigation complaints and hence better spatial ability. Additionally, it was expected that these two tests would correlate with the direct measure of spatial ability used in the questionnaire - the SOT. These correlations were not as strong but reached statistical significance. Both the SBSOD and SSNC had small but significant correlations with the SOT, but in opposite directions. While the SBSOD had a negative relationship with the SOT, the relationship between the SSNC and the SOT was positive. Again, the directions of these relationships were as expected given how each test is scored, and that a lower score on the SOT indicates better performance. Although, the strength of these relationships is not as strong as those previously reported. For example, Friedman et al. (2020) showed a stronger correlation between scores from their computerized version of the SOT and the SBSOD – a finding which was expected here.

The role of sex and age in performance during the direct spatial task and subjective spatial ability was also investigated. Initially, these two variables were assessed separately. Males and females did not differ from one another in any of the tests included in the questionnaire, except in SBSOD scores. This difference in SBSOD scores is not surprising, given that several others have

reported similar findings in both the SBSOD itself (Turano et al., 2009) and in other measures of sense of direction (Cornell, Sorenson & Mio, 2003; Kozlowski & Bryant, 1977). It is surprising, however, that males and females were not significantly different in reporting their subjective navigation complaints (SSNC scores) or in their performance on the SOT. Despite rating their sense of direction more positively than females, males did not perform differently to females on the SOT. It was expected that males would outperform females in this task, as male advantage is commonly reported across spatial tasks (Hoffmann, Gneezy & List, 2011; Jansen & Heil, 2009; Reilly et al., 2016; Yuan et al., 2019; Zancada-Menendez et al., 2016), including perspective-taking tasks (Heydari & Hegarty, 2016), and specifically on the SOT (Zancada-Menendez et al., 2016; Tarampi, Heydari & Hegarty, 2016). The average angular error of males was indeed less than that of females, but this result failed to reach statistical significance. It is possible a significant difference was not detected between males and females in SOT scores because males were outnumbered by females by nearly double in this study. It is a noted limitation that males were underrepresented compared to females in this sample and that this in turn affects interpretation of results.

Participants were categorized into three age groups and performance in each of the tests was analyzed based on age. These groups were referred to as younger (18-24 years), middle-aged (25-44 years) and older (45+ years) groups for the purpose of this analysis. It must be noted that there were not the same number of participants in each age group, and the following findings should be interpreted with this in mind. Regarding SBSOD scores, participants in the 45+ age group rated their own sense of direction significantly higher than both other groups. Since it has been reported that older adults tend to report their own sense of direction as the same if not better than their younger counterparts, this finding was not surprising and is in line with research carried

out by Borella et al. (2014) and Taillade et al. (2016). The older group (45+) also scored lower in SSNC scores compared to the youngest group (18-24). This again is supported by Taillade et al. (2016), who claimed that older adults tend not to report navigational complaints during similar tests.

On the SOT, it was expected that the younger groups would outperform the older group in this task, especially given that an initial decline in spatial ability has been reported to emerge for adults in this age bracket (Zancada-Menendez et al., 2016). The youngest group had significantly lower angular errors on average than both other groups, indicating better performance. This finding is in accordance with previous research which found older adults were at a disadvantage in spatial tasks (Borella et al., 2014) and specifically they tend to have higher angular error on the SOT compared to younger individuals (Kozhevnikov & Hegarty, 2001; Zancada-Menendez et al., 2016). Similar to Taillade et al. (2016), a discrepancy between performance in the direct spatial task and self-reported spatial ability has been found in older adults in the present study. The older age group of participants rated their own sense of direction more positively than the younger group, despite proceeding to perform significantly worse on the SOT compared to the younger group. It is yet to be established whether this might come as a result of older adults overestimating their own spatial abilities, resulting in inconsistencies between actual navigational ability and self-reported sense of direction. Or, if this judgement is truly representative of their daily experiences (i.e., they do not experience navigational issues) and hence complaints are not reported (Taillade et al. 2016). This would give rise to the notion that poorer performance of older adults in spatial tasks can come as a result of the abstract nature of spatial tasks and unfamiliar lab settings (De Beni et al., 2006; Devlin, 2001; Taillade et al., 2016). This is a possible explanation as it has been reported that older adults' navigational performance tends to be worse in unfamiliar environments

than in familiar ones as well as during abstract tasks which hold little ecological value (Taillade et al., 2016). Others have also shown that age-related differences reduce when everyday real-world tasks are used, as opposed to more abstract tasks such as perspective-taking or mental rotation tasks (De Beni et al., 2006; Devlin, 2001). It is possible that participants from the older group do not experience navigation/orientation difficulties in their everyday lives but when faced with an abstract task, such as a perspective-taking task used here, performance is worse than the younger group who possibly can acquire spatial information more quickly and effectively than their older counterpart (Lithfous et al., 2013; Taillade, et al., 2016). Future research should focus on this inconsistency between older adults' subjective and objective performance in spatial tasks.

Despite finding differences between the younger and older group in SOT scores, the older and middle-aged group did not differ in performance. Zancada-Menendez et al. (2016) found that middle-aged individuals performed more similarly to the older group than the younger group on the SOT. This finding has been replicated here, as no differences were found in angular errors between the middle-aged group and the older group, while the youngest group had significantly lower errors on the SOT compared to both other groups. It appears that the performance of the middle-aged group could be likened more to the older group as opposed to the younger group, which Zancada-Menendez et al. (2016) found previously. Although, this was not the case when middle-aged individuals were asked to subjectively report their sense of direction. No differences were found between SBSOD scores of young and middle-aged participants, and the older group scored significantly higher than both these groups. This suggests that the middle-aged participants were more similar to the younger group as opposed to the older group in rating their own sense of direction, despite still performing significantly worse than the younger group on the SOT. These results indicate that the middle-aged group performed most similarly to the younger group in sense

of direction ratings, but their performance in the objective measure of the SOT was no different from the older group. This discrepancy could be explained the same way it was explained for the older group, it is likely that the middle-aged group either overestimate their own spatial ability, or that they do not experience spatial issues in daily life and are more affected by the abstract nature and unfamiliarity of tasks than the younger group (Taillade et al., 2016). One noted limitation of the present study is the inclusion of only one direct measure of spatial ability, including additional direct measures could have helped us better understand the relationship between subjective and objective spatial testing across age groups.

While Jansen and Hail (2009) found that sex differences in a mental rotation task increases with age, this finding was not supported by Zancada-Menendez et al. (2016) who failed to detect an interaction between sex and age in the original version of the SOT/perspective-taking task. Here, we attempted to understand whether an interaction between sex and age was present in SOT scores. No interaction effect was found between sex and age in the present study, although there was a main effect for age but not for sex. This finding is comparable to that of Zancada-Menendez et al. (2016) who did not detect these differences in their study. Although, again, the disproportionate number of participants in each group should be noted here as a limitation in accurately interpreting these findings.

The effect of location in Ireland on test scores was also examined. It was found that counties with greater urban influence achieved higher scores relating to sense of direction and had fewer navigational complaints. The two counties with the highest SOT errors were both rural areas with moderate/no urban influence. CFQ scores did not seem to be affected by location in Ireland. This finding contradicts the work carried out by Coutrot et al. (2018) who found that living in an urban area had a negative impact on spatial ability. While our results are interesting, it should be

noted that these conclusions are based on observation only and further research is needed to fully determine the relationship between spatial ability and urban/rural living. The correlations between test scores showed that counties who reported having higher scores relating to sense of direction also reported fewer navigational complaints, but this finding failed to reach statistical significance. Additionally, a significant strong negative relationship was found between counties SBSOD scores and SOT error. Counties which reported having a better sense of direction also achieved fewer errors on the SOT, and vice versa. It appears some relationship does exist between urban and rural living and spatial ability, but it was beyond the scope of this study to fully investigate this, and further research is required in this area.

It was the aim of this chapter to understand the spatial abilities of Irish adults while also comparing their subjective sense of spatial skill to their objective performance in a direct spatial task. Moreover, we aimed to understand the effect sex, age and location in Ireland has on these spatial abilities. Although males estimated their own sense of direction more positively than females, this confidence in their own spatial ability did not seem to affect their performance in the direct measure of spatial skill, as no sex differences were found on the SOT. Males and females differed only in their SBSOD scores. Regarding age, older adults displayed an inconsistency between self-reporting and actual performance. Despite rating their own sense of direction as better than their younger counterparts, older adults had the poorest performance on the SOT. Middle-aged participants performed most similarly to the older group in the direct spatial task, but they did not rate their sense of direction any differently than the younger group. Location in Ireland seemed to influence how well individuals rated their subjective spatial ability, with urban areas having more positive self-reports than rural areas. The current chapter set out to gain an understanding of the spatial ability of healthy Irish participants as little is known about our level

of spatial skill. The importance of understanding spatial skills of individuals is rising due to evidence suggesting the role spatial ability and particularly spatial navigation and orientation can play in the early detection of AD. Some have even regarded spatial navigation/orientation as a more sensitive maker than episodic memory in diagnosing preclinical AD (Coughlan et al., 2018). And so, having normative values for healthy groups is important to allow direct comparisons to be made to at –risk patient groups.

Chapter 4

General Discussion

4.1 Summary of findings

Early diagnosis is crucial for effective treatment and early intervention plans to slow disease progression (Julayanont et al., 2014) but early detection of MCI or AD is often complicated by the fact the most prevalent cognitive maker for MCI and AD is also recognised in other conditions (Coughlan et al., 2018; Julayanont et al., 2012; Pause et al., 2013). For example, episodic memory is currently the most widely used cognitive marker for AD (Coughlan et al., 2018). However, deficits in episodic memory are not unique to AD and are often presented during healthy ageing as well as in other conditions, including other forms of dementia (Hornberger et al., 2010; Pause et al., 2013). Deficits in spatial navigation and orientation, on the other hand, have recently become of interest to researchers who have found such deficits to be a promising and unique cognitive marker for early MCI and AD detection (Coughlan et al., 2018).

The main goal of the current project was to determine whether tests of spatial cognition might be a valuable clinical tool for the detection of MCI and AD. To achieve this, we first looked at two pen-and-paper cognitive tasks which are currently used in a clinical setting for MCI and AD screening - the MMSE and the MoCA. Baseline and follow-up assessment scores were used from an ADNI sample of cognitively normal, MCI and AD participants. While the MMSE and MoCA are not direct tests of spatial cognition, each test does include subcategories relating to this cognitive domain (e.g., visual spatial, orientation). If these subscales could predict a conversion from MCI to AD, they could possibly be used in a clinical setting as simple indicators. Additionally, initial screening using these subscales could be followed up with more extensive tests specifically aimed at spatial ability. The possible usefulness of more extensive spatial tasks being used in a clinical setting was also explored in the current project. Before such

recommendations could be made, it was necessary to understand how a healthy sample might perform in these tasks and if they would be suitable for administering to a clinical population. In doing so, we could also attempt to gain a better understanding of the general spatial skill level of the Irish population, including age and sex differences in spatial ability.

The spatial subcategories included on the MMSE and MoCA are limited, but as shown by Choe et al. (2020), the MMSE subcategories of memory, orientation and visuospatial ability can be used to distinguish MCI patients who will develop AD from those who will not. From this, we replicated the findings of Choe et al. (2020) by using a different sample (ADNI 2 rather than ADNI 1) while also investigating the usefulness of the equivalent subcategories of the MoCA, since the MoCA contains a wider range of spatial tasks of increased difficulty and is more sensitive in earlier stages of AD (Nasreddine et al., 2005). Similar to Choe et al. (2020), we found the MMSE subscales of memory and orientation were predictive of MCI to AD conversion, but the visuospatial element of the MMSE was not predictive of this progression in our study. Meanwhile, the visuospatial subscales of the MoCA were predictive of MCI to AD conversion. Additional MoCA subscales which could predict MCI to AD conversion were memory, orientation, and language. Our results suggest that the subscales of the MoCA are a more suitable tool to predict MCI to AD conversion than the subscales of the MMSE. While only two subscales of the MMSE could predict conversion in our study, the MoCA had four subscales which predicted conversion. The MMSE items relating to visuospatial ability and language lack complexity compared to the MoCA (Nasreddine et al., 2005) and this is likely the reason deficits in these areas were not detected by the MMSE here. Overall, Chapter 2 identified the MoCA as a more useful tool for determining MCI outcomes compared to the MMSE which may be more useful in later stages of AD (Nasreddine et al., 2005). The utility of MoCA subscales was also suggested, namely those

which assess memory, orientation, visuospatial ability and language were useful for MCI to AD prediction. A particularly important finding was the usefulness of subscales relating to spatial ability (orientation and visuospatial ability) in predicting MCI outcomes, and more specifically MCI to AD progression. These findings support recent literature which has emphasized the important role of spatial cognitive deficits in MCI and AD detection (Coughlan et al., 2018).

Following this, Chapter 3 investigated spatial abilities in a healthy population. Before recommending direct tests of spatial cognition be used in a clinical setting for patient populations, the utility of these tests needed to be explored in a cognitively normal sample. It was the aim of this chapter to assess the usefulness of spatial tasks which are widely used across the literature, but not currently used in a clinical setting for MCI/AD screening. These spatial tests included the Spatial Orientation Task (SOT; Hegarty & Waller, 2004), the Santa Barbara Sense of Direction test (SBSOD; Hegarty et al., 2002), and the Subjective Spatial Navigation Complaints questionnaire (SSNC; Cerman et al., 2018). These tests were deemed suitable since they are widely used and have been regarded as good predicters of large-scale spatial ability (Hegarty et al., 2002; Kozhevnikov et al., 2006).

We found no sex differences between males and females in the spatial tasks, except for the SBSOD. As expected, males rated their own sense of direction more positively than their female counterparts. However, this confidence did not seem to affect performance in the direct spatial task, as no sex differences were found on the SOT. Although sex differences in spatial tasks are widely reported throughout the literature, these differences can be lessened depending on experience (Hoffmann et al., 2011), performance expectation (Tarampi et al., 2016) and strategy employed (Alvarez-Vargas et al., 2020; Gabriel et al., 2011). While no sex effect was evidenced on the SOT, an age effect was observed in this task as older adults had higher angular errors

compared to younger adults. The present findings are in line with previous research which has shown age-related differences across spatial tasks, whereby older adults have been shown to be at a disadvantage compared to younger adults (Borella et al., 2014; Jansen & Heil, 2009). More specifically, this age difference has also been found previously on the SOT (Zancada-Menendez et al., 2016). The spatial tasks used here may be effective for clinical use with MCI and AD patients given that they were useful in the current study with a healthy sample. The utility of these tasks is recognised in the observed age effect in the direct spatial task as well as the fact that this direct task (SOT) correlated in the subjective spatial task (SBSOD) which is widely regarded as a predictive tool of large-scale spatial navigation ability. The tasks used here are simple, quick and easy to administer which also makes them suitable as clinical screening tools. These findings indicate the possible utility of spatial tasks as clinical screening tools, particularly as follow-up assessments to the MMSE and the MoCA.

4.2 Limitations

The current project has a number of limitations. Firstly, the study in Chapter 2 focused only on the MMSE and the MoCA, as these are well-known and widely used clinical tools for MCI and AD diagnosis. During the ADNI2 study, several additional neuropsychological tests were also used to assess cognition. These included the Alzheimer's Disease Assessment Scale – Cognitive Subscale (ADAS-Cog), the Clinical Dementia Rating Scale (CDR) and the Everyday Cognition scale (ECog). It is possible that these tests would have been useful predictive tools as the MMSE and MoCA were. Like the MMSE and the MoCA, these cognitive assessments each contain subscales such as memory, orientation, visuospatial ability and language. Hence, looking at these subscales

in other cognitive assessments may have been beneficial in helping us to understand the deficits associated with MCI to AD progression.

A limitation of the MoCA test has been recognised in the positioning of the visuospatial subscale on the test page. As noted by Demeyere et al. (2016), this subscale of the MoCA can prove difficult for those experiencing left neglect due to its positioning on the top left-hand side of the test. Demeyere et al. (2016) reported that participants with left hemineglect achieved low scores on the MoCA and suggested that performance in the visuospatial subscale of the MoCA can be impaired due to this inability to attend to leftward stimuli. This limitation is of particular importance here, since attention deficits can be present in cases of AD, often as a result of posterior cortical atrophy which can stem from AD pathology (Malhotra, 2019; Mendez et al., 2021). In particular, left unilateral spatial neglect has often been reported in mild to moderate cases of AD (Ishiai et al., 2000; 1996) and has also been shown to worsen as AD patients progress into later stages of the disease (Venneri et al., 1998). Indeed, Cherrier et al. (1999) showed that AD patients were more prone to left-sided errors during a visuospatial construction task compared to healthy controls and VaD patients. The possible impact of unilateral spatial neglect on the assessment of visuospatial ability should be considered during the administration of the MoCA in particular, but also during the design of future visuospatial assessments. This would be especially important to consider should tests of visuospatial ability be used as predictive tools for MCI/AD.

Another limitation of this study can be seen in the low number of MCI-CN participants compared to MCI-MCI or MCI-AD which prevented us from investigating some possible protective factors which result in a reversion to normal cognition as opposed to remaining with MCI or progressing to AD. Understanding why this group reverted to cognitively normal may be

useful for developing potential preventative interventions to help preserve cognitive function and prevent further disease progression. A similar limitation may be observed in the low number of participants who converted from cognitively normal to an AD diagnosis during the study. Understanding factors which contribute to the progression from CN to AD within a short 4-year period would be of benefit to AD research. However, the small number of such cases in the present study meant a deeper investigation into this group was not possible.

While Chapter 3 aimed to understand the general spatial skill of the Irish population, as well as assess the utility of spatial tasks as potential clinical tools, only one direct measure of spatial ability was included in this study (the SOT). Two of the tests in this study were reliant on participant's self-report of their own spatial navigation and orientation ability (SBSOD and SSNC). While self-report measures have been shown to predict performance in real-world spatial tasks (Mitolo et al., 2015), more tests which directly assess spatial cognition could have been included here. There are a number of tasks which might have been useful additions to the study, including the Money Road Map test (Money et al., 1965) and Mental Rotations Test (Vandenberg & Kuse, 1978). This may have provided a more comprehensive understanding of the spatial skills of the sample as well as further supporting the possible use of spatial tasks in a clinical setting. Although, most pen-and-paper based tasks assess small-scale spatial ability as opposed to large-scale ability (Mitolo et al., 2015). And small-scale abilities have been shown to have little to no correlation with large-scale spatial ability which is best assessed in virtual or real-world large-scale environments (Coughlan et al., 2018; Hegarty & Waller, 2004; Mitolo et al., 2015) which are not always feasible (Gazova et al., 2012).

Additionally, the online version of the SOT used here was not compared to the original pen and paper version of the SOT developed by Hegarty and Waller (2004). The computerised version

of the SOT developed by Friedman et al. (2020) showed correlations to the original SOT task, and it's use over the original pen-and-paper task has been warranted. However, the computerised version used here did not follow the same method employed by Friedman et al. (2020). Specifically, our version showed angle values in the question items and asked participants to indicate to the nearest degree the direction of the target object. This may have affected how participants responded in this task, it is possible that participants could have felt restricted by the angle choices or confused by what they signified. Friedman et al. (2020) version may be less demanding since it does not require participants to determine the direction of the object by using specific angles but instead participants indicate the location of the object by clicking the area within the answer circle. Although, computerised versions of tests are usually found to be similar to their pen-and-paper versions (Friedman et al., 2020), the present study could have compared the computerised version used here to the original version of the test to ensure the same skills are being measured.

Improvements to sample size could have also been made in Chapter 3. As previously noted, males were underrepresented in the sample compared to females. This influenced how some of our results were interpreted. For example, no sex differences were found between males and females in the direct spatial task, and it is difficult to decipher whether this might be as a result of inequal group size, or a true reflection of the impact (or lack thereof) sex has on spatial ability. Additionally, the number of older adults in this sample was quite low compared to the number of younger participants. Having a larger and more representative sample size would have been advantageous for understanding the utility of these spatial tasks in a healthy older sample. Since cases of MCI and AD primarily affect adults who are 65 years of age and older, having more

healthy older adults of this age in our sample would have been beneficial for future comparisons to be made between healthy controls and patient populations.

4.3 Future Directions

The subscales of the MoCA have been shown to have good predictive utility here, namely the progression from MCI to AD has been predicted by memory, orientation, visuospatial ability and language subscales. These items were not only predictive of MCI to AD progression but could also distinguish other MCI outcomes. Indeed, present findings suggest that MoCA items relating to memory, orientation, visuospatial and language can determine whether an MCI patient might revert to a cognitively normal state or convert to AD. Research interest into MCI has grown significantly in the last number of years due to the fact MCI is widely regarded as a predementia state and holds a lot of value for AD research (Giau et al., 2019). Future research could focus on MCI patients, attempting to understand further how this state of cognitive impairment might progress, whether that be remaining stable, a reversion to cognitively normal or a conversion to AD. Early diagnosis is an important goal of AD research to ensure treatment and intervention in the earliest stages of the disease (Giau et al., 2019). If this predementia stage of MCI could be fully understood in terms of outcomes which follow, then those at-risk of converting to AD face better opportunity for early intervention with the aim of slowing disease progression and preserving cognitive function.

Using data from the ADNI, we have been able to understand the predictive value of MMSE and MoCA subscale scores for MCI outcomes. The ADNI has an extensive dataset and includes many measures which have not been considered in the present study. The ADNI aims to understand

AD progression through the use of cognitive markers, biomarkers and other clinical measures. The utility of biomarkers as early indicators of dementia is widely accepted (Blennow & Zetterberg, 2018; Humpel, 2011). Biomarkers (such as Aβ plaques or tau tangles) can often be observed years before AD diagnosis and even in preclinical stages of the disease (Sadigh-Eteghad, 2015). Since the present study did not focus on the utility of biomarkers in MCI to AD progression, future research could examine whether biomarkers or cognitive markers are better predictors of AD conversion. Although some have already found cognitive markers (such as those used here) to be more predictive of MCI to AD conversion than biomarkers (Gomar et al., 2011), the combined utility of biomarkers and cognitive markers could also be considered given the widely accepted usefulness of biomarkers in AD detection. This could be investigated using the wide range of data collected for the ADNI.

The utility of spatial subscales in predicting MCI to AD conversion led us to examine spatial cognition in a normal population, with the possibility of suggesting their use as clinical assessments for MCI and AD. The findings presented here have determined these tests as suitable assessments of spatial cognition in a normal population, but correlations between these pen-and-paper type tests and large-scale spatial tasks were not measured in the current study. While we know that the pen-and-paper tasks used here have been shown to predict performance in large-scale spatial tasks, we are not yet aware of their usefulness as screening tools for MCI and AD. Future research could directly compare performance in these pen-and-paper type spatial tasks and large-scale spatial tasks in MCI and AD population samples before they are introduced as clinical screening measures. Suitable tests of large-scale spatial ability might include virtual versions of the Morris Water Maze task, such as NavWell (Commins et al., 2020; Thornberry et al., 2021) and Sea Hero Quest (Coughlan et al., 2019). Virtual Morris Water Maze tasks have shown to be

effective assessments for spatial navigation ability (Commins et al., 2020). Sea Hero Quest is also an effective tool for spatial navigation assessment which holds good ecological validity and can predict performance in real-world spatial navigation tasks (Coughlan et al., 2019). Tests which use virtual environments such as these valuable tools for spatial navigation assessment which allow testing to take place in fully controlled environments which can also be manipulated by the tester (Cogné et al., 2017; Thornberry et al., 2021). Such large-scale tasks have already been demonstrated as useful tools for assessing spatial navigation ability in healthy controls, MCI and AD patients (Cogné et al., 2017; Coughlan et al., 2018). Coughlan et al. (2018) also suggests that understanding key factors relating to tasks such as virtual water maze tasks might aid the development of new pen-and-paper tasks of spatial ability for use in clinical settings. If the tasks presented here were found to be tapping into the same set of spatial skills, this would further justify their use as clinical screening tools for MCI and AD.

It would also be of benefit for future research to understand whether the pen-and-paper type spatial tasks used here can differentiate between various clinical populations, since a major challenge in early AD diagnosis is often the inability to differentiate between AD and other conditions, including various forms of dementia (Humpel, 2011). We are aware large-scale spatial tasks are unique in their ability distinguish AD from other conditions (Coughlan et al., 2018). Specifically, large-scale spatial tasks based in virtual reality environments have shown differences in spatial ability between AD and FTD patients (Tu et al., 2017). Replicating these findings in pen-and-paper spatial tasks such as those used here would be of great benefit for clinicians in terms of diagnostic accuracy as well as quick and easy administration.

4.4 Broader Implications

The current project has demonstrated the effectiveness of MoCA subscales in particular as good predictors of MCI outcomes, most notably the progression from MCI to AD can be predicted with use of memory, orientation, visuospatial and language subscales. These findings may have implications for the clinical use of cognitive tests such as the MoCA. Increasingly busy clinics and competing demands for care have meant that clinicians are seeking time-effective solutions for MCI and AD screening (Farias et al., 2011). Although these tests are brief, some have suggested the MMSE and MoCA be narrowed down even further to allow for quicker screening of cases (Borson et al., 2005; Laske et al., 2014; Mitchell, 2009). Using test subscales in isolation as opposed to administering full cognitive assessments would eliminate the issue of cognitive screening tools being too time-consuming to administer in clinical settings. Subscales relating to memory, orientation, visuospatial and language ability have notable potential as effective clinical screening tools which are both time-efficient and easy to administer to patient populations. However, since we are aware of spatial ability as a unique cognitive marker for MCI and AD (Coughlan et al., 2018), the focus for quick screening should be on subscales relating to these skills, particularly visuospatial and orientation subscales. Additionally, if low scores are evident during initial screening, this could be followed by direct measures of spatial ability. Extensive tests of spatial ability are not currently used in a clinical setting but have been suggested as a useful addition to the current battery of tests (Gazova et al., 2012). The current project has shown how these tasks might be useful as follow-up assessments for those displaying deficits in spatial subscales.

4.5 Concluding Remarks

The current thesis aimed to understand whether direct tests of spatial cognition would be useful as clinical screening tools for the detection of MCI and AD. While further research will be needed before informing clinical practice, the findings of current project are promising. Spatial items on the MoCA have been found to predict various MCI outcomes, including whether an MCI patient might convert to AD or revert to a cognitively normal state. If a patient scores poorly in spatial items of the MoCA during clinical screening, a follow-up assessment using a specialised test of spatial cognition may be warranted. Tests including the Spatial Orientation Test, the Santa Barbara Sense of Direction test or other self-report measures of spatial ability, such as the Subjective Spatial Navigation Complaints questionnaire may be suitable for clinical use, given that they are quick and easy to administer and have been shown previously to correlate with tests of large-scale spatial ability. The current thesis presents evidence for spatial cognition as an effective cognitive marker for MCI and AD and discusses the possibility of integrating specialised tests of spatial cognition into clinical screening procedures to aid early detection of MCI and AD.

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Appendix I – ADNI inclusion criteria for new entrants from ADNI2 Procedures Manual

4. Inclusion Criteria: NEW Participants – CN, EMCI, LMCI, AD

	CN	EMCI	LMCI	AD
1	Subject must be ***free of memory complaints***, verified by a study partner, beyond what one would expect for age	Subject ***must have a subjective memory concern*** as reported by subject, study partner, or clinician	Same as EMCI	Same as EMCI
2	Normal memory function documented by scoring above education adjusted cutoffs on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale –Revised (the maximum score is 25): **a. ≥9 for 16 or more years of education** **b. ≥5 for 8-15 years of education** **c. ≥3 for 0-7 years of education**	Abnormal memory function documented by scoring within the education adjusted ranges on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale –Revised (the maximum score is 25): **a. 9-11 for 16 or more years of education** **b. 5-9 for 8-15 years of education** **c. 3-6 for 0-7 years of education**	Abnormal memory function documented by scoring within the education adjusted ranges on the Logical Memory II subscale (Delayed Paragraph Recall, Paragraph A only) from the Wechsler Memory Scale –Revised (the maximum score is 25): **a. ≤8 for 16 or more years of education** **b. ≤4 for 8-15 years of education** **c. ≤2 for 0-7 years of education**	Same as LMCI
3	Mini-Mental State Exam score between **24 and 30** (inclusive). (Exceptions may be made for subjects with less than 8 years of education at the discretion of the project director)	Same as CN	Same as CN	Mini-Mental State Exam score between **20 and 26** (inclusive) (Exceptions may be made for subjects with less than 8 years of education at the discretion of the project director)
4	Clinical Dementia Rating = **0**. Memory Box score must be **0**	Clinical Dementia Rating = **0.5**. Memory Box score must be at least **0.5**	Same as EMCI	Clinical Dementia Rating = **0.5 or 1.0**
5	**Cognitively normal**, based on an absence of significant impairment in cognitive functions or activities of daily living	**General cognition and functional performance sufficiently preserved such that a diagnosis of Alzheimer's disease cannot be made** by the site physician at the time of the screening visit	Same as EMCI	NINCDS/ADRDA criteria for **probable AD**

4. Inclusion Criteria: NEW Participants – CN, EMCI, LMCI, AD (Cont'd)

	CN	EMCI	LMCI	AD
6	Stability of Permitted Medications for 4 weeks. In particular, subjects may: a. Take stable doses of antidepressants lacking significant anticholinergic side effects (if they are not currently depressed and do not have a history of major depression within the past 1 year). b. Estrogen replacement therapy is permissible c. Gingko biloba is permissible, but discouraged d. Washout from psychoactive medication (e.g., excluded antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.) for at least 4 weeks prior to screening	Stability of Permitted Medications for 4 weeks. In particular, subjects may: a. Take stable doses of antidepressants lacking significant anticholinergic side effects (if they are not currently depressed and do not have a history of major depression within the past 1 year). b. Estrogen replacement therapy is permissible c. Gingko biloba is permissible, but discouraged d. Washout from psychoactive medication (e.g., excluded antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.) for at least 4 weeks prior to screening **e. Cholinesterase inhibitors and memantine are allowable if stable for 12 weeks prior to screen**	Same as EMCI	Same as EMCI

Additional Inclusion Criteria: All Diagnostic Categories

7. Geriatric Depression Scale less than 6.
8. Age between 55-90 (inclusive).
9. Study partner is available who has frequent contact with the subject (e.g. an average of 10 hours per week or more), and can accompany the subject to all clinic visits for the duration of the protocol.
10. Visual and auditory acuity adequate for neuropsychological testing.
11. Good general health with no diseases expected to interfere with the study.
12. Participant is not pregnant, lactating, or of childbearing potential (i.e. women must be two years post-menopausal or surgically sterile).
13. Willing and able to participate in a longitudinal imaging study.
14. Hachinski less than or equal to 4.
15. Completed six grades of education or has a good work history (sufficient to exclude mental retardation).
16. Must speak English or Spanish fluently.
17. Willing to undergo repeated MRIs (3Tesla) and at least two PET scans (one FDG and one Amyloid imaging) and no medical contraindications to MRI.
18. Agrees to collection of blood for GWAS, APOE testing and DNA and RNA banking.
19. Agrees to collection of blood for biomarker testing.
20. Agrees to at least one lumbar puncture for the collection of CSF.

Appendix II – ADNI Exclusion Criteria for new entrants from ADNI2 Procedures Manual

5. Exclusion Criteria: NEW Participants – CN, EMCI, LMCI, AD

	CN	EMCI	LMCI	AD
1	**Any significant neurologic disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities	**Any significant neurologic disease other than suspected incipient Alzheimer's disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.	Same as EMCI	**Any significant neurologic disease other than Alzheimer's disease**, such as Parkinson's disease, multi-infarct dementia, Huntington's disease, normal pressure hydrocephalus, brain tumor, progressive supranuclear palsy, seizure disorder, subdural hematoma, multiple sclerosis, or history of significant head trauma followed by persistent neurologic defaults or known structural brain abnormalities.

Additional Exclusion Criteria: All Diagnostic Categories

2. Screening/baseline MRI scan with evidence of infection, infarction, or other focal lesions. Participants with multiple lacunes or lacunes in a critical memory structure are excluded.
3. Presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body.
4. Major depression, bipolar disorder as described in DSM-IV within the past 1 year. Psychotic features, agitation or behavioral problems within the last 3 months which could lead to difficulty complying with the protocol.
5. History of schizophrenia (DSM IV criteria).
6. History of alcohol or substance abuse or dependence within the past 2 years (DSM IV criteria).
7. Any significant systemic illness or unstable medical condition which could lead to difficulty complying with the protocol.
8. Clinically significant abnormalities in B12, or TFTs that might interfere with the study. A low B12 is exclusionary, unless follow-up labs (homocysteine (HC) and methylmalonic acid (MMA)) indicate that it is not physiologically significant.
9. Residence in skilled nursing facility.
10. Current use of specific psychoactive medications (e.g.,certain antidepressants, neuroleptics, chronic anxiolytics or sedative hypnotics, etc.). Current use of warfarin (exclusionary for lumbar puncture).

Additional Exclusion Criteria: All Diagnostic Categories (Cont'd)

11. Investigational agents are prohibited one month prior to entry and for the duration of the trial.
12. Participation in clinical studies involving neuropsychological measures being collected more than one time per year.
13. Exclusion for amyloid imaging with ^{18}F –AV-45: Current or recent participation in any procedures involving radioactive agents such that the total radiation dose exposure to the participant in any given year would exceed the limits of annual and total dose commitment set forth in the US Code of Federal Regulations (CFR) Title 21 Section 361.1.
14. Exceptions to these guidelines may be considered on a case-by-case basis at the discretion of the protocol director (Dr. Petersen).

GENERAL RULE: Any history of cancer five years prior to screening is exclusionary (history of skin melanoma is not exclusionary)

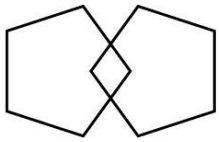
Appendix III – Mini Mental State Examination (MMSE)

MINI MENTAL STATE EXAMINATION (MMSE)

Name:

DOB:

Hospital Number:

One point for each answer	**DATE:**		
ORIENTATION Year Season Month Date Time	...../ 5	...../ 5	...../ 5
Country Town District Hospital Ward/Floor	...../ 5	...../ 5	...../ 5
REGISTRATION Examiner names three objects (e.g. apple, table, penny) and asks the patient to repeat (1 point for each correct. THEN the patient learns the 3 names repeating until correct).	...../ 3	...../ 3	...../ 3
ATTENTION AND CALCULATION Subtract 7 from 100, then repeat from result. Continue five times: 100, 93, 86, 79, 72, 65 (Alternative: spell "WORLD" backwards: DLROW).	...../ 5	...../ 5	...../ 5
RECALL Ask for the names of the three objects learned earlier.	...../ 3	...../ 3	...../ 3
LANGUAGE Name two objects (e.g. pen, watch).	...../ 2	...../ 2	...../ 2
Repeat "No ifs, ands, or buts".	...../ 1	...../ 1	...../ 1
Give a three-stage command. Score 1 for each stage. (e.g. "Place index finger of right hand on your nose and then on your left ear").	...../ 3	...../ 3	...../ 3
Ask the patient to read and obey a written command on a piece of paper. The written instruction is: "Close your eyes".	...../ 1	...../ 1	...../ 1
Ask the patient to write a sentence. Score 1 if it is sensible and has a subject and a verb.	...../ 1	...../ 1	...../ 1
COPYING: Ask the patient to copy a pair of intersecting pentagons 	...../ 1	...../ 1	...../ 1
TOTAL:	...../ 30	...../ 30	...../ 30

MMSE scoring
24-30: no cognitive impairment
18-23: mild cognitive impairment
0-17: severe cognitive impairment

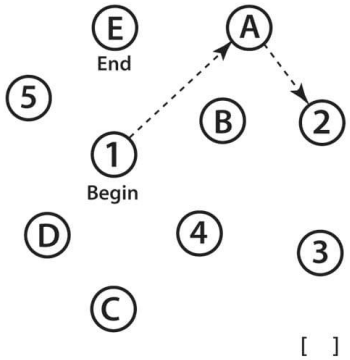
OME Oxford Medical Education

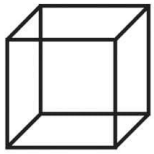
Appendix IV – Montreal Cognitive Assessment (MoCA)

MONTREAL COGNITIVE ASSESSMENT (MOCA)
Version 7.1 Original Version

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

VISUOSPATIAL / EXECUTIVE





Copy cube

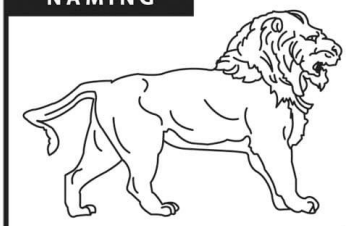
[ ] [ ]

Draw CLOCK (Ten past eleven) (3 points)

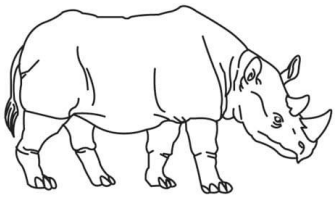
[ ] Contour [ ] Numbers [ ] Hands

POINTS ___/5

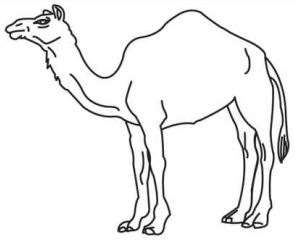
NAMING



[ ]



[ ]



[ ]

___/3

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

	FACE	VELVET	CHURCH	DAISY	RED
1st trial					
2nd trial					

No points

ATTENTION Read list of digits (1 digit/ sec.).
Subject has to repeat them in the forward order [ ] 2 1 8 5 4
Subject has to repeat them in the backward order [ ] 7 4 2 ___/2

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

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

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

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

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

DELAYED RECALL

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

___/5

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

www.mocatest.org
Normal ≥ 26 / 30

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

Administered by: _____

Appendix V – Study Information and Informed Consent

An Examination of Spatial Cognition in the Irish Population

Postgraduate Researchers: Conor Thornberry, Abby Clarke

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Supervisor:
Dr. Sean Commins
Department of Psychology Maynooth University, Co. Kildare, Ireland
Sean.Commins@mu.ie
Ph: 017086182

Your participation is requested in an experimental study taking place with the Department of Psychology at Maynooth University examining certain elements of spatial navigation, memory, learning and cognition in the Irish population, and some of the impacts that you may think, the COVID-19 pandemic has had on some or all of these mechanisms.

What is the study about?

The purpose of this survey is to examine spatial cognition in the general Irish population. These include attention, orientation, awareness, failures and learning, which will all be investigated here. Spatial skills, particularly navigation and memory rely on increased daily movement and routine. Due to the COVID-19 pandemic, many individuals' movements have been heavily restricted, some more than others. As the restrictions on movement ease and the strain of the pandemic lessens on Irish society, we would like to not only gain an insight on the spatial skills of the Irish population, but also, your subjective view of the impact of restricted movement on their spatial skills.

What does it involve? What would I have to do?

There would be one part to your involvement, all of which should take place in a quiet location free from distraction. You may complete this in your own time and when you feel comfortable.

1. You will have been sent a link, familiarize yourself with this information sheet before you consent to participate.

2. You will then be asked to complete short online tasks and questionnaires. Some of these tasks may involve "interactive" elements which involve you having to complete a task that is fully on your screen, returning to the survey afterwards. This will be explained to you when these tasks appear in the survey.

3. You will then finish with some questions related to the lock-down during the pandemic in Ireland, which you are free to not answer should you feel uncomfortable, or for any other reason.

Are there any risks to me?

There are no risks associated with this study. The questionnaires will involve answering questions or completing short, simple tasks in your computer browser.
In the unlikely event that you experience any distress, discomfort or if you have any concerns about any aspect of your performance on these tasks, you should feel free to contact Dr. Sean Commins or contact your own GP with these concerns. Should you be a student of the University you may also avail of the Student Counseling Service (01 708 3554) or Student Health Service (01 708 3878); both are on campus and located very close to the Psychology Department.
We hope to provide a baseline of healthy spatial cognition in the Irish population and explore this based on different demographics. This could be used for comparison and/or help inform us better about some of the brain activity associated with spatial tasks. The COVID-19 questions will shed light on the impact that restricted movement, staying at home and limited social contact may have on spatial skills during everyday tasks.

What happens to my test scores and answers?

The data from your participation (i.e. test scores) will be strictly confidential and will be recorded on a secure password protected server. Only the researcher will have access to this information. Your results will be kept confidential by assigning a random number to each participant instead of your name. Aside from your age, county and gender, no other personal data will be recorded. Except for the researcher(s) involved in running this study, nobody will be allowed to see or discuss any of your data. Your data will be combined with many others and reported in group form – averages etc. – in a scientific paper only.

Can I withdraw from the study?

Yes, you may withdraw your data and involvement in the study at any time up until the completion of your participation.

If you are willing to help us by participating in this study, we will ask you to click and confirm consent, following your reading of the Letter of Consent, which is at the end this information page. We are very grateful for your participation.

You are welcome to discuss this decision with us, but you are under no obligation to do so. Please feel free to study these criteria during a cooling off period of up to one week. Should you choose not to participate, no further action is required. If you have any doubts as to whether or not you are eligible to take place in this study, please inform us so we may determine your eligibility.

I have some health issues – am I still eligible to take part?

Finally, if you suffer from any of the following, you may not be eligible to take part:

- severe visual impairments;
- history of psychological/neurological impairment;
- history of epilepsy or memory issues;
- history of drug or alcohol abuse;
- currently taking psychoactive medication;

Do you suffer from/have suffered from any of the above?

- ○ Yes
- ○ No

INFORMED CONSENT

In agreeing to participate in this research I understand the following:

This research is being conducted by Abby Clarke & Conor Thornberry, postgraduate students at the Department of Psychology, Maynooth University. The method proposed for this research project adheres in principle to the Psychological Society of Ireland (PSI) code of professional ethics. It is, however, the above-named student's responsibility to adhere to ethical guidelines in their dealings with participants and the collection and handling of data. If I have any concerns about participation, I understand that I may refuse to participate or withdraw at any stage.

I have been informed as to the general nature of the study and agree voluntarily to participate.

The total time for your participation will be approximately 20 to 40 minutes in total. There are no known expected discomforts or risks associated with participation.

The results of my participation will be documented by participant number only. No names or individual identifying information will be recorded. With the exception of the researcher(s) involved in running this study, nobody will be allowed to see or discuss any of the individual responses. My responses will be combined with many others and reported in group form in a scientific paper and/or a report submitted to the Department of Psychology. My own data will be available to me at my discretion. I may withdraw my data and involvement in the study at any time, up until the completion of your participation.

At the conclusion of my participation, any questions or concerns I have will be fully addressed.
I may withdraw from this study at any time and may withdraw my data at the conclusion of my participation if I still have concerns.

- ○ I Consent
- ○ I Do Not Consent

Appendix VI– Santa Barbara Sense of Direction Scale, Hegarty et al. (2002)

SANTA BARBARA SENSE-OF-DIRECTION SCALE Participant: _____

The following statements ask you about your spatial and navigational abilities, preferences, and experiences. After each statement, you should circle a number to indicate your level of agreement with the statement. Circle "1" if you strongly agree that the statement applies to you, "7" if you strongly disagree, or some number in between if your agreement is intermediate. Circle "4" if you neither agree nor disagree.

1. I am very good at giving directions.
strongly agree 1 2 3 4 5 6 7 strongly disagree

2. I have a poor memory for where I left things.
strongly agree 1 2 3 4 5 6 7 strongly disagree

3. I am very good at judging distances.
strongly agree 1 2 3 4 5 6 7 strongly disagree

4. My "sense of direction" is very good.
strongly agree 1 2 3 4 5 6 7 strongly disagree

5. I tend to think of my environment in terms of cardinal directions (N, S, E, W).
strongly agree 1 2 3 4 5 6 7 strongly disagree

6. I very easily get lost in a new city.
strongly agree 1 2 3 4 5 6 7 strongly disagree

7. I enjoy reading maps.
strongly agree 1 2 3 4 5 6 7 strongly disagree

8. I have trouble understanding directions.
strongly agree 1 2 3 4 5 6 7 strongly disagree

9. I am very good at reading maps.
strongly agree 1 2 3 4 5 6 7 strongly disagree

10. I don't remember routes very well while riding as a passenger in a car.
strongly agree 1 2 3 4 5 6 7 strongly disagree

11. I don't enjoy giving directions.
strongly agree 1 2 3 4 5 6 7 strongly disagree

12. It's not important to me to know where I am.
strongly agree 1 2 3 4 5 6 7 strongly disagree

13. I usually let someone else do the navigational planning for long trips.
strongly agree 1 2 3 4 5 6 7 strongly disagree

14. I can usually remember a new route after I have traveled it only once.
strongly agree 1 2 3 4 5 6 7 strongly disagree

15. I don't have a very good "mental map" of my environment.
strongly agree 1 2 3 4 5 6 7 strongly disagree

Appendix VII– Subjective Spatial Navigation Complaints Questionnaire, Cerman et al. (2018)

I have had difficulties in the last 3 months with:					
Orientation in my home					
	never	less than once a week	approximately once a week	several times a week	every day
Orientation in my neighborhood					
	never	less than once a week	approximately once a week	several times a week	every day
Orientation in my town					
	never	less than once a week	approximately once a week	several times a week	every day
Orientation outside of my town					
	never	less than once a week	approximately once a week	several times a week	every day
I have been lost in the last 3 months:					
in my flat					
	never	less than once a week	approximately once a week	several times a week	every day
in my neighborhood					
	never	less than once a week	approximately once a week	several times a week	every day
in my town					
	never	less than once a week	approximately once a week	several times a week	every day
in the other town, than where I live					
	never	less than once a week	approximately once a week	several times a week	every day
With respect to places that I visit every day or almost every days, in the last 3 months, my ability to orient myself has been _____ compared to when I was young:					
	same or better	little worse	much worse	significantly worse	
With respect to places that I visit several times a year, in the last 3 months, my ability to orient myself has been _____ compared to when I was young:					
	same or better	little worse	much worse	significantly worse	
In the last 3 months, I have had to ask for directions more often than in the past:					
	never	less than once a week	approximately once a week	several times a week	every day
In the last 3 months, I have had difficulties getting oriented in my supermarket:					
	never	less than once a week	approximately once a week	several times a week	every day
Because of worries that I may get lost, I have had to:					
	reduce traveling out of my town.			yes	no
	reduce traveling to my relatives and friends.			yes	no
	reduce activities around my home (shopping, go to post, *etc.*).			yes	no

Appendix VIII– Spatial Orientation Test (based on Hegarty & Waller, 2004) instructions and example item

Perspective Taking/Spatial Orientation Test

This is a test of your ability to imagine different perspectives or orientations in space. In each of the following questions you will see a picture of an array of objects and an "arrow circle" with a question below about the direction between some of the objects. For each question, you should imagine that you are standing at one object in the array (which will be named in the center of the circle) and facing another object, named at the top of the circle. Your task is to select an arrow from the center object showing the direction to a third object from this facing orientation.

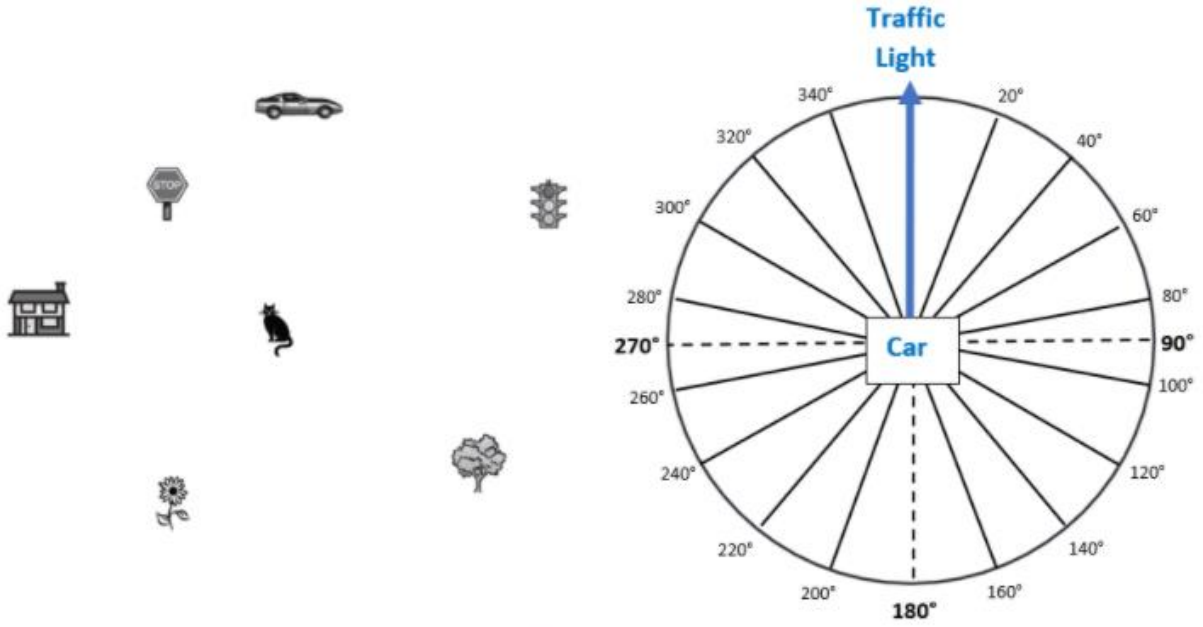
This is the final task to be completed as part of this survey. We appreciate that some might find this test difficult. However, it would be greatly appreciated if you could take time to fully complete this final test to the best of your ability.

Please do not rotate your device or tilt your head while completing this task.

For example:

Look at the sample item below. In this item you are asked to imagine that you are standing at the flower, which is named in the center of the circle, and facing the tree, which is named at the top of the circle. Your task is to choose where the cat is in relation to your position. Each test item will ask you to imagine you are standing at one of the objects in the array, while you are facing some other object. You are then asked to indicate (to the nearest degree) the direction of another object in relation to your position.

In the sample item you are standing at the flower and facing the tree and asked for the direction of the cat. This has been picked for you, the cat is located at the 300° mark. In the following test items your task is to indicate, to the nearest degree, where this arrow should be placed. Can you see below that if you were at the flower facing the tree, the cat would be in this direction?



Imagine you are standing at the **car** and facing the **traffic light**. Please indicate to the nearest degree where the **stop sign** is.

Appendix IX – Cognitive Failure Questionnaire Broadbent et al. (1982)

	Very often	Quite often	Occasionally	Very rarely	Never
1. Do you read something and find you haven't been thinking about it and must read it again?	4	3	2	1	0
2. Do you find you forget why you went from one part of the house to the other?	4	3	2	1	0
3. Do you fail to notice signposts on the road?	4	3	2	1	0
4. Do you find you confuse right and left when giving directions?	4	3	2	1	0
5. Do you bump into people?	4	3	2	1	0
6. Do you find you forget whether you've turned off a light or a fire or locked the door?	4	3	2	1	0
7. Do you fail to listen to people's names when you are meeting them?	4	3	2	1	0
8. Do you say something and realize afterwards that it might be taken as insulting?	4	3	2	1	0
9. Do you fail to hear people speaking to you when you are doing something else?	4	3	2	1	0
10. Do you lose your temper and regret it?	4	3	2	1	0
11. Do you leave important letters unanswered for days?	4	3	2	1	0
12. Do you find you forget which way to turn on a road you know well but rarely use?	4	3	2	1	0
13. Do you fail to see what you want in a supermarket (although it's there)?	4	3	2	1	0
14. Do you find yourself suddenly wondering whether you've used a word correctly?	4	3	2	1	0
15. Do you have trouble making up your mind?	4	3	2	1	0
16. Do you find you forget appointments?	4	3	2	1	0
17. Do you forget where you put something like a newspaper or a book?	4	3	2	1	0
18. Do you find you accidentally throw away the thing you want and keep what you meant to throw away – as in the example of throwing away the matchbox and putting the used match in your pocket?	4	3	2	1	0
19. Do you daydream when you ought to be listening to something?	4	3	2	1	0
20. Do you find you forget people's names?	4	3	2	1	0
21. Do you start doing one thing at home and get distracted into doing something else (unintentionally)?	4	3	2	1	0
22. Do you find you can't quite remember something although it's 'on the tip of your tongue'?	4	3	2	1	0
23. Do you find you forget what you came to the shops to buy?	4	3	2	1	0
24. Do you drop things?	4	3	2	1	0
25. Do you find you can't think of anything to say?	4	3	2	1	0