The role of subjective memory complaints in predicting cognitive impairment associated with future Alzheimer's disease: a community based study

by

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Abstract

Background

In recent years there has been a substantial increase in research examining the role of subjective memory complaints (SMC) in cognitive function and Alzheimer's disease. These studies have related SMC to many different cognitive outcomes, such as retaining normal cognitive function, a fluctuating cognitive performance and the development of Alzheimer's disease. Most of these studies have focused on older populations and have employed a limited assessment of cognitive function. This limits the available evidence regarding the clinical utility of SMC. The literature on the role of SMC in younger subjects is scarce. It is not known whether memory complaints are useful in predicting future cases of Alzheimer's disease in younger community-based subjects.

Aims

The main aim of the present study was to determine whether SMC predict the development of cognitive impairment in a younger cohort of subjects, many of whom were under the age of 70 years (73%), based on their risk profile and neuropsychological assessment. A further aim was to ascertain whether the DRS or 7MS are sensitive screening tools for MCI and examine whether the presence of SMC affects the 3-year cognitive outcome of subjects.

To address these aims, this study consisted of two parts: a cross-sectional design and a longitudinal follow-up component.

Methods

This study was carried out with 86 community-dwelling subjects recruited via advertisement within the catchment area of Central Sydney Area Health Service. The mean age of the subjects was 63.1 years (SD=8.4). Subjective memory complaints were assessed using a single question. Cognitive function was assessed using a comprehensive battery of tests, selected on the basis of their sensitivity to identifying cognitive impairment typically associated with Alzheimer's disease. After the initial analysis between those with SMC and without SMC, subjects were further classified according to their performance on an episodic memory task (i.e., delayed verbal recall, Rey, 1964) as having normal memory function, SMC or aMCI.

Results

Part 1

Subjective memory complaints (SMC) were reported by 63% of the sample. The initial analysis between subjects with SMC (n=54) and without SMC (n=32) suggested an initial relationship between SMC and cognitive functioning. Subjects with SMC had impaired global cognitive functioning on two brief screening tests (7MS and DRS), working memory, verbal recall and visuomotor speed.

However, subsequent screening with the delayed verbal recall test showed that 12 of the 54 subjects with SMC demonstrated significant cognitive impairment, scoring 2 SD below the control group mean. After

these subjects were removed to form the aMCI group, the cognitive differences between subjects with SMC and without SMC were no longer apparent. Subjects with aMCI showed evidence of multiple cognitive deficits (below 1 SD of control group mean) with a high percentage of subjects demonstrating impairment on tests of verbal learning, verbal recall, verbal ability and visuomotor speed.

Further analysis showed a significant association between age and subjects identified as having SMC ($r=-.581$, $p<.001$) and aMCI ($r=.692$, $p<.001$). From the age of 60 onwards, both the SMC and aMCI groups demonstrated a more rapid cognitive decline with increasing age in several cognitive domains.

Part 2

After a mean interval of 3.2 years, 43 subjects were followed up. Subjects with aMCI showed evidence of greater decline on both screening tests (7MS; DRS), whilst the SMC group had significantly higher scores. This trend was also apparent with other neuropsychological testing. The analysis of change over time in cognitive function showed that the majority of subjects (both SMC aMCI) either remained stable or improved their cognitive performance. It is likely that the small sample size and short follow-up interval of the present study contributed to the present observation of no change in cognitive function over time.

Discussion

The present findings suggest that subjective memory complaints are a poor predictor of cognitive function. In isolation, SMC are unlikely to be useful for identifying cases with significant cognitive impairment. This is particularly relevant for subjects under the age of 70 years. However, for subjects over the age of 70 years, SMC are likely to identify significant cases with neuropsychological assessment (such as animal fluency and delayed recall).

Conclusion

The present study showed that SMC are a poor predictor of cognitive function in subjects under the age of 70 years. This study provided evidence that selected and relatively quick to administer formal neuropsychological tests of cognitive function (in particular tests of animal fluency and delayed recall) are better able to identify those at risk of developing cognitive impairment associated with Alzheimer's disease, at an earlier age. This would thus allow exposure to earlier treatment options, such as donepezil, aricept, vitamin E, and memantine".

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List of Abbreviations

AD	Alzheimer's disease
ApoE	Apolipoprotein E
BNT	Boston Naming Test
CD	Clock Drawing
DAT	Dementia of the Alzheimer's Type
DRS	Dementia Rating Scale
DSM-IV-TR	Diagnostic and Statistical Manual of Mental Disorders, 4th ed. text revision (APA, 2000)
GDS	Geriatric Depression Scale
ICD-10	International Classification of Mental and Behavioural Disorders (WHO, 1992)
aMCI	amnestic Mild Cognitive Impairment
MCI	Mild Cognitive Impairment
MMSE	Mini-Mental State Examination
NART	National Adult Reading Test
NINCDS-ADRDA	The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
PAS	Psychogeriatric Assessment Scale
RAVLT	Rey Auditory Verbal Learning Test
ROFCT	Rey-Osterrieth Figure Complex Test
SD	Standard Deviation
7MS	Seven Minute Screen
SMC	Subjective Memory Complaint(s)
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WMS-R	Wechsler Memory Scale – Revised

Chapter 1:

Alzheimer's disease and current challenges

1.1 Synopsis

In 1907, the German physician Alois Alzheimer published the first paper describing the symptoms of a 51 year old female named Auguste D. with what has come to be known as Alzheimer's disease (Maurer, et al., 1997). Auguste presented with a cluster of symptoms and signs including a rapidly deteriorating memory, language difficulties, disorientation and psychotic features. This cluster did not fit any known diagnosis of the time. After Auguste's death, Dr. Alzheimer performed an autopsy. He found shrinkage of the brain and two types of protein deposits he described as senile plaques and neurofibrillary tangles. Today these features are considered neuropathological hallmarks of Alzheimer's disease. Over the last few decades, there has been a substantial increase in Alzheimer research and a resultant increase in publications on this topic. A basic medline search

(using the term Alzheimer*) will illustrate the explosion of Alzheimer research over the last 40 years. There were 14 publications in 1970, 113 in 1980, 1381 in 1990. By 2000 and 2008, it was 3163 and 3856, respectfully.

Slowing the progression or delaying the onset of Alzheimer's disease is urgent from a patient, carer, and economic perspective. A delay in onset of 5 years would reduce the overall prevalence by 50% (Cummings et al., 2007). The most recent information indicates that maximum benefits will be obtained if treatment is initiated early in the course of the disease process before symptoms occur or when mild symptoms first appear. Thus, identifying patients early in the disease processes poses a major challenge to clinicians and the greater scientific community. The introductory chapters review some of the major challenges associated with identification of early treatment populations, risk factors, treatment options and diagnostic issues relating to Alzheimer's disease.

Before beginning any study into Alzheimer's disease, it is important to clarify the existing confusion between dementia and Alzheimer's disease. Often in the literature the terms can be confused, as they may be used interchangeably. Clearly, Alzheimer's disease is the most common type of dementia in the elderly, accounting for more than half of all dementia cases (Brookmeyer et al., 2007), whereas dementia is a clinical syndrome with multiple aetiologies. Also, other dementias, in particular those of vascular aetiology, may co-exist with underlying Alzheimer's disease neuropathology. In the present thesis, the term 'Alzheimer's disease' will be used because it is the most likely cause of dementia in 50 to 70% of cases (Alzheimer's

Association, 2009). The term 'dementia' is used when it is not clear from the literature the exact underlying aetiology of the dementia syndrome.

1.2. Definition

Dementia is a term used to describe a group of disorders which cause a progressive decline in memory and other cognitive functions that interfere with social and occupational functioning (APA, 2000). It is frequently accompanied by neuropsychiatric symptoms, such as depression, psychosis or behavioural problems (Kelley and Petersen, 2007).

Alzheimer's disease is a progressive neurodegenerative brain disease. It is clinically characterized by cognitive deficits in memory, executive functioning and loss of language skills. There are associated impaired activities of daily living and a range of behavioural and psychological symptoms; all with severe debilitating consequences (Bäckman et al., 2004b; Twamley et al., 2006).

The typical early neuropsychological profile of Alzheimer's sufferers consists of prominent complaints of memory difficulty. This is accompanied by deficits in new learning and a disproportionate decline in memory function relative to other cognitive domains. This is a hallmark feature of the disease (Hodges, 2006). The major impairment early in the disease is in anterograde episodic memory. Patients show poor recall of stories, and/or complex figures (Complex Figure Test; Rey, 1964) along with impaired recognition memory for previously studied words and faces (Geldmacher, 2004).

1.3 Epidemiology

Prevalence

A Delphi consensus study (Ferri et al., 2005) estimates that there are 24 million people worldwide with dementia. New cases per year total 4.6 million (i.e. one new case every 7 seconds). By 2016, dementia will surpass depression as the largest cause of disability burden in Australia. It will become the major public health issue in this country (Brodaty et al., 2005).

In Australia, estimates indicate that more than 200,000 are living with dementia (Jorm, 2005). In the absence of a cure, adequate prevention strategies or means to slow its progression, the prevalence of dementia in all of Australia is expected to more than triple (Jorm, 2005).

Incidence

By 2050, over 175,000 new cases of dementia will be diagnosed each year in Australia. Of these, almost half will have Alzheimer's disease. The incidence increases exponentially with age and more than half of all cases of Alzheimer's disease are expected to occur among people older than 75 years (Jorm and Jolly, 1998). Thus, the incidence of Alzheimer's disease is predicted to increase at a faster rate than both the total population and the elderly population (Jorm et al., 2005a), (see **Figure 1.1**).

By 2050, almost one in five Australians will be 65 years or older. After the age of 65, the probability of developing Alzheimer's disease doubles every 5 years (Brookmeyer et al., 2007). As the population is ageing the number of people affected by the Alzheimer's disease will also increase

(Henderson and Jorm, 1998). The very old (>80 years) (who are most likely to suffer from Alzheimer's disease), are expected to increase at a faster rate than either the total population or the young old (55 to 75 years) (Jorm, 2005).

This scenario will be evident worldwide as the numbers of people affected with dementia (including those with Alzheimer's disease) will double every 20 years to reach 81 million by the year 2040 (Ferri et al., 2005).

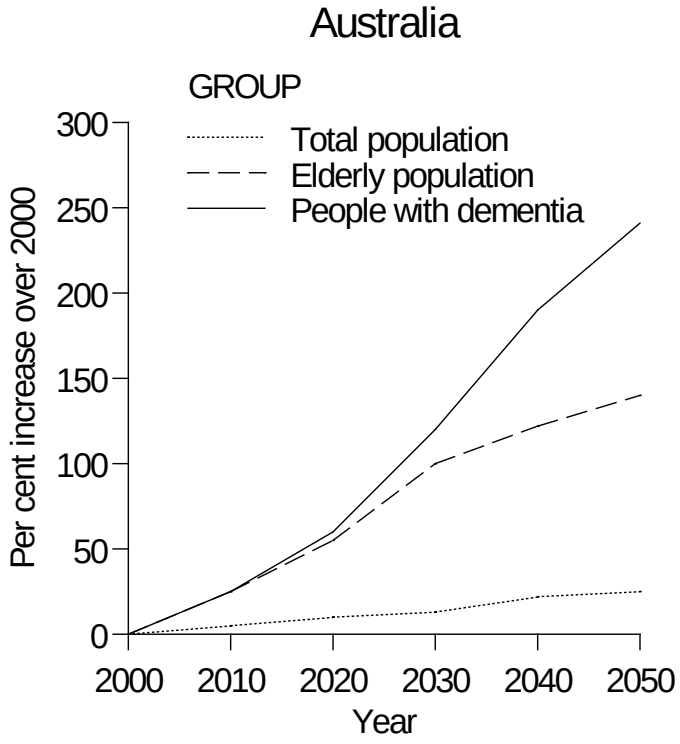


Figure 1.1 *Projected increase in dementia cases, elderly population and total population for Australia, 2000-2050.* Adapted from Jorm et al. (2005a).

1.4 Clinical diagnosis

During the lifetime of the patient, Alzheimer's disease is a clinical diagnosis requiring the patient to have dementia with no other disease established as the cause of the disorder. A brain biopsy may support the clinical findings of Alzheimer's disease; however this diagnostic procedure is very rarely used. A definitive diagnosis is made on the basis of neuropathological findings at autopsy. The hallmarks of Alzheimer's disease are two principal pathological features, namely plaques and neurofibrillary tangles. Both are required for a neuropathological diagnosis of Alzheimer's disease. In-vivo, the diagnosis is based on clinical criteria and there are biological markers available which can help with diagnosing Alzheimer's disease, e.g. brain imaging (Amyloid-Positron Emission Tomography, Flurodeoxyglucose Positron Emission Tomography, Single-Photon Emission Computerised Tomography, Magnetic Resonance Imaging, Computerised Tomography) as well as Cerebrospinal Fluid concentration of tau and b-amyloid.

The most widely used diagnostic systems for Alzheimer's disease are the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders IV-TR, published by the American Psychiatric Association 2000), the ICD-10 (International Classification of Diseases) endorsed by the World Health Organization (1992), and the NINCDS-ADRDA criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Associations (McKhann et al.

1984). These systems are used by clinicians to improve reliability and uniformity of diagnosis.

In research settings, the NINCDS-ADRDA criteria are the most widely used to determine the diagnosis of Alzheimer's disease. According to the NINCDS-ADRDA criteria, Alzheimer's disease can be diagnosed at three different levels of certainty ("definite AD"; "probable AD" and "possible AD"). The clinical diagnostic accuracy has been reported to exceed 90% with patients who are in the mid to late stages of the disease (Dubois et al., 2007). However, it should be emphasized that the diagnostic accuracy of Alzheimer's disease varies greatly depending on where the diagnosis is done, e.g. research memory clinic versus rural areas, general practitioners and general hospital.

In clinical settings, the DSM-IV-TR criteria for dementia of the Alzheimer's type requires the development of memory impairment to be accompanied by impairment in one or more other cognitive domains, (being aphasia, apraxia, agnosia, or executive function, see Table 1.1). The cognitive impairments are gradually progressive, of sufficient severity to impair functional abilities, and exclude other neurologic or psychiatric disturbances, in particular major depressive disorder. Delirium (usually an acute confusional state of sudden onset) also requires exclusion.

The ICD-10 criteria for dementia include an acquired and significant decline of memory and learning function plus the decline in at least one other cognitive domain (e.g., thinking, language abilities, visuospatial

orientation and concentration). The condition needs to be present for at least 6 months and an acute confusional state should be excluded.

Table 1.1 DSM-IV-TR diagnostic criteria for Dementia of the Alzheimer's Type (DAT)

A. Memory impairment in learning or recall and
   One or more of the following
   1. Aphasia: language difficulties
   2. Apraxia: difficulty performing purposeful movements
   3. Agnosia: difficulty recognising people or objects
   4. executive dysfunction
B. Cognitive deficits of sufficient severity to affect social or occupational functioning, representing a significant decline from a previous level
C. Clinical course with gradual onset and progression
D. Other causes for dementia have been excluded
   1. No alternative central nervous system explanation (e.g., stroke, Parkinson's disease)
   2. No alternative systemic conditions
   3. Not due to the effects of substance use
E. Not caused by delirium
F. Not better accounted for by another Axis I disorder (e.g., Major Depression, Schizophrenia)

Adapted from the American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th edition-text revision.* APA Press: Washington, D.C.

1.5 Clinical course

Clinically, the course of Alzheimer's disease is typically divided into three stages, each with different patterns of cognitive and functionalimpairment (Cummings, 2004). The course of the illness varies, as each individual progresses through the disease and may in fact retain some of their abilities. However, the end stage of the disease is very similar.

For research purposes, Alzheimer's disease is considered to have a predementia phase lasting a number of years during which mild cognitive

deficits are apparent on formal testing (Bäckman et al., 2004b; Amieva et al., 2005). During this phase, the person may complain about their memory, however they are able to function independently in the community. A more detailed review of the pre-dementia phase of Alzheimer's disease is discussed in Chapter 3, as it has particular relevance to this study.

The three stages are:

Stage 1. Mild

In the mild stage of clinical AD, there is amnesia for recent events and complaints about memory. The amnesia is characterized by forgetfulness (e.g., asking repetitive questions, misplacing items) and an inability to learn new information (e.g., recalling recent events). In contrast, the retrieval of old information and long-term memory is usually unimpaired. Attention deficits have also been identified (e.g., Chen et al., 2001). The memory deficit has been attributed to pathology of the medial temporal lobe (hippocampus and entorhinal cortex) and the deficit in attention as the first clinical manifestation of a significant involvement of the parietal cortex (Chen, 2001).

These deficits become evident when the patient is exposed to new conditions. Personality change and depressive symptoms, such as disinterest and social withdrawal are also apparent. During this stage, the person is still able to manage independently.

Stage 2. Moderate

In the moderate stage, patients tend to lose things and repeatedly ask the same questions. Language is characterised by an impoverished vocabulary of semantically empty words (e.g., 'thing', 'stuff'), circumlocutions, excessive use of pronouns, gestures, and semantic paraphasias are used to overcome word-finding difficulties in order to maintain the fluency of conversation. Reading and writing are progressively forgotten. Orientation to time and place is poor. Agnosia, apraxia, and deterioration of executive functions become evident, followed by an inability to perform activities of daily living. The memory problems worsen, and the person may not recognise close relatives. Previously intact long-term memory shows impairment.

In the moderate stage, behaviour changes are the norm and patients also manifest labile affect, restlessness, irritability, agitation, aggression and wandering. In many cases the behavioural problems seen in stage 3 are related to the involvement of the frontal lobes. The patient is partly dependent on help from others, especially when faced with new situations or problems.

Stage 3: Severe

In the advanced stage of clinical AD, language is reduced to simple phrases or even single words. However, many patients can receive and return emotional signals long after the loss of verbal language. Patients commonly manifest behavioural problems, apathy, restlessness and

exhaustion. Neurological symptoms, such as apraxia and extrapyramidal disorders are common. The patient needs help and guidance in all basic functions in their everyday life. Patients will ultimately not be able to perform the simplest of tasks independently. They are likely to develop other illnesses and infections.

Deterioration of muscle and mobility will develop, leading the patient to become bedridden and lose the ability to feed them self. Death is usually not due to the disease itself, but rather to a secondary infection such as pneumonia or urinary tract infections. The course of the disease is a gradual and progressive decline with an average duration from diagnosis to death of 8 years (Brookmeyer et al., 2002).

The role of medications during the course of Alzheimer's disease

The role of medication in the management of dementia is multifaceted as it may prevent or delay the onset of the disease by slowing the progression or treating memory problems and reducing secondary symptoms such as depression and hallucinations. A two-year study of vitamin E in patients with Alzheimer's disease showed a significant delay in functional decline, and nursing home placement, compared to selegiline and placebo (Sano et al., 1997). Primary symptoms are often treated with cholinesterase inhibitors (e.g. donepezil, rivastigmine and galantamine), memantine and ginkgo biloba. One RCT study showed that donepezil significantly delayed the progression to dementia in a subgroup of depressed aMCI patients by 1.7 to 2.2 years (Lu et al., 2009) compared to placebo controls. Early

initiation of cholinesterase treatment may temporarily stabilize or delay disease progression (Farlow et al., 2007). These mediations stop the breakdown of acetylcholine and show a modest improvement in cognitive function and behavioural symptoms. Current medications to treat secondary symptoms (e.g., depression and agitation) include anti-depressants, anti-psychotics and mood stabilizers.

Conversion to dementia

It is difficult to pinpoint the precise point at which a person converts to dementia, hence the rapid growth in research into MCI. The boundary between normal ageing, mild cognitive impairment and dementia remain unclear and contentious as noted in Chapter 3. Importantly, longitudinal studies of cognitive ageing do not identify a single point of transition between 'normal' ageing and dementia. When several cognitive domains are used to predict later onset of dementia, cognitive decline is typically non-uniform across domains (Amieva et al., 2005).

1.6 Differential diagnosis

Differentiating among the many causes of cognitive impairment that resemble the clinical state of dementia is vital in terms of treatment and prognosis. The identification of potentially reversible conditions, such as delirium and depression is absolutely necessary. Differential diagnosis begins by conducting a careful history (particularly from significant others), a thorough mental state and physical examination as well as appropriate laboratory investigations to exclude delirium, depression and potentially

medically treatable conditions such as hypothyroidism or vitamin B_{12} deficiencies. It is essential to exclude delirium. The distinguishing feature is an impairment of consciousness, which occurs in delirium and not in dementia. However, a delirium may be superimposed on an underlying dementia (Rahkonen et al., 2000).

The distinction between major depression ("pseudo-dementia") and dementia is also essential. As with delirium, a major depression may also be concurrent with an underlying dementia of the Alzheimer's type (Greenwald et al., 1989). This section discusses differences between major depression and Alzheimer's disease.

Table 1.2 Criteria for Major Depressive Disorder

A. In addition to the presence of depressed mood and/or loss of interest or pleasure, the DSM-IV-TR requires the presence of at least five of the following symptoms to have been present during the same 2-week period.

1. Depressed mood most of the day, nearly every day
1. Markedly diminished interest or pleasure in activities
2. Significant weight loss when not dieting or weight gain
3. Insomnia or hypersomnia nearly every day
4. Observable psychomotor agitation or retardation nearly every day
5. Fatigue or loss of energy nearly every day
6. Feelings of worthlessness or excessive or inappropriate guilt
7. Diminished ability to think or concentrate, or indecisiveness
8. Recurrent thoughts of death, plans or suicide attempts

The symptoms:

B. Do not meet criteria for a Mixed Episode

C. Cause significant impairment in social or occupational functioning

D. Are not due to the effects of substance use or a medical condition

E. Are not better accounted for by bereavement

Adapted from the American Psychiatric Association (2000). *Diagnostic and Statistical Manual of Mental Disorders, 4th ed text revision.* APA Press: Washington, D.C.

Depression

According to DSM-IV-TR criteria, major depressive episode or disorder (major depression) is a mood disorder that produces profound sadness, loss of interest in life, disturbed sleep, appetite change, impaired thinking and energy levels (APA, 2000). An exact definition is adapted from DSM-IV-TR (see Table 1.2).

Depression co-occurs in a number of psychiatric disorders, and is frequently present in dementia. The depression may or may not be "major" in type. When "major", it will often significantly affect cognitive functioning (Steffens and Potter, 2008). In the initial stages, it is often difficult to distinguish between major depression and Alzheimer's disease. Many features of major depression overlap with those found in dementia, such as memory problems, low mood, loss of interest, withdrawal, fatigue, concentration difficulties and sleep difficulties. Further, complicating the distinction is the realization that in 25% to 50% of cases, depression and dementia co-exist (Greenwald et al., 1989).

However, there are some important clinical and neuropsychological differences between patients with major depression and those with early Alzheimer's disease (see Table 1.3).

As shown in Table 1.3, depressed patients typically report more memory complaints. This is likely to reflect the distinct features of major depression, such as negativity, self deprecation along with impaired concentration. Patients with AD frequently underestimate their impairments and engage in confabulation (Geldmacher, 2004) due to the loss of insight

Table 1.3. Clinical and cognitive presentations of Major Depression compared to Alzheimer's disease

Feature	Major Depression	Alzheimer's disease
Age of onset	Above or below 60	Uncommon below 60
Rate and course of cognitive change	Acute; mood congruent changes; either improve with remission or persist	Insidious; progressive decline
Subjective memory complaints	Overestimate	Underestimate
Affect	Sadness $\geq$ apathy	Apathy > sadness in the presence of mood changes; apathy may exist in isolation
Sleep-wake cycle	Disturbed	Variable
Memory	Learning improves with repeated exposure Cueing improves recall Fewer intrusion errors in recall	Learning does not improve despite repeated exposure Rapid forgetting; cueing does not improves recall Greater intrusion errors in recall
Aphasia; Apraxia; Agnosia	Uncommon	Common
Executive functions	Initially impaired; improves when depression lifts	May be initially compromised; declines later in disease
Information processing speed	Slowed	Normal in early stage
Psychomotor speed	Slowed	Normal in early stage
Effort	Impairment on effortful cognitive tasks	Normal effort in response to cognitive demands of task

Adapted from Steffens and Potter (2008).

known to occur in patients with Alzheimer's disease (Clement et al., 2008; Kim et al., 2006). Depressed patients typically demonstrate psychomotor slowing combined with poor effort and cooperation on cognitive testing (e.g., producing incomplete answers). In contrast, decreased performance on cognitively demanding tasks reflects the AD patient's genuine inability to

perform the task, rather than a lack of effort. Moreover, on episodic memory tests; patients with Alzheimer's disease do not benefit from cueing to facilitate remembering, whereas depressed patients benefit from cueing. Major depression as a risk factor for Alzheimer's disease is discussed in Chapter 2.

Diagnostic types

To assist with differential diagnosis, key early presentations of different dementias are listed in Table 1.4 and reviewed in the text.

Vascular Dementia

Vascular dementia involves the loss of cognitive function resulting from ischaemic, hypoperfusive or hemorrhagic brain lesions due to cerebrovascular disease or cardiovascular pathology (Geldmacher, 2004; Roman, 2004). Vascular dementia is a common cause of dementia, second in prevalence only to Alzheimer's disease (Gorelick et al., 2004). Alzheimer's disease and vascular dementia frequently co-exist and account for up to 35% of all dementia cases (Geldmacher, 2004; Zekry et al., 2002). The onset of vascular dementia is typically abrupt, followed by a stepwise deterioration or progressively worsening condition (Schindler, 2005). Patients typically have deficits in encoding or retrieval, but their performance improves with cues, and recognition may be normal. Rapid forgetting is atypical. They are prone to slowed mental processing and disturbances in executive functioning; frequently accompanied by depression. Vascular

dementia has a higher prevalence in men than women, and onset is usually after the age of 70 years.

Table 1.4 Essential differences between Alzheimer's disease and other dementias

	AD	VaD	FTD	DLB
Onset	Insidious	Sudden, staggered or insidious	Insidious	Insidious
Course	Slowly progressive	Stepwise, fluctuating, variable or insidious	Gradual progression	Often rapidly progressive and may fluctuate on a daily basis
Cognitive deficits	Multiple cognitive deficits	Focal deficits; mental slowness;	Cognition reasonably preserved in early stages; language more affected earlier than AD	Visuo-perceptual skills + attention; +letter fluency
Functional / Behavioural findings	Executive dysfunction; apathy; loss of insight; emotional withdrawal	Incontinence; executive dysfunction; preserved insight; gait disturbances; depression	Disinhibition; apathy; loss of insight; emotional blunting	Executive dysfunction; apathy; depression; Psychosis (esp. visual hallucinations) more common than AD; Parkinsonian features

AD=Alzheimer's disease; VaD=Vascular Dementia; FTD=Frontotemporal Dementia; DLB=Dementia with Lewy bodies.

Adapted from APA (2000); Ferman et al. (2006); Hodges et al. (1992); Geldmacher (2004); McKeith (2007); Neary et al. (1998).

Frontotemporal dementia

Frontotemporal dementia describes a group of clinical syndromes associated with damage to the prefrontal and anterior temporal lobes and presents with non-Alzheimer type pathology (Hodges et al., 1992; Neary et al., 1998; Mesulam, 2001). In the early stages, frontotemporal dementia is frequently misdiagnosed as a psychiatric disorder or Alzheimer's disease (McKhann et al., 2001). Frontotemporal dementia can present as either the behavioural/frontal variant or aphasic variant. Symptoms indicating the behavioural variant include; disinhibition, impulsivity, apathy, obsessive compulsive disorder in the context of good cognitive skills. Patients also experience emotional blunting and loss of insight resulting in disturbed in social comportment (Liscic et al., 2007). Communication abilities remain preserved until later stages of the disease. Frontotemporal dementia occurs between 45 and 65, at an age when many patients are still employed, but in a quarter of cases the onset is over the age of 65 years (Hodges, 2001).

The aphasic variant can be further divided into two subtypes: Semantic Dementia and progressive non-fluent aphasia.

a. Semantic Dementia

Semantic dementia was initially coined by Snowden et al. (1989) to describe a form of frontotemporal dementia, associated with deterioration of semantic memory as a consequence of focal atrophy of the left temporal lobe. Patients with semantic dementia typically have fluent, effortless, grammatical speech which lacks content. Patients with semantic dementia

can be identified by their high endorsement of semantic complaints not found in other patient groups (Ahmed et al., 2008). They often experience difficulty retrieving words, understanding the meaning of words and visual information. These deficits are often accompanied by surface dyslexia and/or dysgraphia, and visual recognition deficits for faces and objects (Hodges, 2001). In contrast, episodic memory remains intact, with normal performance on recognition-based tests with visual material and preservation of recent autobiographical memory (Hodges and Graham, 1998).

b. Progressive Non-fluent Aphasia

Progressive non-fluent aphasia is characterised by progressive language deficits in the absence of memory, visual processing, and personality changes in the early stages (Mesulam, 2001). Initial language deficits typically include difficulties with effortful speech production, errors in grammar and phonological production, and difficulties with word retrieval. In contrast, semantic comprehension remains well preserved. However, as the disease progresses, language further deteriorates to the point where the patient may use unintelligible grunts to communicate, or may become mute (Mesulam, 2001).

3. Dementia with Lewy bodies

Dementia with Lewy bodies consists of primary dementia characterised by visuoperceptual and executive dysfunction, accompanied by prominent visual hallucinations, fluctuating attention and Parkinsonian

(McKeith, 2007). In contrast to Alzheimer's disease, visual hallucinations may become evident early in the course and deficits in executive function are among the earliest cognitive problems (Geldmacher, 2004). The cognitive/behavioural and Parkinsonian signs typically evolve within one year of each other (McKeith, 2007). Compared to pathologically proven Alzheimer's patients, patients with Dementia with Lewy bodies have better performance on memory and object naming tasks and greater deficits in attention, letter fluency and visuo-spatial abilities (Ferman et al., 2006). Visuospatial disturbances are prominent and other changes include general slowness of thought and action and rigidity. Apathy and depression are also common features.

Table 1.4 identified several types of dementia syndromes. However, it is important to recognise that this table is not exclusive and that there are many other types of dementias. Some of these include: Creutzfeld Jacob Disease (a prion disease), Korsakoff's dementia, (an amnestic disorder secondary to thiamine deficiency) and Progressive Supranuclear Palsy. Whilst some of these are easier to distinguish from Alzheimer's disease (e.g., Creutzfeld Jacob Disease, Korsakoff's dementia due to the underlying cause), others such as Progressive Supranuclear Palsy are more clinically challenging.

1.7 Disease mechanisms/Pathophysiology

There are a number of possible mechanisms for the aetiology of Alzheimer's disease (Bertram et al., 2008; Eckman and Eckman, 2007; Ertekin-Taner, 2007). The classical ones are discussed here.

Neuropathology

Examination of the AD brain reveals cortical atrophy that exceeds that observed in a normal elderly brain (McEvoy et al., 2009). This is an important characteristic feature of Alzheimer's disease. The two key neuropathological features of Alzheimer's disease, first described by Alzheimer in 1906 are amyloid plaques and neurofibrillary tangles. These features are thought to underpin much of the clinical and behavioural observations of the disease. However, these two features have been implicated in normal ageing and in patients with mild cognitive impairment (e.g., Aizenstein et al., 2008; Morris, 2006). Other notable changes associated with Alzheimer's disease include neuronal degeneration in the nucleus basalis of Meynert (Rosengarten et al., 2006) and decreased levels of acetycholine (Eggers et al., 2006).

According to Braak et al. (1991; 1995) the distribution of amyloid plaques varies among patients with no specific evolution of the pattern over the course of the disease. However, the distribution of tangles follows a specific pattern. Tangles are prominent in the hippocampal and entorhinal regions during the early stages of Alzheimer's disease. They then spread to limbic structures and cortical association areas, (predominantly the parietal and temporal lobes) and later to the frontal lobes.

The Amyloid Cascade Hypothesis

The deposition of extracellular amyloid plaques is probably an early pathologic event, preceding the clinical symptoms of Alzheimer's disease

(Engler et al., 2006; Jack et al., 2008). Plaques consist mainly of aggregates of the amyloid β-peptide (Glenner and Wong, 1984; Masters et al., 1985) and have been found to induce neuronal death (apoptosis).

It is still uncertain whether amyloid plaques or tau proteins are the more important lesion in Alzheimer's disease (Eckman and Eckman, 2007; Tiraboschi, 2004). Initially the amyloid cascade hypothesis suggested that abnormal accumulation of amyloid β-peptide caused Alzheimer's disease (Hardy et al., 1992). As cognitive decline is not well correlated to the amount of amyloid deposits in the brain (McKee et al., 1991), this theory has not been supported. Levels of soluble amyloid β-peptide may be better correlated to both synaptic density and cognitive decline (McLean et al., 1999). There is growing evidence that they might be the principal neurotoxic agent in Alzheimer's disease, whereas insoluble fibrils are relatively inert or even protective (Walsh and Selkoe, 2007). Therefore, the main focus of the theory today is amyloid β-peptide aggregation rather than plaques, as the primary cause of Alzheimer's disease (Hardy et al., 2006; Masters, 2006).

Neurofibrillary tangles consist mostly of aggregated hyper-phosphorylated tau protein that forms inside the neuron. The normal function of tau is to bind tubulin and thereby stabilize microtubules in neuronal axons, allowing nutrients and neurotransmitters to be transported along the axons between the cell body and the synapses. Tau is a non-specific bio-marker which is elevated in other brain diseases as well. In Alzheimer's disease, hyperphosphorylated tau detaches from the

microtubules and aggregates into paired helical filaments and neurofibrillary tangles (Iqbal et al., 1986). Support for the amyloid hypothesis, which looks at amyloid β-peptide as the common initiating factor for Alzheimer's disease, is that studies on a transgenic mouse model for Alzheimer's disease, tangles appear to be an event secondary to amyloid β-peptide plaques, where amyloid β-peptide might induce or aggravate the aggregation of tau (Oddo et al., 2004).

Amyloid Precursor Protein

Glenner and Wong (1984) published the purification and sequence of the protein, now referred to as amyloid β-peptide, from cerebrovascular amyloidosis in patients with Alzheimer's disease. The amyloid β-peptide was shown to be derived from a larger precursor protein, the amyloid precursor or APP mapped to chromosome 21 (Kang et al., 1987). Amyloid precursor protein consists of multiple structural and functional domains. It has been proposed to function as a cell surface receptor, and is involved in cell adhesion and synaptic plasticity (Zheng and Koo, 2006). Homozygous APP knock-out mice are viable and fertile, but are smaller and less active than wild type mice (Zeng et al., 1995).

St George-Hyslop et al. (1987) subsequently demonstrated a linkage to the same region of chromosome 21 in four early onset Alzheimer's disease families. Goate et al. (1991) demonstrated the first mutation in the APP gene causing familial Alzheimer's disease. Mutations within the APP sequence are all in exons 16 or 17, where the sequence for amyloid β-

peptide is located. Mutations affecting the y-secretase cleavage site alter the processing of APP into more amyloid β-peptide 42, whereas mutations affecting the β-secretase cleavage site lead to the production of more total amyloid β-peptide. There are also mutations located within the amyloid β-peptide sequence that increase the aggregation rate of amyloid β-peptide.

The observation that patients with Down's syndrome (who have trisomy of chromosome 21) frequently, develop Alzheimer-like neuropathology by middle age (Olson and Shaw, 1969) supports a theory that chromosome 21 abnormalities may underlie Alzheimer's disease. Once the APP gene was mapped to chromosome 21, the co-occurrence of Down's syndrome and early-onset Alzheimer's disease could be explained by a gene dose effect due to the extra copy of the APP gene. Recent reports have indicated that duplications of APP, in the absence of trisomy 21, can cause familial early-onset Alzheimer's disease with cerebral amyloid angiopathy (Sleegers et al., 2006). There are also reports that polymorphisms in the promoter of the APP gene affecting expression levels are associated with Alzheimer's disease (Theuns et al., 2006). These findings demonstrate that an increased expression of APP is sufficient enough to cause Alzheimer's disease, even when the sequence of APP is not altered. For further discussion of the genetics of Alzheimer's disease see Chapter 2.

1.8 Treatment

There is no cure for Alzheimer's disease and currently available treatments remain symptomatic with no beneficial effect on the disease

process (Sano, 2003). At present, treatment often involves cholinesterase inhibitors (donepezil, galantamine, rivastigmine, or rarely tacrine); and in moderate to severe cases, memantine, an NMDA (*N*-methyl-D-aspartate) antagonist (Lipton, 2006; Walker et al., 2005).

Slowing cognitive decline and hence postponing functional and behavioural impairment is important in the treatment of Alzheimer's disease (Hermann and Gauthier, 2008). Cholinesterase inhibitors work by increasing synaptic concentrations of the neurotransmitter acetylcholine (Stahl, 2000). They can modestly improve cognitive performance or delay cognitive decline in many patients. In some patients, cognitive performance is improved to levels observed 6 to 12 months earlier. Evidence suggests that early treatment with these medications may provide greater benefits over the long term, such as slowing the progression of the disease and reducing the risk of institutionalization (Lopez et al., 2005).

The behavioural and psychological symptoms of dementia (BPSD, such as aggression and psychosis can be treated with neuroleptic antipsychotic drugs (Sink et al. 2005). Whilst these drugs have been shown to modestly reduce these behavioural problems, serious side-effects of, cerebrovascular events, movement difficulties, or cognitive decline, often limit their use in clinical practice (Sink et al., 2005). It should be highlighted here that the current guidelines, e.g. from the International Psychogeriatric Association (IPA) are not to treat behavioural problems with antipsychotic as first line treatment, but with non-pharmacological interventions should and

only if they fail or there is acute risk involved should medication be considered.

Several new agents are being developed as molecular targets for treating or even preventing Alzheimer's disease (Cummings et al., 2007). These exciting developments include: 1) antiamyloid agents, which target the toxicity associated with Aβ peptide, 2) neuroprotective agents. These may reduce the damage associated with processing abnormal amyloid protein. Examples are antioxidants, anti-inflammatory agents or tau-related therapies, and 3) neurorestorative approaches, such as neurotrophic and nerve growth strategies, transplantations, and stem-cell related interventions (Cummings et al., 2007). These new approaches offer some hope in the future treatment of Alzheimer's disease. However, as a rule treatment needs to be initiated early in order to achieve the maximum benefits (Cummings et al., 2007).

1.9 Summary

This introductory chapter reviewed some of the challenges involved with identification of early treatment populations, and diagnostic issues related to Alzheimer's disease, and treatment options. The next chapter provides information on risk factors associated with Alzheimer's disease, including genetic as well as environmental factors that may help to identify subjects with a high risk of developing Alzheimer's disease and cognitive disorders in later life.

Chapter 2:

Risk factors for

Alzheimer's disease

2.1 Introduction

Alzheimer's disease is considered to be a multi-factorial disease, resulting fro a complex interplay of different factors (Borenstein et al., 2006). Recent studies suggest that various genetic and environmental factors are likely to contribute to the risk of dementia, including early-life brain development, body growth, socioeconomic conditions, environmental enrichment, head injury, and education status (Borenstein et al., 2006; Fratiglioni and Wang, 2007). Many studies have considered the importance of these factors in their attempts to identify causes of Alzheimer's disease or identify high-risk individuals for treatment.

This section reviews the literature on well known risk factors for Alzheimer's disease; some of which are modifiable by lifestyle changes or medical treatment (obesity, hypertension, diabetes). For ease of reference, the term dementia will be used unless findings specifically refer to Alzheimer's disease.

2.2 Age

Advancing age is considered to be the principal risk factor for Alzheimer's disease. The prevalence of the disease increases exponentially between the ages of 65 and 85, doubling every five years after the age of 60 (Bondi et al., 2008). Several studies have identified the age of 70 as a critical turning point for significant cognitive decline and dementia (Arauz et al., 2005; Ritchie and Kilda, 1995; Wang et al., 2004a). A number of studies suggest that women have a slightly greater risk for Alzheimer's disease than men (Heun et al., 2006). This has been attributed to women's longer life expectancy, hormones and genes.

It has been proposed that dementia might be an inevitable consequence should one live long enough (Drachman, 1994). However, some studies indicate that dementia is "age-related" rather than an "ageing-related" disorder (Ritchie and Kilda, 1995). These authors reported a fall in the prevalence of dementia in the age range 80 to 84, and around 95 years of age the prevalence levelled off to about 40%. Thus, the very elderly have a reduced risk of dementia, having survived the period when dementia presents. This supports the hypothesis that dementia is not a normal part of ageing.

2.3 Lifestyle and environmental factors

There is increasing awareness that lifestyle factors contribute significantly to an increased risk of dementia. The Western lifestyle which includes an excessive consumption of unhealthy food and a lack of exercise

is known to contribute to a variety of conditions such as, heart disease, high cholesterol, high blood pressure, obesity, and diabetes mellitus (Type 2) (Fillit et al., 2008).

Many reports have examined the effects of these lifestyle and environmental factors on the risk of dementia (e.g., Anstey et al., 2007; Foley and White, 2006; Larson et al., 2006; Lautenschlager et al., 2008; Luchsinger et al., 2007; Rosendorff et al., 2007; Scarmeas et al., 2006). Table 2.1 summarizes some of the risk factors associated with mild cognitive impairment (MCI) and Alzheimer's disease.

Table 2.1 Risk factors for Mild Cognitive Impairment (MCI) and Alzheimer's disease

Epidemiologic	Genetic	Physiologic
Age	ApoE-e4 genotype	Hypothyroidism
Female sex	SORL1 genotype	Hypercholesterolemia
History of head trauma	Family hx of dementia or AD	Diabetes Mellitus (Type 2)
Hx of midlife hypertension		Hyperinsulinemia
History of stroke		Elevated serum
Small head circumference		homocysteine levels

Adapted from Cummings et al. (2007).

2.3.1 Diet

Observational data suggest that the low risk of dementia in some developing countries can be attributed to the type of diet (Lushinger et al., 2007). Diets rich in fruits, vegetables, and fibre improve human well-being and significantly reduce development of the pathological processes that are characteristic of neurodegenerative disorders (Martin et al., 2002).

The Mediterranean diet has been shown to reduce risk for cardiovascular disease, cancer, and increase longevity (Knoops et al., 2004). The Mediterranean diet consists of a high intake of fruits and vegetables, legumes, cereals, fish, monounsaturated fats (e.g., olive oil), small amounts of meat and poultry, dairy products (in the form of cheese and yogurt) and wine with meals. A study by Scarmeas et al. (2006) examined the link between the Mediterranean diet and the risk of Alzheimer's disease by following 2258 non-demented elderly subjects for an average of 4 years. These authors reported that subjects who most closely followed the Mediterranean diet had a 40% to 54% reduced risk for Alzheimer's disease compared to those who were least likely to follow the diet.

The low incidence of dementia despite increased longevity in Okinawa, an island south of Japan, is consistent with their traditional low caloric and low fat diet. The diet primarily consists of lean meat, fish, tofu and vegetables, (especially dark green leafy vegetables and sweet potato). The significance of these dietary factors is reinforced by the finding that when the Okinawa's migrate, they develop Western world diseases, such as heart disease, dementia and cancer (Yamada et al., 2002).

Chinese studies suggest that regular tea drinking might be protective against Alzheimer's disease (Wang et al., 2004b). A recent study by Eskelinen et al. (2009) examined the association between coffee and tea consumption and the risk of dementia and Alzheimer's disease later in life. This study followed 1409 individuals (aged from 65-79) for 21 years and found that the coffee drinkers amongst them had the lowest risk of dementia

and Alzheimer's disease compared to those drinking little or no coffee. A 65% reduced risk was observed in those who drank three to five cups of coffee per day. This study did not find tea to have a protective effect.

2.3.2 Exercise

Recent studies have shown the beneficial effects to patients who exercise moderately (three times per week) in improving their cognitive function. Lautenschlager et al. (2008) found that non-demented older subjects (>50years) who were assigned to a 6 month exercise program of moderate intensity (1/2 hr of exercise 3 times per week) showed an improvement of 1.3 points in cognitive functioning, as defined by the ADAS-cog compared to the non-exercise group. Notably, the benefits of exercise persisted for a further 12 months after the exercise intervention had stopped.

Likewise, physical activity was associated with a reduced incidence of dementia in subjects aged $\geq$ 65 years who exercised 3 or more times per week (relative risk, 0.68; CI 0.48 to 0.96) compared to those who exercised fewer than 3 times per week (Larson et al., 2006). Additionally, exercise was further associated with the greatest risk reduction in subjects who had poor physical functioning at baseline.

2.3.3 Smoking

The relationship between smoking, cognitive function and dementia is not well established. Studies have generally provided conflicting results

(Epping Jordan, 1998). Observational data by Anstey et al. (2007) suggests a positive link between smoking and Alzheimer's disease. This study assessed cognitive decline and incidence of dementia in 26,374 subjects (mean age=74) and found that current smokers had an increased risk of Alzheimer's disease (relative risk, 1.79; CI 1.43 to 2.23). Those who were current smokers had a significantly greater decline in cognitive ability compared to those who had never smoked or those who were former smokers (relative risk, 1.70, CI 1.25 to 2.31). However, this study did not take into account the influence of other health and lifestyle factors associated with smoking that may also explain these associations (e.g., poor nutrition and less physical activity).

The association between smoking and Alzheimer's disease is supported by Luchsinger et al. (2005) who demonstrated that current smoking was strongly related to a higher risk of Alzheimer's disease both independently and in the context of other vascular risk factors.

2.4 Education and the cognitive reserve hypothesis

Illiteracy or low educational achievement has been reported to be a robust risk factor for dementia (Borenstein et al., 2006). The cognitive reserve hypothesis assumes that favourable hereditary and environmental factors increase the brain reserve, which in turn, may delay the clinical onset of dementia (Allen et al., 2005; Fratiglioni and Wang, 2007). It has been shown that higher levels of education lower the risk of Alzheimer's disease, even in the presence of pathological changes, compared to those with less

education (Roe et al., 2008). Cognitive changes would be less noticeable in highly educated persons because of higher pre-morbid functioning compared to those with less education. However, one should keep in mind that lower rates of education may also be linked to poverty or lower socioeconomic status. These have been associated with poorer health, less access to health care which may increase the risk of dementia (Prince et al., 2003).

Moreover, studies have demonstrated that transgenic mouse models of Aβ deposition raised in an enriched environment (e.g., running wheels, coloured tunnels and toys) had less Alzheimer pathology (e.g., reduced Aβ levels and amyloid deposits in the brain) compared to mice raised in a "standard environment" (Lazarov et al., 2005). This study suggests a gene environment interaction and that exercise and environmental enrichment may be protective against developing or delaying the onset of Alzheimer's disease.

2.5 Trauma

The risk of Alzheimer's disease is doubled for individuals with a history of head injury that led to a loss of consciousness or hospitalization (Mortimer et al., 1991). Retired professional football players with a history of concussion showed greater cognitive impairment in later life than did retired players without a history of concussion (Guskiewicz et al. 2005). Similarly, a condition can develop in ex-boxers with neurological sequelae known as "Punch Drunk Syndrome" (Roberts et al., 1990).

2.6 Medical conditions

Cardiovascular risk factors

It is well established that Alzheimer's disease and cardiovascular disease share many common risk factors, such as hypertension, hypercholesterolemia, and Type 2 diabetes mellitus (de la Torre, 2008; Papademetriou, 2005).

Vascular risk factors have been implicated in the pathogenesis of Alzheimer's disease (Kloppenburg et al., 2008; Luchsinger et al., 2005). In a review of studies, Kloppenburg et al. (2008) found Type 2 diabetes mellitus and obesity were consistently associated with an increased risk of dementia, increasing the risk for any dementia by 1.5 times.

Luchsinger et al. (2005) followed 1138 non-demented subjects (mean age=76.2) for 5.5 years and found the risk of Alzheimer's disease increased with the number of vascular risk factors present. Type 2 diabetes mellitus and current smoking were the strongest independent risk factors. Having three or more vascular risk factors increased the risk of developing Alzheimer's disease three-fold.

Diabetes Mellitus

Type 2 diabetes mellitus is a well-known risk factor for cardiovascular disease (Arvanitakis et al., 2004; Schnaider et al., 2004). Type 2 diabetes develops in the context of insulin resistance, frequently accompanied by other vascular risk factors such as hypertension, dyslipidaemia and obesity.

Each of these risk factors has been associated with cognitive decline and dementia (e.g., Fillit et al., 2008).

Evidence for Type 2 diabetes mellitus as a risk factor for dementia is provided by Luchsinger et al., (2005) who demonstrated that Type 2 diabetes mellitus was the strongest predictor of dementia beyond the age of 65 years from among the vascular risk factors. One recent study showed that individuals with both type 2 diabetes and the ApoE e-4 allele had a five times higher risk for developing Alzheimer's disease compared to those with neither risk factor (Irie et al., 2008). This shows that risk factors for Alzheimer's disease can be additive.

Hypertension and stroke

There is strong evidence linking hypertension to dementia through its association with cerebrovascular disease. Hypertension increases the risk of stroke, which, in turn increases the risk of Vascular Dementia and Alzheimer's disease (Honig et al., 2003). Patients with a history of stroke are between 3.5 and 6 times more likely to develop dementia than those without stroke (Lays et al., 2005). Hypertension is a mid-life risk factor and by late life, usually before the dementia diagnosis is made, blood pressure drops. Kloppenburg et al. (2008) reported the risk of dementia was highest in subjects with midlife hypertension, accounting for 30% of cases of late life dementia.

Luchsinger et al. (2005) reported that hypertension clustered with other cerebrovascular risk factors, such as Type 2 diabetes mellitus, heart

disease, and current smoking contributed to a higher risk of Alzheimer's disease compared to hypertension alone. This study suggests that hypertension may cause cognitive impairment and dementia through its association with other cerebrovascular risk factors. Another report showed that non-demented subjects (n=918; aged $\geq$ 65 years) with a history of hypertension have an increased risk of MCI by 1.5 times (Reitz et al., 2007).

Obesity

Obesity has been linked to a number of medical conditions, including hypertension, stroke, Type 2 diabetes mellitus, and cardiovascular disease and poor cognitive performance (Kopelman, 2000). Midlife obesity has been associated with an increased risk of dementia and Alzheimer's disease in later life (Kivipelto et al., 2005). In turn all of these conditions have been linked to an increased risk of dementia via their association with vascular risk factors.

There has been increased emphasis on central obesity (abdominal distribution of fat) which is considered to be a more potent risk factor for vascular disease than Body Mass Index (Luchsinger, 2008). A recent study spanning 36 years reported an independent association of midlife central obesity with an increased risk of dementia by three times (Whitmer et al., 2008).

Parkinson's disease with dementia

Parkinson's disease is a neurological condition characterized by motor slowing, tremor, rigidity along with executive dysfunction (set-shifting and

temporal sequencing difficulty) and impairment in memory retrieval. Parkinson's disease typically begins with unilateral motor signs, such as tremor in one hand. However, patients with Parkinson's disease are six times more at risk of dementia compared to age-matched controls (McKeith, 2007).

Parkinson's disease with dementia describes the dementia that occurs in the context of well established Parkinson's disease. This dementia can present in three forms: 1) as a prominent dysexecutive syndrome (common); 2) as dementia with Lewy bodies with prominent fluctuations in cognition and hallucinations (common); or 3) as an amnestic "Alzheimer-like" syndrome (less common); (McKeith, 2007). This condition is slightly more prevalent in men and onset is between 40 and 70 years.

2.7 Depression

There is ongoing controversy as to whether major depression represents an actual risk factor or is a prodrome of dementia (Dal Forno et al., 2005; Kral and Emery, 1989). Some studies indicate that major depression may be an independent risk factor for Alzheimer's type dementia (Geerlings et al., 2008; Ownby et al., 2006; Wilson et al., 2008). Geerlings et al. (2008) examined the link between a history of major depression (26.6% of sample) and Alzheimer's disease in 503 non-demented subjects (age range 60 to 90). Over a 6-year follow-up, 33 subjects developed Alzheimer's disease. Subjects with a history of late-onset major depression were 2.5 times more likely to develop Alzheimer's disease than those without

a history. The risk was even higher in subjects whose major depression occurred before 60 years of age. They were four times more likely to develop Alzheimer's disease compared to those without major depression.

However, Bartolini et al. (2005) found an increase in depressive symptoms one year prior to diagnosis of Alzheimer's disease in non-demented subjects (mean age=69.2; SD=4.8) referred to a memory clinic after complaining of memory problems. At baseline, of the 222 subjects, 124 met the criteria DSM-III-R for major depression. In 31 of the 124 (25%), the increase occurred in motivation-related (concentration difficulties, loss of interest) rather than mood-related (dysphoria, feelings of guilt) symptoms of major depression. This observation led the authors to conclude that motivational symptoms of depression are cognitively loaded as they were linked to the subject's basic processing resources, such as the ability to focus attention on the task at hand, while closing out irrelevant information. This study suggests that certain aspects of major depression are a prodrome of dementia.

However, it remains difficult to determine whether major depression contributes to the cognitive difficulties or if it is secondary to the memory problems. In effect major depression may impair memory functioning.

2.8 Genetics

Early onset Alzheimer's disease has a strong genetic component but only a small percentage of all AD cases are early-onset (before 65 years of age). Of these, approximately 40% are sporadic. The remaining 60% have

a familial dominantly inherited Alzheimer's disease with mutations in any of three genes: APP on chromosome 21, presenilin 1 on chromosome 14 and presenilin 2 on chromosome 1 (Levy-Lahad et al., 1995; Sherrington et al., 1995). However, these three genes do not explain all cases of familial Alzheimer's disease. The majority of AD cases are late-onset (after the age of 65 years), of which approximately 75% are sporadic, probably caused by a genetic predisposition in combination with environmental factors. The remaining 25% of late-onset cases have a family history of Alzheimer's disease where several genes have been implicated (Bertram and Tanzi, 2008). To date, only the Apolipoprotein E gene (ApoE) remains accountable for more than 50% of the risk associated with late onset Alzheimer's disease (Corder et al., 1993).

First degree relatives of a person with Alzheimer's disease have a greater risk of developing the disease than those without a family history. Twin studies have estimated heritability for Alzheimer's disease to be as high as 79% (Gatz et al., 2006). In addition, estimations of concordance have demonstrated that if one twin develops Alzheimer's disease, the other twin will also develop the disease in 59% of the monozygotic twin pairs, whereas this only occurs in 32% of same-sex dizygotic twins and in 24% of opposite-sex dizygotic twin pairs. As twins are assumed to share not only genes but also the environment during a critical period for brain development, this demonstrates a high genetic component to Alzheimer's disease (Gatz et al., 2005).

2.9 The role of the ApoE

The ApoE-ε4 allele on chromosome 19 was the first genetic risk factor to be identified for late-onset Alzheimer's disease (Corder et al., 1993; Strittmatter et al., 1993). Subsequent studies have confirmed the ApoE as the single most important susceptibility gene for sporadic and late-onset familial Alzheimer's disease yet identified (National Institute on Ageing/Alzheimer's Association Working Group, 1996; Raber et al., 2004).

It has been suggested that the ApoE isoforms may affect amyloid deposition, tangle formation, cholinergic function or neuronal plasticity and repair (Mahley and Rall, 2000). However, one should keep in mind that, ApoE is neither sufficient nor necessary for the development of Alzheimer's disease, as not all Alzheimer's patients have an ApoE-ε4 allele and not all individuals with an ApoE-ε4 allele will develop Alzheimer's disease. Therefore, ApoE should not be used as a sole diagnostic test for Alzheimer's disease (Liddell et al., 2001).

Three different alleles, ε-2, ε-3 and ε-4, encode the isoforms of ApoE. These base pair substitutions result in changes in the relative affinity of the ApoE protein for receptors and lipoproteins. In the brain, ApoE is synthesized by astrocytes and microglia, whereas ApoE in the periphery is mostly synthesized in the liver. It is a lipid transporter in cerebrospinal fluid and plasma and the primary protein component of lipoproteins in the central nervous system. Through the interaction with cell surface lipoprotein receptors it is involved in cholesterol homeostasis. The ApoE4 is associated

with increased levels and ApoE2 with decreased levels of cholesterol in plasma, compared to ApoE3 (Davignon et al., 1988).

The six possible ApoE genotypes (epsilon 2/2, 2/3, 2/4, 3/3, 3/4 and 4/4) differ in their frequency of occurrence in the population. ApoE epsilon-3 is the most common allele occurring on more than 75% of chromosomes in Caucasian populations. The average frequencies of ε-2 and ε-4 are 8% and 15%, respectively.

2.9.1 ApoE ε4 as a risk factor

The ApoE 4 genotype represents an important biological risk factor for Alzheimer's disease world-wide (Pericak-Vance et al., 2000). A pioneering study by Farrer et al. (1997) found the ApoE epsilon 4 allele increased the relative risk of developing Alzheimer's disease. Carriers of the epsilon 4 allele (ε2/4, ε3/4) had an odds ratio between 2.2 and 4.4 of developing Alzheimer's disease compared to people with the epsilon ε3/3 genotype. The most common variant, ε3, is neutral for Alzheimer's disease risk. Carriers of the epsilon 4 (ε4/4) have an odds ratio ranging from 5.1 to 34.3.

The ε2 allele is the most unusual of the three and is considered somewhat protective for Alzheimer's disease (Corder et al., 2004). Carriers of the ε2:ε2 genotype are under represented in Alzheimer's disease and over represented in populations of healthy centenarians. It has been associated with longevity, successful ageing and protection against Alzheimer's disease (Panza et al., 2004; Talbot et al., 1994).

According to Farrer et al. (1997) women are more vulnerable to Alzheimer's disease irrespective of their ApoE status, possibly due to independent factors such as estrogens. Comparison of ApoE 4 heterozygous men and women showed that women had an increased risk of developing Alzheimer's disease two-fold.

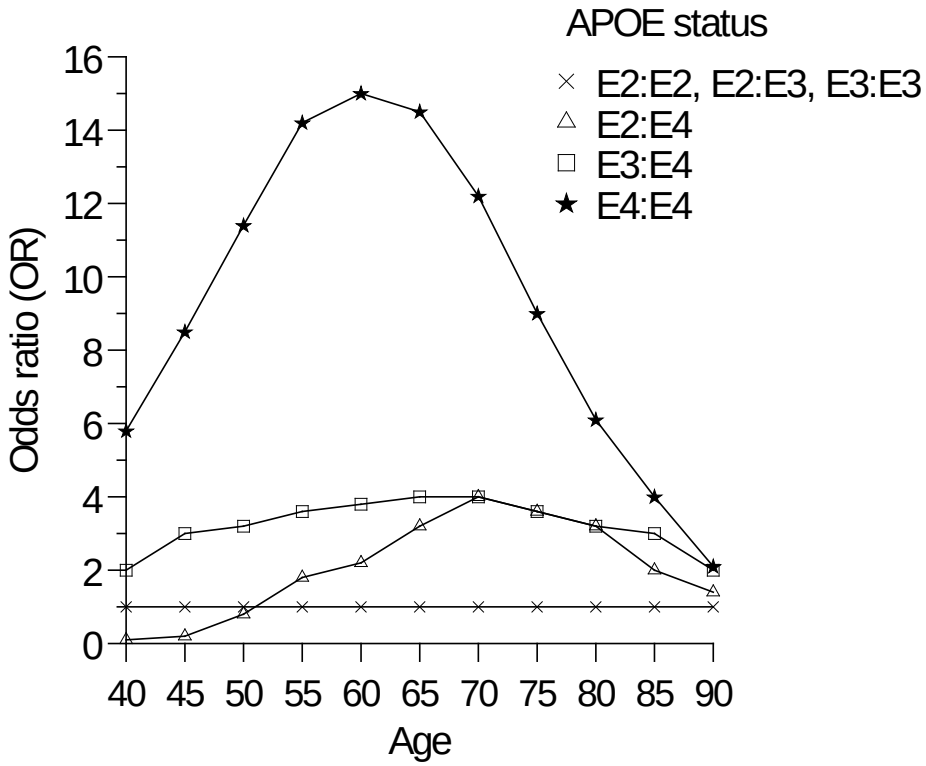


Figure 2.1. *Age of onset and the risk of Alzheimer's disease for different carriers of ApoE genotypes. Adapted from Farrer et al. (1997).*

2.9.2 ApoE and age of onset

As shown in **Figure 2.1**, ApoE 4 genotype has a significant role in the age-of onset of Alzheimer's disease (Bird, 2008, Farrer et al., 1997). Each additional epsilon 4 allele shifts the age of onset to a younger age. Corder et al. (2004) reported that in families with histories of late-onset Alzheimer's disease, the risk of Alzheimer's disease increased from approximately 20% to over 90% and mean-age-of-onset decreased from 84 to 68 years with increasing number of epsilon 4 alleles.

2.9.3 ApoE and cognitive decline and dementia

Whilst the role of the ApoE ε4 in Alzheimer's disease is well established, its role in cognitive decline remains uncertain (Kleiman et al., 2006; Fliesher et al., 2007). Many studies have attempted to model the effects of the ApoE ε4 to examine whether it provides independent information on risk of future cognitive decline. The outcomes of these studies have varied widely. Some studies indicate that the ApoE ε4 may accelerate decline in those with cognitive impairment or Alzheimer's disease (Consentino et al., 2008; Fratiglioni et al., 2004). Another study reported that the ApoE ε4 does not affect patients with preclinical Alzheimer's disease (Estevez-Gonzalez et al., 2004). The ApoE ε4 has also been shown to impair specific domains such as episodic memory (Kozauer et al., 2008). One study indicated that the ApoE ε4 provides an independent contribution to the risk of cognitive decline, especially after the age of 50 (Caselli et al., 2004). The

ApoE ε4 has also been related to a faster decline in non-demented samples (Small et al., 2004).

A recent study showed that the ApoE ε4 allele appears to accelerate cognitive decline in patients with early stage Alzheimer's disease (Consentino et al., 2008; Fratiglioni et al., 2004). To examine the effect of ε4 on the rate of cognitive decline in patients with Alzheimer's disease, Consentino et al. (2008) recruited patients from two longitudinal cohort studies and one clinic-based sample. The 3 samples studied included: 199 (48%) incident Alzheimer's disease; 215 (54%) prevalent Alzheimer's disease, and 156 (71%) patients diagnosed with Alzheimer's disease. Over a 4-year follow-up period, in the incident sample, the presence of the ε4 allele was associated with more rapid cognitive decline, even after demographic adjustments. In contrast, ε4 was not associated with the rate of change in either of the other groups. However, after adjustment for disease severity or exclusion of severely impaired subjects, a faster decline in e4 carriers was also apparent. This study shows that the ApoE ε4 influences cognitive decline in the earliest stages of disease with minimal effects or none in the moderate to severe stages.

In a large epidemiological study, Jorm et al. (2007) examined the effects of ApoE ε4 allele on cognitive functioning in 6,560 subjects and observed no association. The subjects were aged 20-24, 40-44, and 60-64 and all received cognitive testing. Whilst, the cross-sectional analysis showed differences in cognitive performance across the age categories, these authors failed to find an effect of the ApoE ε4 genotype on cognitive

functioning across the age categories or an age by genotype interaction. In this study, normal cognitive ageing between the ages of 20 and 60 years could not be attributed to the effects of the ApoE ε4 (Jorm et al., 2007).

In a subsequent study, these same authors Christensen et al. (2008) re-examined the effects of the ApoE ε4 allele on cognitive function in a sample of 2,021 subjects, aged between 65-69 years. This is the age when the ApoE ε4 exerts its maximal effect (Blacker et al., 1997). Over a follow-up period of 4-years, MMSE scores were significantly lower for ε4 homozygotes than heterozygotes or non-carriers. The effects of the ApoE ε4 on cognitive decline were found on the MMSE and Symbol-Digit Modalities test, after controlling for risk factors, such as previous head injury or low education. Christensen et al. (2008) suggested that it is possible for ApoE ε4 carriers to be more vulnerable to greater cognitive decline in the presence of other risk factors between the ages of 65-69 years.

In healthy ageing, the ApoE ε4 appears to have some influence in global cognitive function, however only in some specific domains. A meta-analysis of 38 studies (Small et al., 2004) reported that ApoE ε4 carriers scored modestly but significantly poorer in the areas of global cognitive function, episodic memory and executive functioning compared to ApoE ε3/ε3 carriers. Notably, ApoE ε2 carriers performed better than the controls in global cognitive function. This is consistent with the protective effect of the ApoE ε2 against Alzheimer's disease.

In a retrospective analysis, using patients with established Alzheimer's disease, Estevez-Gonzalez et al. (2004) used formal assessment to examine

the association between the ApoE ε4 allele and memory profile in 24 patients in the preclinical stage of Alzheimer's disease who were either ApoE ε4 carriers (n=13) or ApoE ε3 homozygotes. (N=11). A one-way analysis of variance comparing ApoE ε4 carriers and patients with ApoE ε3 homozygosity showed that 2 years prior to AD diagnosis both genotype groups had similar memory performance on a number of tasks, including working memory, declarative memory and non-declarative memory.

Similarly, Caselli et al. (2004) examined whether memory loss could be identified in subjects prior to the onset of MCI by recruiting 180 subjects from the community at increased risk for Alzheimer's disease due to the presence of the ApoE ε4 allele. A total of 180 subjects (mean age=60; SD: 6.2) were classified as normal on the basis of their MMSE scores=29.6 $\pm$ 0.7; 45 were ApoE ε4/ε4 homozygotes, 42 ApoE ε3/ε4 heterzygotes, and 93 ApoE ε4 non-carriers. Over the 33-month interval, carriers of the ApoE ε4 had poorer performance on multiple measures of verbal memory tests including (total score on Auditory Verbal Learning Test (AVLT); delayed recall; and Selective Reminding Test (SRT), free and cued recall) compared to non-ApoE ε4 carriers. Additionally, these authors reported that carriers of the ApoE ε4 aged between 50 to 59 showed greater declines on the AVLT delayed recall, SRT free and cued recall, and Complex Figure Test. This study suggests that prior to the onset of MCI or dementia; ApoE ε4 carriers show a modest decline in memory skills commencing from the age of 50 onwards.

2.10 Summary

To summarise, Alzheimer's disease is considered to be a multi-factorial disease. The risk for Alzheimer's disease is not likely to be determined in any single time period but results from a complex interplay between genetic and environmental exposures throughout one's life (Borenstein et al., 2006). All of these factors are likely to have synergistic or additive effect on the risk of Alzheimer's disease which increases with age. Also, the role of ApoE ε4 status in memory function remains controversial. It is not clear whether ApoE has a direct effect on memory in the absence of disease or acts only through association with Alzheimer's disease. This may be attributed to the small effect size related to the ApoE and that very large samples (n>1000) may be required to find subtle associations or to determine the mechanism of action. Nevertheless, several studies have reported a higher proportion of ApoE ε4 carriers in patients with advanced Alzheimer's disease and thus remain an important risk factor for developing the disease. The next chapter examines the risk of Alzheimer's disease associated in individuals with subjective memory complaints or mild cognitive impairment.

Chapter 3: Normal ageing, memory complaints and Alzheimer's disease

3.1 Cognitive decline and normal ageing

It is well known that old age is accompanied by a loss of memory (Collie et al., 2001; Geslani et al., 2005; Maruff et al., 2004). However, along the cognitive continuum, a loss of memory can also indicate the onset of a dementia syndrome (McKhann et al., 1984; American Psychiatric Association, 2000) or be a predictor of future Alzheimer's disease (Saxton et al., 2004). Scientific evidence has shown that the cognitive domains known to be impaired in preclinical Alzheimer's disease, such as episodic memory, executive function and perceptual speed have also been implicated in normal cognitive ageing (Bäckman et al., 2004a; Twamley et al., 2006; Bäckman and Small, 2007). Thus, the boundary that separates normal ageing from pathological ageing is not entirely clear.

In normal ageing, memory problems tend to reflect a generalized decrease in the efficiency by which information is processed and retrieved. Memory functioning is generally well maintained up until the age of 60 years (Allen et al., 2005). In non-demented elderly there are clear signs of age-related cognitive decline, from the mid 70s onwards (De Ronchi et al., 2005). These changes have been reported to occur primarily on tasks of new learning, speed and flexible adjustments (cognitive flexibility) to new situational demands. In contrast, tasks that draw on previously acquired knowledge have limited speed demands or are highly automatic show little or no age-related decline. These are summarized below and discussed further in Chapters 5 and 6.

Episodic Memory

Increasing age is accompanied by a gradual decrease in episodic memory functioning. This decrement in performance can also be observed in the oldest old. Age-related impairments in free recall of stories and word lists are evident by age 50. When cognitive support or structure is provided by the use of recognition testing, more study time, or cueing to facilitate episodic memory functioning, the age-related differences diminish. This suggests that as we age there is a greater impairment of retrieval processes than of encoding or retention (Bäckman and Small, 1998; Bäckman et al., 2004a). In contrast, transferring information from a temporary storage to a more permanent memory store becomes increasingly difficult with advancing age (Bäckman et al., 2004a).

Working memory

Working memory is typically well-preserved unless there is high demand placed on processing capacity. Performance on Digits Forward (a task involving repeating sequence of numbers) is robust to age-related decline, because this task places few demands on working memory. By contrast, performance on Digits Backward declines with increasing age, because this task places demands on working memory. In this task the information needs to be manipulated in a relatively untransformed fashion, which is cognitively taxing.

Information processing speed

A prominent impairment that accompanies increasing age is a decrease in performance in information processing speed (Craik and Rabinowitz, 1984). This slowing down can be observed on tests of cognitive speed, such as Trail A and Trail B tasks (Tombaugh, 2004). Even in the very old, the age-related differences observed in Trail-Making have been isolated to the speed with which the task could be completed, and not to accuracy (Bäckman et al., 2004a). Although, Trail B, places additional demands on executive function, the age-related slowing observed in Trail-Making has been reported to result from impairments in visuomotor tracking (Bäckman et al., 2004a).

Semantic memory

A moderate age-related decline has been observed on both letter and category fluency tasks, especially in the very old. Thus, although different mechanisms assist with fluency tasks, (switching and clustering), both fluency tasks are affected equally in the old, and suggest that the underlying processes are similarly impaired (Bäckman et al., 2004a, Tulving, 2002).

3.2 The concept of early detection

There has been a recent shift to thinking about Alzheimer's disease in pre-dementia terms (Ganguli, 2006; Petersen et al., 2007; Winblad et al., 2004). This is evident in the literature where patients presenting with cognitive impairment have been depicted by a variety of terms, such as mild cognitive impairment (MCI: Ganguli et al., 2004; Gauthier et al., 2006), subjective memory complaints/impairment (or subjective cognitive impairment) (SMC: Abdulrab and Heun, 2008; Geerlings et al., 1999; Jungwirth et al., 2004; Reisberg et al., 2008; Schofield et al., 1997), age-associated cognitive decline (Schonknecht et al., 2005), as well as cognitive impairment no dementia (CIND: Palmer et al., 2002; 2003), questionable dementia (Lam et al., 2005a; 2005b) and isolated memory impairment (Bowen et al., 1997; Tierney et al., 1996). Each of these terms has been used to identify a pre-dementia stage of cognitive impairment (e.g., aMCI), with variable prognosis.

The use of the term 'preclinical' denotes a clinical condition with high progression to Alzheimer's disease, whilst the use of the word 'predementia'

denotes a stage of cognitive impairment with variable prognosis. It is important to emphasize that some persons might have a clinical presentation of cognitive impairment in the predementia state.

The MCI criteria have undergone significant change over the last 10 years. In 1958 Kral introduced the term "benign senescent forgetfulness" or (mild memory loss) to describe a mild memory disorder in the elderly that accompanied old age but was not considered to be abnormal or become pathological. Since this initial report, MCI has undergone a significant evolution over the past 10 years with a number of related concepts having emerged to describe memory impairment in old age. Some of these include: 'Cognitive Impairment no Dementia' (Jacova et al., 2008), 'Age Associated Memory Impairment' (Goldman and Morris, 2001). All of these terms have different criteria to identify a type of memory impairment that inevitably leads to dementia and Alzheimer's disease. Hence MCI research findings that are often disparate are likely to be partly due to this.

However, AD development is associated with objective cognitive decline prior to clinical diagnosis, it is vital to improve the diagnostic tools, such as brief screening tests able to detect the disease (Oksengard et al., 2004). This will facilitate the early detection. Recently, there has been increased awareness that persons who complain about their memory should be taken seriously and be assessed for dementia (Dufoil et al., 2005; Coley et al., 2008). In this setting, general practitioners are a critical point of early intervention (Brodaty et al., 2006; Ganguli et al., 2004)

In primary care, several brief screening tests have been proposed by Brodaty et al. (2006), including the GP Assessment of Cognition; the Mini-Cog and the Memory Impairment Screen. However none have been as universally accepted as the Mini-Mental State Examination (MMSE: Folstein et al., 1975) which continues to be used widely in clinical practice (Lavery et al., 2007). The question is whether brief screening tests, such as the MMSE or Mini-Cog are able to detect early signs of Alzheimer's disease, especially in high functioning individuals. The next section provides a more detailed discussion of the limitations of brief screening tests and the need for formal assessment.

3.2.1 Screening for early dementia

It has been suggested that neuropsychological assessment will play a pivotal role in the new diagnostic challenges faced by all clinicians (Bondi et al., 2008; Cummings et al., 2007). However, identifying subjects who are in the earliest phases and are likely to progress to Alzheimer's disease is not straightforward.

There are current concerns regarding the ability of brief screening tools such as the MMSE to identify impairment in cognitive domains other than memory. With new evidence identifying impairments in semantic memory and executive function (Ahmed et al., 2008; Hodges et al., 2006; Rouch et al., 2008), the sole reliance on brief screening tools seems inappropriate.

The MMSE is thought to be an insensitive screening tool for identifying both MCI and dementia (Tariq et al., 2006), especially in pre-morbidly high-functioning individuals with memory complaints (Geerlings et al., 1999; van Oijen et al., 2007). This has been attributed to its ceiling effect and lack of delayed recall condition (Chen et al., 2000). Also, impairments in those with MCI are mild and subtle (Gallassi et al., 2008) and not easily detected by simple global screening tasks.

In addition, the cut-off score to define impairment in those with MCI may not be appropriate. Solomon et al. (2002) reported that in a research clinic, an MMSE cut-off score of 24 and above, accurately identified Alzheimer's disease in 98 of 110 (89%) patients (mean age= 71.6, SD=7.5) with very mild impairment (mean MMSE score on initial assessment = 25.7 $\pm$ 1.4). This suggests that the MMSE is useful in identifying individuals in the later phases of the disease.

There are alternative screening tests highly relevant in the study of dementia, such as the Seven Minute Screen (7MS). The 7MS has been shown to reliably distinguish Alzheimer's disease from normal ageing and other dementias (e.g., Meulen et al., 2004; Solomon et al., 1998). However, it has not been examined in the study of subjective memory complaints (SMC). The 7MS is highly sensitive and specific in the identification of Alzheimer's disease (92.9%; 93.5%, respectively) and performance is not affected by age, sex or education (Solomon et al., 1998). It includes several tests, selected because they examine areas typically compromised in early Alzheimer's disease (orientation, memory, clock drawing and animal fluency).

Similarly, the Dementia Rating Scale (DRS: Mattis et al., 1976) is highly sensitive in identifying cognitive impairment that is associated with dementia. It also consists of several domains of cognitive functioning in addition to memory. The sensitivity and specificity of the DRS is 74% and 93%, respectively (Vangel and Lichenberg, 1995). Unlike the MMSE, age, education and IQ do not affect performance on the DRS (Chan et al., 2001).

The process of intervention begins with being able to identify deficits related to SMC by examining a wide range of cognitive functions. Neuropsychological assessment and more sensitive screening tests may help identify those with suspected cognitive compromise. As mentioned in Chapter 1 (Section 1.7), the early identification of Alzheimer's disease provides therapeutic opportunities for intervention at an earlier stage rather than waiting for significant decline to occur.

3.3 Mild cognitive impairment (MCI)

Mild Cognitive Impairment (MCI) is a research term proposed to denote a transitional stage between the cognitive changes of normal ageing and early dementia or Alzheimer's disease (Winblad et al., 2004; Petersen, 2004). Mild cognitive impairment manifests by presenting as cognitive impairment which is abnormal for age with preserved activities in daily living, but does not meet the criteria for dementia (Gauthier et al., 2006; Petersen, 2007). The memory loss is subtle and formal psychometric testing is needed to measure the decline. This occurs once the patient (or a reliable informant) has complained about their memory. The concept of MCI has

recently emerged as an important clinical entity, which has been proposed for entry into the DSM-V (Petersen and O'Brien, 2006).

Whilst many reports acknowledge MCI as a transitional stage between normal ageing and dementia (e.g., Allegri et al., 2008; Burns and Zaudig, 2002; Mariani et al., 2007; Orgogozo, 2006), not all accept MCI as a risk factor for dementia. Some reports indicate that MCI identifies subjects who already have the disease in the prodrome stage (Morris, 2006). Other reports describe MCI as a predementia stage which inevitably leads to Alzheimer's disease (e.g., Orgozozo, 2006).

The prevalence of MCI varies considerably and has been reported to be as high as 65% per year (Busse et al., 2006) in different studies. It has been estimated that patients with MCI progress to dementia at inconsistent rates, ranging anywhere from 10% to 15% per year (Luis et al., 2003) compared to healthy elderly who progress to dementia at a rate of 1 to 2% per annum (Petersen et al., 2001). In a clinical setting, Gabryelewicz et al. (2007) reported an annual progression rate of 7.3%. The variability in outcome has been attributed to many factors including, age of subjects, inconsistent application of the criteria, use of different tests to define impairment, different follow-up time periods, different entry levels and study setting. All of these factors vary widely between studies (Bondi et al., 2008; Small et al., 2007).

The working group of Winblad et al. (2004) revised the criteria for MCI to acknowledge non-amnestic presentations which may occur in the preclinical stage (Ribero et al., 2006; Ringman, 2005). The clinical syndrome

of MCI was divided into two broad subtypes: amnestic MCI (aMCI) characterized by the presence of isolated memory impairment, and non-amnestic MCI (naMCI) in which other cognitive functions rather than memory are mostly impaired (Winblad et al., 2004). The general criteria for MCI are provided in Table 3.1.

Table 3.1. General criteria for Mild Cognitive Impairment (MCI)

a. Absence of dementia according to DSM-IV or ICD-10
b. Self and/or informant reported cognitive decline
c. Impairment on cognitive tasks, and
d. preserved basic activities of daily living or minimal impairment in complex instrumental function

Adapted from Winblad et al. (2004).

Mild cognitive impairment (MCI) was divided further into three categories; i) single non memory domain MCI, with isolated impairment of a cognitive domain other than memory; ii) multiple domain amnestic MCI, characterised by a slight impairment of multiple cognitive domains including memory; and iii) multiple domains non amnestic MCI, with a slight impairment of multiple cognitive domains but without memory deficits (Petersen, 2007).

In terms of risk factors for Alzheimer's disease, there is consensus that aMCI represents the highest risk subtype and is described as the 'AD prodrome' (Gauthier et al., 2006; Lehrner et al., 2005). This supports the hypothesis that isolated memory loss favours a diagnosis of Alzheimer's

disease (Bowen et al., 1987; Petersen et al., 2001). However, one report indicated that there was no distinction between the two and that amnestic MCI is really just early Alzheimer's disease (Bruscoli and Lovestone, 2004). Likewise, some consider mdMCI to represent a more advanced stage of the AD prodrome (Alexopolous et al., 2006) and therefore greater risk. By contrast, the cognitive prognosis of the multiple domains MCI and single domain non-amnestic MCI subtypes appear more varied. These include; normal ageing, vascular dementia, frontotemporal dementia, dementia with Lewy body dementia, primary progressive aphasia or Alzheimer's disease (Guarch et al., 2008; Levey et al., 2006; Small et al., 2007).

Mild cognitive impairment is a highly debated concept that has been challenged on several grounds (e.g., Visser, 2007). The primary issue relates to MCI as a risk factor for Alzheimer's disease. Mild cognitive impairment is perceived to have poor predictive validity for Alzheimer's disease (e.g., Visser et al., 2006; Whitehouse et al., 2006). Research on MCI has shown that none of the MCI subtypes necessarily progress to Alzheimer's disease, but many remain stable or even improve their cognitive performance (e.g., Ganguli et al., 2004; Ganguli, 2006; Palmer et al., 2003; Perri et al., 2007; Visser et al., 2006).

Furthermore, there is no universally accepted approach to the objective identification cognitive impairment or agreement on the degree of objective impairment necessary to constitute decline. There is also confusion on how to define 'minimal impairment' or alterations in instrumental activities of daily living (Hodges, 2006). All of these factors

influence outcome. The inclusion of SMC in the criteria that define MCI is also disputed, and this is discussed in Section 3.4.

Despite ongoing controversies, MCI represents a step towards early diagnosis of Alzheimer's disease and the possibility of earlier therapeutic treatment of symptoms. It provides some indication of the boundary between normal ageing and dementia. Currently, MCI is hindered by the inconsistent application of the criteria, lack of consensus regarding the tests used to measure cognitive impairment and the role of SMC. A consensus on these issues may improve sensitivity and therefore prediction. Also, the issues surrounding memory complaints need to be resolved before MCI can be accepted into the DSM-V as a clinical syndrome. Thus, the challenge which remains for MCI is to consistently identify high-risk individuals with MCI who will progress to a dementia of the Alzheimer's type and other dementias from those who will not. It is also important to achieve a consensus regarding the criteria included in the diagnosis of MCI (Levey et al., 2006; Touchon, 2006). This will pave the way for the early diagnosis of Alzheimer's disease and allow identification of subjects with high or ultra high risk. This will enable the development of strategies for early intervention.

3.4 The neuropsychology of Alzheimer's disease

As we progress towards early identification and treatment of Alzheimer's disease, understanding the neuropsychological impairments in different pre-dementia states will become increasingly important. This

section commences with a discussion of the typical language impairments observed in Alzheimer's patients, and then proceeds to highlight the consistency of impairment observed on tasks of episodic memory, as measured by delayed recall. To date, there is considerable agreement that episodic memory impairment remains one of the most defining neuropsychological observations during the preclinical phase of Alzheimer's disease, and represents the hallmark of the syndrome of dementia of the Alzheimer's type.

3.4.1 Language impairment

Alzheimer's disease is characterized by disorders in the semantic system affecting various aspects of language ability (Bayles and Tomoeda, 1983; Gainotti, 1992; Hodges and Patterson, 1995; Vogel et al., 2005). Language deficits occur very early in the course of the disease and are evident on tasks including: the 'Supermarket Task' (Martin and Fedio, 1983), verbal fluency (Hodges et al., 1991), confrontation naming (Gainotti, 1992), object sorting (Martin et al., 1986), free-word association (Abeysinghe et al., 1990), and naming of famous faces (Thompson et al., 2002). These deficits contrast with speech, which remains fluent and articulate (Kertesz et al., 1986) well into the later stages of the disease.

The most sensitive test to identify early Alzheimer's disease is category fluency (Hodges et al., 2006; Salmon et al., 2002). An early decline in category fluency performance has been reported to occur in the pre-dementia phase of Alzheimer's disease (Raoux et al., 2008) and in the

absence of other semantic deficits (Monsch et al., 1992). It contrasts with letter fluency, which remains unimpaired. The deficit in category fluency is demonstrated by the Supermarket Task, when asked to generate items found in a supermarket, patients with Alzheimer's disease generate fewer examples from each category in addition to providing the category label to which an item belongs rather than the item (e.g., vegetable instead of carrot) (Martin and Fedio, 1983).

Confrontation naming impairment is also a prominent feature of early Alzheimer's disease, which remains insensitive to the effects of normal ageing (Flicker et al., 1997). It is thought that naming deficits tend to reflect a loss of detailed subordinate category level information (Rosch et al., 1976). The deficit in naming is apparent when patients with Alzheimer's disease are asked to name an object, the same pattern of impairment observed on category fluency emerges, in addition to providing the name of another object from the same semantic category (e.g., naming a "banana" an "apple") (Bayles and Tomoeda, 1983).

However, the mechanisms underlying semantic deficits in Alzheimer's disease are controversial. Some reports argue that these deficits reflect difficulty accessing a semantic system, which is essentially intact (Hillis et al., 1995; Nebes, 1989), whilst others argue that there has been a loss of semantic knowledge (Chertkow et al., 1992; Flicker et al., 1997; Garrard et al., 2005; Hodges et al., 1991; Martin and Fedio, 1983). The evidence favours the latter account of a loss of semantic knowledge (e.g., Chertkow et al., 1992; Gainotti, 2006) as observed by item consistency in an animal

decision task. The report by Chertkow et al. (1992) demonstrated a striking item-to-item correspondence, such that when a patient could not correctly identify an animal on an Animal Decision task, they could not answer probe questions about the animal.

This argument was further extended to include the issue of category-specificity within the semantic system and whether patients with Alzheimer's disease are more impaired on living items (e.g., animals) than non-living items (e.g., baseball bat). The issue of category specificity has been criticized as being experimentally induced by the test material used. Category-specific semantic impairments have been attributed to item familiarity, name frequency and visual complexity of the items (Parkin and Stewart, 1993). Thus, better performance is expected on living items that are identified primarily by their visual properties, which provide preferential access to stored knowledge. In contrast, non-living items are identified in terms of their functional properties, which make identification more difficult, because the person must draw on semantic knowledge (Chertkow et al., 1992). In spite of the ongoing controversy, evidence strongly favours categories of knowledge (Gainotti, 2006; Rosch et al., 1976).

These findings are of interest because of their implications for the early diagnosis of Alzheimer's disease. These issues highlight the potentially confounding effects of test material and the deficits that will manifest as a consequence. This is relevant for new concepts such as mild cognitive impairment (MCI), which relies on sensitive tests not influenced by the inherent properties of the test material. Consideration of these issues may

help to clarify the importance of semantic memory deficits that have been increasingly recognized as impaired during the dementia prodrome (e.g., Amieva et al., 2005; Hodges et al., 2006; Saxton et al., 2004).

3.4.2 Neuropsychological predictors of Alzheimer's disease

Alzheimer's disease is characterised by a long preclinical stage of cognitive decline during which impairments have been demonstrated across a range of cognitive domains including, episodic and semantic memory, psychomotor speed, attention, verbal ability, visuospatial skill and global indicators of cognition, such as the MMSE (Amieva et al., 2005; Arnaiz and Almkvist, 2003; Bäckman et al., 2005; Bäckman and Small, 2007; Morris, 2006; Orgogozo, 2006). Despite the multiple nature of the impairments (Bäckman et al., 2004b; Twamley et al., 2006), there is agreement that deficits in episodic memory, especially if isolated to this domain, predict Alzheimer's disease. However, there is a lack of consensus regarding how early the deficit appears and the sequence of deficit acquisition leading to Alzheimer's disease. These deficits have been shown by many longitudinal studies examining cognitive decline over time using healthy older people and patients at increased risk of Alzheimer's disease due to family history or MCI (De Jager et al., 2003; Fox et al., 1998; Ganguli et al., 2004; Guarch et al., 2008; Howieson et al., 2008; Visser et al., 2006).

Episodic memory impairments

There is no doubt that deficits in episodic memory represent the hallmark of Alzheimer's disease and can be observed many years before clinical onset of the disease (Bäckman et al., 2005; Bondi et al., 2008). Of the many cognitive tasks studied, deficits in episodic memory, especially in delayed recall, appear to be the most sensitive early clinical indicator of the dementia prodrome (Bondi et al., 1995; Butters et al., 1987; Chen et al., 2001; Elias et al., 2000; Linn et al., 1995; Perri et al., 2007; Solomon et al., 1998; Tierney et al., 1996; 2005). The deficit typically manifests in terms of a poor ability to learn and remember new information after a short period of delay, such as in a word-list learning task (Andersson et al., 2006; Bäckman and Small, 1998; Gainotti et al., 1998; Guarch et al., 2008). Recent evidence has identified accelerated forgetting rates and increased sensitivity to non-word lists during retrieval (Manes et al., 2008). The impairment in episodic memory is consistent with the critical role of the medial temporal lobe and hippocampus in the formation of new memories (Tulving and Markowitsch, 1998), which is affected in the early stages of Alzheimer's disease.

The Rey Auditory Verbal Learning Test (RAVLT)

The predictive value of the RAVLT (Rey, 1964) in determining which aspects of episodic memory are more impaired in preclinical Alzheimer's disease is well established (Andersson et al., 2006; Bäckman et al., 2001; Estevez-Gonzalez et al., 2003; Gainotti and Mara, 1994; Gainotti et al., 1998;

Saxton et al., 2004; Woodard et al., 1999). Patients who are likely to develop Alzheimer's disease lose more information over a brief delay than other patients with amnesia or other dementing disorder (Gainotti et al., 1998). In particular, poor delayed recall combined with a failure to benefit from semantic cues to facilitate remembering may be an index of more rapid progression to Alzheimer's disease (Andersson et al., 2006; Buschke et al., 1999; Dubois and Albert, 2004; Estevez-Gonzalez et al., 2003; Grober et al., 2000; Lehrner et al., 2005; Perri et al., 2007; Saxton et al., 2004; Sarazin et al., 2007). Thus, tests of delayed recall are now frequently used to identify subjects at high risk of Alzheimer's disease (e.g., Andersson et al., 2006; Cargin et al., 2007 and 2008; Estevez-Gonzalez et al., 2003; Lerhner et al., 2005; Saxton et al., 2004).

Based on evidence that the RAVLT is an early neuropsychological marker of Alzheimer's disease, Estevez-Gonzalez et al. (2003) recruited 70 subjects (mean age 67) from the community with SMC to examine if the RAVLT could identify which subjects with SMC would develop AD over the next 2 years. Two years later, 27 (39%) patients with SMC were diagnosed with probable AD; 26 (37%) with MCI and 17 (24%) remained cognitively normal. The authors reported the profile of impairment which characterised the 27 Alzheimer's patients, consisted of a profound amnestic disorder as evidenced by lower baseline test scores and frequently recalling zero words in the delayed recall test (Trial 6) unadjusted for age or having a percentage of forgetting (difference between Trial 5 and Trial 6) of more than 75%.

3.5 Subjective memory complaints (SMC)

Memory complaints are common among older adults and often considered an initial symptom of cognitive impairment; possibly heralding the onset of a dementia syndrome (Reisberg et al., 2008). This is evidenced by their inclusion in the criteria that define MCI. Subjective memory complaints (SMC) refers to reports of concern about memory performance in relation to everyday functioning, such as remembering names and recalling where one has placed things in response to a question on memory (Coley et al., 2008; Mitchell, 2008b).

Self-reports of memory loss are generally perceived as problematic and have been criticised on several grounds (Ahmed et al., 2008; Jungwirth et al., 2004). The techniques used to assess SMC vary widely across studies; some use a single question on everyday abilities or probe about changes in memory (Estevez-Gonzalez et al., 2003; Palmer et al., 2003; Kim et al., 2006), whilst others use questionnaires to define SMC (Perri et al., 2007), such as the Memory Assessment Clinic-Questionnaire. The clinical significance of each method remains to be determined, as not all measurement techniques are equal. The lack of consensus on the criteria that define and quantify SMC has produced inconsistent reports regarding its clinical utility (Abdulrab and Heun, 2008; Mitchell, 2008a).

Furthermore, the complaint is not always detected on psychometric testing or spontaneously disclosed when questioned directly (Lavery et al., 2006), despite being consciously aware of a change in their memory (Lam et al., 2005b; Wong et al., 2006). In this regard, subjects with a clinically

significant disorder can be excluded, underestimating the clinical utility of MCI and progression rates to dementia (Mitchell, 2008b). Jungwirth et al. (2004) reported that a significant number of their subjects with objective memory impairment (94%) did not complain about their memory. This issue is problematic for the concept of MCI and has led to calls for the removal or separation of SMC from MCI (Purser et al., 2006; Mitchell, 2008b).

It has been demonstrated that patients with more severe cognitive impairment or with Alzheimer's disease underestimate their memory difficulties compared to informant information (Farias et al., 2005). A meta-analysis examining the clinical significance of SMC reported that 60% of people with dementia do not complain of simple memory complaints even on specific questioning (Mitchell, 2008b). It has been suggested that patients in the early to mild stages of Alzheimer's disease have poor insight into their memory difficulties (Kim et al., 2006). In this regard, recommendations specify this information can be provided by a relative or reliable informant, such as a general practitioner (Mackinnon et al., 2003; Winblad et al., 2004). However, whilst this is important in severely impaired subjects, the information provided by an informant may introduce bias. Some subjects may be able to hide problems by the use of lists and other strategies. Thus, only those with more severe impairment would be noticed by informants.

It remains unclear, however, whether SMC are a useful clinical indicator. Some studies of elderly subjects have reported an association between SMC and a subsequent diagnosis of dementia (Geerlings et al., 1999; Jorm et al., 2005b; St John and Montgomery, 2002; Wang et al.,

2004a; Wong et al., 2006). Jorm et al. (2005b) reported older males who developed dementia had SMC at least 3 to 6 years earlier, often before objective deficits could be measured on tests of episodic memory, orientation and language. Other studies have not supported the association (Cargin et al., 2008; Jessen et al., 2007; Minett et al., 2008) and have attributed it to older age (Park et al., 2007; Treves et al., 2005). Further discussion of the relationship between memory complaints and objective memory impairment and dementia is provided in section 3.6.

Subjective memory complaints are common across a range of clinical disorders, and are consistently reported to be associated with psychoaffective disorders, such as depression, anxiety (Jorm et al., 2001; Jungwirth et al., 2004; Lautenschlager et al., 2005; Minett et al., 2005; Minett et al., 2008; Wong et al., 2006), personality disorders and neuroticism (Dux et al., 2008). A report by Lautenschlager et al. (2005) showed that SMC are more prevalent in subjects with depression and anxiety than with dementia. Psychoaffective factors could lead to an overestimation of memory problems, especially in those with MCI (Kumar et al., 2006). It is well known that subjects with depression overestimate their memory difficulties and complain more spontaneously (Steffens and Potter, 2008). However, not all studies support the link between depression and SMC (St. John and Montgomery, 2002).

The connection between memory complaints and Alzheimer's disease is rather complex and many factors have been implicated in the relationship. Some of these include; older age, psychological factors and different

measurement and techniques. This makes the cognitive burden incurred by patients presenting with SMC difficult to objectively measure, especially in the early stages of disease when memory complaints are difficult to assess. All of these factors have made it difficult for SMC to consistently predict dementia.

Nevertheless, SMC play an important role in the pathway to care for persons with cognitive disorders. Whilst SMC may be non-specific to a number of disorders and their role in diagnostic criteria may require further refinement, they do seem to increase the likelihood that the individual will seek medical attention. Thus, identifying a cohort that may better respond to the available treatment therapies.

Collectively, these issues have led to uncertainty about the clinical significance of SMC, especially in defining MCI. Disagreement remains with respect to the aetiology and clinical significance of SMC. Reports are now calling for memory complaints to be separated from MCI (Allegri et al., 2008; Mitchell, 2008) and for a consensus to be reached on the criteria to define SMC that reliably predict progression to MCI (Reisberg et al., 2008). The separation of SMC from MCI may help to clarify the role of SMC in cognitive function and possibly represent a step towards earlier diagnosis.

3.6 The predictive role of subjective memory complaints

Prompted by the recent availability of effective symptomatic treatment and the prospect of identifying a pre-dementia diagnosis of Alzheimer's disease, clinical inquiry into the role of SMC in cognitive impairment and

dementia has significantly escalated in recent years (Abdulrab and Heun, 2008; Ahmed et al., 2008; Coley et al., 2008; Mitchell, 2008; Reisberg et al., 2008; Reisberg and Gauthier, 2008). Subjective memory complaints by self-report or an informant are part of the criteria for MCI. Whilst, MCI is a clinical condition with an increased risk of developing dementia, the risk of developing dementia by people with SMC is much less clear.

Numerous studies have considered the importance of memory complaints as a predictor for future cognitive decline and dementia with variable prognosis. The parameters and brief outcome of these studies are listed in **Table 3.3**. This section will provide a brief review of recent evidence exploring potential relationships between SMC and cognitive function drawing on findings from community-dwelling residents; longitudinal population-based studies, memory clinics, tertiary referrals, and primary care outpatients. Also, despite the many terms used to describe memory complaints, for ease of reference the term SMC will be adopted to describe all memory complaints.

3.6.1 Subjective memory complaints (SMC) and dementia

Several recent cross-sectional studies examining the association between SMC and dementia have reported inconsistent findings (e.g., Archer et al., 2006; Clement et al., 2008; Jessen et al., 2007; Minett et al., 2008; Park et al., 2007; Rouch et al., 2008; Snitz et al., 2008). For example, Jessen et al. (2007) examined the association between SMC, cognitive function and depression in 2389 non-demented subjects (mean age 80) from

a population-based cohort and identified a relationship between SMC in tasks of daily living with depressive symptoms. However, these authors also reported an association between SMC and lower scores on verbal delayed

Table 3.2 Longitudinal studies examining subjective memory complaints (SMC) as a predictor of cognitive decline or dementia

Study Setting	Screening Test Score; n	Age; mean years (SD)	Proportion with SMCs	SMC quantified	F/UP (years)	Outcome
Community						
Cargin et al. (2008)	32 normal 68 memory declining	69 (8)	60% normal 75% declining	Single question CFQ	2.5	No association
Estevez-Gonzalez et al. (2003)	70 subjects with SMCs	67 (NR)	100%	Single question	2	AD (27; 39%); MCI (26; 37%); Normal (17; 24%)
Geerlings et al. (1999)	2169 non-demented	65-84	11.5%	Single question	3.2	Alzheimer's disease (77; 4%)
Jungwirth et al. (2008)	382 normal; 202 questionable impairment	75-76	49% of normal gp 58% impaired gp	Four single questions	2.5	AD in 46 (12%) normal subjects; AD in 44 (22%) subjects with questionable impairment,; Association between verbal memory and AD in both normal and impaired groups
Kim et al. (2006)	686 non demented; included 133 (19%) with MMSE<21	71.3 (5.2)	19.7%	GMS	2.4	Dementia (57; 8.3%) 3.4% per annum
Purser et al. (2006)	3673: 72% normal; 25% MCI; 3% severe impairment	> 65	34%	Self-rating	10	Cognitive decline; no association
St. John et al. (2002)	1416 normal subjects	76 (NR)	21%	Single question	5	Dementia in 22.6% of total sample; CIND in 18.8% of total sample
Wang et al. (2004a)	1,883 non-demented	74.6 (5.8)	4.6%	SMRS	5.2	Cognitive decline and dementia in 21% of sample
Memory Clinic						
Gallassi et al. (2008)	92 non-demented subjects with SMCs	67.4 (10.4)	100%	MAC-Q	.75	MCI (49; 53%)
Glodzik-Sobanska et al. (2007)[1]	230	67.0 (8.4)	81%	GDS	8.4	MCI or dementia (84; 37%); normal (111; 48%); unstable (35; 15%)
Huen et al. (2006)	757 non-demented	> 55	50.6%	Single question	4.7	AD (38; 5%)
Lehrner et al. (2005)						6.5%
Guarch et al. (2008)[1]	34 normal; 47 AD; 43 with SMCs	67 (NR)	35%	Single question;	2	AD in 10 subjects with SMCs; associations low baseline global scores, esp. episodic and visual memory
Treves et al. (2005)	211 subjects with SMCs	67.4 (9.4)	100%	Single question	3	Dementia (5%)
Population-based						
Crowe et al. (2006)	55 subjects with aMCI	$\geq$65	N/A	6 item of the PIC; 14 items of the MFQ; 2 single qus.	2	Cognitive decline on MMSE; no association

Dufoil et al. (2005)	733 MMSE 27.6±2.1; range 18-30	59-71	NR	CDS	4 and 6	Cognitive decline on MMSE , WAIS and Delayed Recall
Jorm et al. (2005)	3734 CASI > 74	71-93	NR	4 single questions	6	Dementia in 52; associations with episodic memory
Mol et al. (2006)	557	55-85	26.6%	Single question	6	Cognitive decline at baseline in some specific domains (Delayed recall, info processing speed); no association at follow-up
Palmer et al. (2003)	1435 dementia free	75-95 years	48%	Single question	3	Alzheimer's disease and dementia (18%)
van Oijen et al. (2007).	6927	69.5 (9.1)	19%	Single question	9.1	Alzheimer's disease (568; 8%)

NR=Not reported;
CFQ= Cognitive Failures Questionnaire
GMS=Geriatric Mental State Schedule;
SMRS=Subjective Memory Rating Scale
MAC-Q=Memory Assessment Clinic-Questionnaire
CDS=Cognitive Difficulties Scale;
IPC= Personality in Intellectual Aging Contexts
MFQ=Memory Functioning Questionnaire
CASI=Cognitive Abilities Screening Instrument

recall in non-depressed subjects, which they interpreted as indicating the presence of early Alzheimer's disease.

Similarly, Minett et al. (2008) also examined the association between SMC, cognitive function and depression in 114 non-demented subjects (≥50 years) with and without SMC at baseline from a geriatric clinic. These authors reported an association between SMC and depression as evidenced by the lack of difference in cognitive function in subjects with and without SMC. A domain specific association in non-depressed subjects with SMC was apparent in animal fluency.

In contrast, Snitz et al. (2008) examined the association between SMC and memory performance in 276 older primary care outpatients (mean age=73.2) with MMSE scores >19. These authors found SMC were significantly associated with memory test performance, even after controlling for depressive symptoms and education. A limitation of this study is that patients with dementia may have been included as evidenced by the low MMSE cut-off score.

Likewise, a community study by Rouch et al. (2008), examined the association between memory complaints, cognitive and executive function and affective disorders in 937 non-demented community-dwelling subjects (mean age=65). These authors reported an association between cognitive complaints with lower scores on verbal memory (Free and Cued Selective Reminding Test) and executive function (Digit Symbol Substitution Test, Trail Making B), independent of affective problems.

Whilst the above studies suggest a potential association between SMC and cognitive impairment, they highlight that additional information on the role of SMC can be obtained by using different neuropsychological tests other than brief screening instruments. Although these cross-sectional studies provide some clinical information, they cannot examine cognitive changes associated with SMC over time. Hypotheses relating to SMC and cognitive decline are more appropriately addressed by longitudinal studies (Jungwirth et al., 2008; Sinforiani et al., 2007).

There are many studies that have examined the course of SMC on cognitive decline over varying time intervals (see Table 3.3). Several studies have consistently reported associations in older subjects with SMC and normal baseline rather than impaired cognition, frequently measured by the MMSE. Most of the studies reporting a positive relationship have used a single question to measure SMC. These studies are in support of the hypothesis that SMC predict cognitive decline and Alzheimer's disease.

In an assessment of SMC, Geerlings et al. (1999) recruited 2169 randomly selected elderly subjects (age range 65-84) from the community and categorized them as having either normal baseline cognition (MMSE= 26-30; n= 1956) or impaired baseline cognition (MMSE <26; n=213). After a mean interval of 3.2 years, SMC, measured by a single question were associated with a threefold increase in the risk of developing Alzheimer's disease among young elderly subjects (aged 65-74) with high MMSE scores ($\geq$26). A total of 77 patients developed Alzheimer's disease. Notably, no

association was found among those with low MMSE scores (<26), SMC and Alzheimer's disease.

In a similar study examining the association between SMC and Alzheimer's, Jungwirth et al. (2008) recruited 584 non-demented community residents aged 75-76 years at baseline. Subjects were categorized as either cognitively healthy (n=382), defined by a MMSE score of ≥28 (28-30) or as having questionable cognitive impairment (n=202), defined by a MMSE score ranging from 23-27. Over a follow-up period of 2.5 years, a univariate analysis showed that SMC as quantified by four single questions predicted Alzheimer's disease in 46 subjects with normal baseline cognition compared to none of the subjects with questionable cognitive impairment. Additionally, a multivariate analysis showed that only impaired verbal memory and anxiety predicted Alzheimer's disease in normal subjects, whilst memory performance independently predicted Alzheimer's disease in 44 subjects with cognitive impairment. Like the previous study, both studies concluded that SMC have merit in predicting dementia, despite the lack of supportive evidence from the MMSE.

A study by van Oijen et al. (2007) examined education level on SMC and risk of Alzheimer's disease in 6927 non-demented subjects recruited from a population-based cohort, mean age 69.5 (SD=9.1) years. Over a follow-up period of 9.0 years, endorsement of a single question on SMC was associated with three times the risk of Alzheimer's disease in subjects who were highly educated and without objective deficits (MMSE score ≥29) compared to subjects with low education and equally high MMSE score

(≥29); their risk of Alzheimer's disease was 1.5 times. However, as performance on the MMSE deteriorated, the risk of Alzheimer's disease associated in highly educated subjects was similar to that of persons with low education.

Gallassi et al. (2008) examined the outcome of SMC as either NCI (No Cognitive Impairment; MMSE score >23.8) or MCI according to established criteria Winblad et al. (2004) by recruiting 92 non-demented outpatients (MMSE=28.1 ± 2.0; mean age=67.4 ± 10.4) with SMC from a tertiary setting. Over a follow-up period of 9 months, self-reported SMC, measured with the Memory Assessment Clinic Questionnaire predicted MCI in 49 subjects with SMC. Notably, many of the MCI patients had mild impairment usually confined to a single cognitive domain. Comparison of the two groups showed that the 43 NCI patients were on average younger (63.3±11.2 and 71.1±8.1), had higher education (10.8 and 8.0 years) and higher MMSE scores (29.09 and 27.30) compared to the MCI patients who had more severe depression and irritability. This study highlights the effects of age on memory complaints. That is, there is a strong association with age in those identified as having MCI.

However, not all studies have reported SMC as a prerequisite for cognitive decline and dementia (St. John and Montgomery, 2002; Wang et al., 2004a). In an assessment of SMC on future dementia, Wang et al. (2004a) recruited 1, 883 non-demented community-based subjects (mean age of 74.6 ± 5.8) from a population-based cohort with no baseline objective cognitive impairment on the basis of their score of >91 on the Cognitive

Ability Screening Instrument. Over a 5-year follow-up interval, SMC was associated with cognitive decline and dementia in 15% of subjects with SMC and 6% without SMC. Notably, the risk of dementia was 6 times greater in subjects reporting SMC at the age of 70 compared to a risk of 1.6 times at the age of 80.

However, other studies examining the role of SMC have included subjects with questionable cognitive impairment as evidence by the low MMSE cut-off scores (<24) or have included subjects with baseline cognitive impairment, such as aMCI (e.g., Crowe et al., 2006; Dufouil et al., 2005; Kim et al., 2006; Lerhner et al., 2005; Palmer et al., 2003; Treves et al., 2005), adversely influencing cognitive decline. In spite of using a population with lower baseline cognitive abilities, these studies also report positive associations between SMC and cognitive impairment.

Dufouil et al. (2005) recruited 733 subjects (aged from 59-71) from a population-based longitudinal study to explore whether the number of cognitive complaints can be used to predict future cognitive decline. Their mean baseline MMSE scores were (27.6 $\pm$ 2.1, range 18-30). After an interval of 4 years, those who endorsed a greater number of SMC, measured with the Cognitive Difficulties Scale were associated with greater prior cognitive decline as measured by the MMSE, WAIS, and Delayed Recall. Also, more SMC at 4-year follow-up were associated with greater cognitive decline in MMSE scores 2 years later, compared with subjects with no apparent cognitive decline in the 4-year period preceding the cognitive complaint assessment. This study supports the use of SMC as a useful

indicator of measured cognitive decline and in predicting future decline, prior to observable detection by testing.

In an assessment of SMC on cognitive decline, Crowe et al. (2006) recruited 55 subjects $\geq$65 years (mean age = 74 years) from a population-based cohort who met the criteria for aMCI at baseline. Inclusion into the study was based on obtaining a score $\geq$23 on the MMSE; the presence of SMC was not a compulsory inclusion criterion. Multiple regression analysis showed that, over a two-year follow-up period, those with SMC at baseline predicted future decline in memory in subjects with aMCI. Whilst this study suggests that patients with aMCI have some insight into their memory difficulties; a limitation of this study is the presence of baseline cognitive impairment.

Likewise, Kim et al. (2006) examined the association between changes in self-reported memory complaints and dementia in 686 non-demented subjects (mean age=71.3, SD=5.2) living within the community. Over a follow-up period of 2.4 years, SMC, measured using the Geriatric Mental State Schedule was associated with a higher rate of dementia in subjects with persistent SMC (present on both occasions) and transient SMC (present only at baseline) compared to the subjects without SMC at both points. The incidence of dementia was 3.4% per annum. Subjects with persistent SMC had 4.8 times greater risk of dementia, whilst subjects with transient SMC had a dementia risk of 2.3 times. Notably, dementia was not associated with new complaints at follow-up. However, when adjustment was made for baseline cognitive impairment (n=133, defined by MMSE $\leq$

21), the association between baseline SMC and dementia was weakened.

However, not all studies have supported the role of SMC with cognitive impairment (e.g., Cargin et al., 2008; Dik et al., 2001; Jungwirth et al., 2004; Mol et al., 2006; Purser et al., 2006), irrespective of baseline functioning. This may be partially attributed to methodological differences.

Mol et al. (2006) assessed SMC on cognitive function by recruiting 557 healthy subjects (mean age=67.7, SD) from the Maastricht Ageing Study who at baseline had MMSE scores >24. At baseline, SMC, measured with a single question was associated with lower scores on both the information processing speed task and delayed recall task. However, over a mean interval of six years, baseline SMC no longer predicted a change on any cognitive task in subjects with and without SMC. These authors found that SMC had higher correlations with symptoms of depression and anxiety, compared to subjects with cognitive decline alone. A limitation of this study concerns the exclusion of 78 subjects with SMC who were not worried or hindered by their forgetfulness. It is possible that some of these SMC subjects may have developed demonstrable cognitive decline at follow-up.

Cargin et al. (2008) examined SMC by recruiting high functioning non-demented subjects residing in the community (mean age=69, SD=8) on the basis of scoring $\geq$28 on the MMSE or above the age appropriate limit on the Short Blessed Test. Subjects were grouped according to their performance on a task of Delayed Recall identified as either normal controls (n=68) or memory declining (n=32). Over a follow-up period of 2.5 years, SMC, as measured by the Cognitive Failures Questionnaire were unrelated to

objective cognitive functioning in both normal controls and those with objective memory decline. These authors reported stronger associations between SMC and the subject's level of depression, anxiety and general mental health.

In a retrospective assessment of SMC on cognitive decline and dementia, Glodzik-Sobanska et al. (2008) examined the medical records of 230 cognitively normal elderly subjects (mean age=67.0, SD=8.4 years) attending a memory clinic. Nineteen percent had a Global Deterioration Scale rating of 1 and 81% had a rating of 2, where a rating of 1 indicated no SMC and a rating of 2 indicated awareness and complaint of memory change in the absence of objective evidence. Over a period of 8.4 years, SMC, measured using the Memory Assessment Clinic Questionnaire, predicted both future decline to MCI or dementia, and an unstable diagnosis. The outcome consisted of: cognitively normal (n=111), declining to MCI or dementia (n=84), and diagnostically unstable (n=35). Compared to the unstable group, the declining group was older, had lower depression scores and greater deficits in delayed memory. The presence of more severe complaints did not further increase the risk of cognitive decline in this group. In contrast, the risk of an unstable diagnosis was associated with a higher level of anxiety, more severe memory complaints, and younger age. Despite the retrospective nature, this study gives some support to SMC predicting cognitive decline (MCI) and dementia in these cognitively normal subjects attending a memory clinic.

3.7 Summary and conclusions

In this review of the literature, the clinical utility of SMC to identify subjects who are likely to have cognitive impairment or develop dementia remains unclear. The studies reviewed have varied widely in the depth and type of assessment of SMC and cognitive function and the populations being examined. The differing methodologies are likely to have contributed to the variable cognitive prognosis associated with SMC. These being: retaining normal cognitive function, a fluctuating course to developing a dementia syndrome. In addition to cognitive function, SMC have also been linked to different clinical conditions, such as depression.

A large extent of the data examining the relationship between SMC and cognitive function has been obtained from studies using older populations. The average age of the subjects has been > 70 years (see Table 3.3). As the prevalence of SMC increases with age, deficits in older subjects might be reflective of normal ageing. Much less is known about the role of SMC in middle-aged subjects and whether they can be used to predict cognitive impairment or dementia.

It is interesting that the majority of the studies have employed a very limited assessment of cognitive ability. Namely, much of the current knowledge on SMC is provided by studies that have employed simple measures of global cognitive functioning (e.g., MMSE). This is relevant because the initial deficits are often subtle (Clement et al., 2008) and can be missed by the use of these tasks. Many studies have neglected to consider a

wider array of cognitive tasks which limits the available evidence regarding the clinical utility of SMC.

This review has shown that very few studies have examined the role of SMC in predicting cognitive impairment in subjects below the age of 70 years, especially for community samples. Far fewer studies have used formal cognitive assessments to examine SMC and other risk factors to examine their importance in identifying younger subjects who develop dementia later in life.

Chapter 4: Aims and Hypotheses

4.1 Rationale for study

As shown in this review of the literature, the clinical utility of SMC to identify subjects who develop dementia is unclear. SMC have been related to many different cognitive outcomes. These include retaining normal cognitive function, a fluctuating cognitive performance and the development of a full dementia syndrome of the Alzheimer's type (Gallassi et al., 2008; Glodzik-Sobanska et al., 2008; Jungwirth et al., 2008; van Oijen et al., 2007).

Much of what is currently known about SMC has been obtained from studies that have predominantly used older subjects, brief screening instruments or a limited range of tests (Geerlings et al., 1999; Palmer et al., 2003). Also, a majority of these studies have recruited subjects from ongoing studies on healthy ageing, such as the Maastricht Ageing Study by Mol et al. (2006) or the Iowa 65 + Rural Health Study by Purser et al. (2006). These studies have not employed fully comprehensive cognitive assessments. It remains unclear whether the use of SMC can predict the subsequent development of cognitive impairment in subjects under the age of 70 years.

The studies reviewed have differed in their methodology, which may also account for the observed discrepancies regarding the role of SMC in cognitive impairment.

Firstly, many studies have examined memory complaints in older subjects over the age of 70 (e.g., Palmer et al., 2003; Jungwirth et al., 2008). Since the prevalence of SMC increases with age, some of these findings may reflect normal ageing rather than the effects of memory complaints on cognition. Much less is known about the role of SMC in younger subjects under the age of 70 years. Current available evidence examining younger subjects is scarce (Cargin et al., 2008; Dufoil et al., 2005; Jorm et al., 2004; Rouch et al., 2008) It is not known whether memory complaints are useful in predicting dementia in younger subjects.

In addition, many of the studies reviewed have used simple measures of global cognitive functioning (e.g., MMSE). The MMSE is considered to be insensitive for identifying both MCI and dementia (Tariq et al., 2006). This is relevant because the initial deficits are often subtle (Clement et al., 2008) and can be missed by the use of these tests. Based on earlier evidence provided by Solomon et al. (2002) the MMSE may be more appropriate for identifying individuals in the later phases of the disease. Many studies do not consider a wider array of cognitive tasks. This limits the available evidence regarding the role of SMC in cognitive function. The few studies that have used several neuropsychological tests to examine other cognitive domains frequently report domain specific associations, even when no

impairment on the MMSE is apparent (Jessen et al., 2007; Minett et al., 2008; Mol et al., 2006; Rouch et al., 2008).

Finally, a methodological issue relates to the techniques used to quantify SMC. These have varied widely across studies. Some use a single question; others employ questions about everyday abilities, or memory questionnaires. This has rendered comparisons between studies difficult. Of the studies reviewed, the use of questionnaires has to lead to the exclusion of subjects who did not meet the threshold for having SMC, despite reporting a memory complaint (e.g., Mol et al., 2006; Wang et al., 2004a).

The current study was specifically designed to address these issues. The main aim of the present study was to identify subjects who are at greater risk of developing Alzheimer's disease at an earlier age, based on their risk profile and neuropsychological assessment. Therefore, this study examines the role of SMC as well as established risk factors (i.e. age, family history) on cognitive function using a comprehensive neuropsychological test battery. These tests assessed cognitive processes thought most likely to be impaired in the early phases of a dementia of the Alzheimer's type.

To identify subjects at greater risk of developing Alzheimer's disease at an earlier age, community-dwelling subjects (aged from 50-79) were recruited. GP referrals, or those under the care of a specialist in a memory clinic, are likely to have a more advanced stage of cognitive impairment or dementia and were deemed to be unsuitable candidates for this study.

As SMC has been linked with an increased risk of cognitive decline and dementia (Jungwirth et al., 2008; Gallassi et al., 2008; Geerlings et al.,

1999), this study recruited subjects from the community with SMC. However, as SMC has also been linked to different psychoaffective states, a well-validated episodic memory task was used to further classify the subjects into three groups (discussed below). This occurred after the initial analysis of both subjects with SMC and without SMC.

As reviewed in Chapter 2, there are many risk factors which contribute to an increased risk of Alzheimer's disease. Therefore, this study applied exclusion criteria to minimise the possibility that SMC were due to other psychiatric (e.g., depression) medical conditions (e.g., stroke), drug or alcohol problems and head trauma. However, subjects with mild (non-major) depression were not excluded because we were also interested in examining the relationship between SMC and mild depression.

To maximise the possibility of identifying subjects with an increased risk of Alzheimer's disease, subjects were screened to identify their ApoE genotype. The present study was also interested in examining whether the ApoE ε4 affects cognitive function over time in subjects with SMC. Previous research indicated that over a 33 month interval, ApoE ε4 carriers aged between 50 and 59, showed a modest decline in memory skills from the age of 50 onwards (Caselli et al., 2004). There have been few studies that have examined the effect of the ApoE ε4 and its association with cognitive decline using younger subjects (Caselli et al., 2004; Christensen et al., 2008; Jorm et al., 2007), especially in subjects with SMC (Cargin et al., 2008).

As discussed in Chapter 3, deficits in episodic memory, especially in delayed recall, appear to be sensitive early clinical indicators of the

Alzheimer's dementia prodrome (Andersson et al., 2006; Howieson et al., 2008; Guarch et al., 2008). Therefore, performance on the delayed recall task was used to classify subjects as having normal memory, SMC or aMCI.

It is important to emphasize that in the present study subjects with aMCI were not defined using the strict criteria of Winblad et al. (2004). To maximise subject numbers, those with impairment in other cognitive domains were not excluded. All subjects were classified according to their performance on delayed recall and response to a single question on memory difficulties. A more detailed discussion of group classification is provided in Chapter 5 (Methods).

4.2 Aims and Hypotheses

The aims are as follows:

1. To determine whether age and/or other factors such as mild depression influence the relationship between SMC and objective measures of cognitive function;

2. To ascertain whether the DRS or 7MS are sensitive screening tools to identify MCI;

3. To examine whether the presence of SMC affects the 3-year cognitive outcome of subjects

4. To examine whether the ApoE ε4 affects cognitive function over time in subjects with SMC.

Hypotheses

The hypotheses related to these aims are as follows:

1. Subjects with SMC will demonstrate significant cognitive impairment on formal neuropsychological assessment compared to those without SMC;

2. There is in existence screening tests that are both sensitive and relatively easy to administer and can be used to potentially identify subjects with MCI;

3. Subjects with SMC will demonstrate evidence of worsening cognitive function over a 3-year interval;

4. Subjects with SMC and the ApoE e4 allele will show evidence of worsening cognitive function over time;

The next chapter describes in detail the neurocognitive test battery used for the formal clinical assessment of cognitive function and discusses the different aspects of memory and cognition measured by each test. It also lays the foundation of the pattern analysis for assessing deficits to single and multiple cognitive domains.

Chapter 5: Neuropsychological assessment of memory

5.1 Cognitive domains and neuropsychological tests of memory

Formal neuropsychological testing is essential to "identify cognitive impairments in a maximally objective manner" (Lindeboom and Weinstein, 2004, p. 83). It is invaluable for quantifying the degree of cognitive impairment (Arnaiz and Almkvist, 2003), assists in differential diagnosis and may complement clinical judgement. Thus, when these strengths are combined, neuropsychological assessment can play a pivotal role in the early detection of Alzheimer's disease.

In this section, a description of the tests used in the neuropsychological evaluation of all individuals in the present study is provided. A brief summary of the test battery categorized by cognitive domain is presented in **Table 5.1** and is attached to the Appendix. The psychometric properties of these tests are provided in Chapter 6 (Methods), which discusses the unique and overlapping components of each test and the influence of confounding variables; such as the age and education. This

background information will lay the foundation for understanding the different types of neuropsychological impairments reported in Alzheimer's disease.

Additionally, the similarities subtest (from the WAIS-R, Wechsler, 1981) was also administered to the subjects even though it was not included in the evaluation of global functioning.

Many neuropsychological tests share common underlying cognitive components. Thus, impairment on a single test cannot exclusively be attributed to one cognitive domain, primarily because of the inter-relationships between tests. There are many studies that use the same neuropsychological test for different purposes. For example, category fluency, a test of semantic memory has also been used as a test of executive function (e.g., Bäckman et al., 2004a). Similarly, digit span has been used as a test of attention and also working memory. The interpretation of test results requires consideration of the common underlying cognitive mechanisms of the test.

The categorisation of neuropsychological tests into composite cognitive scores to reflect common cognitive domains is a useful way to conceptualise performance and overcome some of the difficulties associated with the use of a single test. This method facilitates comparisons between studies and has recently been used in a study on memory complaints in patients with MCI (Clement et al., 2008).

Table 5.1 Brief description of neuropsychological tests used in this study, grouped by cognitive domain

Cognitive domain and test	Source and task
1. Current intellectual functioning (IQ)	
Full scale IQ	**NART:** National Adult Reading Test Pronouncing 50 irregular words
2. Working memory (WM)	
Digit span (forward)	**WAIS-R:** given series of numbers to repeat forward and backward
Digit span (backward)	
Serial 7's (score 2 if correct, 1 or 0 if incorrect)	**WMS:** Counting backwards from 100 by 7
3. Verbal learning/acquisition (VL)	
RAVLT: trials 1-5 (total)	**RAVLT:** Rey Auditory Verbal Learning Test Learning a list of 15 words over 5 trials, and repeating the list back to the examiner after each trial
4. Verbal recall (VR)	
RAVLT: immediate recall	**RAVLT** Recalling words from the list in trials 1 to 5, without a subsequent presentation
RAVLT: delayed recall (20 min)	Recalling words from the list in trials 1 to 5 (immediately) and after a 20 min delay
Recognition A (maximum 15)	Correctly identifying the words from the list in trials 1 to 5 from amongst foils
5. Verbal ability (language skills) (VA)	
F A S (total number of words)	Naming words starting with letters F, A and S, in one minute for each
Category fluency (total number of words)	Naming as many animals in one minute
Boston Naming Test	Correctly naming 60 pictures of line drawings
6. Visual recall (VsR)	
Rey Complex Figure Test (recall)	**ROCFT:** Rey-Osterrieth Complex Figure Test Drawing a complex visual picture from memory
7. Visuospatial ability (VsA)	
Rey Complex Figure Test (copy)	**ROCFT** Copying a complex visual figure from a diagram
Praxis (maximum 60 points)	Ability to initiate action commands
8. Visuomotor speed (VsS)	
Trail Making-A (seconds)	**Trail A** Time to complete a simple paper pencil task connecting digits (1, 2, ... 25)
9. Cognitive flexibility/Executive function (EF)	
Trail Making-B (seconds) (max 300 sec)	**Trail B** Time to complete a more complex task alternating digits and letters (1-A, 2-B, etc to 12-L)

5.2 Domain 1: Intellectual functioning

The National Adult Reading Test (NART: Nelson and Willison, 1991)

The National Adult Reading (NART) is an oral, single word reading test, and was chosen because it can reliably estimate pre-morbid cognitive functioning in subjects suspected of having brain damage. In this test, subjects read aloud fifty irregularly spelled words that violate the traditional rules of grapheme to phoneme correspondence (e.g., naïve, chord) and are listed in order of increasing difficulty of pronunciation (e.g., deny, puerperal). Performance is expressed in terms of the number of errors, with high scores reflecting poor performance. Thus, the subject's predicted IQ and optimum level of intellectual ability is based on an estimate derived from the number of pronunciation errors (Nelson and Willison, 1991). This may be further adjusted for age and education.

NART is impervious to the presence of mental disease, such as early Alzheimer's disease, where reading ability is generally well maintained (Hodges, 1994). Performance on NART declines in the later stages of the disease. This has been attributed to impairment within the semantic system (Patterson et al., 1994).

5.3 Domain 2: Working memory

Digit Span subtest (WAIS-R: Wechsler, 1981)

The digit span subtest from the WAIS-R (Wechsler, 1981) is commonly used to measure both attention and short-term working memory capacity, which are closely related to the integrity of executive function.

Testing included both the digits forward and the digits backward components. In both conditions, a string of digits was read aloud to the subjects at the rate of 1 digit per second. Subjects were asked to repeat the digits back to the candidate. The number of digits in both conditions progressively increased upon successful repetition on 2 trials of the same string of digits. If the subject scored a zero on both trials of an item, the test was discontinued.

Digit span forward is sensitive to immediate memory (short-term memory storage capacity). Backward digit span is sensitive to working memory in which the information held in the short-term memory store is manipulated mentally. According to Baddeley (1986), backward digit span requires temporal reorganization of digits, and thus poses demands on working memory (Baddeley, 1986). There is disagreement regarding what this test measures. Some consider this to be *the* classical test of attention (van Zomeren and Brouwer, 1994), whereas others consider it a test of working memory (Baddeley, 1986). In this study, digit span was used as a test of short-term working memory.

Serial Sevens Subtraction (WMS: Wechsler, 1945)

Serial Sevens Subtraction is a test of mental control and calculating ability. In this test, the subjects were asked to subtract 7 from 100, and to continue subtracting 7 from their answer until they were told to stop. The time limit was 76 seconds. One point was deducted for each error. An error free performance within the time limit was given a score of 2, which was the

maximum score. Some consider this test to measure attention and mental control (Tierney et al., 1996). In this study it was used as a test of working memory. Deficits in mental control have been reported to occur in preclinical Alzheimer's disease and in subjects with memory complaints (Tierney et al., 1996). The scores of all three tests were averaged to assess working memory.

5.4 Domains 3 and 4: Verbal learning and verbal recall

Rey Auditory Verbal Learning Test (Rey, 1964; Schmidt, 1996)

The Rey Auditory Verbal Learning Test (RAVLT) is a verbal serial learning test consisting of two lists of 15-high frequency, semantically unrelated words. It measures the ability to encode, consolidate, store and retrieve verbal information (Schmidt, 1996). It is critically dependent on episodic memory and provides a measure of immediate recall, evaluates learning over consecutive trials, and assesses confabulation and susceptibility to interference (Gainotti and Marra, 1994). The RAVLT is sensitive to identification of impairment in the medial temporal lobe. It was chosen because it engages the memory systems maximally.

In this test, the candidate read aloud the 15 words (List A; see page A20) with a 1-s interval between each word for five consecutive trials (Trials 1 to 5). Each trial was followed by a free-recall test. Subjects were advised to listen carefully to a list of 15 words because they would be asked to repeat back as many of the words that they could recall. The order of presentation of the words remained fixed across the trials. Instructions were

repeated before each trial to minimize forgetting. After Trial 5, an interference list (List B) was read aloud by the candidate and each subject was asked to freely recall words from this list. Following this recollection, each subject was asked to recall as many words from the original list (List A) used in Trials 1 to 5, without a further presentation of that list.

After a 20-minute period of delay that was filled with other psychometric tasks, subjects were again asked to recall the words from List A. This formed Trial 6 (Delayed Recall). Subjects were also asked to recognize as many of the target words (Lists A and B) from amongst a list of 50 words, which included the 30 targets and 20 foils mixed randomly. This became the delayed recognition score for the list of words presented in Trials 1-5.

The following indices were computed according to previously described and commonly reported indices in the literature (Estevez–Gonzales et al., 2003; Gainotti and Marra, 1994).

1. number of correct responses given in each Trial (1 to 5);
2. immediate recall score: the sum of all correct responses given in the five consecutive Trials (maximum score=75);
3. delayed recall: the number of words recalled from List A after a 20 minute delay (Trial 6, maximum=15);

The RAVLT is considered to be one of the most sensitive tests for identification of preclinical Alzheimer's disease, especially the Delayed Recall subtest. Profound impairment in delayed recall has been reported to

consistently predict progression to Alzheimer's disease, ranging anywhere from two to nine years (in non-demented subjects) prior to disease onset (e.g., Amieva et al., 2005; Estevez-Gonzalez et al., 2003; Saxton et al., 2004). A useful diagnostic measure for identifying preclinical Alzheimer's disease is to compare immediate and delayed recall performance on word list learning tasks. A discrepancy between the two is thought to be indicative of a dementia syndrome of the Alzheimer's type (Gainotti et al., 1998).

Additionally, RAVLT is sensitive to memory deficits in different patient groups and can thus be used to distinguish between Alzheimer's disease and other causes of cognitive impairment. Woodard et al. (1999) reported that normal ageing was characterised by learning deficits rather than consolidation deficits on RAVLT. In contrast, both learning and consolidation deficits are more apparent in patients with Alzheimer's disease (Woodard et al., 1999). Similarly, Gainotti and Marra (1994) reported that Alzheimer's patients could be characterized by the presence of many intrusions errors on delayed recall.

5.5 Domain 5: Verbal ability

Word Fluency 'FAS' (Benton et al., 1983)

Verbal fluency was measured using the 'FAS' task (Benton et al., 1983) and the animal naming task (Borbowski et al., 1967). Word fluency critically depends on the integrity of semantic memory as well as the ability to initiate systematic search and retrieval strategies (Fabrigoule et al., 1998). In category fluency, multiple cognitive mechanisms are involved in successful

retrieval and recall of words. Identifying which aspect of category fluency is impaired is not always straightforward. The cognitive mechanisms implicated in category fluency are presented in **Table 5.2.**

In the present study, word fluency was assessed using both the initial letter and category fluency tasks (part of 7 Minute Screen). Although both tasks evaluate word fluency, they differ in terms of difficulty in the strategies that are required for successful performance. The former relies on switching and the latter relies on clustering. Successful performance on a category fluency task depends on the ability to organize output in terms of *clusters* (i.e., producing words within a given semantic category) of meaningfully related words (Estes, 1974). In contrast, successful performance on a letter fluency task depends on *switching* (i.e., finding new semantic categories) (Bäckman et al., 2004a). Theoretically, clustering is thought to be an automatic process that depends upon the availability of memory storage for words. In contrast, switching is an effortful process that requires speed as well as cognitive flexibility and is thought to be dependent on the effectiveness of the subject's search processes (Troyer et al., 1997).

In the initial letter fluency task, subjects were asked to generate as many words as they could think of beginning with the letters F, A and S, respectively. A one-minute time limit was given for each letter. Subjects were instructed not to give proper names, numbers, or words as well as repetitions of words with different suffixes (e.g., rain, rained, and raining). The total score was the sum of the number of words generated for all three

Table 5.2 Cognitive mechanisms underlying verbal retrieval and recall

Auditory attention;
Ability to initiate and maintain word production set;
Cognitive flexibility (in rapidly shifting from one word to the next within a selected category);
Response inhibition capacity;
Speed of mental processing;
Response speed;
Long-term vocabulary storage and executive functions;
Short-term memory of keeping track of the words that have already been said;

Adapted from Mitrushina et al. (2005). *Handbook of Normative Data for Neuropsychological Assessment, 2nd edition*. Oxford University Press: New York

letters. The lowest acceptable total for elderly subjects of low educational attainment is around 25 words (Hodges, 1994).

Category fluency is a useful test to identify Alzheimer's disease, because it is highly sensitive to frontal 'executive' dysfunction and subtle degrees of semantic memory impairment. It is also one of the best indicators of the spread of pathology beyond the medial temporal lobe (Hodges, 1994). Patients with early Alzheimer's disease are frequently more impaired on category fluency than letter fluency (Butters et al., 1987). It is thought that category fluency is more affected by deterioration in the structure of semantic knowledge in Alzheimer's disease (Martin and Fedio, 1983; Monsch et al., 1992). Depending on bias, some reports conceptualize category fluency as a test of executive functioning. In this study it was used as a test of semantic memory (verbal ability and language skills).

Boston Naming Test (BNT: Kaplan et al., 1983)

The Boston Naming Test (BNT) is a visual confrontation naming test that was initially designed to examine aphasic patients. This is demonstrated by the design of the test in which the items to be named decrease in their frequency of occurrence within the English language. The BNT is frequently used in the assessment of Alzheimer's disease, notably for identifying impairment and documenting severity. Naming is critically dependent on the integrity of semantic memory, which is compromised in the early stages of Alzheimer's disease (Bayles and Tomoeda, 1983; Gainotti, 1992). As such the BNT was chosen for this reason.

In this test, subjects were required to name line pictures (60 line drawings), which ranged from simple, high frequency items ("tree") to less common items ("abacus") (see page A24). As the test progresses, the pictured items become increasingly less familiar and difficult to name.

Subjects were allowed up to 20 seconds to name each object and were given various prompting cues, depending on the nature of their error. If an error was spontaneously self-corrected, full credit was given. If the subject did not produce the name spontaneously, various prompting cues were provided. If the subject did not know the answer or gave a response that indicated a misperception of the object (e.g., "spear" instead of asparagus for item 49), a stimulus cue was given that provided some conceptual information about the picture (e.g., "it is something to eat"). If a general or vague response was given about the object (e.g., "animal" for camel for item 17), the subject was asked to provide a more specific

response (e.g., “could you be more specific?” or “could you tell me what type of animal?”). If the subject responded correctly to this question, this was recorded as a stimulus-cued response rather than as a spontaneous response.

A phonemic cue (the sound produced by the first few letters of the object) was given (a) after a stimulus cue did not result in the correct answer, or (b) when an incorrect response was given and a stimulus cue was not appropriate (“horse” rather than unicorn for item 57). The appropriate phonemic cue would be, “it’s not a horse, and it’s a uni...”. If a subject gave the correct response after being informed that their answer was incorrect, but before the phonemic cue, the answer was scored as a stimulus cue. The maximum score is 60. This is comprised of both the number of spontaneously correct responses and the number of correct responses following a stimulus cue.

5.6 Domains 6 and 7: Visual recall and visuospatial ability

Rey-Osterrieth Complex Figure Test (ROCFT: Rey, 1964)

The Rey-Osterrieth Complex Figure Test (ROCFT) is a test of visuospatial constructional ability (copy trial) and visual memory (delayed recall copy trial). Initially, subjects were asked to copy the figure without a time restriction. After a delay of 30 minutes and without prior warning, subjects were asked to redraw the figure “from memory” (see page A8 for copy figure). The accuracy of the copied and recalled versions were scored using a standardized scoring system, which assigned a maximum of two

points to each of the 18 elements within the figure, depending on the level of accuracy achieved. The two ROCFT measures used were the copy score and the recall score.

This test is extremely sensitive to detecting visual neglect in patients with lesions. By definition, unilateral (or hemi-spatial) neglect refers to a lack of attention to events and actions in one-half of space (Humphreys and Riddoch, 1984). Unilateral visual neglect may be observed by failure to copy one-half of the diagram. By observing the method that the individual uses when performing the task and, noting which details are omitted from the figure, the presence or absence of neglect can be determined as can the presence of a possible lesion.

Praxis (WMS-R: Wechsler, 1981)

Praxis consists of 20 items which require the subject to make purposeful movements in response to a command. The body movements were further divided into 4 categories, which included: the upper limb; facial; instrumental and complex. The commands ranged in difficulty from “make a fist” to “pretend to play the piano”. A score of 3 points was given for good performance; 2 points for an approximate performance or good performance on imitation only; and a score of 1 point for an approximate performance on imitation. The total score was summed over items with a maximum score of 60. Slight impairments in instrumental and complex functions may be evident early in the course of a dementia syndrome as highlighted by their inclusion in the criteria for MCI (Winblad et al., 2004; Petersen, 2007).

5.7 Domains 8 and 9: Visuomotor speed and executive functioning

Trail-Making Test (Reitan, 1958)

Trail Making is a test of attention, speed and mental flexibility (Strauss et al., 2006). This test requires the subject to draw upon multiple cognitive skills for successful performance. This test was administered in two parts (A and B). Part A consisted of 25-circled numbers randomly arranged on a page (see page A14). Subjects were asked to draw a line connecting the numbers in sequential order from 1 to 25, in as short a time as possible. Part A is regarded as a classical visual test of selective attention that primarily draws on attentional skills and psychomotor speed (van Zomeren and Brouwer, 1994). These skills are also necessary for successful performance in Part B.

Part B is a more cognitively complex because of the increased demand in speed of processing and the executive functions of working memory and set-shifting. Part B consists of both circled numbers and letters randomly arranged on a page (see page A15). Subjects were asked to draw a line connecting the numbers and letters in a sequential and alternating order (1-A, 2-B, 3-C up to 12-L-13) as quickly as possible. In Part B, the demands on working memory are increased because subjects must hold information both of the alphabet and of calculation, whilst manipulating this information in an orderly fashion. It is extremely easy to become confused on this task due to the increase in visually interfering stimuli (Gaudino et al., 1995). Part B is considered to be a test of divided attention (van Zomeren and Brouwer, 1994). Errors were pointed out to the subject, as they

occurred, to allow for correction. The subject was timed on both parts of the test and scored as the number of seconds taken to complete the task. If the time taken to complete the task was greater than 5 minutes, a maximum score of 300 was recorded. Both tasks are sensitive to the early cognitive changes associated with progression to Alzheimer's disease (e.g., Chen et al., 2001).

5.8 Tests not assigned to a domain

Similarities subtest (WAIS-R: Wechsler, 1981)

Similarities are a test of abstract reasoning ability and semantic knowledge. In this task, the candidate read aloud word pairs in reference to either an object or situation. The subject was asked to explain what each pair of seemingly unrelated words had in common. The word pairs ranged in the level of abstraction required (and hence difficulty), from 'orange-banana' to 'work-play'. To keep the overall assessment time to a minimum, a subset of 7 word pairs was used in this study (see page A22). They were items 1, 2, 3, 4, 7, 9 and 12. Therefore, a total maximum score of 14 was possible. The scoring system was hierarchical in nature (Rosch et al., 1976), in that categorisations that identified the super-ordinate category (general properties in common with other objects, e.g., fruits, animals) were given a score of two. Naming one or more common properties or functions was given a score of one. A score of zero was given when the response was only relevant for one member of the pair, or if they indicated a difference existed between the pair, or if the demonstrated only a generalised understanding of

the word pair e.g. “You can eat them both”.

The use of this test was theoretically motivated by reports that patients with early Alzheimer’s disease have difficulty understanding the conceptual relationship between objects (Chertkow et al., 1992; Fabrigoule et al., 1996). For example, when patients with Alzheimer’s disease are asked to say in what way an orange and a banana are alike or similar, they often respond that they are not alike, thus demonstrating impairment in forming abstract relations between objects.

5.9 Summary

This chapter provided a detailed discussion of the tests (as grouped by cognitive domain) used for the clinical assessment of all test subjects in this study. The next chapter will discuss the Methods and study procedures. It will also detail the psychometric properties of each of the neuropsychological tests used in the test battery.

Chapter 6:

Methods

6.1 Subjects and recruitment

Community-dwelling subjects aged between 50 to 79 years, living in the catchment area of Central Sydney Area Health Service, were recruited into the study. The subjects were recruited via advertisement in local newspapers and flyers placed on community and hospital bulletin boards. The notices invited individuals with or without memory difficulties or a family history of Alzheimer's disease to participate in a research study on ageing and Alzheimer's disease (see page A25 for Flyer).

All subjects underwent a screening procedure prior to inclusion. Subjects were required to be free of any relevant underlying medical, neurological, or psychiatric illness, by self-report; and be willing to participate in the study procedures. In addition, to minimise the likelihood of including into the study, those who may develop vascular dementia at a later date, subjects with a history of major vascular disease (e.g., atrial fibrillation or cerebral infarcts) were excluded. Subjects with a history of diabetes mellitus (Types 1 and 2) and those taking medication capable of producing sedation or reduced mental alertness were also excluded.

The present study was initially designed to investigate fMRI changes in patients with preclinical Alzheimer's disease. However, during the course of the study, the principal supervisor left the organisation to pursue other career interests. This prompted a change in supervision. Also due to the departure of the principal supervisor, funding for the fMRI scans was no longer available which prompted a slight modification in the study design. An increased focus was placed on the role of subjective memory complaints (SMC) and neuropsychological testing. Although the separation of SMC subjects into groups with and without objective impairment was not part of the original design, these subjects were nevertheless separated due to the availability of information on SMC.

Consequently, the change in study design prompted a change in the use of the depression scale was made in order to more reliably measure symptoms of depression in subjects under the age of 65 years. The reasons for this are discussed in section 6.5.3 as is the method of aligning scores on the two scales. The minor adjustments to the protocol did not affect the study outcome. A copy of the initial advertisement recruiting subjects for neuropsychological testing and fMRI is attached in the Appendix (see page A26).

All subjects were either cognitively normal or demonstrated mild impaired cognitive deficits. All subjects spoke fluent English, had adequate vision and hearing and were able to understand task instructions. The subjects lived at home with no assistance and many were not working or retired (77%).

Prior to the initial assessment, a brief telephone screening interview was conducted with all potential subjects to determine suitability for participation. The subjects answered questions in relation to concerns about their memory, family history of Alzheimer's disease, psychiatric and medical history, involvement in a major car accident and drug and alcohol problems.

6.1.1 Ethical approval

This study was approved by the Human Research Ethical Committees of the Royal Prince Alfred Hospital (X99-0116, X02-0324); Concord Hospital (CH62/612002-108) and The University of Sydney (6705). These committees are governed by guidelines set out by the National Health and Medical Research Council (NH&MRC). All subjects provided written informed consent prior to the initial interview. Subjects were given information on the study (page A27) and were provided with the results of their cognitive testing. The candidate further explained the procedure involved with venepuncture. The ethical issues involved in testing for ApoE were addressed both verbally and within the handout (see page A30).

6.2 Study design and procedure

6.2.1. Initial assessment

This study was divided into two stages: initial assessment and follow-up assessment. After initial screening, all subjects underwent a cognitive assessment using a standard neuropsychological test battery (see Section 6.6). In addition, two other tests were included to examine their potential as

tools for early detection of subjects that might have dementia (Dementia Rating Scale and 7 Minute Screen). Subjects were also screened for stroke and depressive symptoms (Psychogeriatric Assessment Scale and Geriatric Depression Scale), as well as a question examining subjective memory. Relevant demographic information was also obtained.

Between 1999 and 2003, subjects were assessed at the Royal Prince Alfred Hospital. Between 2004 and 2005 subjects were primarily assessed at Concord Repatriation General Hospital. The candidate was flexible regarding the place of assessment. Most of the assessments were conducted on weekdays early in the morning when subjects were more likely to be alert and feeling refreshed. On both campuses the room was well lit, comfortable and quiet. During the process of testing, noise and visual distractions were kept to a minimum level. There was no clock in the room, since providing an estimation of time was part of the assessment.

6.2.2 Follow-up assessment

The candidate wrote to all the subjects inviting them back for a re-assessment of their memory. The letter asked subjects to indicate their interest in a second memory test by placing a tick in one of the appropriate boxes. The options available on the letter were: 'Yes, I wish to be contacted'; 'No, I do not wish to be contacted' and 'the above mentioned person does not live here anymore, please give forwarding address if known'. Non-responses were followed-up with a phone-call after a period of 2 weeks. Although, it would have been desirable to have a 100% follow-up

rate, the first wave of subjects were not expecting to be followed up as they were initially assessed for an fMRI scan. Notwithstanding this, 42 (49%) subjects from the first wave returned for a second interview.

The follow-up assessment was conducted after an average period of three years to allow sufficient time to assess changes in cognitive function. A longitudinal approach is invaluable as it provides further information regarding the stability of any relationship between SMC and cognitive function observed in cross-sectional studies. It has been suggested that in subjects with memory complaints, a period of 5 years is desirable for cognitive impairment to manifest (Wang et al., 2004a). Some reports consider SMC to be a stage that occurs prior to MCI in the evolution of Alzheimer's disease and lasts for approximately 15 years (Prichep et al., 2006; Reisberg et al., 2008; Reisberg and Gauthier, 2008). In the present study, three years was deemed to be an acceptable minimum time interval to allow deficits to occur and did not extend beyond the period of candidature. Many studies that have employed similar time frames report a significant relationship between SMC and cognitive decline (Geerlings et al., 1999; St John and Montgomery, 1992).

The same research battery of neuropsychological tests used in the initial assessment was used in the follow-up assessment. Subjects who consented to be re-tested underwent the same screening procedure that was employed in the initial assessment.

6.3 Measurement of memory complaints

In the literature, memory complaints have been referred to by a variety of terms including, subjective memory complaints, subjective memory impairment, subjective cognitive impairment, and subjective cognitive complaints (Cargin et al., 2008; Mitchell, 2008a; Petersen and O'Brien, 2006; Reisberg and Gauthier, 2008). The present study used the term subjective memory complaint to refer to complaints of memory by self-report.

Subjective memory complaints were quantified using a single question administered at initial assessment ("Do you have a problem with your memory"). Previous research indicates this is sufficient to demonstrate a significant correlation between memory complaints and test performance (Geerlings et al., 1999; Jorm et al., 2005b; Lam et al., 2005b; Minett et al., 2008; Palmer et al., 2003; Snitz et al., 2008; van Oijen et al., 2007). Responses were coded "Yes" or "No". This question was simple and straightforward and made no suggestions about memory loss. This question made no direct reference to a specific time frame for the perceived memory loss. Therefore it allowed for a subjective opinion of memory encompassing elements of the remote past, present and future. Information from an informant was not collected, because the study focused on the subject's perception of their own memory difficulties. This will be taken up later in the discussion.

The subjects reported recurrent episodes of memory loss, which caused them sufficient concern. The defining feature of the memory complaint was based on their own self awareness that their memory had

changed. They presented with subjective feelings of memory loss for simple everyday activities which did not have a negative effect on their everyday lives. Some examples of the types of memory complaints reported by the subjects included: misplacing objects, forgetting the names of familiar people, unable to recall recent events and forgetting familiar telephone numbers.

6.4 Classification of memory status

The subjects were classified according to two criteria; (1) their response to the question "Do you have a problem with your memory?" and (2) performance on initial assessment on a task of word list delayed recall (RAVLT, Rey, 1964). They were then classified as having normal memory (normal controls; no SMC and a recall score $\geq$ 4 words on the RAVLT), SMC (the presence of a SMC and a recall score $\geq$ 4 words on the RAVLT) or aMCI (the presence of a SMC and a recall score < 4 words on RAVLT). The process of determining the appropriate cut-off on the RAVLT is discussed in section 7.5 (page 147).

The classification occurred after the initial assessment when comparisons were made between subjects with and without SMC. As this study was partially designed to be exploratory in nature rather than diagnostic, subjects were not informed of their group. The implication of this is addressed in Feedback to subjects (page 132). The three groups were formed based on their risk of developing dementia at a later date.

6.4.1 Normal control group

Subjects who answered "No" to the question "Do you have a problem with your memory?" and had a delayed recall score on the RAVLT of $\geq$4 (i.e. no objective evidence of memory impairment) were considered to have normal memory functioning and formed the normal control group. Individuals aged between 50 and 79, fulfilling these criteria had various education levels, normal orientation and social functioning within the community. They may or may not have had a family history of Alzheimer's disease. Notwithstanding ApoE status, it was hypothesized these subjects would have the lowest risk of developing Alzheimer's disease in the future based on this risk factor profile.

6.4.2 Subjective memory complaint (SMC) group

Subjects who answered "Yes" to the question: "Do you have a problem with your memory?" were grouped as having SMC. For some of the analyses, the subjects were further grouped according to their performance with delayed recall on the RAVLT. That is, subjects with SMC who scored $\geq$4 on the RAVLT (i.e. no objective evidence of memory impairment) were considered to have SMC. Subjects with SMC fulfilled the following criteria:

1. a memory complaint by self-report;
2. a recall score $\geq$4 on the delayed word recall test of the RAVLT;
3. normal orientation and apparent adequate social functioning within the community;

6.4.3 Amnestic mild cognitive impairment (aMCI) group

Subjects who answered "Yes" to the question "Do you have a problem with your memory?" and had a delayed recall score on the RAVLT of <4 (objective evidence of memory impairment) were considered to have amnestic Mild Cognitive Impairment (aMCI: Peterson, 2007; Winblad et al., 2004). Based on initial findings, these subjects scored 2.0 standard deviations (SDs) below the mean for the normal controls. This cut-off score is consistent with previous studies (Guarch et al., 2004; 2008) that reported subjects with SMC who developed Alzheimer's disease within 18 months, were defined by a deficit of 2.0 SDs below the mean on an episodic memory tasks that was unadjusted for age (delayed verbal memory). The deficit in delayed verbal memory predicted 80.5% of cases (Guarch et al., 2008).

This allowed the candidate to include into this group subjects with typical aMCI as defined by Winblad et al. (2004). To maximise subject numbers, those with impairments in others domains were not excluded. Thus, in the present study, aMCI is not used in the strict sense as defined by Windbald et al. (2004). The Winblad criteria allow also for the patient to *not* self-complain as long as someone else who knows them well complains. Subjects with aMCI fulfilled the following criteria:

1. a memory complaint by self-report;
2. normal orientation and apparent adequate social functioning within the community;
3. a recall score < 4 on the delayed word recall test of the RAVLT;

There were no subjects without a SMC and recall score of < 4, hence there was no need for further categorisation. The criteria for MCI are discussed in Chapter 3, Section 3.3.

6.5 Screening tests

The screening tests included the 7 Minute Screen (Solomon et al., 1998); the Mattis Dementia Rating Scale (Mattis, 1976); the Geriatric Depression Scale, Short Form (Sheikh and Yesavage, 1986) and two scales within the Psychogeriatric Assessment Scale (Jorm and MacKinnon, 1995; Jorm et al., 1995) (i.e. the Stroke Scale and Depression Scale). The details of these tests are provided below and were part of the overall assessment procedure.

6.5.1 The 7 Minute Screen (7MS: Solomon et al., 1998)

The Seven-Minute Screen Neurocognitive battery is a brief screening test for cognitive impairment aimed at early identification of dementia (Solomon et al., 1998). It consists of four tests (temporal orientation, short- and long-term memory, naming, visuospatial organisation, semantic processing and storage), selected because they examine cognitive domains typically impaired in Alzheimer's disease (see pages A9-A12). Abnormalities in these domains are considered highly sensitive in identifying early stage Alzheimer's disease (Solomon et al., 1998). The 7MS has excellent predictive validity and can reliably distinguish Alzheimer's disease from normal ageing and other dementias, such as fronto-temporal dementia (e.g.,

Drake et al., 2003; Meulen et al., 2004).

Solomon et al. (1998) validated the test in a community sample of 60 patients with Alzheimer's disease and 30 healthy controls. He reported an overall test/retest reliability in the range of 0.83 to 0.92 and an inter-rater reliability of 0.93. The 7MS classified 92% of patients with Alzheimer's disease correctly and 96% of control subjects correctly. Unlike the MMSE, scores on the 7MS are not influenced by age, sex or education.

The 7MS has been widely accepted as a screening test for identifying early Alzheimer's disease due to its good diagnostic power and reliability (e.g., Del Ser et al., 2006; Drake et al., 2003; Meulen et al., 2004; Skjerve et al., 2007; Tsolaki et al., 2002). Meulen et al. (2004) reported a high level of sensitivity of 92.9% for Alzheimer's disease and 89.4% for other types of dementias, and equally high specificity in both populations (93.5%). However, in Meulen's et al. (2004) study, performance was influenced by age, sex and education.

Compared to the MMSE, Meulen et al. (2004) reported the 7MS is more sensitive in identifying Alzheimer's disease. Others have indicated the 7MS is a useful brief screening tool for deciding who would benefit from further neuropsychological assessment (Henderson, 2004; Solomon et al., 1998).

6.5.1.1 7MS subscales

The 7MS consists of the following 4 subscales:

1. Benton Temporal Orientation (BTO): In this test, orientation to time is measured and quantified by the degree of error. The subject is asked the

date (day-month-year) and time. The fewer errors made, the more likely the full score is given. For example, 10 points are subtracted for each year off the target year, 5 points for each month off the target month, 1 point for each date and day of the week off the target date and day, and 1 point for each 30 minutes off the correct time. However, when a question is met with a non-response or a response of "I don't know", the subject is asked to guess. If they refuse to guess, no points are deducted. The maximum total error score is 113, which indicates the worst possible performance. The best score is 0. For the purpose of analysis, only errors are recorded as high scores indicate poor performance.

2. Memory (Enhanced cued recall: ECR): Enhanced cued recall is a memory test that induces semantic processing and encoding, and is sensitive to early Alzheimer's disease (Grober et al., 1988). Patients with Alzheimer's disease are typically unable to benefit from semantic cues to facilitate remembering. This test consists of 16 pictures, which are presented four at a time on four individual cards. During the learning trial of each pictured item, the subject is given a semantic cue to assist with learning the to-be-remembered item. For example, "There's an insect on this page; what is it?" Immediately after presentation of all items, the subject is asked to free recall as many of the pictures as possible. After a short interval, during which a distracter task is presented, the subject is asked to free recall all pictures. The appropriate semantic cue is provided for unnamed pictures. For example, "I showed you a picture of a musical instrument; what was it?" Scores range between 16 (maximum) and zero.

3. Clock Drawing (CD): Clock Drawing measures visuo-spatial memory and visuo-constructional ability, which are usually impaired in mild and moderate Alzheimer's disease (Brodaty and Moore, 1997; Esteban-Santillan et al., 1998). In this test, the subject is asked to draw the face of a clock and place the hands at a fixed time "twenty-to-four". Points are deducted for different types of errors. These include missing numbers, incorrect order and position of numbers. Points are also deducted if both hands are not present, the hour or minute number is not indicated and if the hands are proportionally incorrect. The best score is 7, which is the maximum total score; the lowest is zero.

4. Category fluency (CF): Category fluency measures the integrity and ability to access semantic memory and is a sensitive marker of Alzheimer's disease (Monsch et al., 1992). In this test, the subject is asked to generate as many words as possible from the semantic category *animals* and is given a 60-second time limit. The total number of animals named is the score recorded. The best score is 45. If no animals are named, a score of zero is assigned.

6.5.1.2 Calculating the 7MS total score

To determine the degree to which the 7MS discriminated between control subjects and patients with Alzheimer's disease, Solomon et al. (1998) estimated a logistic regression model using the raw scores of the four subtests as predictor variables:

$$\mathbf{Ln\,[P/(1-P)] = 35.59 - 1.303*ECR - 1.378 * CF + 3.298 * BTO - 0.838 * CD}$$

P indicates the probability of having Alzheimer's disease, and ECR, VF, BTO, and CD are the scores for the Enhanced Cued Recall, Category Fluency, Benton Temporal Orientation, and Clock Drawing tests, respectively. The natural logarithm (Ln) of P/(1-P) is equal to the total 7MS score of the above logistic regression formula. The probability of having dementia decreases with a lower total score. For example if the total score is -24.6, the probability of having dementia is less than 1%. If the total score is 0, the probability of dementia is 50%. Finally, when the total score is more than 7 the risk is more than 99.9% (Solomon et al., 1998).

In Solomon et al's. (1998) initial study, total scores from the 7MS that fell between the normal control threshold (probabilities less than 0.3) and dementia (p>0.7) were not categorised (diagnosis deferred) and it was recommended to re-test these subjects 3-6 months later. This indicated that the subject's performance did not fit neatly into either category.

6.5.2 The Dementia Rating Scale (DRS: Mattis et al., 1976)

The DRS is a reliable screening test for dementia and is capable of measuring the progression of cognitive decline in older persons well into the later stages of dementia (Mattis, 1976; Salmon et al., 1990). The DRS was used to provide an estimate of global cognitive function within the study population (see Appendix A16 for a list of questions). The DRS total score is derived from five sub-scales of specific cognitive functioning. These are: 1) attention (e.g., digit span), 2) initiation and performance (e.g., category fluency), 3) construction (e.g., copying designs), 4) conceptualisation (e.g.,

similarities), and 5) verbal and non-verbal short-term memory (e.g., sentence recall and design recognition). The total summary score has good concurrent and predictive validity (Strauss et al., 2006).

Scores using all the DRS questions range from 0-144. A score of 123 (lower 95% confidence interval of norms) is commonly used to identify subjects with dementia (Mattis, 1976). According to Strauss et al., (2006) the simple cut-off score of (<123) is inappropriate because it is based on a small well-educated sample size. In the present study, two items in the memory subscale (orientation) were not used as they were more relevant to USA populations. These two items were questions about the 'city mayor' (which may be confused with city of Sydney or local shire mayor) and the 'governor' (which may be confused with the state Premier who actually 'governs' the state, not the Governor General or the NSW Governor). Thus, the DRS maximum in the current study was 142. Moreover, the cut-off criteria for dementia was lowered from 123 to 121".

The DRS is highly sensitive to identifying cognitive impairment associated with dementia. Vangel and Lichenberg (1995) successfully classified 87% of their healthy sample from amongst a group of 105 cognitively impaired elderly subjects using a cut-off score of 120. The sensitivity and specificity was reported to be 74% and 93%, respectively. Age, education and IQ have been documented to affect performance on the DRS (Chan et al., 2001; Schmidt et al., 1994b). In this regard, the norms provided by Schmidt et al. (1994b) are highly sensitive because they are adjusted for age and education.

Further reliability data are provided by Mattis (1988) who reviewed evidence from several reports, which indicated that the total score had a one week test re-test reliability of (0.97), a split-half reliability of (0.90) and internal consistency estimates (Cronbach alpha) between (0.75 to 0.95) for each of the subtests. However, Schmidt et al. (1994a) reported different degrees of internal consistency for the individual subtests, with Construction, Conceptualization, Memory and Total Score having the highest (0.70), and Initiation and Perseveration, (0.45), having the lowest.

6.5.3 Screening for major depressive disorder

All subjects were screened for past and present major depressive symptoms. It has been documented that depression amongst the elderly is grossly underestimated (Snowdon and Lane, 2001) and may be concealed by an increase in somatic symptoms, such as fatigue and sleep problems. Whilst depression is common in the early stages of Alzheimer's disease (van Oijen et al., 2007) it may also be a prodrome to dementia of the Alzheimer's type (Wilson et al., 2008). Thus, clinical judgement is required in combination with the use of scales when screening for major depression and identifying other underlying causes.

During the course of the study, two self-report scales were used to screen for depression. Initially, when the focus of the study was based on clinical referrals, the Depression Scale from the Psychogeriatric Assessment Scales (Jorm and Mackinnon, 1995; Jorm et al., 1995) was used. However, when the study was modified in 2001 (and subjects under the age of 65

years were included), the GDS-15 (Sheikh and Yesavage, 1986) was subsequently used to screen for depression.

To align the scoring systems of both screening scales, the cut-off scores from both scales; Depression Scale (PAS) and GDS were used to categorize subjects as 0, (no depression), to indicate the absence of clinically significant depressive symptoms (i.e., the subject scored within the normal range); 1, to indicate mild depressive symptoms (i.e., the subject scored between 5-7 on the PAS or 8-9 on the GDS), and 2 to indicate clinical signs of depression (i.e., the subject scored $\geq$10). This allowed for both groups to be rated for depression on the same scoring system, despite the use of two different scales. The cut-off scores on the GDS-15 are similar to those employed by Freidman et al. (2005). Friedman et al. (2005) looked at depression in subjects over the age of 65 (mean age=80) and used a similar cut-offs to the present study to determine the severity of depression. That is, Friedman et al. used a score from 6-10 to classify subjects as having mild depression and a score from 11-15 to classify subjects as having severe depression.

Subjects were excluded if they scored within the depression range on either assessment. In the present study, subject number 75 was rated as having clinical signs of depression. This subject spoke about stress and anxiety in her life and felt overburdened caring for her grandchildren. This subject was advised to see her GP for treatment and was excluded from the analysis. Eight subjects who were rated as having mild depressive

symptoms were not excluded from the analysis, but were used to assess the influence of increased depressive symptomatology on memory complaints.

6.5.3.1 The Psychogeriatric Assessment Scale (PAS) (Jorm and MacKinnon, 1995)

The Stroke Scale

The Stroke Scale is part of the Psychogeriatric Assessment Scale (Jorm and MacKinnon, 1995). This scale evaluates six symptoms of cerebrovascular disease. It provides an indication of whether cognitive impairment might be due to vascular dementia or non-vascular types of dementia (mainly Alzheimer's disease) (see page A3). Subjects with vascular dementia obtain higher than average scores on this scale. The validity of the Stroke Scale is demonstrated by its correlation with the Hachinski Ischemic Score; 0.71 and 0.65 (Jorm et al., 1995). Approximately, 80% of vascular dementia cases obtain a score of one or more (Jorm and MacKinnon, 1995). The scores range from 0 to 6 with scores of 2 or more indicating the possibility of vascular dementia. None of the subjects in the present study reported a history of stroke or transient ischaemic attacks (T.I.A).

The Depression Scale

The Depression scale evaluates 12 symptoms of depression over the previous two weeks (see page A4). For example, "Have you had trouble sleeping over the past two weeks?" The scale focuses on the physical and cognitive symptoms of depression. The reference population used for determining the psychometric properties of the scale consisted of 134

geriatric and psychogeriatric patients from Sydney and Geneva, over the age of 70 years. Reports indicate that the Depression Scale performs well as a screening test for major depression (Jorm et al., 1995). Test-retest reliability for the Depression Scale is high and the validity of the scale is supported by its correlation with the Goldberg depression and anxiety scales, 0.67 and 0.60 respectively. Approximately 80% of major depression cases obtain a score of four or more (Jorm and MacKinnon, 1995).

6.5.3.2 The Geriatric Depression Scale (Sheikh and Yesavage, 1986)

The Geriatric Depression Scale (GDS) is a reliable and valid screening tool to detect the presence of a major depressive disorder amongst older persons in different settings (Sheikh and Yesavage, 1986). It is used extensively in geriatric populations (Almeida and Almeida, 1999; D'Ath et al., 1994; Friedman et al., 2005; Jongenelis et al., 2007) and is favoured because it excludes somatic symptoms of depression known to occur in the elderly that frequently are related to causes other than depression. In the present study, subjects were administered the GDS-15 Short Form which has been validated for a diagnosis of major depressive episode according to the ICD-10 and DSM-IV criteria, for research and clinical purposes (Almeida and Almeida, 1999). The GDS-15 consists of 15 questions enquiring about different aspects of depression in relation to mood and activity, e.g., 'Do you think it is wonderful to be alive now?' Subjects either responded with a 'yes' or 'no' answer to each question (see page A7). The responses to the 15 questions were summed to give a total score from 0 to 15, with higher

scores indicating more depressive symptoms. A cut-off score of 5 or more indicates probable depression, but not necessarily major depression (D'Ath et al., 1994).

Reliability data supports the clinical utility of the GDS-15 for measuring depression. D'Ath et al. (1994) screened elderly subjects over 75 years for depression using a cut-off score of 4/5, and reported high sensitivity (91%) and specificity (72%). The internal consistency for the GDS-15 is also high (Cronbach's alpha = 0.80) and all of the 15 items are significantly associated with the total score and hence 'caseness' (D'Ath et al., 1994). However, internal consistency declines with increasing severity of dementia. The GDS-15 has high test-retest reliability (0.84 to 0.85) for short intervals (less than 2 weeks). This test correlates well with other measures of depression, (e.g., Beck Depression Inventory (r=0.84) and the Zung Self-Rating Depression Scale (r=0.68) which are used for assessing depression in younger age groups.

6.6 Clinical assessment of memory

All subjects were evaluated with a standard neuropsychological battery consisting of 15 tests (see Chapter 5). This included (a) one test of pre-morbid IQ (Nelson and Willison, 1991); (b) three tests of working memory; Digit span Forward and Backward (Wechsler, 1981), the Serial 7's subtest from the Wechsler Memory Scale (Wechsler, 1945); (c) three memory tests (verbal learning and recall), the Rey Auditory Verbal Learning Test (Rey, 1964), Rey-Osterrieth Complex Figure Test (delayed recall of 30

min; Rey, 1964); (d) three language tests; Verbal Fluency for letters "FAS" and for categories "Animals' (Benton et al., 1983) and the Boston Naming Test (Kaplan et al., 1983); (e) two tests of visuo-spatial ability; Rey Complex Figure Test; copy (Rey, 1964) and the subtest Praxis from the Wechsler Memory Scale-Revised (Wechsler, 1981); (f) one test of visuomotor speed; Trail Making Test-Part A (Reitan, 1958); and (g) one test of executive function (EF); Trail Making Test-Part B (Reitan, 1958). Similarities (Wechsler, 1981) were administered as a test for abstract reasoning ability and semantic knowledge. Each test is described below and the entire list of questions and items are provided in the Appendix.

All of these tests have been empirically demonstrated to be useful, valid and reliable for the study of different cognitive functions (Lezak, 1995; Strauss et al., 2006). The individual tests were further organized into eight categories of cognitive ability on the basis of the typical association between tests and ability domains seen in the neuropsychological literature (Lezak, 1995; Mitrushina et al., 2005; Strauss et al., 2006).

NART was used only for the purpose of providing an estimate of the subjects' intelligence and was not incorporated in some of the analyses.

The National Adult Reading Test (NART: Nelson and Willison, 1991)

NART was used to estimate pre-morbid intelligence in the study population because performance on NART relies heavily on previous knowledge and not on current cognitive abilities (Nelson and Willison, 1991; Crawford et al., 2001). In a review of studies, Strauss et al. (2006) reported

NART to be among the most reliable tests in clinical practice. NART has high levels of internal consistency (alpha=0.90), test-retest reliability (0.98), and inter-rater reliability (κ>0.88).

NART is unrelated to some demographic variables, such as age, gender and ethnicity. These have little effect on the subject's performance in this test (Anstey et al., 2000). However, performance is correlated with education level and social class. NART errors systematically decrease with increasing full score. In terms of construct validity, NART correlates highly with measures of intelligence (especially verbal IQ and full-scale IQ) on the WAIS-R (r=0.85). Among verbal subtests, NART errors correlate the highest with Vocabulary and Information.

The reliability of NART was demonstrated by Crawford et al. (2001) who administered an IQ test to 177 individuals at age 11 and again at age 77. The NART scores obtained at age 77 were highly correlated (r=0.73; p<0.001) with the individual's IQ scores obtained at age 11. In the Crawford et al. (2001) study, NART accounted for more than 50% of the variance in the intelligence of the subjects, measured at age 11. In these individuals, NART was impervious to the effects of age, education and general socio-economic influences encountered after 11 years of age.

The Wechsler Adult Intelligence Test - Revised (WAIS-R Wechsler, 1981)

There is strong evidence to support the validity of the WAIS-R as a measure of global intelligence. The psychometric properties of the three

individual subtests from WAIS-R (Digit Span, Similarities and Mental Control) are discussed under its parent test the WAIS-R (Wechsler, 1981). The WAIS-R has been well standardized and is considered to be a reliable and valid instrument, which correlates highly with other IQ tests (Strauss et al., 2006). The reliability coefficients (internal consistency) for performance IQ, verbal IQ and full IQ range between 0.93 and 0.97. The split-half reliability of the WAIS-R is also very high (0.95).

The Rey Auditory Verbal Learning Test (RAVLT: Rey, 1964)

The RAVLT is a sensitive measure of verbal learning and memory that correlates moderately well with other measures of learning and memory such as, the WMS-R Logical Memory and Visual Reproduction subtests, and the California Verbal Learning Test (Strauss et al., 2006). The RAVLT is also sensitive to verbal memory deficits in different patient groups (Strauss et al., 2006). The RAVLT has been reported to distinguish patients with pseudo-dementia from those with Alzheimer's disease (Gainotti and Marra, 1994).

According to Strauss et al. (2006), the most reliable measures are the total score, the delayed recall score, and Trial 5 score. The internal reliability (Cronbach alpha) of the total score is high (0.90). Over a one-year period, more adequate retest reliability has been reported for trial 5 and delayed-recall trials (0.60 to 0.70). The delayed-recall score correlates highly with the total score ($r>0.75$), adding to the concurrent validity of RAVLT.

Performance on RAVLT is affected by age, education and intelligence (Strauss et al., 2006). Age becomes increasingly important, (especially after

the age of 60) for the number of words recalled on immediate and delayed recall trials. This is because forgetting is reported to increase with advancing age (Salthouse, 1996).

Word Fluency (Benton et al., 1983)

Word fluency is a measure of language ability. The internal consistency (Cronbach alpha) for each letter 'FAS' is high (0.83). The test-retest reliability for both the letter and semantic fluency tasks is consistently high (0.70) for both short and long intervals. Word fluency correlates well with other language tests such as the Visual Naming Test (r=0.76 to 0.86).

Increasing age is accompanied by a decrease in verbal fluency and category fluency (Bäckman et al., 2004a). Benton et al. (1981) reported a decline in verbal fluency after the age of 80 based on a sample of 65-84 year olds. Education level significantly influences scores on both fluency tasks, and higher levels of education have been associated with better performance (Bäckman et al., 2004a). Tombaugh et al. (1999) reported FAS is more sensitive to the effects of education, whilst animal naming is more sensitive to the effects of age.

Boston Naming Test (BNT: Kaplan et al., 1983)

The BNT is a reliable measure of visual confrontation naming. The internal consistency for the 60-item form ranges from 0.78 to 0.96. The test-retest reliability of the BNT is consistently higher over shorter intervals (0.91) of 1 to 2 weeks than over longer intervals. For example, over a, one-

year period, the test re-test reliability has been reported to range from 0.62 to 0.89. The BNT correlates well with other language tests such as the Visual Naming Test (r=0.76 to 0.86) from the Multilingual Aphasia Examination and to measures of intelligence (Strauss et al., 2006).

The BNT is sensitive to the effects of age. Scores on the BNT decrease with age, with the greatest decrease occurring after the age of 70 (Mitrushina et al., 2005). However, increasing age is accompanied by increasing variability in the standard deviation, suggesting that some older groups maintain their performance, whilst others decline. This may also represent the inter-individual differences that accompany increasing age (Christensen, 2001).

Performance on the BNT is also affected by verbal intelligence, full-scale IQ and educational achievement. There is less of an age effect in more highly educated individuals (Welch et al., 1996). The effects of education and intelligence can be seen by the high correlation that BNT scores have with Verbal IQ and vocabulary subtests of the WAIS-R (Thompson and Heaton, 1989). Thus, it is important to consider premorbid ability when interpreting BNT performance.

Rey-Osterrieth Complex Figure Test (ROCFT: Rey, 1964)

The ROCFT is a valid measure of a number of cognitive processes, including constructional ability (copy) and memory (recall and recognition). Memory and visuo-motor ability contribute significantly to performance. This is demonstrated by the significant correlation that the copy and recall

conditions have with tasks that require memory and constructional ability (e.g., RAVLT Trial 5 and Trail-Making B). Also, ROCFT measures correlate more strongly with performance subtests (e.g., Perceptual Organisation from WAIS-R) than with verbal subtests (e.g., Verbal Comprehension from WAIS-R).

ROCFT scores correlate well with measures of general intellectual ability (Strauss et al., 2006). ROCFT has high split-half reliability and Cronbach alpha (>0.60) for the copy condition and (>0.80) for the recall condition, suggesting the tests tap into a single factor (Strauss et al., 2006). Test-retest reliability is high for delayed recall (r=0.89) and recognition (r=0.87). No data are available for copy because most normal subjects perform close to full score and this reduces the test-retest correlation coefficient.

Increasing age is accompanied by a robust age-related decline in copy and recall scores as well as an increase in variability (Mitrushina et al., 2005; Strauss et al., 2006). A consistent discrepancy has been reported in recall performance between older subjects (60-80 years) and younger subjects (20-59 years). Older subjects score much lower than younger subjects (Strauss et al., 2006). This has been attributed to the less efficient encoding and retrieval strategies, which accompany increasing age (Bäckman et al., 2004a).

Trail-Making Test (Reitan, 1958)

The Trail-Making Test is a measure of attention, speed, and mental flexibility and is highly sensitive to cognitive impairment. In a review of studies, Strauss et al. (2006) reported that test-retest reliability is low for Part A (r=0.46) and high for Part B (r=0.89). The inter-rater reliability has been reported to be high for both Part A (κ=0.94) and Part B (κ=0.90).

Both parts of the Trail-Making Test correlate moderately with each other (r=0.31), suggesting a common underlying component, despite measuring different functions. Part B places greater demands on motor speed and visual-perceptual processes (Strauss et al., 2006). Part B also correlates well with other tests of executive function and frontal lobe dysfunction (Strauss et al., 2006).

Performance on Trails A and B is strongly affected by age and has been shown to decline with increasing age (Bäckman et al., 2004a). It is thought that age-related differences are related to the speed with which both tasks are completed. Age is unrelated to the accuracy in performing the tasks (Bäckman et al., 2004a). Although lower education and low IQ are associated with poor test scores, education may have a greater effect on Trail B for subjects over the age of 54 years (Tombaugh, 2004).

After the cognitive testing, the raw scores of the control group were compared with published norms matched for age and education on each of the cognitive tasks. This occurred prior to performing the z transformations on each of the nine cognitive domains. The purpose of this was to determine whether a bias was present in the data because there was a

higher proportion of subjects with a family history of Alzheimer's disease compared to the general population. This was due to the initial advertisement which requested first degree family members in order to maximise the chance of finding subjects carrying the ApoE ε4 allele.

6.7 Apolipoprotein E (ApoE) genotyping

Following the cognitive assessments, subjects were asked to provide a blood sample to allow for the identification of their ApoE genotype. This occurred on site at either the Royal Prince Alfred Hospital or Concord Repatriation Hospital.

Blood samples (5ml) from each subject were collected in EDTA tubes. The genotype of each DNA sample at the ApoE locus was extracted by using standard methods in which DNA was amplified by the polymerase chain reaction (PCR: Poirier et al., 1993). In this method a DNA solution is prepared from the whole blood using the Dynabeads DNA Direct Kit. The DNA is bound to super-paramagnetic polymer particles and washed free from matrix and inhibitors using a magnetic particle concentrator. After elution into buffer, the isolated DNA is then amplified using the PCR initiated by the enzyme Taq polymerase. The DNA product is subsequently cut using a restriction enzyme (Cfo 1). Electrophoresis on polyacrylamide gel identifies patterns of base pair fragments, which can be related to the ApoE gene structure. Genotypes were determined by Biochemists whom were blind to subject status.

Funding for ApoE genotyping was acquired in March 2003. As a

result, not all subjects in this study were able to undergo ApoE genotyping. However, some subjects assessed before 2003 had a follow-up assessment and were then genotyped. Two blood samples were lost due to administrative errors and were unavailable for analysis.

6.8 Role of candidate

The candidate played the primary role in all aspects of subject recruitment, data collection, management and interpretation. This included:

Study design

The design of the study was performed in collaboration with and under the guidance of the primary supervisor. The candidate was solely responsible for researching and reviewing the literature and creating study information, in addition to selecting a neuropsychological test battery for testing the hypotheses of interest.

The neuropsychological test battery examined nine domains of cognitive function. The cognitive interview took an average of two to three hours to complete. Subjects who had mild cognitive difficulties took longer to complete the test. It is well documented that cognitive impairment increases the testing time of the individual (e.g., Meulen et al., 2004; Solomon et al., 1998). Due to the extensive nature of the testing, most of the subjects were given short breaks to assist with feeling refreshed.

Recruitment and data collection

The candidate was solely responsible for recruiting all subjects, which included placing advertisements, arranging the interviews and blood tests.

The candidate performed all of the face-to-face initial and follow-up neuropsychological assessments and entered all of the data into the SPSS program prior to data analysis.

Blood collection

The candidate played a supportive role in the process of blood collection. After testing, the candidate accompanied the subject to the Pathology Department within one of the two hospital settings. Here a registered nurse extracted 5ml of blood from a vein in one of the subject's arms. The candidate then ensured that the blood was forwarded to the Biochemistry Department at the Royal Prince Alfred Hospital for ApoE genotyping. The candidate communicated directly with the Biochemistry department regarding the dissemination of blood test results.

Statistical design and analysis

The candidate, under the supervision and guidance of the primary supervisor, performed the design, planning and execution of the statistical analysis. The candidate was responsible for collecting, entering and management of the data along with the interpretation of statistical analyses.

Feedback to subjects

The candidate provided each subject with a short report of their cognitive performance. Subjects were not given a diagnosis. Subjects who demonstrated cognitive impairment or remained concerned about their memory were advised to see their GP for follow-up support or referral to a specialist. The subject did not receive feedback regarding their ApoE status. Research indicates that although the ApoE e4 allele is overrepresented in

patients with Alzheimer's disease in comparison with the general population (Saunders et al., 1993) and is recognized as a risk factor for Alzheimer's disease, evidence for a direct causation is lacking. Thus, this information was not disclosed to the subjects unless they requested it. However, a total of 11 subjects requested their ApoE status. The candidate advised these subjects on the relationship between the ApoE e4 allele and Alzheimer's disease.

6.9 Statistical analysis

To investigate cognitive differences between the groups, comparisons using one-way analysis of variance were conducted for each of the cognitive tests completed at both assessment intervals. Demographic factors and clinical variables were examined between the groups using one-way analysis of variance for continuous data. Categorical data were presented as percentage frequencies and were compared between groups using chi-square analysis, with the Pearson chi-square value reported.

To statistically control for the effects of potentially confounding variables such as age and years of education, analysis of covariance (ANCOVA) was used. If a significant main effect for group emerged and there were more than two groups, post-hoc tests were conducted using the Tukeys' B method. Bivariate Pearsons' coefficient of correlation was used to evaluate interrelationships between continuous variables, such as age and scores on formal tests (RAVLT, Trail making etc). Where appropriate, Bonferroni corrections were used to correct for family wise error.

To obtain an overview on the pattern of performance across the spectrum of cognitive domains, data from raw test scores were transformed into normally distributed z-scores based on the mean values and standard deviations from the normal control group on initial and follow-up testing. The use of z-scores allows the direct comparison of performance in different cognitive domains. The measures chosen for each composite cognitive domain were those deemed to load most heavily upon the cognitive function reported to be measured by the test (see Chapter 5).

Three of the tests (non-list errors, Trail Making-A and B) were reverse scored so that higher z-scores indicated better functioning on each of the cognitive domains. Domain z-scores were calculated by averaging tests within each domain. Individual scores below 1 SD from the mean were summed over eight of the domains for each subject to reflect overall cognitive function.

To determine whether change in cognitive function had occurred over time, and whether the pattern of performance differed between the three groups on all of the composite cognitive domains, a repeated measures multivariate analysis of variance (MANOVA) was conducted. To further investigate the interrelationships between independent and dependent variables, multiple regression analysis was conducted. The model identified demographic factors, which contributed significantly to composite z scores (average z scores of domains 2-9). In this model, a simultaneous multiple regression analysis was chosen, due to the exploratory nature of this analysis. In this method, all independent variables are entered together in

the model as one block (Tabecknick and Fidell, 2003).

All tests used were two-tailed and the statistical significance level for comparisons was set at 0.05. Data were analyzed using Statistical Package for Social Sciences (SPSS) for Windows, Version 13 (SPSS Inc. 2005) and SYSTAT, Version 8.

Chapter 7: Results, Initial assessment

7.1 Introduction

This chapter reports on the initial assessments of 86 subjects recruited from the community. The subjects were screened prior to assessment to exclude those with a current or past relevant medical, psychiatric, or neurological illness. Subjects taking medication that may compromise their cognitive function (e.g., antidepressant medication, corticosteroids) were also excluded. Demographic, clinical and neuropsychological data are presented for all subjects.

The chapter commences by analyzing risk factors for cognitive impairment, such as age, education years, subjective memory complaint (SMC), family history of dementia of the Alzheimer's disease, and depression. Information on the assessment of aMCI is provided. The clinical utility of other screening tests that can be used as alternatives to the 7MS, DRS and delayed recall to identify cognitive deficits was also examined.

Comparisons were then made between subjects with (n=54) and without (n=32) SMC on each of the cognitive tasks. It was noted that 12 of the 54 individuals with SMC also fulfilled the criteria for aMCI. Therefore, two sets of analyses are presented; one with two groups and one with three groups to test specific hypotheses on how they relate to cognitive deficits. The next section examines the inter-correlations between age and cognitive domains for the three groups. A multiple regression analysis was then carried out to examine the influence of age, education years, SMC, family history of Alzheimer's disease, and depression using the global z-score for domains 2-8. The results of the follow-up assessment will be presented in Chapter 8.

7.2 Demographic background

Between April 1999 and November 2003 a total of 108 potential subjects who responded to the community advertisement were screened over the phone. Twenty-two subjects were excluded as they did not meet the inclusion criteria. Seven subjects reported they had a medical or psychiatric illness. Three of these subjects had a history of vascular disease, two had diabetes and two were treated for a major depressive disorder. A further 15 subjects were excluded due to their age falling outside the designated age range of 50 to 79 years. This resulted in a total sample size of 86 subjects, consisting of 53 females and 33 males who consented to a neuropsychological interview (**Table 7.1**). Most of the subjects were born in Australia (70%) and were of Caucasian origin (93%).

Table 7.1 Demographic data for males and females on initial assessment (mean±SD)

Characteristics	Males (n=33)	Females (n=53)	Total (n=86)	P value
Age	64.2 ± 7.8	62.5 ± 8.7	63.1 ± 8.4	.368
(range)	(51 to 79)	(50 to 79)	(50 to 79)	
Years of education	14.3 ± 4.6	13.4 ± 3.7	13.8 ± 4.1	.308
Born in Australia	23 (70%)	37 (70%)	60 (70%)	.991
Race: Caucasian	31 (94%)	49 (93%)	80 (93%)	.792
Family history +AD	17 (52%)	24 (45%)	41 (48%)	.574
Subjective Memory Complaint (SMC)	23 (70%)	31 (59%)	54 (63%)	.296
Depression				
PAS total (n=43)	1.2 (1.7)	1.5 (1.8)	1.3 (1.7)	.593
GDS total (n=43)	1.2 (1.3)	2.6 (2.4)	2.1 (2.2)	.038*
(rated as mildly depressed)	1 (3%)	7 (13%)	8 (9%)	.114
Stroke score >1	2 (6%)	0	2 (2%)	.070
DRS total	133.6 (6.2)	132.8 (6.3)	133.1 (6.2)	.606
(range)	(118 to 141)	(109 to 142)	(109 to 142)	
Abnormal DRS (<121)	3 (9%)	4 (8%)	7 (8%)	.800
7 Minute Screen (7MS) total	-11.7 ± 14.3	-14.7 ± 8.7	-13.5 ± 11.2	.234
(range)	(-39 to 32)	(-38 to 4)	(-39 to 32)	
Abnormal 7MS (≥1)	4 (12%)	2 (4%)	6 (7%)	.139
aMCI(Delayed Recall<4)	8 (24%)	4 (8%)	12 (14%)	.087

*Statistically significant at p<.05

Subjects had a median age of 63 years and an average of 13.8 years of education. The majority of the sample was under the age of 70 (73%). There were no differences between the genders for any of the demographic items or for the majority of the clinical variables excluding depression.

On the Geriatric Depression Scale (GDS), females had significantly higher scores, $F(1,41)=4.61$, $p=.038$ compared to males. No gender

differences were apparent on the depression section of the Psychogeriatric Assessment Scale (PAS).

On the GDS, subjects frequently endorsed questions in relation to life satisfaction (26%), dropping many activities (23%), fear that a bad event would befall them (21%), having more memory problems in relation to peers (21%), and feeling full of energy (35%). On the PAS depression scale, subjects frequently endorsed items in relation to feeling depressed and sad (23%), trouble sleeping (16%), feeling worn out or little energy (21%) and trouble concentrating (19%). Overall, more females (13%) had scores indicative of mild depression compared to males (3%), but this did not reach statistical significance (P = .114).

Three (9%) men and four (8%) women had abnormally low DRS scores in the dementia range. Four (12%) men and two (4%) women scored above the abnormal threshold on the 7MS. More males (24%) fulfilled the aMCI criteria compared to females (8%), but this was not statistically significant (p=.087).

Stroke history

Two male (6%) subjects scored greater than one on the Stroke Scale (PAS: Jorm et al., 1995). This scale asks subjects if they have ever had a stroke or mini-stroke in the past and to elaborate upon symptoms suggestive of a stroke. None of the subjects responded “Yes” to two critical questions about a history of stroke, which were; “Have you ever had or been told that you had a stroke?” and “Have you ever experienced or been told that you

had a mini-stroke such as collapsing for no apparent reason or becoming disorientated?"

Both subjects who scored greater than one had other physical ailments, which may have encouraged them to respond 'yes' to other questions on this scale. These conditions included: arthritis (hence one of these subjects responded 'yes' to the question, "Have you ever had a sudden weakness on one side which got better?"), rheumatism and cataracts.

Both subjects responded 'yes' to the question on memory difficulties, "Have you ever had or been told that you had a sudden severe difficulty with your memory?" The answer to the question can be misconstrued by the researcher as a sign of a stroke, although the subject may have responded to this question in terms of their general difficulties and concerns with their memory, rather than a memory deficit that could be attributed to a stroke.

It was concluded that a history of stroke was unlikely for either subject, especially as both had responded negatively to the question "have you ever had a stroke?" during the initial telephone screening interview. Thus, neither subject was excluded from the study.

7.3 Risk factors for Alzheimer's disease

This section examines the role of established risk factors and their association with cognitive function, such as family history and age. It also examines the role of education and SMC on cognitive function.

To investigate the role of family history, the sample was dichotomised by the presence or absence of a family history of Alzheimer's disease.

7.3.1 Family history

In the present study, 48% of subjects had a first degree family history of Alzheimer's disease. The majority of the affected family members were parents (95%). Eleven of these were part of a combination with other family members such as parents and/or siblings, aunty/uncle or grandparents. A total of 5% had siblings with a history of Alzheimer's disease. Of those who were family history positive, 73% had one family member and 27% had two known family members.

Table 7.2 Subjects with and without a first degree family history of Dementia of the Alzheimer's Type (mean ± SD)

Risk factors	No family history (n=45)	Family history (n=41)	P value
Age	64.4 ± 9.3	61.7 ± 7.1	.137
Gender			
Males	16 (36%)	17 (42%)	.574
Females	29 (64%)	24 (59%)	
Education	13.4 ± 3.9	14.2 ± 4.3	.376
Subjective memory complaint	27 (60%)	27 (66%)	.575
ApoE-ε4 positive*	8 (28%)	10 (37%)	.449
Dementia Rating Scale (total)	132.8 ± 6.5	133.5 ± 5.9	.587
(range)	(109-142)	(119-142)	
Abnormal DRS (<121)	4 (9%)	3 (7%)	.790
7 Minute Screen (7MS) total	-12.2 ± 13.1	-15.1 ± 8.4	.231
(range)	(-39 to 32)	(-38 to 2)	
Abnormal 7MS (≥1)	5 (11%)	1 (2%)	.115

*Not all subjects were tested for ApoE-ε4

*Total number of subjects tested for ApoE-ε4; n=56, which consists of No Family History n=29; Family History n=27

Table 7.2 presents data on different risk factors for subjects with and without a first degree family history of Alzheimer's disease. There were no

differences between the two groups for any of the demographic variables. Both groups had a similarly high percentage of subjects who complained about their memory, 60% and 66%. No differences were apparent for carriers of the ApoE-ε4 on both dementia screening tests.

7.3.2 Age

To investigate the role of age in relation to cognitive function, the sample was categorised by age (decades) and analyses were performed on different demographic variables.

Table 7.3 provides demographic data for subjects across three age categories. There were no differences between the groups for any of the demographic variables. There were also no differences in cognitive functioning in the two younger age groups (50-59, 60-69), whereas cognitive differences were apparent in the older age group (70-79 years).

On the DRS, the older group (70-79) had a significantly lower DRS total score, $F(2,83)=6.3$, $p=.003$, including lower scores on initiation ($p=.014$) compared to the younger age groups (59-59, 60-69) and lower scores on memory ($p=.002$) compared to the 50-59 year age group. The older group (70-79 years) also had a higher percentage of subjects with abnormally low DRS scores in the dementia range (26%) compared to subjects aged 50-59 years (3%).

On the 7MS, the older group (70-79) had significantly lower 7MS total scores, $F(2,83)=6.9$, $p=.002$ and animal fluency scores, $F(2,83)=3.7$, $p=.028$ compared to the younger groups (50-59, 60-69). Moreover, the older group (70-79 years) had a significantly higher percentage of subjects who scored

Table 7.3 Demographic data categorized by age (decades) on initial assessment (mean ± SD)

Characteristics	50-59 (n=35)	60-69 (n=28)	70-79 (n=23)	P value
Males	10 (29%)	15 (54%)	8 (35%)	.118
Females	25 (71%)	13 (46%)	15 (65%)	
Years of education	14.7 ± 3.9	13.7 ± 4.0	12.4 ± 4.1	.104
Family history positive	19 (54%)	15 (54%)	7 (30%)	.154
Subj. memory complaint	21 (60%)	19 (68%)	14 (61%)	.794
Dementia Rating Scale				
a) attention	17.7 (.60)	17.9 (.45)	17.7 (.63)	.353
b) initiation	34.0 (3.8)	34.1 (3.9)	31.1 (5.1) [a,b]	.014*
c) construction	6.0 (0)	6.0 (0)	6.0 (0)	-
d) conceptualisation	35.6 (2.0)	35.3 (2.3)	34.3 (3.3)	.125
e) memory	41.5 (.74)	40.9 (1.4)	40.3 (1.6)[a]	.002*
DRS total	134.8 (4.9)	134.0 (4.6)	129.4 (8.1)[a,b]	.003*
(range)	(122 to 141)	(124 to 142)	(109 to 142)	
Abnormal DRS (<121)	1 (3%)	0	6 (26%)	.001*
7 Minute Screen (7MS)				
Orientation (error)	.03 (.17)	.57 (1.0)	1.4 (3.7)[a]	.033*
Enhanced cued recall	15.6 (.69)	15.7 (.77)	15.7 (.54)	.833
Clock drawing	7.0 (.17)	6.9 (.31)	6.6 (.89)[a]	.028*
Animal fluency	19.1 (5.8)	19.0 (6.0)	15.3 (5.3)[a,b]	.028*
7MS total	-16.9 (8.0)	-14.9 (9.3)	-6.8 (14.4)[a,b]	.002*
(range)	(-38 to -4)	(-39 to 2)	(-28 to 32)	
Abnormal 7MS (≥1)	0	1 (4%)	5 (22%)	.004*
aMCI(Delayed Recall<4)	1 (3%)	4 (14%)	7 (30%)	.039*

* Statistically significant at p<.05

[a] Statistically significant at p<.05 compared to the 50-59 year age group (post hoc test)

[b] Statistically significant at p<.05 compared to the 60-69 year age group (post hoc test)

above the abnormal threshold on the 7MS (22%) compared to the 60-69 year age group (4%). The older group (70-79) also had lower scores on temporal orientation (p=.033) and clock drawing (p=.028) compared to the 50-59 year age group. A significantly higher percentage of the older group (70-79 years) (30%) fulfilled the aMCI criteria compared to the younger

groups (50-59, 60-69) (17%). The effects of age are further examined in section 7.5.2 and 7.9 examining correlations with dementia screening tests and cognitive domains.

7.3.3 Education

To assess the role of education on cognitive function, the sample was dichotomised by total years of education (<12 years or ≥12 years). This cut-off was chosen because it fits the typical Australian education system which consists of 6 years of primary school and 6 years of high school.

Table 7.4 indicates there were no differences between the groups for any of the demographic variables. Subjects with <12 years of education reported slightly more memory complaints (73%) compared to subjects with ≥12 years of education (58%), but this was not statistically significant (p=.194). On the DRS, subjects with <12 years of education had significantly lower DRS total scores compared to subjects with ≥12 years of education, $F(1,84)=11.9$, p=.001. A significantly higher percentage of subjects with <12 years of education had an abnormal 7MS score (15%) compared to subjects with >12 years of education (3%), (χ^2 = 4.06; df=1; p=.044; however two cells had low expected counts). Education is further assessed in section 7.11 on global function in the multiple regression analysis.

Table 7.4 Demographic data for the sample based on years of education (mean±SD)

Risk factors	< 12 years (n=26)	≥ 12 years (n=60)	P value
Age	65.4 ± 8.4	62.1 ± 8.1	.101
Gender			
Males	9 (35%)	24 (40%)	.637
Females	17 (65%)	36 (60%)	
Subjective memory complaint	19 (73%)	35 (58%)	.194
Family history positive	11 (42%)	30 (50%)	.512
Dementia Rating Scale (total)	129.8 ± 7.0	134.5 ± 5.3	.001*
(range)	(109 to 142)	(119 to 142)	
Abnormal DRS (<121)	3 (12%)	4 (7%)	.448
7 Minute Screen (7MS) total	-10.5 ± 10.5	-14.9 ± 11.3	.093
(range)	(-26 to 23)	(-39 to 32)	
Abnormal 7MS (≥1)	4 (15%)	2 (3%)	.044*

*Statistically significant at p<.05

7.3.4 Subjective memory complaint (SMC)

To address the role of SMC in cognitive function, the sample was dichotomised by the presence or absence of SMC and analyses were performed on different demographic and cognitive variables. **Table 7.5** provides demographic data for subjects with (n=32) and without (n=54) SMC. The high percentage of subjects (63%) reporting a memory complaint was expected as the advertisement had requested subjects with memory difficulties. The two groups did not differ on any of the demographic variables. Subjects with SMC had significantly lower scores on the DRS total score, $F(1,84)=11.5$, $p=.001$.

Table 7.5 Demographic data for subjects with and without subjective memory complaint (SMC) on initial assessment (mean ± SD)

Characteristics	No SMC (n = 32)	SMC (n = 54)	P value
Age	62.4 ± 8.9	63.5 ± 8.1	.565
Gender			
Male	10 (31%)	23 (43%)	.296
Female	22 (69%)	31 (57%)	
Years of education	14.6 ± 3.4	13.2 ± 4.3	.117
Family history	14 (44%)	27 (50%)	.575
Depression			
PAS total (n=43)	.94 (1.6)	1.6 (1.7)	.208
GDS total (n=43)	2.4 (2.5)	2.0 (2.1)	.554
(mildly depressed)	4 (13%)	4 (7%)	.432
Stroke history	1 (3%)	1 (2%)	.705
Dementia Rating Scale			
a) attention	17.9 ± .39	17.6 ± .62	.026*
b) initiation	35.2 ± 2.1	32.1 ± 4.8	.001*
c) construction	6.0 ± 0	6.0 ± 0	-
d) conceptualisation	35.5 ± 2.0	35.0 ± 2.8	.375
e) memory	41.3 ± .98	40.9 ± 1.5	.186
DRS total	135.8 ± 3.3	131.5 ± 6.9	.001*
(range)	(127-142)	(109-142)	
(rated $\leq$ 121)	0	7 (13%)	.034*
7 minute screen (7MS)			
Temporal orientation (error)	.19 ± .59	.81 ± 2.5	.167
Enhanced cued recall (ECR)	15.8 ± .56	15.6 ± .74	.262
Clock drawing	6.9 ± .34	6.8 ± .61	.722
Animal fluency	20.0 ± 4.8	16.9 ± 6.3	.020*
7MS total	-17.6 ± 6.4	-11.1 ± 12.7	.008**
(range)	(-38 to –7)	(-39 to 32)	
Abnormal 7MS ($\geq$1)	0	6 (11%)	.051

*Statistically significant at p<.05, **p < .01

On the DRS, subjects with SMC had lower scores on attention (p=.026) and initiation (p=.001). Seven (13%) subjects with SMC had abnormally low DRS total scores in the dementia range (≤121, note: 2 items were not used in the present study as these related to USA-related topics) compared to none of the subjects without SMC, (χ^2=4.52; df=1; p=.034; however two cells had low expected counts).

Table 7.5 further shows subjects with SMC had lower 7MS total scores compared to subjects without SMC, F(1,84)=7.36, p=.008. Subjects with SMC had lower scores on animal fluency, F(1,84)=5.58, p=.020, which contributed significantly to this difference. Six subjects in the SMC group scored above the abnormal threshold on the 7MS (≥1) indicating the presence of probable dementia. None of the subjects in the group without SMC had abnormal 7MS scores. Thus, SMC had good specificity on both dementia screening tests (100%), but unacceptably low sensitivity (<15%).

It should be emphasized that a subgroup of those with SMC do have MCI (n=12). This information is presented in detail in section 7.5 (page 151).

7.4 The Rey Auditory Verbal Learning Test (RAVLT)

One of the aims of the study was to identify subjects with a high risk of developing Alzheimer's disease. This section examines performance on the Delayed Recall subtest from the RAVLT. **Table 7.6** shows the performance of subjects with and without SMC on the RAVLT, which has been analysed on the basis of its individual subtests: immediate memory,

new learning, and delayed recall.

Subjects with SMC had significantly lower scores on delayed recall compared to subjects without SMC, $F(1,84)=5.4$, $p=.022$. It is noteworthy that the two memory complaint groups did not significantly differ in their

Table 7.6 Data on the Rey Auditory Verbal Learning Test for subjects with and without SMC (mean ± SD)

RAVLT	No SMC (n=32)	SMC (n=54)	P value
Verbal learning:			
Trial 1 (max 15)	5.9 ± 1.8	5.2 ± 2.0	.131
Trial 2 (max 15)	7.3 ± 1.9	7.3 ± 2.4	.924
Trial 3 (max 15)	9.3 ± 1.8	8.7 ± 2.6	.200
Trial 4 (max 15)	10.5 ± 2.5	9.5 ± 3.1	.135
Trial 5 (max 15)	10.9 ± 2.5	10.2 ± 3.1	.252
Sum of Trials 1-5 (max 75)	44.0 ± 8.6	40.9 ± 11.5	.189
Delayed recall score:			
Trial 6 after 20 min delay (max 15)	9.2 ± 2.7	7.4 ± 3.8	.022*
Delayed recall score:			
Score = 0	0	2 (4%)	.271
Score < 4	0	12 (22%)	.004*
Score < 6	3 (9%)	16 (30%)	.029*

*Statistically significant at p<.05

performance on all five learning trials (trials 1-5) and were able to learn a similar number of total words (sum of trials 1-5). Further analyses are conducted below to identify subjects in the SMC group with pronounced deficits on delayed recall.

7.5 Classification of amnestic mild cognitive impairment (aMCI)

In this section, the delayed recall subtest of the RAVLT was used as a screening test to identify objective cognitive impairment and classify subjects as having aMCI. To aid classification, a range of cut-off scores for

impairment were considered (0, <4, and 6) and applied to subjects with and without SMC. **Table 7.6** shows if a cut-off score of zero was applied to the current data, two (4%) subjects in the SMC group would be classified as having impairment compared to none in the No SMC group. By applying a cut-off score of <6, a total of 16 (30%) subjects in the SMC group would be classified as having impairment compared to three (9%) in the No SMC group.

However, if a cut-off score <4 on delayed recall was applied to the data, 12 (22%) of the subjects in the SMC group would be classified as having impairment compared to none of the subjects in the No SMC group. A cut-off score of <4 seemed realistic and demonstrated good separation between the groups. This score is also about 2 SD below the mean for the SMC group. This score was chosen to define impairment because it produced the best sensitivity and specificity balance and was similar to thresholds used by others (Guarch et al., 2008) to classify subjects as having aMCI. The present study did not use cut-off scores adjusted for age. This would have been preferable, however due to the small sample size this would have resulted in skewed information.

7.5.1 Demographics

This section provides demographic and cognitive data to help examine differences between the three groups: controls, SMC and aMCI.

As shown in **Table 7.7**, the aMCI group was slightly older, $F(2,83)=5.44$, $p=.006$ and had fewer years of formal education,

F(2,83)=3.88, p=.025 compared to the control and SMC groups. All three groups had a high proportion (44-50%) of subjects with a first degree family history of Alzheimer's disease. There were no significant differences between the groups for depressive symptom scores. Four (13%) subjects in the control and four (13%) in the SMC groups were rated as having mild depression. None of the subjects in the aMCI group had scores in the mild depression range.

Table 7.7 Demographic data for the three groups after screening for cognitive impairment (mean ± SD)

Characteristics	Normal Controls (n = 32)	SMC (n = 42)	aMCI (n =12)	P value
Age	62.4 ± 8.9	61.6 ± 7.3	70.1 ± 7.2[a,b]	.006*
(range)	(50-79)	(50-78)	(57-79)	
Gender				
Male	10 (31%)	15 (36%)	8 (67%)	.087
Female	22 (69%)	27 (64%)	4 (33%)	
Years of education	14.6 ± 3.4	13.9 ± 4.1	11.0 ± 4.6[a,b]	.025*
Born in Australia	21 (66%)	31 (74%)	8 (67%)	.726
Race: Caucasian	28 (88%)	41 (98%)	11 (92%)	.234
Family history	14 (44%)	21 (50%)	6 (50%)	.854
ApoE-ε4 positive**	8 (42%)	6 (20%)	4 (57%)	.086
Depression				
PAS total (n=43)	.9 (1.7)	1.9 (1.8)	1.0 (1.4)	.237
GDS total (n=43)	2.4 (2.5)	2.0 (2.2)	2.0 (1.2)	.841
(rated as mildly depressed)	4 (13%)	4 (10%)	0	.445
Stroke history	1 (3%)	0	1 (8%)	.223

*Statistically significant at p<.05

[a] Statistically significant at p<.05 compared to the control group

[b] Statistically significant at p<.05 compared to the SMC group

** Not all subjects were tested for ApoE-ε4

** Total number of subjects tested for ApoE-ε4; n=56, which consists of Controls n=19; SMC n=30; aMCI n=7

7.5.2 Cognitive function

Table 7.8 shows the aMCI group had lower DRS total scores compared to the control and SMC groups, F(2,83)=9.66, p=.001, including significantly lower scores on conceptualization (p=.012) and memory (p=.001). On the initiation subscale, the aMCI group had lower scores compared to the control group (p=.004). Four (10%) subjects in the SMC and three (25%) in the aMCI groups had abnormally low DRS scores in the dementia range (≤121) compared to none of the subjects in the control group (χ^2=7.50; df=2; p=.023; however three cells had low expected counts).

On the 7MS, the aMCI group had lower scores compared to the control group, F(2,83)=4.30, p=.017, including significantly lower scores on clock drawing (p=.006) and animal fluency (p=.048). On the enhanced cued recall task, the aMCI group had lower scores compared to both the control and SMC groups (p=.017). Three (7%) subjects in the SMC and three (25%) subjects in the aMCI groups had an abnormal 7MS score (≥1) indicating the presence of probable dementia, compared to none of the subjects in the control group (χ^2=8.41; df=2; p=.015; however three cells had low expected counts).

A Pearson Chi-square test was used to analyse whether performance on the 7MS and DRS was independent of age for the three groups. This is illustrated in **Figures 7.1 and 7.2**. Both screening instruments were

Table 7.8 Clinical data for the three groups on initial assessment (mean ± SD)

Characteristics	Normal Controls (n=32)	SMC (n=42)	aMCI (n=12)	P value
Dementia Rating Scale				
a) attention	17.9 ± .39	17.6 ± .62	17.6 ± .67	.082
b) initiation	35.2 ± 2.1	32.3 ± 4.8 [a]	31.5 ± 4.7 [a]	.004*
c) construction	6.0 ± 0	6.0 ± 0	6.0 ± 0	-
d) conceptualisation	35.5 ± 2.0	35.5 ± 2.4	33.2 ± 3.5 [a,b]	.012*
e) memory	41.3 ± 1.0	41.3 ± .94	39.3 ± 2.1 [a,b]	.000*
DRS total	135.8 ± 3.3	132.6 ± 6.1	127.6 ± 8.5 [a,b]	.000*
(range)	(129-142)	(119-137)	(109-136)	
(rated +, score ≤ 121)	0	4 (10%)	3 (25%)	.023*
7 minute screen (7MS)				
Orientation (error)	0.19 ± 0.59	0.79 ± 2.6	0.92 ± 2.3	.379
Enhanced cued recall (ECR)	15.8 ± .55	15.7 ± .59	15.2 ± 1.0 [a,b]	.017*
Clock drawing	6.9 ± .34	7.0 ± .22	6.4 ± 1.2 [a,b]	.006*
Animal fluency	20.0 ± 4.8	17.3 ± 6.5	15.7 ± 5.3 [a]	.048*
7MS total	-17.6 ± 6.4	-12.0 ± 12.5	-8.1 ± 13.1 [a]	.017*
(range)	(-38 to –7)	(-39 to 32)	(-27 to 23)	
Abnormal 7MS	0	3 (7%)	3 (25%)	.015*

[a] Statistically significant at p<.05 compared to the control group (post-hoc test).

[b] Statistically significant at p<.05 compared to the SMC group (post-hoc test).

moderately correlated with the subject's age (r=0.28; n=86; p=0.008 for the 7MS and r=-0.30; n=86; p=0.005 for the DRS). Age was significantly correlated with higher scores on the 7MS for subjects with aMCI (r=.63; n=12 p<.05), but not for the control and SMC groups (r=-.16; n=32 p>.05 and r=-.18; n=42; p>.05), respectively. Moreover, there was no significant correlation between age and scores on the DRS for any of the three groups, indicating that age was not associated with performance on the DRS. The lack of correlation between the two scales and the groups are likely due to small sample sizes of individual groups and smaller range in scores.

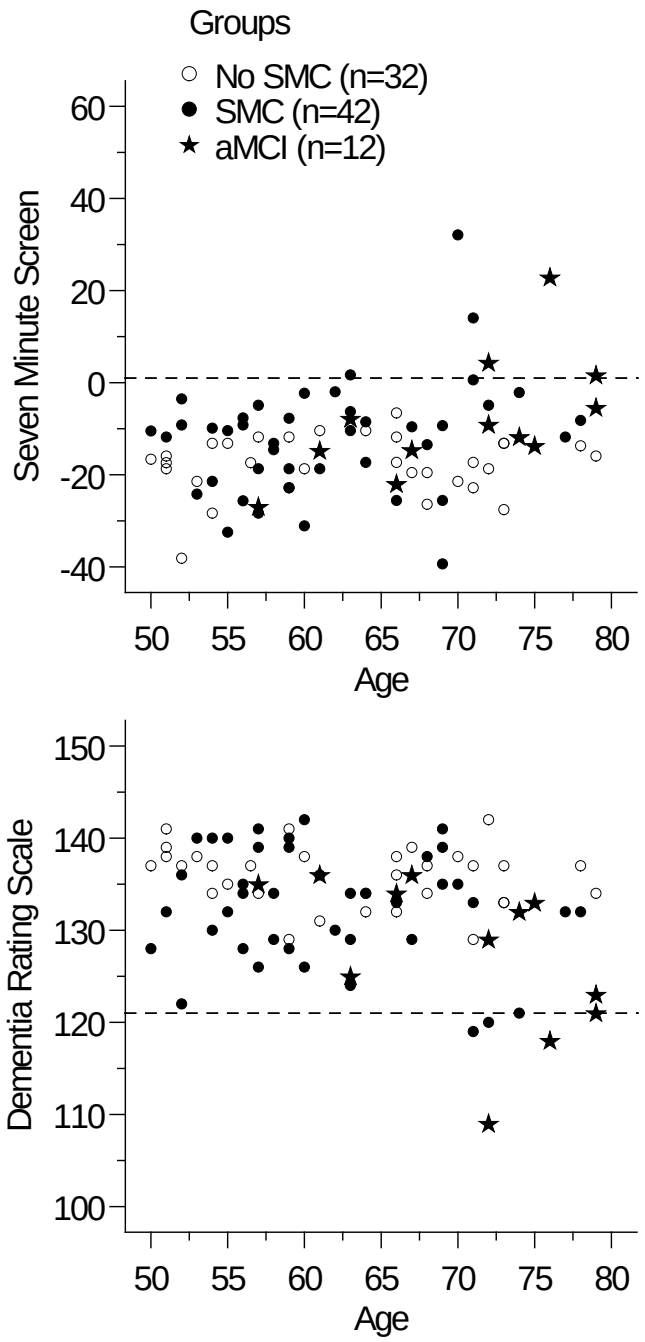


Figure 7.1 (above) *Graph showing the relationship between age and 7MS scores for the three groups.*

Figure 7.2 (below) *Graph showing relationship between age and DRS scores for the three groups*

A Pearson bivariate correlation was used to examine the interrelationship between the 7MS and DRS (see **Figure 7.3**). There was a strong negative linear correlation between the 7MS and the DRS (r=-.65; n=86; p=.001). Thus, higher scores on the 7MS were associated with lower scores on the DRS. Threshold scores for the two tests are indicated by dotted lines showing there was strong disagreement between the two instruments for two SMC subjects with normal DRS scores (~135) and 7MS scores >10 (see filled circles, quadrant 2). It should also be noted that two subjects in the aMCI group had abnormal scores on both tests (see filled stars, quadrant 1).

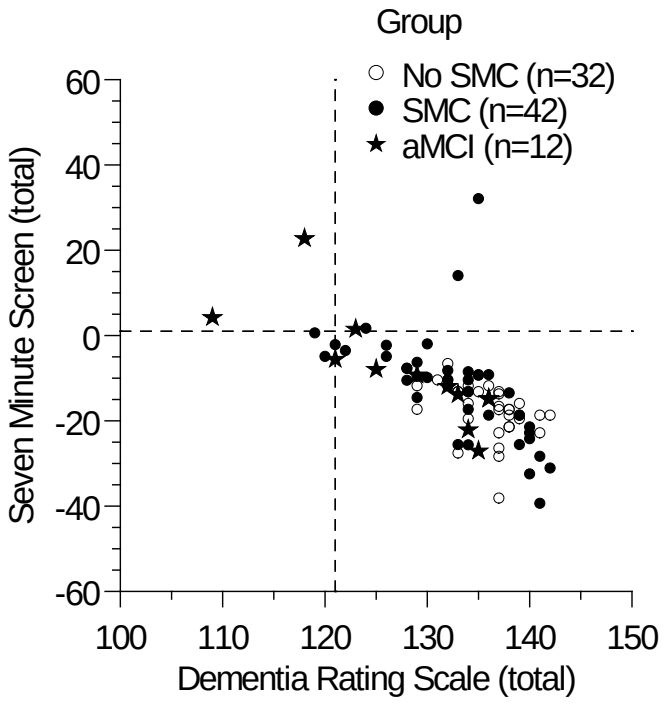


Figure 7.3 *Graph showing the correspondence between the 7 Minute Screen and Dementia Rating Scale in identifying cognitive impairment in the three groups.*

7.6 Other screening tests for dementia

This section briefly describes the clinical utility of other screening measures that have been used to screen for cognitive impairment. **Table 7.9** lists five tasks that are either part of the 7MS (Clock drawing and animal naming) or others that are quick and easy to use, such as verbal fluency (FAS words), similarities and the Trail Making-B task. The percentage of subjects with abnormal scores using published thresholds indicates the task with the best sensitivity and specificity was animal naming. None of the control and SMC groups had abnormal scores on the Clock Drawing task, but it was less sensitive than animal naming which identified deficits in 36% of subjects with SMC. Verbal fluency identified deficits in 21% of subjects with SMC, whilst Trail-B identified deficits in 14% of subjects with SMC. Scores on Similarities did not differentiate between the groups.

Table 7.9 Alternative screening tests using standard thresholds to detect dementia

Task (threshold)	Controls (n=32) % abnormal	SMC (n=42) % abnormal	aMCI (n=12) % abnormal	χ^2 value (df=2)
Clock drawing (≤5)	0	0	1 (8%)	6.24*
Animal naming (≤14)	2	15 (36%)	6 (50%)	11.90**
Verbal fluency–FAS total (≤27)	3 (9%)	9 (21%)	7 (58%)	12.18**
Trail-B (> 120 sec)	4 (13%)	6 (14%)	6 (50%)	9.12**
Similarities (≤ 6)	5 (16%)	9 (21%)	3 (25%)	NS

Threshold values were sourced from Solomon et al. (1998) for Clock Drawing; Monsch et al. (1992) for Animal naming and Verbal Fluency and Tombaugh, 2004 for Trail b test. Note age and education levels were not taken into consideration for determination of abnormality.

*p<.05, **p=.001

7.7 Normative data on healthy ageing

In this section, the raw scores for the present study of the controls (n=32) are compared to published norms on healthy ageing for each of the tests grouped by cognitive domain. The purpose of this was to demonstrate the similarity in cognitive functioning between the control data in the present study with published norms prior to transforming the raw data to z-scores. A further aim was to examine the influence of age and/or education on each of the cognitive tests.

7.7.1 Intelligent quotient (IQ)

The National Adult Reading Test (NART)

The intelligent quotient of the sample was assessed using NART. **Table 7.10** shows the raw NART scores for this study using only the controls (n=32) compared to healthy subjects from Australian published norms (n=244; Collie et al., 1999). Subjects in the published norms were over the age of 44 (mean age 63.1), and were recruited through media or contact with the research institute. They scored > 28 on the MMSE, and were free of mental and psychiatric illness. The majority of these subjects were well educated and of above average intelligence.

Performance on NART for both studies was comparable across the age categories. There were some small differences on NART for subjects in the present study with less than 12 years of education compared to the same subset in the published norms. There was a trend for higher NART

Table 7.10 Comparison of performance on the National Adult Reading Test (NART) between the present study control values with Australian published norms by age and educational level

	Present study		Collie et al. 1999	
Education Level (years)	50-64 years	65-79 years	50-69 years	70+ years
<12 years				
N	3	4	77	31
Mean	115.7	118.3	126.9	119.2
SD	2.1	5.2	5.8	4.7
≥ 12 years				
N	14	11	111	25
Mean	116.6	119.5	121.4	121.8
SD	5.9	5.3	4.1	4.3

Source: Collie et al. (1999) Norms and the effects of demographic variables on a neuropsychological battery for use in healthy ageing Australian populations. Australian and New Zealand Journal of Psychiatry: 33: 568-575.

scores in subjects with greater than 12 years of education. This was evident in both studies and reflects the influence of education on NART (Strauss et al. et al., 2006). Age had little effect on performance. A two-way ANOVA using age and education as factors indicated that NART was not affected by age, $F(1,28)=1.4$, $p=.245$ or education $F(1,28)=0.22$, $p=.642$. The NART scores should be interpreted with caution, given the low subject numbers in the present study.

To avoid duplication of normative data, published data on healthy subjects for subtests from the WAIS-R (digit span, similarities and mental control) are not presented. The WAIS-R highly correlates with NART (Crawford et al., 2001; Strauss et al., 2006) and performance on WAIS-R can be predicted by performance on NART (Nelson and Willison, 1991).

7.7.2 Episodic memory

The Rey Auditory Verbal Learning Test (RAVLT)

The RAVLT assessed verbal episodic memory and was classified as a test of verbal learning and recall. **Table 7.11** shows the raw RAVLT scores for the present study using only the control group (n=32) compared to healthy subjects from Australian published norms (n=62; Geffen et al., 1990). Subjects in the published norms were physically healthy and free of neurological symptoms by self-report. They had an average education of 11.2 (2.2) years, with a range of 7-22 years. Their average estimated IQ (derived from error scores on the NART) was 116 (7.3), with a range of 94-127.

Table 7.11 Comparison of performance on the Rey Auditory Verbal Learning Test (RAVLT) between the present study control values with Australian published norms by age (mean, SD)

	Present study (norms) by age			Published norms by age		
RAVLT items	50-59 (n=14)	60-69 (n=9)	70-79 (n=9)	50-59 (n= 20)	60-69 (n=22)	70-86 (n=20)
trials 1-5 (New learning)	45.2 (5.9)	48.1 (8.2)	37.9 (9.8)	47.6 (8.1)	42.9 (7.8)	37.1 (7.5)
Recall after interference	9.1 (2.9)	10.8 (2.0)	7.6 (3.0)	9.8 (2.9)	8.5 (2.2)	7.1 (1.8)
Recall after 20 min delay	9.6 (2.9)	10.2 (1.3)	7.3 (2.6)	10.1 (2.7)	8.7 (3.1)	7.0 (2.4)
Recognition of List A	14.1 (1.2)	14.2 (.83)	12.8 (2.2)	13.8 (1)	13.1 (2.0)	12.6 (2.3)

Source: Geffen, Moar, O'Hanlon et al., 1990: Data for healthy Australian adults stratified by age group

As shown in **Table 7.11** the scores of individual subtests on the RAVLT in the present study were comparable to the Australian published norms of Geffen et al. (1990). In both studies there was a trend for a steady decline in performance with increasing age on the total amount of words recalled after an interference list. This declining trend was also observed for the 20-minute delayed recall component. In the present study, subjects aged 60-69 years had slightly higher scores. However, the data remained comparable because the means for this age group fell within the SD of the published norms. Both data sets highlight that increasing age is accompanied by a decline in performance on episodic memory tasks, especially those which tax the memory system.

As previously discussed, since recall of Trial 1 is considered a measure of short-term memory, and approximates Digit Span (WAIS-R) to within one or two points (Hodges, 1994), the control values in the present study will therefore approximate published norms on Digit Span. This is supported by the similar performance on RAVLT between the control values in the present study with published Australian norms.

Rey-Osterrieth Complex Figure Test (ROCFT)

The ROCFT test assessed visual episodic memory and was classified as a test of visual recall and visuo-spatial ability. **Table 7.12** shows the raw ROCFT scores for the present study using only the control group (n=32) compared to published control values (n=698; Strauss et al., 2006).

Subjects in the published norms were well educated (mean=14 years), physically healthy and free of neurological symptoms.

Table 7.12 Comparison of performance on the Rey-Osterrieth Complex Figure Test (ROCFT) between the present study control values with published norms by age (mean, SD)

	Present study (norms) by age			Published norms by age		
ROCFT	50-59 (n=14)	60-69 (n=9)	70-79 (n=9)	50-59 (n=144)	60-69 (n=220)	70+ (n=334)
Copy	35.1	35.7	35.9	31.2	30.8	29.6
SD	(1.7)	(0.71)	(0.33)	(3.7)	(4.2)	(3.4)
Recall	14.0	16.8	13.7	14.9	14.2	11.7
SD	(4.4)	(6.6)	(7.0)	(7.0)	(7.5)	(6.1)

Source: Strauss et al. (2006)

Table 7.12 shows the copy scores on the ROCFT in the present study were slightly higher than the published norms for different age categories (Strauss et al., 2006). The recall scores in both data sets were comparable (means are within 1 SD of each other) and showed the classical discrepancy in performance between copy and recall, which is greater for the 70+ age group than for the younger age groups.

7.7.3 Semantic Memory

Word Fluency

Word fluency assessed semantic memory and was classified as a test of verbal ability. **Table 7.13** shows the word fluency scores for the present study using only the control group (n=32) compared to healthy subjects recruited from Canadian published norms (n=698; Tombaugh et al., 1999).

The Canadian subjects were healthy volunteers recruited from different sources within the community (e.g., shopping centres). They were free of psychiatric and neurological illness and spoke English as a first language.

Table 7.13 Comparison of performance on word fluency between the present study control values with published norms by age (mean, SD)

	Present study (norms) by age			Published norms by age		
Word Fluency	50-59 (n=14)	60-69 (n=9)	70-79 (n=9)	50-59 (n=144)	60-69 (n=220)	70+ (n=334)
Animals	20.4 (5.7)	19.4 (4.7)	20.0 (3.9)	20.1 (4.9)	17.6 (4.7)	16.1 (4.0)
FAS total	45.1 (11.5)	39.1 (13.1)	36.0 (11.1)	42.1 (11.1)	38.5 (13.7)	34.8 (12.8)

Source for word fluency: Tombaugh et al., 1999: Data for the FAS and animal naming for a sample of healthy adults stratified by demographic groups.

As shown in **Table 7.13**, performance on word fluency for animals and letters was similar in both studies for subjects aged 50-59 and 60-69. This is shown by the similar means and SDs. In the present study, animal fluency scores were slightly higher (20) than in the published norms (16) for subjects aged 70-79. However, the data remained comparable because the SDs overlapped each other. Both data sets further show a decline in performance on category fluency and verbal fluency with increasing age.

The Boston Naming Test (BNT)

The BNT assessed semantic memory and was also classified as a test of verbal ability. **Table 7.14** shows the raw BNT scores for the present study using only the control group (n=32) compared to healthy subjects from Australian published norms (n=136; Worrall et al., 1995). Subjects in

the published norms consisted of independently living older persons, recruited through advertisements. All subjects were free of neurological disease and spoke English as a first language. The mean age for the sample was 70.4 (SD=7.8) years.

Table 7.14 Comparison of performance on the Boston Naming Test (BNT) between the present study control values with Australian published norms by age (mean, SD)

	The present study (norms)		Worrall et al. (1995)		
BNT	50-64	65-79	55-64	65-74	75+
	(n=17)	(n=15)	(n=36)	(n=66)	(n=34)
Mean	54.8	53.8	53.1	53.2	48.0
SD	(5.7)	(6.3)	(4.4)	(5.4)	(7.2)

Source: Worrall et al., 1995 Data for a sample of healthy older Australians

As shown in **Table 7.14** comparison of the raw naming scores for the controls in the present study with the Australian published norms of Worrall et al. (1995) shows a similar pattern of performance for both studies across the age categories. This is supported by the SDs within the present study which overlapped with published data.

7.7.4 Visuomotor speed and executive functioning

Trail-Making A and B

The Trail-Making test A and B assessed visuo-motor speed and executive functioning, respectively (see Methods). **Table 7.15** shows the raw Trail-Making test scores for the present study using only the control group (n=32) compared to healthy subjects from Canadian published norms (n=287; Tombaugh, 2004). Subjects from the published norms were

recruited from the community (e.g., shopping centres) and were free of neurological, psychiatric and medical symptoms by self-report. Their mean age and years of education were 58 (21.7) and 12.6 (2.6), respectively. All subjects had MMSE scores >23.

Table 7.15 shows there was generally good agreement between the Trail Making A and B scores with the healthy control data in the present study and published norms (Tombaugh, 2004). Both studies showed a trend for increased task time with increased task complexity, especially in subjects aged 70-79 years with lower levels of education. The differences in the standard deviations in the present study reflect low subject numbers for some of the data cells.

Table 7.15 Comparison of performance on the Trail-Making Test between the controls in the present study with published norms (mean seconds, SD)

	Present study (norms) by age			Published norms by age		
Education Level, yrs	50-59 (n=14)	60-69 (n=9)	70-79 (n=9)	55-59 (n=95)	60-64 (n=86)	70-74 (n=106)
<12						
Trail A	22.7	43.4	30.7	35.10	33.22	42.47
(SD)	(.84)	(29.8)	(2.1)	(10.94)	(9.10)	(15.15)
12 +						
Trail A	28.4	26.9	39.7	31.72	31.32	40.13
(SD)	(6.8)	(6.7)	(8.7)	(10.14)	(6.96)	(14.48)
<12						
Trail B	188.0	78.3	81.0	78.84	74.55	109.95
(SD)	(158.4)	(36.3)	(23.0)	(19.09)	(19.55)	(35.15)
12 +						
Trail B	79.6	91.1	97.0	68.74	64.58	86.27
(SD)	(25.3)	(52.7)	(35.0)	(21.02)	(18.59)	(24.07)

Means and SDs are expressed in seconds. Lower scores indicate better performance. The time limit for Trail B is 300 seconds. A score of 300 is recorded if the task is not completed within this period.

Source: Tombaugh, 2004. Data for a sample of healthy Canadian adults stratified by Age and Education

In summary, the controls in the present study were comparable to healthy aged-matched norms on all the neuropsychological tests reviewed. The mean scores were found to be either very close or within 1 SD of published norms. Thus, the controls in the present study were considered to represent a group of subjects with normal cognitive functioning between the age of 50 and 79.

The z-scores derived from the control group data were therefore used to compare the performance of subjects using a neuropsychological test battery. The z-scores were calculated for each of the cognitive tests and then aggregated, if necessary, for each of the cognitive domains. The next section provides a discussion on z-scores.

7.8 Profile of neuropsychological functioning

This section summarises the profile of neuropsychological functioning for two groups (subjects with and without SMC) and for three groups (controls, SMC and aMCI) on initial assessment. Performance across the individual tests and their composite cognitive domains were expressed as a z-score.

7.8.1 Computing and understanding z-scores

The z-score represents, in standard deviation units, the amount a score deviates from the mean of the control group, which is represented by the zero line with a theoretical standard deviation of one. The rationale for transforming raw data to z-scores is to more easily compare individual and

group data for the various domains that otherwise would have different units of measurement and variance.

The following is an example of how to calculate the z-score of a subject using raw test scores and evaluate the subject's performance in relation to a control reference group. For example, from the aMCI group, subject number 78 was able to generate a total of 53 words on Verbal Fluency using the letters 'FAS'; scored 34/75 immediate learning (List A) and completed Trail A in 23.41 seconds. The first raw test score (Verbal Fluency) is entered into the following equation:

z-score = (subjects' score - controls' mean)/controls' SD

The Verbal Fluency score of 53 would be entered as follows: z-score = (53-40.8438)/12.14724 where; 40.8438 is the control's mean for Verbal Fluency and 12.14724 is the control's SD. Rounded control means (and SDs) can be found in Tables 7.16 and 7.17 for cognitive domain 5 (verbal ability). This produces a z-score of +1.00 and shows normal performance in Verbal Fluency skills.

Consider the raw score of 34 on total new learning (List A) from the RAVLT. This score would be entered as follows: z-score=(34-43.9688)/8.5628. This produces a z-score of -1.16 and shows deficits in episodic memory. For variables in which higher scores indicate poorer performance, the subject's score and control mean were reversed. The z-score equivalent is (control mean-subject score)/control SD. The Trail A score of 43.4 would be entered as follows: (31.8063-43.4)/11.73939. This produces a z-score of -1.00 and shows deficits in visuomotor speed.

In summary, z-scores provide a convenient way to assess test results that use different units of measurement based on a standardized normal population. The degree of difference from the standardized mean to define 'abnormality' case-ness is based on probability theory (Dawson-Saunders & Trapp, 1994). It is proposed that 66.7% of the normal population will have scores between –1 and 1 and only 2.5% of the population will have scores below 1.96. As a rule, z-scores are most commonly used to compare different attribute/test profiles and interpreting individual performance based on percentile difference of the population mean.

7.8.2 Cognitive function

In this section two analyses were used to examine cognitive function in those with and without SMC and those grouped by aMCI (Controls, SMC, and aMCI). The raw data means and SDs for each cognitive test are summarized in **Tables 7.16** and **7.17** together with the z-scores for each of the nine cognitive domains. As shown in **Table 7.16**, subjects with SMC scored significantly lower than subjects without SMC on working memory (p=.032), verbal recall (p=.038) and visuo-motor speed (p=.044).

Analysis of the data by three groups (**Table 7.17**) showed significant group differences on six of the nine cognitive domains. Post hoc analysis showed that the aMCI group scored significantly lower than the control and SMC groups on verbal learning F(2,83)=14.6, p=.000, verbal recall F(2,83)=29.5, p=.000, verbal ability F(2,83)=5.4, p=.006, visuo-motor speed F(2,83)=5.5, p=.005 and executive functioning F(2,83)=9.2, p=.000.

The aMCI group also had significantly lower scores on visual recall compared to the SMC group. There were no significant group differences in working memory and visuo-spatial ability. The aMCI group scored lower on IQ compared to the other two groups, but this was not significant (p=.060).

Table 7.16 Summary profile of performance on different cognitive domains (Z transformed) and raw test scores for each domain in subjects with and without SMC (mean ± SD)

Cognitive domain and tests	No SMC (n=32)	SMC (n=54)	P value
1. Intellectual functioning	**-0.00 ± 1.00**	**-0.41 ± 1.12**	**.088**
Full scale IQ (NART)	117.7 ± 5.4	115.5 ± 6.0	
2. Working memory (WM)	**-0.00 ± 0.80**	**-0.39 ± 0.79**	**.032***
Digit span (forward)	10.3 ± 2.1	9.6 ± 2.4	
Digit span (backward)	8.3 ± 2.3	7.2 ± 2.4	
Serial 7's	1.1 ± .10	0.76 ± .97	
3. Verbal learning (VbL)	**-0.00 ± 1.00**	**-0.36 ± 1.34**	**.189**
RAVLT: trials 1-5	44.0 ±8.6	40.9 ± 11.5	
4. Verbal recall (VbR)	**-0.00 ± 0.74**	**-0.42 ± 0.96**	**.038***
RAVLT: immediate recall	9.2 ± 2.9	7.8 ± 3.8	
RAVLT: delayed recall	9.2 ± 2.7	7.4 ± 3.8	
List A recognition	13.8 ± 1.6	13.3 ± 2.0	
Non-word list recognition	2.7 ± 2.2	3.2 ± 2.8	
5. Verbal ability (VbA)	**-0.00 ± 0.84**	**-0.36 ± 0.91**	**.072**
F A S (total)	40.8 ± 12.1	35.1 ± 12.8	
Boston naming test	54.3 ± 5.9	52.9 ± 6.8	
6. Visual recall (VsR)	**-0.00 ± 1.00**	**0.20 ± 1.15**	**.433**
REY complex figure test (recall)	14.7 ± 5.8	15.8 ± 6.7	
7. Visuo-spatial ability (VsA)	**-0.00 ± 1.00**	**-0.11 ± 1.11**	**.634**
Rey complex figure test (copy)	35.5 ± 1.2	35.3 ± 1.4	
8. Visuomotor speed (VmS)	**-0.00 ± 1.00**	**-0.57 ± 1.40**	**.044***
Trail Making-A	31.8 ± 11.7	38.5 ± 16.3	
9. Executive functioning (EF)	**0.00 ± 1.00**	**-0.16 ± 1.10**	**.506**
Trail Making-B	92.3 ± 50.1	100.2 ± 54.5	

*Statistically significant at p<.05

Table 7.17 Summary profile of performance on different cognitive domains (Z transformed) and raw test scores for each domain (mean ± SD) by three groups

Cognitive domain and tests	Controls (n=32)	SMC (n=42)	aMCI (n=12)	P value
1. Intellectual functioning	**-0.00 ± 1.00**	**-0.28 ± 0.97**	**-0.86 ± 1.50**	**.060**
Full scale IQ (NART)	117.7 ± 5.4	116.2 ± 5.2	113.1 ± 8.02	
2. Working memory (WM)	**-0.00 ± 0.80**	**-0.38 ± 0.83**	**-0.41 ± 0.68**	**.100**
Digit span (forward)	7.0 ± 1.2	6.5 ± 1.6	6.7 ± .89	
Digit span (backward)	5.0 ± 1.4	4.5 ± 1.5	4.1 ± 1.1	
Serial 7's	1.1 ± 1.0	.74 ± .96	.83 ± 1.0	
3. Verbal learning (VbL)	**-0.00 ± 1.00**	**0.04 ± 1.21**	**-1.78± 0.65**[a,b]	**.000**
RAVLT: trials 1-5	44.0 ± 8.6	44.3 ± 10.3	28.8 ± 5.6	
4. Verbal recall (VbR)	**-0.00 ± 0.74**	**-0.05± 0.72**	**-1.71± 0.48**[a,b]	**.000**
RAVLT: immediate recall	9.2 ± 2.9	9.0 ± 3.4	3.8 ± 1.9	
RAVLT: delayed recall	9.2 ± 2.7	8.8 ± 3.0	2.3 ± 1.2	
List A recognition	13.8 ± 1.6	13.9 ± 1.3	11.3 ± 2.6	
Non-word list recognition	2.7 ± 2.2	2.9 ± 2.4	4.4 ± 3.9	
5. Verbal ability (VbA)	**-0.00 ± 0.84**	**-0.20± 0.72**	**-0.95± 1.30**[a,b]	**.006**
F A S (total)	40.8 ± 12.1	37.0 ± 11.9	28.3 ± 14.1	
Boston naming test	54.3 ± 5.9	53.9 ± 5.5	49.3 ± 9.6	
6. Visual recall (VsR)	**-0.00 ± 1.00**	**0.41 ± 1.10**	**-0.56 ± 1.11**[b]	**.017**
REY complex figure test (recall)	14.7 ± 5.8	17.1 ± 6.2	11.5 ± 6.4	
7. Visuo-spatial ability (VsA)	**-0.00 ± 1.00**	**0.01 ± 0.84**	**-0.56 ± 1.75**	**.237**
Rey complex figure test (copy)	35.5 ± 1.2	35.5 ± 1.0	34.8 ± 2.2	
8. Visuomotor speed (VmS)	**-0.00 ± 1.00**	**-0.34± 1.10**	**-1.40± 2.01**[a,b]	**.005**
Trail Making-A	31.8 ± 11.7	35.8 ± 12.6	47.9 ± 23.6	
9. Executive functioning (EF)	**0.00 ± 1.00**	**0.14 ± .67**	**-1.20± 1.60**[a,b]	**.000**
Trail Making-B	92.3 ± 50.1	85.3 ± 33.8	152.3 ± 79.2	

[a] Statistically significant at p<.05 compared to the control group (post-hoc test).

[b] Statistically significant at p<.05 compared to the SMC group (post-hoc test).

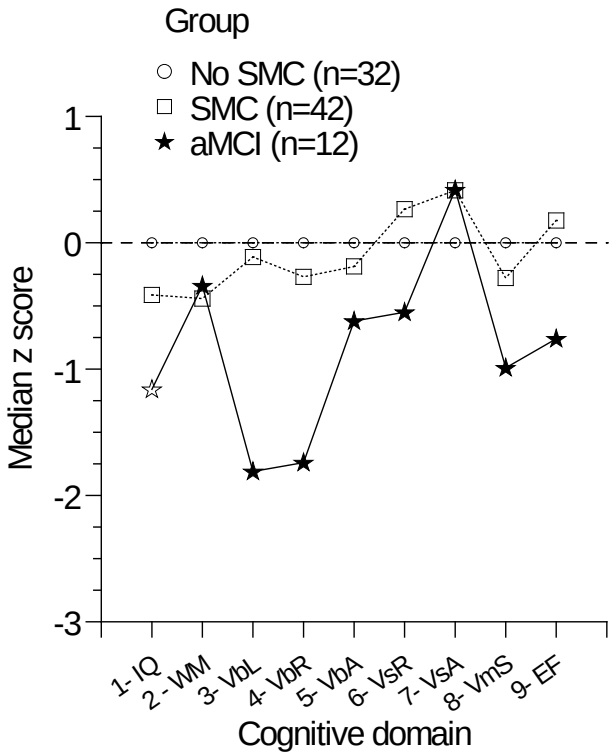


Figure 7.4 *Median z-scores for each cognitive domain for the three groups. By definition, scores for the control group have a mean of 0 and a standard deviation of 1 (dotted line).*

Figure 7.4 illustrates the median z-score profile of cognitive functioning for the SMC and aMCI groups in comparison to the control group (dotted line). The median scores are displayed for the cognitive domains, as they are less prone to skewed data. Visual examination of the profiles suggests that the aMCI group scored more poorly on seven of the cognitive domains and had pronounced deficits (<-1) on IQ, verbal learning, verbal recall and visuo-motor speed. None of the SMC group scored <.05 SD below the group mean for any of the cognitive domains.

7.9 Cognitive profiles and age

Figure 7.5 illustrates that age is a strong predictor of cognitive function based on results of a neurocognitive test battery. The vast majority of subjects under the age of 70 had normal cognitive function on formal testing. For those over 70 years of age, about 60% had deficits (below 1.0 SD of norm z-score) in two or more cognitive domains and more domains were affected if they fulfilled the aMCI criteria.

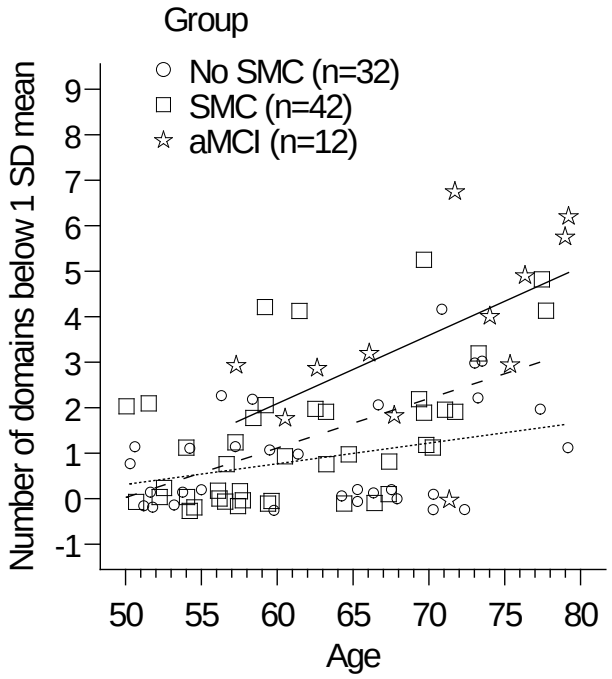


Figure 7.5 *Graph showing the relationship between age and the number of domains with cognitive deficits greater than one SD of the norms for each of the three groups. Dotted line indicates line of best fit for the control group (open circles), dashed line for the SMC group (open boxes) and the solid line for the aMCI group (stars).*

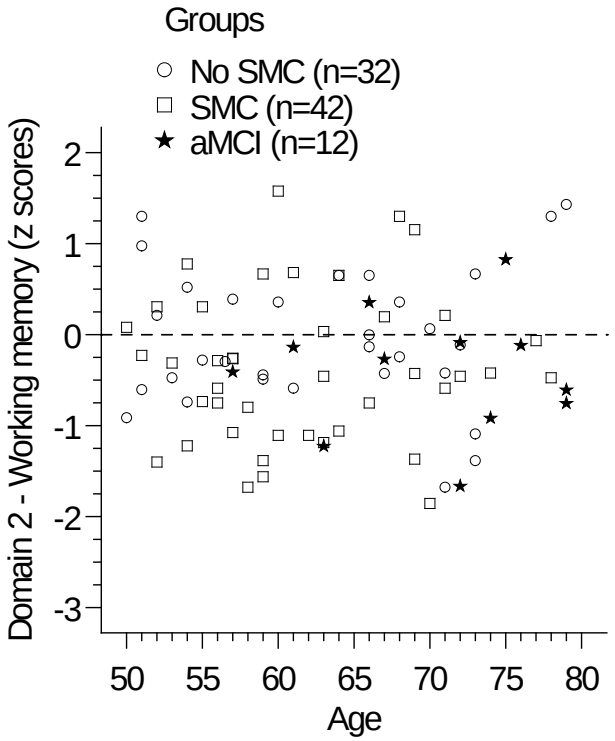
The Pearson correlation coefficients of the relationship between age and each of the cognitive domains are presented in **Table 7.18** and illustrated in **Figures 7.6 to 7.13**.

Table 7.18 shows many of the cognitive domains were highly inter-correlated (for example verbal learning and verbal recall (D3 and D4) had a correlation of 0.84 and the trail making tasks A and B (D8 and D9) had an r value of 0.53. Full IQ and working memory (Domains 1 and 2) were unrelated to age (r=.04 and -0.02, p>.05) (Table 7.18 and Fig 7.6). In contrast, age was significantly and negatively related to verbal learning (Domain 3, r= -0.51, p<.01, Fig. 7.7), verbal recall (Domain 4, r= -0.42, p<.01, Fig 7.8), verbal ability (Domain 5, r= -0.37, p<.01, Fig 7.9) and visual recall (Domain 6, r= -0.28, p<.05, Fig 7.10). Age was not related to

Table 7.18 Correlation matrix (Pearson *r* values) summarizing the association between age and the nine cognitive domains (D1-D9, n=86)

Variable		D1	D2	D3	D4	D5	D6	D7	D8
	Age	IQ	WM	VbL	VbR	VbA	VsR	VsA	VmS
D1-IQ	.04	-----							
D2-WM	-.02	.50**	------						
D3-VbL	-.51**	.10	.12	------					
D4-VbR	-.42**	.04	.05	.84**	------				
D5-VbA	-.37**	.52**	.43**	.36**	.31**	------			
D6-VsR	-.28*	.05	-.09	.30**	.30**	.35**	------		
D7-VsA	-.21	.12	.18	.26*	.24*	.16	.18	------	
D8-VmS	-.47**	.07	.21	.33**	.29**	.43**	.28**	.19	------
D9-EF	-.31**	.25*	.30**	.36**	.31**	.45**	.24*	.23*	.53**

*Statistically significant at p<.05, **p<0.01, Bonferroni corrected probabilities.
see Table 7.17 for explanation of abbreviations for each of the domains.



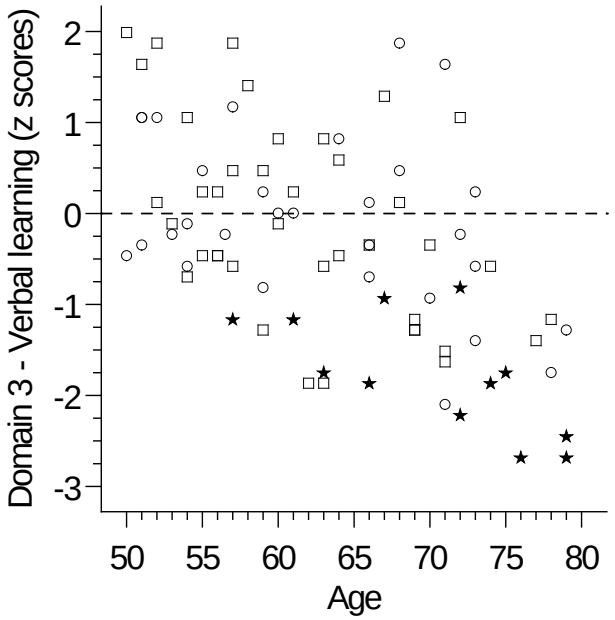
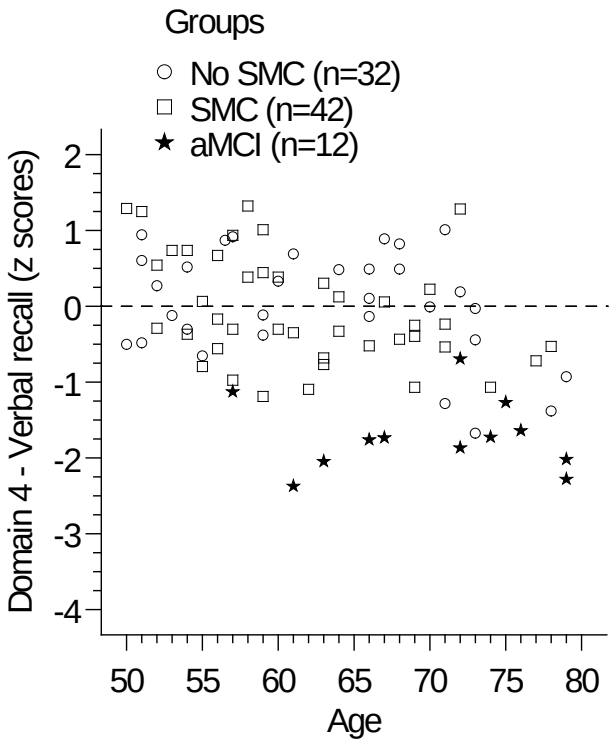


Figure 7.6 (above) *Graph showing that age was unrelated to working memory (z-scores). Dotted line indicates control mean. Scores above the line indicate better performance. See Table 7.17 for further explanation of domains and tasks used to quantify z-scores.*

Figure 7.7 (below) *Graph showing that age was related to deficits in verbal learning.*



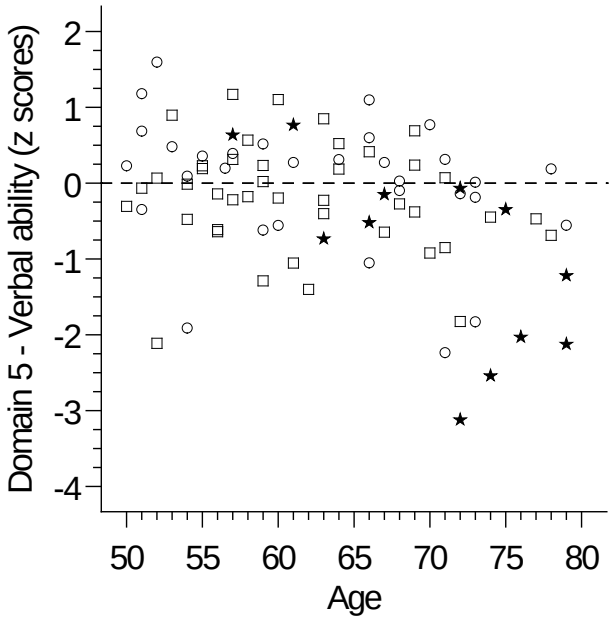


Figure 7.8 (above) *Graph showing that age was related to deficits in verbal recall.*

Figure 7.9 (below) *Graph showing that age was related to deficits in verbal ability.*

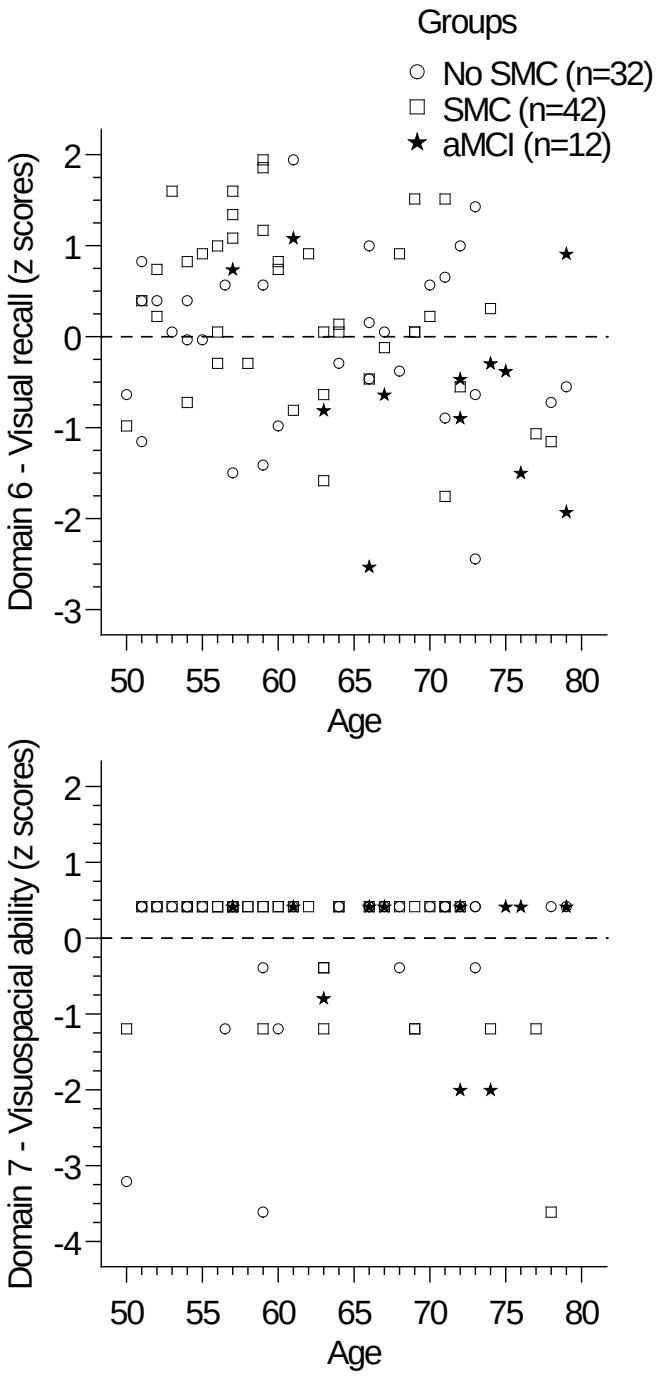


Figure 7.10 (above) *Graph showing that age was related to deficits in visual recall.*

Figure 7.11 (below) *Graph showing that age was unrelated to visuo-spatial ability. Approximately half the subjects had a maximal score which explains the similar scores above the line (ceiling effect).*

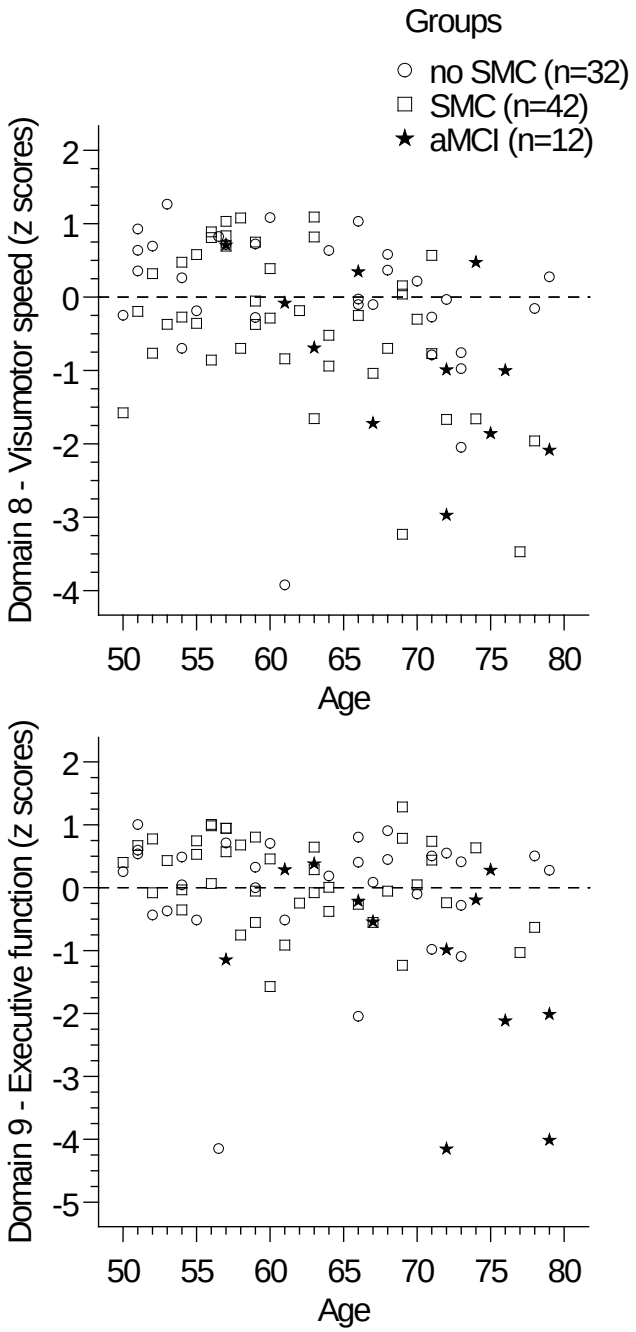


Figure 7.12 (above) *Graph showing that age was related to deficits in visuomotor speed.*

Figure 7.13 (below) *Graph showing that age was related to deficits in executive function.*

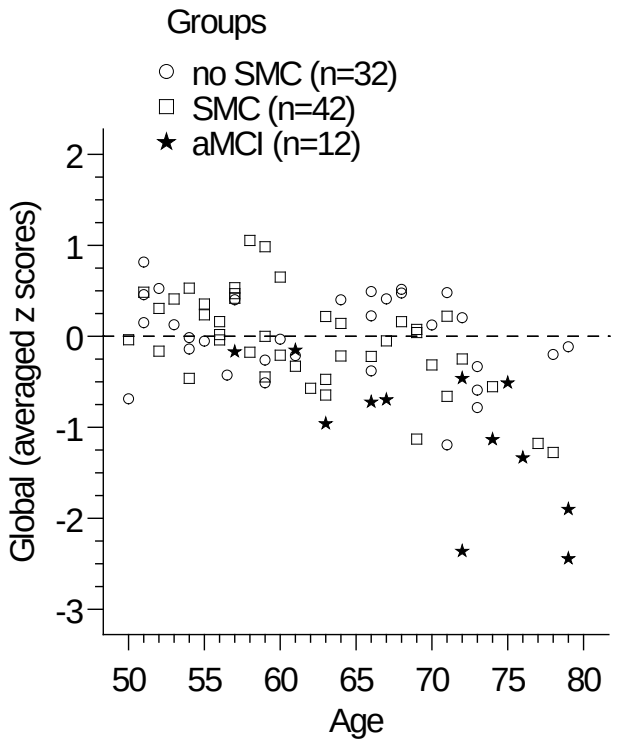


Figure 7.14 *Relationship between age and global average (mean z-score cognitive domains 2 to 9).*

visuo-spatial ability (Domain 7, r= -.21, p>.05, Fig 7.11), however age was significantly and negatively related to visuo-motor speed (Domain 8, r= -0.47, p<.01, Fig 7.12), and executive function (Domain 9, r= -.31, p<.01, Fig 7.13).

Figure 7.14 illustrates the relationship between age and the average z-score for cognitive domains two to nine for the three subject groups. Age was unrelated to average z scores for the Control group (r=-.220, p>.001), but was related to the SMC (r=-.581, p<.001), and aMCI groups (r=-.692, p<.001).

7.10 Impaired cognitive domains

In this section, a Pearson Chi-square test was used to identify the number of subjects in each group scoring within the impaired range (more than one SD below the mean). Based on evidence that premorbid IQ remains stable in early Alzheimer's disease (as measured by NART) and that IQ was not significant in Tables 7.16 and 7.17, IQ was not a variable of interest and was thus excluded from multiple regressions in Table 7.19.

Table 7.19 Number of cognitive domains with scores below 1 SD of control mean on initial assessment

Cognitive Domain	Controls (n=32) n (%)	SMC (n=42) n (%)	aMCI (n=12) n (%)
2. Working memory	3 (9%)	12 (29%)	2 (17%)
3. Verbal learning	4 (13%)	10 (24%)	10 (83%)
4. Verbal recall	4 (13%)	4 (10%)	11 (92%)
5. Verbal ability	4 (13%)	5 (12%)	5 (42%)
6. Visual recall	4 (13%)	4 (10%)	3 (25%)
7. Visuo-spatial ability	4 (13%)	8 (19%)	3 (25%)
8. Visuomotor speed	2 (6%)	8 (19%)	5 (42%)
9. Executive functioning	3 (9%)	3 (7%)	5 (42%)
Total (summed over domains 2-9)			
0	16 (50%)	17 (41%)	1 (8%)
1	8 (25%)	9 (21%)	0
2	5 (16%)	10 (24%)	2 (17%)
3	2 (6%)	1 (2%)	4 (33%)
4-5	1 (3%)	5 (12%)	2 (17%)
6+	0	0	3 (25%)

Table 7.19 shows the number and percentage of subjects in each group who scored one SD below the control mean (z-score<–1) on each of the cognitive domains and the group aggregate for the number of impaired domains (2-9). A higher percentage of subjects with aMCI (92%) and SMC (38%) had multiple domain deficits compared to the control group (25%). The aMCI group had a high percentage of subjects with impairments on

tests of verbal learning (83%) and verbal recall (92%). Twenty-four percent of the SMC group had impairments in verbal learning.

7.11 Assessment of risk factors for dementia on global functioning

The following analysis was undertaken to assess which variables accounted for the variation in global functioning. A multiple regression analysis was performed with global z-score averaged over domains 2-8 as the dependent variable. Cognitive domain 1 was omitted from the global function z-score due to reasons discussed in section 7.10. A summary of the multiple regression analysis is presented in Table 7.20. The independent variables were age, education years, SMC, family history of Alzheimer's disease and minor depression (from GDS and PAS). The latter three variables were coded as present (coded 1) or absent (coded 0). ApoE status was not used in the analysis as only 56 cases provided blood and this would have reduced the number of cases to too few.

Table 7.20 shows the correlations between the variables (first five rows and columns), the unstandardized regression coefficients (B) and intercept, the standardized regression coefficients (β, beta), the semi-partial correlations (sr^2) and R^2, and adjusted R^2. The overall R for regression (.612) was significantly different from zero, $F(5,80)=9.60$, $p=.001$. Age was the only factor which significantly contributed to the prediction of global cognitive functioning whilst SMC, family history and depression did not contribute significantly to the equation. Although the correlation between years of education and global functioning was .31, education did not

contribute significantly to the regression. Presumably, the relationship between education and global functioning is influenced by the subject's age.

Table 7.20 Standard multiple regression of age, subjective memory complaint (SMC), family history of AD, education years and depression using global cognitive functioning (average of Z-scores Domains 2-8) as the dependent variable

	Global (DV)	Age	SMC	AD FHx	Education Years	Depn	B	beta	sr^2 Unique
Age	-.54						0.039**	-.502	.222
SMC	-.20	.06					-0.225	-.168	.027
AD FHx	.20	-.16	.06				0.148	.115	.018
Edu years	.31	-.25	-.17	.10			0.022	.135	.016
Depn	-.04	-.19	-.09	.02	-.05		-.309	-.139	.018
						Intercept	2.09		
Mean	-.17	63.1	0.63	0.48	13.8	.09		R^2	0.375
SD	.65	8.4	.48	.50	4.1	.30		Adj R^2	0.336
								R	0.612

n=86, *p<0.05, **p<0.01

unique variability =.301, shared variability = .074

subjective memory complaint, AD family history and minor depression were coded 0=absent, 1 = present

Moreover, as illustrated in **Figure 7.15**, the regression analysis showed a good fit between the predicted and observed cumulative probabilities. Inspection of the residual analysis (**Figure 7.16**) showed that assumptions of normality, linearity and homoscedasticity were met as these were not correlated to the residuals.

Therefore, age was the only variable which contributed significantly to prediction of global cognitive functioning, age (sr^2=0.222). Together the five predictor variables contributed .301 in unique variability and another .074 in shared variability. In combination these explained 38% of the variability in global functioning.

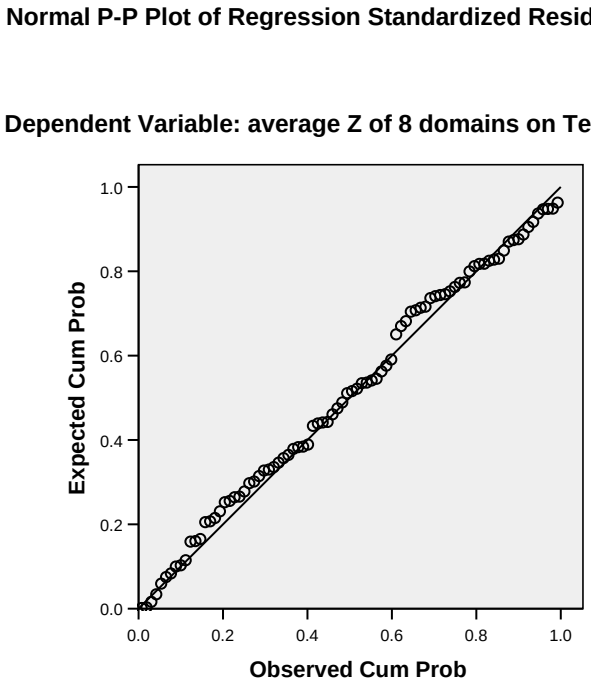


Figure 7.15 *Probability plot of the multiple regression analysis shown in Table 7.20.*

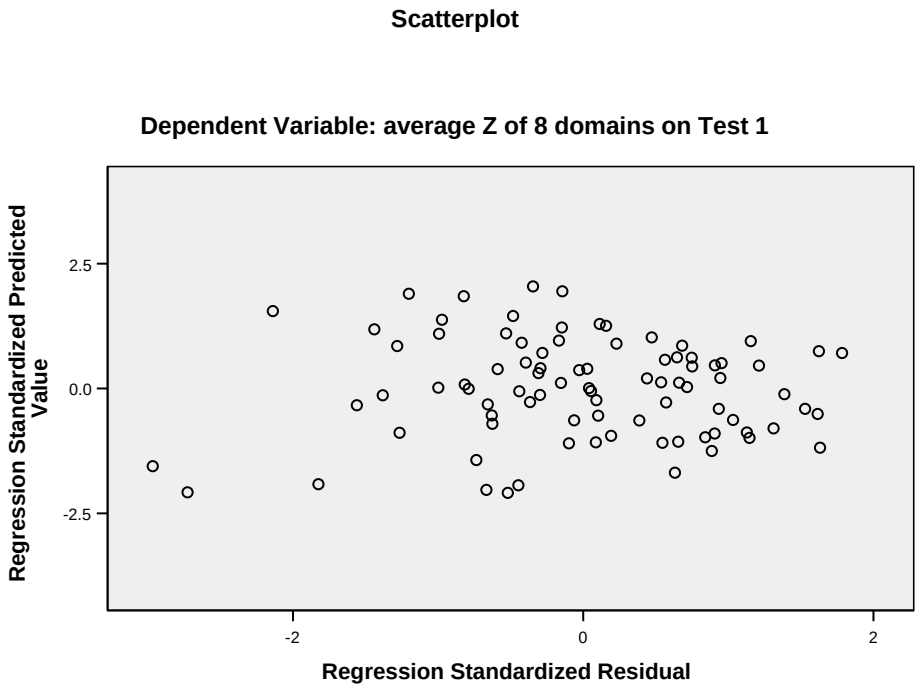


Figure 7.16 *Scatterplot of standardized residuals and predicted values for the multiple regression analysis.*

In summary, of the five variables examined (age, education years, SMC, family history of Alzheimer's disease and depression) in the multiple regression analysis, age was by far the largest predictor of global functioning. This effect was independent of SMC, family history and depression. For those without a memory complaint or a family history, significant changes would not be expected between assessments spaced 5-10 years apart (0.20 and 0.39 change in global z-scores). Conversely, changes greater than -0.5 SD units would indicate a significant decline in cognitive functioning between tests conducted a few years apart. This issue will be taken up in the next chapter describing follow-up assessments.

Chapter 8:

Results,

Follow-up assessment

8.1 Introduction

This chapter presents data for 43 subjects who returned for a follow-up test after an average period of three years. A high proportion of subjects did not attend for follow-up testing. A total of 50% declined to be re-tested or were unable to be contacted. The reasons and implications of the follow-up response rate are considered in the discussion. None of the subjects who returned for follow-up testing had experienced a relevant medical or psychiatric illness over the intervening period. Nor had any commenced a medication that could compromise their performance. The same neuropsychological test battery that was administered at the initial assessment was employed for the follow-up assessment.

The first section analyzes the characteristics of subjects who returned and those who did not attend a follow-up test to identify areas of potential bias. Comparisons were made between subjects with SMC (n=28) and without SMC (n=15) on different demographic variables to examine group

differences between assessments. Two separate analyses were carried out; one examined group differences between assessments. The other analysis assessed change over time in subjects with amnestic mild cognitive impairments (aMCI) compared to the control and SMC groups (repeated measures).

The influence of the ApoE ε4 allele on cognitive function in the context of risk factors such as age, family history of Alzheimer's disease, depression and level of education was then examined. A multiple regression analysis was performed to assess the influence of these factors on global cognitive performance as measured by the global z-score of 8 cognitive domains at time 2.

8.2 Follow-up interviews

The follow-up tests took place between February 2002 and November 2005. As shown in **Table 8.1**, the follow-up sample consisted of 43 subjects (50% of the total study sample) who consented to a second memory test. The mean follow-up period between tests was 3.2 years.

A total of 43 persons did return for a second test. As advised by relatives, one of the subjects died from cancer (subject #1, a 68 year old female). Twenty subjects declined to be re-tested; four of these subjects stated they were unable to take time off work. Four of the subjects had their initial test after October 2004 and consequently did not complete the 2-3 year interval required for re-testing. Sixteen subjects did not respond and were considered non-contactable (lost to follow-up).

Table 8.1 Demographic and clinical characteristics of subjects who returned for a follow-up test compared with those who did not return for a follow-up test (mean ± SD)

Characteristics	Not followed-up (n=43)	Had a follow-up test (n=43)	P value
Age (years)	62.1 ± 8.7	64.1 ± 8.0	.275
(range)	(50-79)	(51-79)	
Gender			
Male	17 (40%)	16 (37%)	.825
Female	26 (60%)	27 (63%)	
Education (years)	13.7 (4.0)	13.8 (4.1)	.906
Family history positive	19 (44%)	22 (51%)	.517
Subjective memory complaint	26 (61%)	28 (65%)	.665
Depression			
GDS total (n=43)	2.3 (2.1)	2.0 (2.3)	.644
(rated as mildly depressed)	4 (9%)	4 (9%)	1.0
Dementia Rating Scale	132.1 ± 6.7	134.1 ± 5.5	.140
(range)	(109-141)	(121-142)	
(rated ≤ 121)	5 (12%)	2 (5%)	.237
7 Minute Screen (total score)	-13.7 ± 10.7	-13.4 ± 11.7	.896
(range)	(-39 to 23)	(-33 to 32)	
Abnormal 7MS (>1)	2 (5%)	4 (9%)	.397

According to the reports of relatives, one subject (#12) was diagnosed as having Alzheimer's disease by her treating specialist. It is likely that this subject had dementia, but in the absence of a full assessment and rigorous application of dementia criteria, such a diagnosis cannot be confirmed. At last contact, this patient was residing in a nursing home. Another subject (#75) was rated as having clinical signs of depression according to the Psychogeriatric Assessment Scale (PAS) and was excluded.

To identify potential bias in the follow-up sample, the characteristics of subjects who returned for a follow-up test were compared to those who

did not attend a follow-up test. As shown in **Table 8.1**, there were no demographic or clinical differences between the groups for any of the variables. Both groups had similar mean ages and proportions with a positive family history, and SMC (61% VS. 65%). Both groups had four subjects who were rated as having mild depressive symptoms.

On the DRS, five (12%) subjects who dropped out of the study scored below the threshold for dementia. Whilst two subjects (5%) who returned for a follow-up test scored below the threshold for dementia. On the 7MS, two (5%) subjects who dropped out of the study scored within the abnormal range. Whilst four (9%) subjects who returned for a follow-up test scored within the abnormal range. Moreover, based on the similarities between the two groups, subjects in the follow-up cohort were considered to be representative of the total sample of subjects who had an initial test.

8.3 Subjective memory complaint

The data on SMC are based on information collected from the baseline assessment. As can be seen in **Table 8.2,** there were no demographic differences between subjects with SMC and subjects without SMC. On initial testing, subjects with SMC had lower DRS scores, $F(1,41)=7.76$, $p=.008$, but not on follow-up testing, $F(1,41)=2.78$, $p=.103$. Two subjects (7%) with SMC had abnormally low DRS scores on both tests. On the 7MS, there were no significant differences between subjects with SMC and subjects without SMC at either time point. Four (14%) subjects with SMC scored within the abnormal range on initial testing and one (4%) on follow-up testing.

Table 8.2 Characteristics of subjects in the follow-up sample with and without subjective memory complaint (mean ± SD)

Characteristics	No SMC (n=15)	SMC (n=28)	P value
Age	63.2 ± 8.2	64.6 ± 8.0	.606
Gender			
Male	8 (53%)	11 (39%)	.377
Female	7 (47%)	17 (61%)	
Months-between tests	38.5 ± 5.9	37.5 ± 7.8	.646
Years of education	14.9 ± 3.6	13.2 ± 4.3	.191
Family history positive AD	10 (67%)	18 (64%)	.876
Stroke score >1 (T1 & T2)	0	1 (4%)	.459
Geriatric depression (Test 1)	1.2 ± 2.2	1.5 ± 1.9	.604
Geriatric depression (Test 2)	1.5 ± 2.0	1.8 ± 2.0	.562
Dementia Rating Scale (Test 1)	137.1 (3.5)	133.0 (5.8)	.008*
(range)	(129-142)	(121-142)	
DRS+ (rated ≤ 121)	0	2 (7%)	.289
Dementia Rating Scale (Test 2)	136.3 ± 4.0	132.9 ± 7.5	.103
(range)	(129-141)	(105-142)	
DRS+ (rated ≤ 121)	0	2 (7%)	.289
7 Minute Screen total (Test 1)	-17.7 ± 4.3	-11.1 ± 13.7	.076
(range)	(-23 to -7)	(-33 to 32)	
Abnormal 7MS (>1)	0	4 (14%)	.124
7MS total (Test 2)	-16.7 (5.9)	-14.9 (13.6)	.626
(range)	(-24 to –6)	(-34 to 35)	
Abnormal 7MS (>1)	0	1 (4%)	.459

*Statistically significant at p <.05

8.4 Cognitive changes on dementia screening tests

In this section, the results for change on two dementia screening tests (DRS and 7MS) are presented in **Tables 8.3** and **8.4**. Initial analyses that compared those with and without SMC did not reveal any group differences between testing, nor were there any changes over time. Therefore, data are reported using three groups. To investigate change over

time, a MANOVA was performed on each variable. If significant differences were obtained for any of the variables, further one-way analyses of variance (ANOVA) were used to identify group differences (this contrast feature is not available on SPSS using MANOVA).

The analysis of change over time showed a decline on two of the DRS subtests (**Table 8.3**). The control group had significantly lower scores on attention $F(1,40)=5.58$, $p=.023$, whilst the aMCI group had significantly lower scores on initiation $F(1,40)=9.25$, $p=.004$.

Table 8.3 Assessment of change in global functioning as measured by the DRS (mean ± SD)

Dementia Rating Scale	Initial (Time 1)	Follow-up (Time 2)	Change Over time
Controls (n=15)			
Total Score	137.1 ± 3.5	136.3 ± 4.0	__
a) attention	17.9 ± .52	17.5 ± .52	d
b) initiation	36.1 ± 1.4	34.7 ± 2.7	__
c) construction	6.0	6.0	__
d) conceptualisation	35.6 ± 2.6	36.5 ± 2.5	__
e) memory	41.4 ± .83	41.6 ± .83	__
SMC (n=23)			
Total Score	133.5 ± 5.4	134.6 ± 4.7	__
a) attention	17.8 ± .52	17.9 ± .42	__
b) initiation	33.1 ± 4.5	34.1 ± 3.6	__
c) construction	6.0	6.0	__
d) conceptualisation	35.7 ± 2.4	35.3 ± 2.0	__
e) memory	41.2 ± 1.0	41.3 ± .89	__
aMCI (n=5)			
Total Score	127. 8 ± 5.6[a,b]	124.8 ± 12.7[a,b]	__
a) attention	17.8 ± .45	17.8 ± .45	__
b) initiation	30.8 ± 4.2[a]	27.0 ± 5.2[a,b]	d
c) construction	6.0	6.0	__
d) conceptualisation	33.8 ± 1.6	34.0 ± 4.7	__
e) memory	39.4 ± 2.3[a,b]	40.0 ± 2.8[a,b]	__

[a] indicates significant difference from controls at Time 1 or Time 2

[b] indicates a significant difference from SMC group at Time 1 or Time 2

[d] indicates a significant decline over time within a group

The analysis of group differences at time 1, showed the aMCI group had significantly lower scores on the DRS total score, F(2,40)=7.2, p=.002 and memory subtest F(2,40)=6.1, p=.005 compared to the control and SMC groups. Also at time 1, the aMCI group had significantly lower scores on the initiation subtest compared to the control group, F(2,40)=4.9, p=.012.

At time 2, the aMCI group had significantly lower scores on the DRS total score, F(2,40)=7.6, p=.002, initiation F(2,40)=9.9, p=.001, and memory F(2,40)=3.3, p=.045 compared to the control and SMC groups. On the memory subtest, the difference was very small as noted by the mean score (40.0).

The analysis of change over time showed a change on several 7MS subtests (**Table 8.4**). The aMCI group had significantly lower scores on enhanced cued recall (ECR), F(1,40)=13.56, p=.001 and animal fluency, F(1,40)=4.30, p=.045. The aMCI also had a significantly higher score on the 7MS total score, F(1,40)=6.98, p=.012, indicating a decline in cognitive ability. The SMC group had significantly higher scores on temporal orientation (error), F(1,40)=5.17, p=.028, animal fluency, F(1,40)=5.84, p=.020, and the 7MS total score F(1,40)=13.20, p=.001.

The analysis of group differences at time 1 showed the aMCI group had significantly lower scores compared to the other two groups on clock drawing. At time 2, the aMCI group had significantly lower scores compared to the control and SMC groups on temporal orientation, enhanced cued recall (ECR), and animal fluency and the 7MS total score.

Table 8.4 Assessment of change in global functioning as measured by the 7-Minute Screen (mean ± SD)

7-minute screen (7MS)	Initial (Time 1)	Follow-up (Time 2)	Change Over time
Temporal orientation (error)			
Controls (n=15)	.33 ± .82	.13 ± .35	-
SMC (n=23)	1.3 ± 3.4	.04 ± .21	c
aMCI (n=5)	.40 ± .90	1.4 ± 3.1[a,b]	-
Enhanced cued recall (ECR)			
Controls (n=15)	15.9 ± .26	15.9 ± .26	-
SMC (n=23)	15.7 ± .54	15.9 ± .34	-
aMCI (n=5)	15.6 ± .55	13.4 ± 4.2[a,b]	d
Clock drawing			
Controls (n=15)	6.9 ± .26	7.0 (0)	-
SMC (n=23)	7.0 ± .21	7.0 ± .21	-
aMCI (n=5)	6.6 ± .55 [a,b]	6.8 ± .45	-
Animal fluency			
Controls (n=15)	20.2 ± 2.4	18.9 ± 3.9	-
SMC (n=23)	18.1 ± 6.2	20.1 ± 6.7	c
aMCI (n=5)	14.8 ± 4.9	11.2 ± 3.5[a,b]	d
7MS total			
Controls (n=15)	-17.7 ± 4.3	-16.7 ± 5.9	-
SMC (n=23)	-11.4 ± 14.7	-18.5 ± 9.4	c
aMCI (n=5)	-9.3 ± 8.7	1.6 ± 18.9[a,b]	d

[a] indicates significant difference from controls at time 1 or time 2

[b] indicates a significant difference from the SMC group

[c] indicates an improvement over time within a group

[d] indicates a decline over time within a group

Pearson's correlation coefficient was used to assess the relationship between age, the 7MS and DRS for the three groups. As illustrated in **Figures 8.1** and **8.2**, age was positively related to lower scores on the 7MS (higher scores indicating impairment) (r=0.50, p=.001) and negatively related to the DRS (lower scores indicating impairment) (r=-0.45, p=.003). This indicated age had a significant effect on both screening tests.

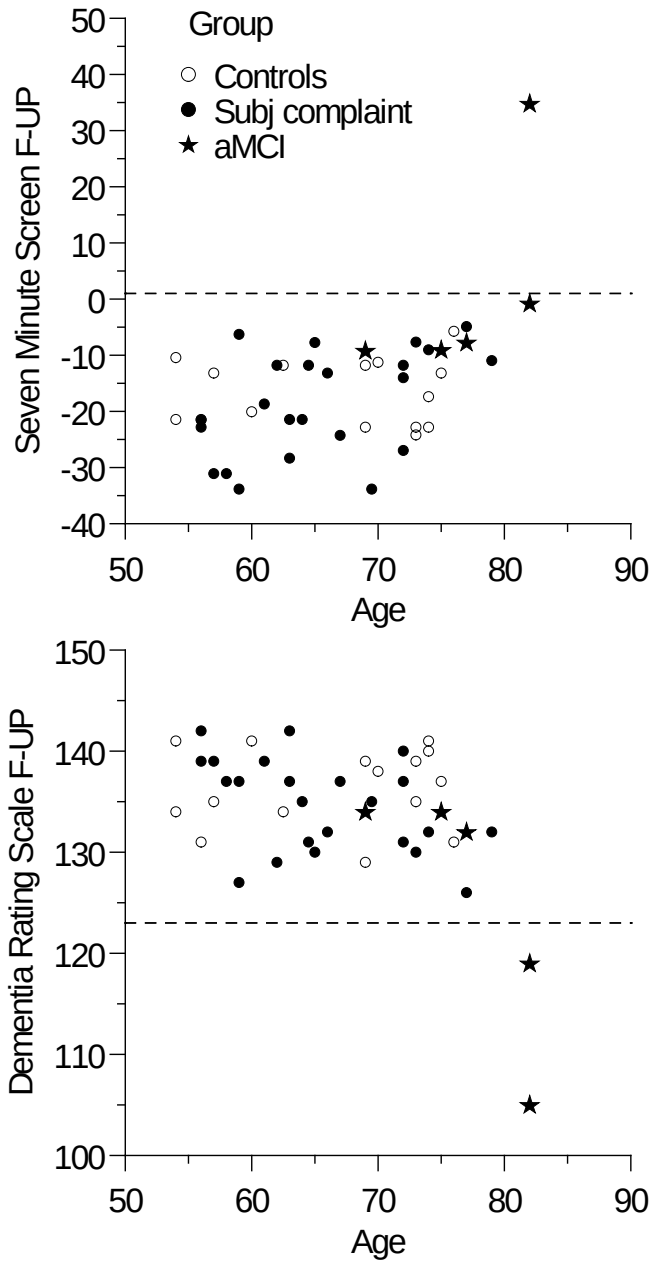


Figure 8.1 (above) *Graph showing the relationship between age (T2) and performance on the 7MS on follow-up assessment. Scores above the line indicate poorer performance.*

Figure 8.2 (below) *Graph showing the relationship between age (T2) and performance on the DRS on follow-up assessment. Scores above the line indicate better performance.*

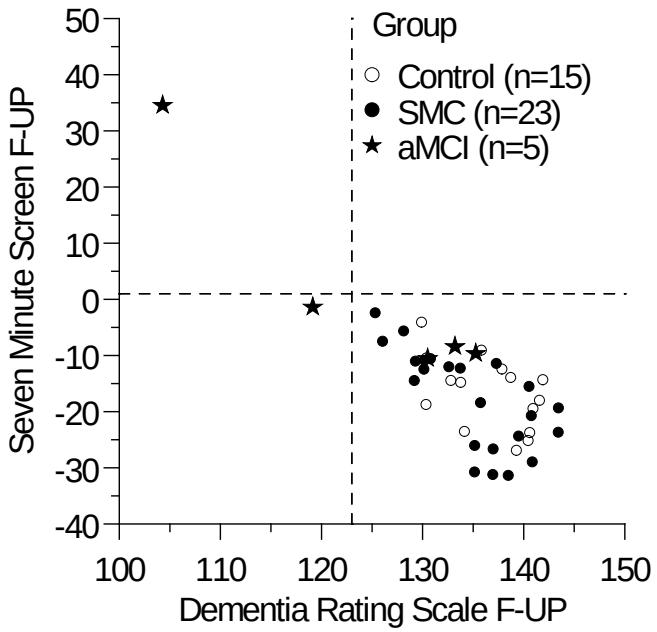


Figure 8.3 *Graph showing the strong correspondence (r= -0.84) between the 7MS and DRS on follow-up assessment. Dotted lines indicate threshold values for the two measures.*

In agreement with initial testing (see Figure 7.3, page 160) **Figure 8.3** illustrates a strong negative linear correlation between the 7MS and DRS (r= -0.84, p=.001). Higher scores on the 7MS were associated with lower scores on the DRS.

8.5 Neuropsychological changes over time

This section presents results for change on individual tests grouped by cognitive domain for the three groups (controls, SMC, aMCI). These are presented in **Tables 8.5** and **8.10**. Two analyses were used. One investigated change over time on each of the 8 cognitive domains. If

significant differences were obtained for any of the cognitive domains, further one-way ANOVAs were used to identify group differences.

Working memory (Domain 2)

As can be seen in **Table 8.5**, the analysis of change over time in working memory showed the SMC group had significantly higher scores on digit span forward, $F(1,40)=4.30$, $p=.045$, whilst the control group had a significant decline in performance on digit span backwards, $F(1,40)=5.36$, $p=.026$.

Table 8.5 Assessment of change in working memory (domain 2) (mean ± SD)

Working memory	Initial (Time 1)	Follow-up (Time 2)	Change Over time
Digits forward			
Controls (n=15)	6.7 ± .96	6.6 ± 1.1	__
SMC (n=23)	6.3 ± 1.7	6.8 ± 1.3	c
aMCI (n=5)	6.4 ± .55	6.2 ± 1.5	__
Digits backward			
Controls (n=15)	4.7 ± 1.3	4.0 ± 1.3	d
SMC (n=23)	4.8 ± 1.5	5.0 ± 1.6	__
aMCI (n=5)	4.4 ± .55	4.2 ± .84	__
Serial 7's (errors)			
Controls (n=15)	.87 ± 1.0	.67 ± .98	__
SMC (n=23)	.70 ± .97	1.1 ± 1.0	__
aMCI (n=5)	.80 ± 1.1	.40 ± 0.90	__

[c] indicates a significant improvement over time within a group

[d] indicates a significant decline over time within a group

Verbal learning (Domain 3)

As can be seen in **Table 8.6**, the analysis of change over time in verbal learning showed the SMC group had significantly higher scores on verbal learning, F(1,40)=6.17, p=.017.

Table 8.6 Assessment of change in verbal learning (domain 3) (mean ± SD)

Verbal learning	Initial (Time 1)	Follow-up (Time 2)	Change Over time
Trials 1-5			
Controls (n=15)	43.5 ± 9.0	46.1 ± 7.0	__
SMC (n=23)	41.9 ± 9.1	45.2 ± 11.2	c
aMCI (n=5)	27.4 ± 6.2[a,b]	28.2 ± 5.9[a,b]	__

[a] indicates a significant difference from controls

[b] indicates a significant difference from SMC group

[c] indicates a significant improvement over time within a group

Trials 1 –5 = total learning over trials on the Rey Auditory Verbal Learning Test

The analysis showed the aMCI group scored significantly lower on verbal learning compared to the control and SMC groups at both time points, F(2,40)=6.63, p=.003 (Time 1) and F(2,40)=7.41, p=.002 (Time 2).

Verbal recall (Domain 4)

As can be seen in **Table 8.7**, the analysis of change over time in delayed recall showed the SMC group had significantly higher scores on delayed recall, F(1,40)=5.06, p=.030.

The analysis of group differences at time 1, showed the aMCI group had significantly lower scores on immediate recall, F(2,40)=9.37, p=.001 (T1), delayed recall, F(2,40)=17.23, p=.001 (T1), and recognition of List A words F(2,40)=6.1, p=.005 compared to the control and SMC groups.

Table 8.7 Assessment of change in verbal recall (domain 4) (mean ± SD)

Verbal recall	Initial (Time 1)	Follow-up (Time 2)	Change Over time
Immediate recall			
Controls (n=15)	9.9 ± 2.2	9.4 ± 2.2	__
SMC (n=23)	8.0 ± 3.5	9.0 ± 3.0	__
aMCI (n=5)	3.2 ± 2.4[a,b]	2.8 ± 2.6[a,b]	__
Delayed recall			
Controls (n=15)	9.3 ± 2.6	9.3 ± 3.5	__
SMC (n=23)	8.1 ± 2.4	9.2 ± 3.0	c
aMCI (n=5)	2.2 ± 1.3[a,b]	2.6 ± 2.4[a,b]	__
List A: recognition			
Controls (n=15)	13.9 ± 1.8	14.1 ± 1.8	__
SMC (n=23)	13.9 ± 1.3	14.0 ± 1.3	__
aMCI (n=5)	11.0 ± 3.2[a,b]	9.2 ± 6.3[a,b]	__
List B: recognition			
Controls (n=15)	5.1 ± 3.0	6.5 ± 3.8	__
SMC (n=23)	7.2 ± 2.5	7.0 ± 3.6	__
aMCI (n=5)	5.0 ± 2.0	5.2 ± 4.6	__

[a] indicates a significant difference from controls

[b] indicates a significant difference from SMC group

[c] indicates a significant improvement over time within a group

RAVLT = Rey Auditory Verbal Learning Test

At time 2, the aMCI group had significantly lower scores on immediate recall $F(2,40)=12.45$, $p=.001$, delayed recall, $F(2,40)=9.92$, $p=.001$ (T2) recognition of List A words $F(2,40)=8.40$, $p=.001$ compared to the other two groups.

Verbal ability (Domain 5)

As can be seen in **Table 8.8**, the analysis of change over time in verbal ability showed the SMC group had significantly higher scores on FAS word generation, $F(1,40)=13.15$, $p=.001$.

Table 8.8 Assessment of change in verbal ability (domain 5) (mean ± SD)

Verbal ability	Initial (Time 1)	Follow-up (Time 2)	Change over time
BNT			
Controls (n=15)	53.0 ± 8.2	54.7 ± 5.9	__
SMC (n=23)	54.7 ± 5.5	55.5 ± 4.6	__
aMCI (n=5)	47.4 ± 10.4	47.6 ± 10.6[a,b]	__
FAS (total)			
Controls (n=15)	40.1 ± 12.7	39.3 ± 15.4	__
SMC (n=23)	36.9 ± 12.7	43.5 ± 13.7	c
aMCI (n=5)	23.8 ± 10.3[a,b]	22.8 ± 15.2[a,b]	__

[a] indicates a significant difference from controls

[b] indicates a significant difference from SMC group

[c] indicates a significant improvement over time within a group

FAS = Letter fluency; BNT = Boston Naming Test

The analysis of group differences at time 1, showed the aMCI group had significantly lower scores on FAS word generation, F(2,40)=, p=.050 compared to the control and SMC groups. At time 2, the aMCI group had significantly lower scores on FAS word generation, F(2,40)=4.21, p=.022 and on the BNT, F(2,40)=3.68,p=.034 compared to the other two groups.

Visual copy and recall (Domains 6 and 7)

As can be seen in **Table 8.9**, the analysis of change over time in visual copy and recall showed the aMCI group's recall performance increased on the second assessment, but this was not significant (p=.058).

Analysis of group differences at time 1, showed the aMCI group obtained significantly lower scores on visual copy, F(2,40)=4.2, p=.026, and visual recall, F(2,40)=4.4, p=.018, respectively compared to the control and SMC groups.

Table 8.9 Assessment of change in visual copy (domain 6) and recall (domain 7) (mean ± SD)

Visual copy and recall	Initial (Time 1)	Follow-up (Time 2)	Change over time
ROCFT: Copy			
Controls (n=15)	35.7 ± .60	35.7 ± .70	__
SMC (n=23)	35.5 ± .85	35.7 ± .69	__
aMCI (n=5)	34.0 ± 3.1[a,b]	35.2 ± 1.8	__
ROCFT: Recall			
Controls (n=15)	16.2 ± 5.0	17.6 ± 6.5	__
SMC (n=23)	18.2 ± 5.9	18.7 ± 5.6	__
aMCI (n=5)	9.7 ± 8.0[a,b]	15.5 ± 11.7	__

[a] indicates a significant difference from controls

[b] indicates a significant difference from SMC group

ROCFT = Rey-Osterrieth Complex Figure Test

Visuomotor speed and executive functioning (Domains 8 and 9)

As can be seen in Table 8.10, the analysis of change over time in visuomotor speed and executive functioning (Trail A and B) showed no changes over time for any of the three groups.

Table 8.10 Assessment of change in visuomotor speed (domain 8) and executive functioning (domain 9) (mean ± SD)

Visuomotor speed & Executive functioning	Initial (Time 1)	Follow-up (Time 2)	Change over time
Trail A			
Controls (n=15)	29.5 ± 7.7	29.6 ± 9.2	__
SMC (n=23)	34.8 ± 14.1	34.2 ± 16.3	__
aMCI (n=5)	52.7 ± 34.3[a,b]	60.1 ± 30.1[a,b]	__
Trail B			
Controls (n=15)	93.3 ± 62.1	73.1 ± 17.5	__
SMC (n=23)	85.0 ± 33.3	86.1 ± 56.3	__
aMCI (n=5)	166.3± 80.0[a,b]	176.2 ± 92.0[a,b]	__

[a] indicates a significant difference from controls

[b] indicates a significant difference from SMC group

Analysis of group differences at time 1, showed the aMCI had significantly higher scores compared to the other two groups on Trails A and B, $F(2,40)=4.07$, $p=.025$ and $F(2,40)=5.29$, $p=.009$, respectively. At time 2, the aMCI group had significantly higher scores compared to the other two groups on Trails A and B, $F(2,40)=6.71$, $p=.003$ and $F(2,40)=7.71$, $p=.001$, respectively. The large SDs on Trail B indicates two subjects did not complete the task and obtained a score of 300 (sec).

Assessment summary of individual tests

On the brief screening tests, the aMCI group showed greater decline over time on the 7MS total score and two subtests; verbal fluency and enhanced cued recall. The SMC group obtained significantly higher scores on the 7MS total score, verbal fluency and temporal orientation. On the DRS, the aMCI showed minimal change over time. However, in the analysis of group differences, the aMCI group had significantly lower scores on the DRS total score, initiation and memory compared to the other two groups.

On the composite cognitive domain tests, the analysis of change over time showed the SMC group had higher scores on working memory, verbal learning, verbal recall and verbal ability, whilst the aMCI group declined on working memory. The aMCI group had consistently lower scores compared to the other two groups on all of the cognitive domains and maintained a stable performance over time.

8.6 Profile of neuropsychological impairment at follow-up

This section provides a summary profile of change over time, using repeated measures MANOVA for the individual cognitive domains expressed as z scores. The subjects are grouped by SMC (**Table 8.11**), and also by aMCI (**Table 8.12**). Analysis of the data by two groups (**Table 8.11)** showed significant changes on four of the nine cognitive domains. Both subjects with and without SMC had significantly higher scores on intellectual functioning $F(1,41)=14.24$, $p=.001$ and $F(1,41)=16.35$, $p=.001$, respectively. The SMC group had significantly higher scores on working memory, $F(1,41)=6.67$, $p=.013$, verbal learning, $F(1,41)=18.84$, $p=.000$ and verbal ability, $F(1,41)=10.70$, $p=.002$.

Analysis of the data by three groups (**Table 8.12**) showed significant group differences on four of the nine cognitive domains. All three groups had significantly higher scores on intellectual functioning (IQ), $F(1,40)=16.67$, $p=.001$ (controls), $F(1,40)=8.33$, $p=.006$ (SMC), and $F(1,40)=8.00$, $p=.007$ (aMCI). The SMC group had significantly higher scores on working memory, $F(1,40)=13.08$, p.001, verbal learning, $F(1,40)=14.32$, $p=.001$, and verbal ability, $F(1,40)=14.20$, $p=.001$. The aMCI group had significantly higher scores on verbal learning, $F(1,40)=4.15$, $p=.048$. This contrasted with the aMCI group's performance on verbal recall, which remained stable. The aMCI group had a slight decrease in performance in visuomotor speed as noted by the one point change in the SD, but this was not significant.

Table 8.11 Summary profile of changes in each cognitive domain (Z transformed) in subjects with and without SMC on initial and follow-up assessment (mean ± SD)

Cognitive domain and tests	Initial (Time 1)	Follow-up (Time 2)	Change over time
1. Intellectual functioning			
No SMC (n=15)	.00 ± 1.0	.43 ± .70	c
SMC (n=28)	.00 ± 1.1	.30 ± .96	c
2. Working memory (WM)			
No SMC (n=15)	.00 ± .69	-.11 ± .58	__
SMC (n=28)	-.04 ± .89	.23 ± .96	c
3. Verbal learning (VbL)			
No SMC (n=15)	.00 ± 1.0	.19 ± 1.2	__
SMC (n=28)	-.85 ± 1.2	-.23 ± 1.3	c
4. Verbal recall (VbR)			
No SMC (n=15)	.00 ± .69	-.32 ± .98	__
SMC (n=28)	-.90 ± 1.0	-.74 ± 1.3	__
5. Verbal ability (VbA)			
No SMC (n=15)	.00 ± .88	.07 ± .84	__
SMC (n=28)	-.19 ± .72	.05 ± .91	c
6. Visual recall (VsR)			
No SMC (n=15)	.00 ± 1.0	.27 ± 1.3	__
SMC (n=28)	.10 ± 1.4	.38 ± 1.4	__
7. Visuo-spatial ability (VsA)			
No SMC (n=15)	.00 ± 1.0	.00 ± 1.2	__
SMC (n=28)	-.81 ± 2.6	-.15 ± 1.6	__
8. Visuomotor speed (VmS)			
No SMC (n=15)	.00 ± 1.0	-.01 ± 1.2	__
SMC (n=28)	-1.1 ± 2.6	- 1.2 ± 2.8	__
9. Executive functioning (EF)			
No SMC (n=15)	.00 ± 1.0	.33 ± .28	__
SMC (n=28)	-.10 ± .86	-.14 ± 1.1	__

[c] indicates a significant improvement over time within a group

Table 8.12 Summary profile of changes in each cognitive domain by three groups on initial and follow-up assessment (mean z score ± SD)

Cognitive domain and tests	Initial (Time 1)	Follow-up (Time 2)	Change over time
1. Intellectual functioning (IQ)			
Controls (n=15)	.00 ± 1.0	.43 ± .70	c
SMC (n=23)	.16 ± .93	.41 ± .85	c
aMCI (n=5)	-.76 ± 1.4	-.24 ± 1.3	c
2. Working memory (WM)			
Controls (n=15)	.00 ± .69	-.11 ± .58	—
SMC (n=23)	-.03 ± .95	.36 ± .98	c
aMCI (n=5)	-.08 ± .55	-.35 ± .68	—
3. Verbal learning (VbL)			
Controls (n=15)	.00 ± 1.0	.19 ± 1.2	—
SMC (n=23)	-.44 ± .92	.16 ± 1.0	c
aMCI (n=5)	-2.7 ± .51[a,b]	-2.0 ± .81[a,b]	c
4. Verbal recall (VbR)			
Controls (n=15)	.00 ± .70	-.32 ± .98	—
SMC (n=23)	-.62 ± .85	-.34 ± .93	—
aMCI (n=5)	-2.2 ± .59[a,b]	-2.5 ± .94[a,b]	—
5. Verbal ability (VbA)			
Controls (n=15)	.00 ± .88	.07 ± .84	—
SMC (n=23)	-.02 ± .59	.29 ± .69	c
aMCI (n=5)	-.98 ± .81[a,b]	-1.0 ± 1.1[a,b]	—
6. Visual recall (VsR)			
Controls (n=15)	.00 ± 1.0	.27 ± 1.3	—
SMC (n=23)	.40 ± 1.2	.50 ± 1.1	—
aMCI (n=5)	-1.3 ± 1.6	-.15 ± 2.3	—
7. Visuospatial ability (VsA)			
Controls (n=15)	.00 ± 1.0	.00 ± 1.2	—
SMC (n=23)	-.36 ± 1.4	.01 ± 1.2	—
aMCI (n=5)	-2.9 ± 5.2	-.90 ± 3.0	—
8. Visuomotor speed (VmS)			
Controls (n=15)	.00 ± 1.0	-.01 ± 1.2	—
SMC (n=23)	-.70 ± 1.8	-.62 ± 2.1	—
aMCI (n=5)	-3.0 ± 4.5[a,b]	-4.0 ± 3.9[a,b]	—
9. Executive functioning (EF)			
Controls (n=15)	.00 ± 1.0	.33 ± .28	—
SMC (n=23)	.13 ± .54	.12 ± .91	—
aMCI (n=5)	-1.2 ± 1.3[a,b]	-1.3 ± 1.5[a,b]	—

[a] indicates a significant difference from the control group

[b] indicates a significant difference from the SMC group

[c] indicates a significant improvement over time within a group

Figure 8.4 illustrates the mean z-score profile of neuropsychological functioning for both the SMC and aMCI groups in comparison to the control group on re-testing. Examination of Figure 8.4 shows that most of the control and SMC groups obtained a similar or higher score on re-testing three years later. Whilst the aMCI group did not decline, their performance significantly contrasted with the control and SMC groups in a number of cognitive domains, including verbal learning, verbal recall, verbal ability, visuomotor speed and executive functioning

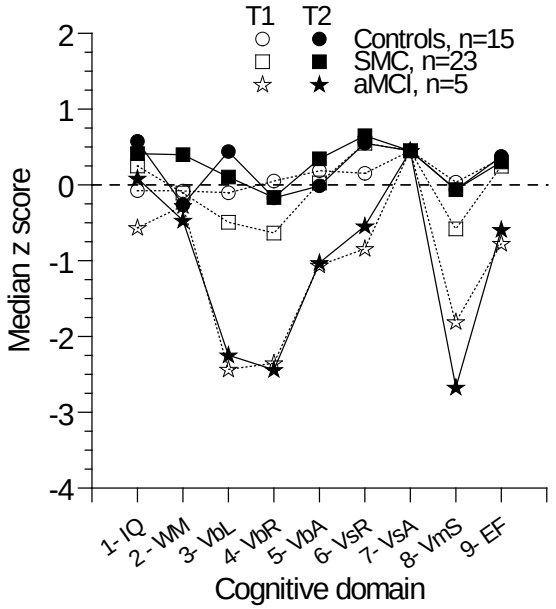


Figure 8.4 *Mean z-scores for each cognitive domain for the three groups on initial (T1) and follow-up assessment (T2). Scores for the control group (represented by the zero line) have a mean of 0 and a standard deviation of 1. Scores below –1 indicate significantly lower functioning.*

8.7 Impaired cognitive domains

In this section, a Pearson Chi-square test was used to identify the number of subjects in each group scoring within the impaired range (more than one SD below the mean) on both assessments.

Table 8.13 shows the number and percentage of subjects in each group who scored one SD below the control mean (z-score<–1) on each of the cognitive domains and the group aggregate for the number of impaired domains (2-9).

Table 8.13 Number of cognitive domains with scores below 1 SD of control mean on initial and follow-up assessment (mean ± SD)

Cognitive Domain	Controls Time 1 (n=15) (n=%)	SMC Time 1 (n=23) (n=%)	aMCI Time 1 (n=5) (n=%)	Controls Time 2 (n=15) (n=%)	SMC Time 2 (n=23) (n=%)	aMCI Time 2 (n=5) (n=%)
2. Working memory	1 (7%)	5 (22%)	0	0	1 (4%)	1 (20%)
3. Verbal learning	1 (7%)	7 (30%)	4 (80%)	1 (7%)	3 (13%)	4 (80%)
4. Verbal recall	1 (7%)	8 (35%)	5(100%)	3 (20%)	6 (26%)	5(100%)
5. Verbal ability	3 (20%)	1 (4%)	3 (60%)	2 (13%)	0	3 (60%)
6. Visual recall	3 (20%)	3 (13%)	2 (40%)	3 (20%)	2 (9%)	2 (40%)
7. Visuospatial ability	3 (20%)	6 (26%)	2 (40%)	2 (13%)	3 (13%)	1 (20%)
8. Visuomotor speed	2 (13%)	2 (26%)	3 (60%)	4 (27%)	9 (39%)	3 (60%)
9. Executive functioning	1 (7%)	0	2 (40%)	0	2 (9%)	2 (40%)
Total (sum of 2-9)						
0	8 (53%)	7 (30%)	0	6 (40%)	10(44%)	0
1	4 (26%)	7 (30%)	0	5 (33%)	6 (26%)	1 (20%)
2	1 (7%)	3 (13%)	1 (20%)	3 (20%)	4 (17%)	0
3	1 (7%)	3 (13%)	1 (20%)	0	2 (9%)	1 (20%)
4-5	0	3 (13%)	1 (20%)	1 (7%)	0	2 (40%)
6+	1 (7%)	0	2 (40%)	0	1 (4%)	1 (20%)

At follow-up, the percentage of subjects in each group with multiple domain deficits remained higher for the aMCI (100% at T1 vs. 80% at T2) and SMC groups (39% at T1 vs. 30% at T2) compared to the control group (39% at T1 vs. 27% at T2). On both assessments, the aMCI group had a high percentage of subjects with impairments on tests of verbal learning

(80%), verbal recall (100%), verbal ability (60%) and visuomotor speed (60%).

Figure 8.5 shows that at follow-up, age remained a strong predictor of cognitive function based on the number of domain deficits on formal testing (r=0.43, p=.003). The vast majority of control subjects under the age of 70 had normal cognitive function with few deficits on formal testing.

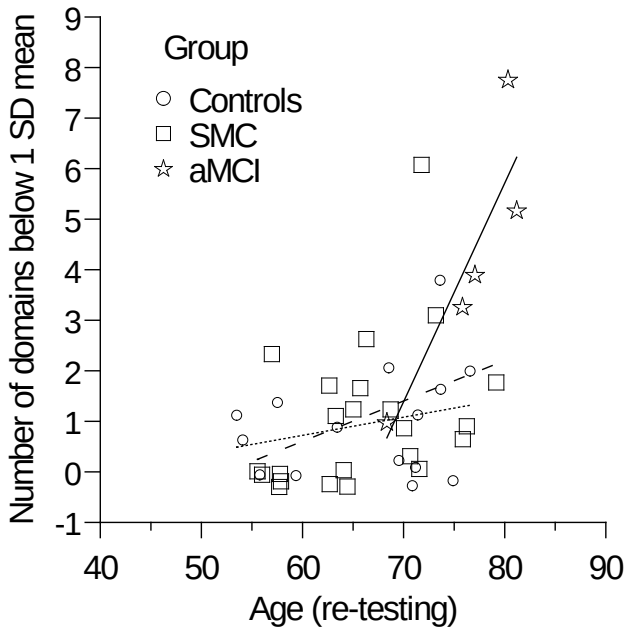


Figure 8.5 *Graph showing the relationship between age and the number of domains with cognitive deficits greater than one SD of the norms for each of the groups on follow-up assessment. Dotted line indicates line of best fit for control group (open circles), dashed line for the SMC group (open boxes) and the solid line for the aMCI group (stars).*

8.8 Apolipoprotein-ε4 (ApoE-ε4)

Table 8.14 shows the characteristics of subjects with and without the ApoE-ε4 allele on initial and follow-up assessment. Three subjects were not tested for the ApoE-ε4.

Table 8.14 Characteristics of subjects with and without the ApoE-ε4 allele on follow-up assessment (mean ± SD)

Characteristics	Non ApoE-ε4 (2/3, 3/3) (n=26)	ApoE-ε4 (2/4, 3/4, 4/4) (n=14)[a]	P value
Age	64.4 ± 8.0	65.0 ± 8.1	.840
Gender			
Male	13 (50%)	4 (29%)	.191
Female	13 (50%)	10 (71%)	
Years of education	13.3 ± 3.6	14.8 ± 4.8	.279
Family history of AD	15 (58%)	10 (71%)	.392
Subjective memory complaint	18 (69%)	8 (57%)	.445
7 Minute screen total (Test 1)	-11.8 ± 12.9	-17.1 ± 9.3	.184
(range)	(-26 to 32)	(-33 to -2)	
Abnormal 7MS	3 (12%)	0	.186
7 Minute screen total (Test 2)	-14.5 ± 13.0	-17.3 ± 9.3	.470
(range)	(-34 to 35)	(-31 to -1)	
Abnormal 7MS	1 (4%)	0	.457
Dementia Rating Scale (Test 1)	134.1 (4.7)	134.3 (6.6)	.925
(range)	(123-142)	(121-142)	
rated ≤ 121	0	2 (14%)	.048*
Dementia Rating Scale (Test 2)	133.2 ± 6.9	135.2 ± 6.4	.363
(range)	(105-142)	(119-142)	
rated ≤ 121	1 (4%)	1 (7%)	.648

* Statistically significant at p<.05

[a] Includes one subject who had a copy of the ApoE-ε2/ε4 allele

Fourteen subjects (35%) carried at least one ApoE-ε4 allele. There were no statistically significant differences between ApoE-ε4 and non-ApoE-ε4 carriers for the majority of the demographic and clinical variables. At time 1, a slightly higher percentage of ApoE-ε4 (14%) carriers compared to none in the non- ApoE-ε4 carriers had a DRS score below the threshold for dementia (<121), which reached significance at, χ^2=3.9; df=1; p=.048.

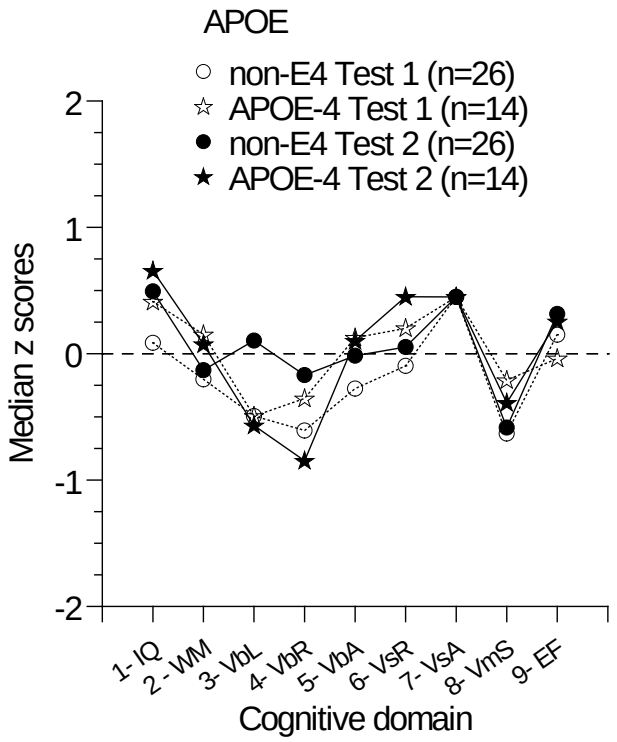


Figure 8.6 *Relationship between mean z-scores for each cognitive domain for Apolipoprotein-ε4 status on initial (time 1) and follow-up assessment (time 2). Scores for the control group (represented by the zero line) have a mean of 0 and a standard deviation of 1. Scores below –1 indicate significantly lower functioning.*

Figure 8.6 summarizes the pattern of cognitive ability and ApoE-ε4 status on initial and follow-up testing. Examination of the graph shows that ApoE-ε4 status had little effect on the mean z-scores for any of the cognitive domains. In most cases performance improved or remained stable on retesting regardless of ApoE-ε4 genotype.

8.9 Assessment of risk factors for dementia on global functioning

To assess which variables contributed to global functioning at time 2, a multiple regression analysis was performed with global z-score averaged over domains 2-8 as the dependent variable. The independent variables tested were age, education years, SMC, family history of Alzheimer's disease and mild depressive symptoms. The latter three variables were coded as present (coded 1) or absent (coded 0). The results of the multiple regression analysis are summarised in **Table 8.15**. One case (#59) was not included due to outlier values on the global z-score.

Table 8.15 Standard multiple regression of age, subjective memory complaint, family history and education years on global cognitive functioning (average of Z-scores Domains 2-8) on follow-up assessment

	Global (DV)	Age	SMC	AD FHx	Education Years	Depn	B	Beta	sr^2 Unique
Age (yrs)	-.53**						-.063*	-.647	.388
SMC	-.09	.04					-.127	-.083	.007
AD FHx	.22	.07	.00				.467*	.299	.088
Edu years	-.09	-.23	-.19	.00			-.051*	-.284	.073
Depression	-.26	-.09	.10	.09	-.10		-.679**	-.360	.125
						intercept	4.71		
Mean	-.04	66.9	.64	.67	13.9	.12		R^2	.535
SD	0.74	7.7	.49	.48	4.1	.40		Adj R^2	.470
								R	.731

n=42, **p<0.05

unique variability =.681, shared variability = .05

subjective memory complaint, AD family history and minor depression were coded 1= Yes, 2= No

The multiple regression analysis showed a significant contribution of four risk factors to the variance in global z scores, R^2= .535; (p=.001). As can be seen from the regression coefficients four factors, age (beta=-.647; p=.001), depression score (beta=-.360; p=.004), family history (beta=..299;

p=.013) and education (beta=-.284; p=.023) explained the largest proportion of variance in global cognitive function. The presence of SMC did not contribute significantly to the regression model. Examination of the residual analysis (**Figure 8.7**) showed that assumptions of normality, linearity and homoscedasticity were met as these were not correlated to the residuals.

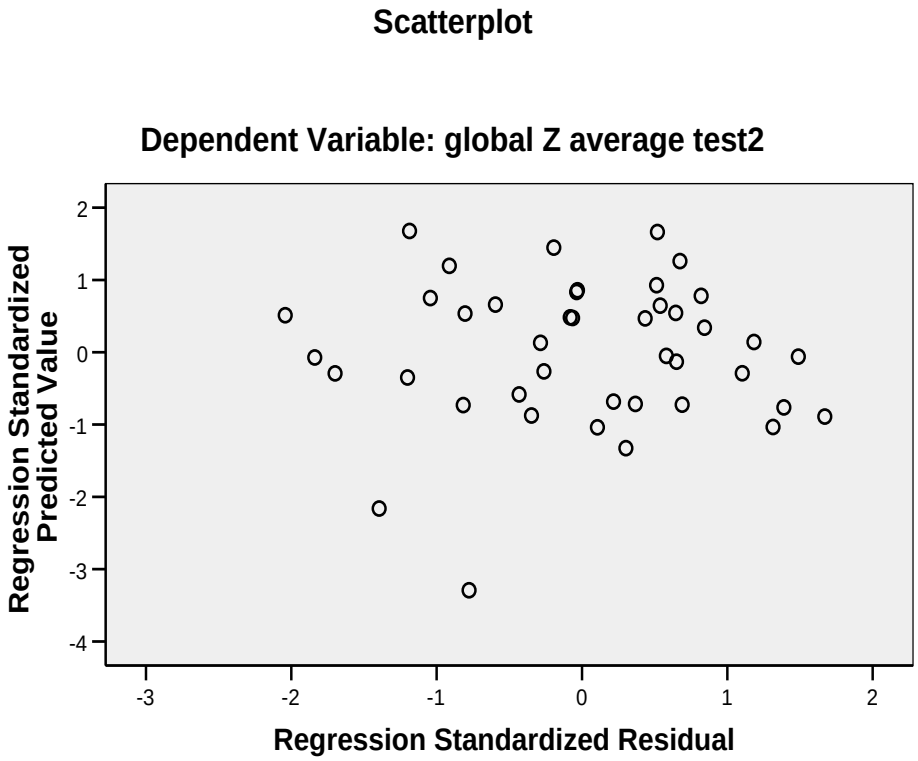


Figure 8.7 *Scatterplot of standardized residuals and predicted values for the multiple regression analysis.*

In summary, the multiple regression analysis indicates that collectively, four variables (age, minor depression, AD family history and education years), accounted for 54% of the total variance in global cognitive functioning. Together the four predictor variables contributed .681 in unique variability and another .05 in shared variability. Closer inspection of the

correlations and beta value sizes indicate inverse relations between global z-scores and years of education and minor depression.

A further multiple regression analysis was performed using change in global z scores between assessment 1 and 2, using the same variables, but this was not significant.

Chapter 9:

Discussion

9.1 General overview

The main aim of the present study was to determine whether SMC predict the development of cognitive impairment in a younger cohort of subjects, many of whom were under the age of 70 years (73%), based on their risk profile and neuropsychological assessment. In order to purse this line of inquiry, this study was conducted in two parts. The initial cross-sectional design examined in detail the role of SMC as well as established risk factors (i.e. age, family history and verbal learning deficit) on cognitive function. The follow-up component was implemented to examine whether the presence of SMC affects the 3-year cognitive outcome of subjects.

In this chapter, the principal findings will be drawn together and a discussion of the results will be presented in the following sections: 1) Cross-sectional findings; 2) Longitudinal findings. In addition, the results will be addressed in terms of their clinical significance for the early detection of Alzheimer's disease. They will also raise methodological issues relevant to this study and provide directions for future research.

I. Initial assessment

9.2 Summary

The initial analysis suggested a relationship between SMC and cognitive impairment in a younger cohort of subjects. This was documented by impaired performance on two screening tests for dementia (e.g. 7MS and DRS) and neuropsychological assessment. This relationship occurred independently of depression. Further analysis of the data showed that when a group of subjects with SMC (n=12) demonstrated impairment on tests of delayed recall and animal fluency. Once these subjects were removed from the SMC group to form the aMCI group, the relationship between SMC and cognitive impairment in younger subjects was no longer apparent.

These initial findings are important as they indicate that SMC in younger subjects are less likely to be related to cognitive impairment. In isolation, SMC are unlikely to be useful for identifying cases with significant cognitive impairment. In particular, the use of sensitive tests such as animal fluency and delayed recall are more reliable indicators of cognitive impairment compared to current brief screening methods for subjects with SMC. Subjective memory complaints were more likely to be associated with cognitive impairment in older subjects (>70 years). Many current studies do not adequately screen for objective memory impairment in persons with memory complaints. This is likely due to the use of simple measures of global cognitive functioning, such as the MMSE.

Subjective memory complaints

Prior to comparing the present study with the literature on memory complaints, the concept of measuring and quantifying SMC needs to be acknowledged. A straight forward comparison between studies is precluded by the fact that a range of questions and scales (e.g., Cognitive Difficulties Questionnaire; MacNair Scale) has been used across studies. There is no agreement or uniformity on the choice of these methods. Additionally, the questions to identify memory difficulties have varied widely, with many tapping into different aspects of cognitive functioning and time frames.

The obvious repercussion of the usage of various measurements of memory complaints is that a meaningful comparison and interpretation of results is less readily achievable. The main reason for this difficulty is that there exists no strong evidence of a correlation between these different techniques in measuring the same construct (Mitchell, 2008a). Ahmed et al. (2008) reported that patients with Semantic Dementia frequently endorse semantic complaints, such as word finding difficulty and understanding the meaning of names (Ahmed et al., 2008). These same authors reported that the "worried well" and patients with Alzheimer's disease could not be distinguished on the basis of their memory complaints. This suggests that the use of differing questions may fail to identify cases of significant cognitive impairment or dementia syndromes. Thus, it is important to consider these issues when comparing the relationship between SMC and cognitive functioning across different studies.

Depression

It is important to emphasize that SMC is frequently linked to major depression (Cargin et al., 2008; Jessen et al., 2007; Jorm et al., 2004; Lautenschlager et al., 2005). It is well documented that impaired memory and concentration difficulties are part of the core symptomatology of major depression (APA, 2000; Steffens and Potter, 2008). Whilst some reports indicate that major depression is a prodrome to dementia (Wilson et al., 2008), major depression may also appear co-morbidly with an underlying dementia. Undoubtedly, the relationship between SMC, depression and dementia is rather complex. This is demonstrated by several lines of inquiry into correlates of SMC indicating relations with both depression and cognitive impairment (e.g., Jessen et al., 2007; Minett et al., 2008).

In the present study, those with scores on the GDS and PAS in the depression range were excluded. Subjects with a self-reported previous history of major depression were also excluded. Subjects taking medications, such as corticosteroids and anti-depressants which could influence mood and potentially affect cognitive functioning were also excluded. However, subjects with mild depressive symptoms were not excluded as this was unlikely to significantly affect cognitive performance.

Prevalence of SMC

In the present study, 63% of subjects reported SMC as defined by a single question. This proportion is higher than the 10.6% to 21% reported in several previous community studies that have also used a single question

(Geerlings et al., 1999; Jungwirth et al., 2004; St. John and Montgomery, 2002). The relatively high rate of subjects reporting a memory complaint in the present study was likely due to the advertisement requesting subjects with memory difficulties.

However, the variation in the reported rates of SMC might also be related to the methods used to define and quantify SMC. Purser et al. (2006) showed that when community-dwelling subjects were asked in more detail about their memory difficulties using a memory scale, rather than a single question requiring a "Yes" or "No" response, a prevalence of 32% was observed. Thus, the variation in the reported rates of SMC may also be the result of the different techniques used to quantify SMC. Nevertheless, the rate of memory complaints in the present study is comparable to a recent community study by Cargin et al. (2008). They reported an average rate of 67.5% in normal controls and memory declining groups.

9.3 Subjective memory complaints

Hypothesis 1: *Subjects with SMC will demonstrate significant cognitive impairment on formal neuropsychological assessment compared to those without SMC.*

The present study initially showed that in this cohort of predominantly younger subjects with SMC (73%), a simple question "Do you have problems with your memory?" was associated with cognitive impairment on formal neuropsychological assessment. This was demonstrated by the use of two brief screening tests and neuropsychological assessment (Tables 7.5, and

7.16). This observation is further discussed below.

9.3.1 Brief screening tests findings

In subjects with SMC, the 7MS and DRS identified an overall global cognitive deficit, including sub-clinical deficits on attention, initiation, memory and animal fluency compared to the No SMC group.

Moreover, seven subjects in the SMC group had DRS total scores below the threshold for impairment compared to none in subjects without SMC. Similarly, six subjects in the SMC group scored above the abnormal threshold on the 7MS compared to none of the subjects without SMC.

9.3.2 Neuropsychological findings

The SMC group could be differentiated from the No SMC group on tests in three of the eight cognitive domains, including working memory; verbal recall and visuomotor speed (see Table 7.16, page 170). These deficits occurred independently of depression as shown in the multiple regression analysis (Table 7.20, page 182). This analysis showed that depression was a non-significant predictor of global cognitive function.

Relevant literature findings

The present observation of a relationship between SMC and cognitive impairment is in agreement with a recent community-based study by Rouch et al. (2008). Rouch et al. (2008) investigated the association between SMC, affective disorders and objective memory in 937 non-demented community-

dwelling subjects (mean age=65). Memory complaints were quantified using the MacNair scale, which is a self-rating scale exploring memory difficulty in everyday life. Their results showed a significant association between memory complaints and lower scores on verbal memory (Free and Cued Selective Reminding Test) and executive function (Digit Symbol Substitution Test, Trail Making B). Similar to our study, the association occurred independently of affective disorders, such as depression and anxiety.

However, in the study by Rouch et al. (2008), animal fluency did not correlate with memory complaints, but rather with depression. This finding contrasts with the results of the present study. Both studies were comparable regarding mean age (63 yrs and 65 yrs, respectively). The discrepancy may be explained by two methodological issues. Firstly, Rouch et al. (2008) allowed their subjects 2 minutes to generate animals, whilst in the present study only a 1 minute time period was allowed. Another factor that might explain the difference is sample size. Namely, sample size which was much larger for Rouch et al. compared to the present study (n=937 and n=86, respectively).

However, other studies have failed to support the present finding: Minett et al. (2008) studied the relationship between SMC, cognitive function and depression in 114 non-demented subjects (aged $\geq$ 50 years). Their results showed a relationship between SMC and depression, but not with cognitive function. Despite the lack of association, these authors reported that subjects with a memory complaint had significantly lower scores on animal fluency compared to subjects without a complaint.

Another study, by Jessen et al. (2007), also failed to report a relationship between SMC and cognitive function. These authors reported a relationship between SMC and depression in 2389 non-demented subjects (mean age=80 years). In addition to this finding, an association between SMC and verbal delayed recall was also reported. The use of the MMSE as a simplistic screening test might have precluded both Minett and Jessen from observing any difference between subjects with SMC and those without SMC. The lack of association might also be attributed to the different techniques used by Minett and Jessen to measure SMC. Namely, both authors used a combination of questions and scales to define the presence of SMC. Nevertheless, both Minett and Jessen observed impairments on animal fluency and verbal delayed recall, which are part of the 7MS. This observation reinforces the greater sensitivity of the 7MS (Solomon et al., 1998; Del Ser et al., 2006) to identifying cognitive impairment compared to the MMSE.

The results of the present study provide limited support for the hypothesis that SMC are associated with impairments in several cognitive domains amongst community dwelling subjects over the age of 50 years.

However, the regression analyses presented in tables 7.20 and 8.15 found that when age is taken into account, SMC were insignificant in the prediction of global cognition. This is discussed further in section 9.4.

9.4 The role of age

The present study was able to show significant neuropsychological evidence of cognitive impairment in subjects identified as having SMC and aMCI (Table 7.8; page 174). This observation was more strongly related to age, as shown by the more rapid decline in cognitive function in subjects with aMCI with advanced age (Figure 7.5, page 173).

The relationship between age, SMC and cognitive function is clearly an important area for investigation. With the exception of several investigators known to target younger populations, such as Jorm and Christensen, much of the literature has focused on older subjects (e.g., Jungwirth et al., 2008; Howieson et al., 2008; Palmer et al., 2003). Thus, whether SMC can be used to help identify subjects at an earlier age is not well known. However, this area is fraught with difficulties, as the effects of normal ageing begin from the age of 60 onwards. There is considerable debate within the literature to say when age-related cognitive decline begins (Salthouse, 2009). Normal ageing is characterized by a decrease in the efficiency by which information is processed and retrieved. From the mid 70s onwards (De Ronchi et al., 2005) cognitive decline occurs on tasks of new learning, speed and flexible adjustments to new situations. This needs to be taken into consideration, especially when evaluating studies examining older subjects.

The relationship between age, SMC and global cognitive functioning is further illustrated in Figure 7.14 (page 179). It was observed that the association between age, SMC and global cognitive function differed

according to whether there was evidence of SMC and/or cognitive impairment (i.e. the subject group). In control subjects, there was no association between age and global cognitive functioning as indicated by the non-significant correlation. In subjects with SMC and aMCI, age was significantly and negatively correlated to global cognitive functioning, commencing from the age of approximately 65 onwards. This indicated that increasing age was accompanied by lower cognitive functioning. More specifically, verbal learning, verbal recall, verbal ability, visuomotor speed and executive functioning significantly correlated with age (Figures 7.7 to 7.9 and 7.12, 7.13, pages 175-176 and 178).

Furthermore, Figure 7.5 (page 173) showed that subjects with SMC had on average deficits in two or more cognitive domains (below 1SD of the control group mean), commencing from the age of 60 onwards. The multiple regression analysis (Table 7.20, page 182) showed that of the five variables examined (age, SMC, family history of AD, education and depression), age was the best predictor of global cognitive functioning (z scores) accounting for 39% of the variance.

Relevant literature findings

The present observation of an association between age, SMC, aMCI and lower global cognitive functioning is consistent with the findings of Wang et al. (2004a). Wang et al. (2004a) examined the association between SMC and future dementia in 1,883 community subjects (mean age=74.6). Subjects had no baseline objective cognitive impairment as

defined by a score of >91 on the Cognitive Ability Screening Instrument. Wang et al. (2004a) defined a memory complaint as being present in subjects who scored 20 or more on a 5-point Likert scale. Despite the different measurement techniques, Wang et al. (2004a) also identified the age of 70 as a beginning of cognitive decline in subjects with memory complaints.

As 73% of our sample was under 69 years (Table 7.4, page 147), our study shows that in subjects identified as having either SMC or aMCI, multiple cognitive deficits can appear between the ages of 60 to 65. Compared to Wang et al's (2004a), our study has identified an earlier age when cognitive impairment begins to manifest in those with memory complaints.

It is important to emphasize that the aMCI group in the present study were slightly older (mean age=70) and had fewer years of education (mean years 11). Thus, the demographic profile of our aMCI group (Table 7.7, page 153) is consistent with the profile reported by previous studies linking older age to clinical conditions, such as MCI (e.g., Gallassi et al., 2008). In the study by Gallassi et al. (2008) patients with SMC who developed MCI after a period of 9 months, were older (mean age=71.1) and had lower levels of education (8 years) and lower global cognitive function based on the MMSE scores.

However, other studies have failed to support the present findings: Park et al. (2007) investigated the association between SMC and objective cognitive function in 9477 subjects with a mean age of 72.6. Their results

showed that age was associated with SMC, irrespective of the cognitive status of the individual. These authors reported no association between SMC and advanced age in subjects with cognitive impairment, but observed an association in elderly subjects without cognitive impairment.

The inconsistency between both studies is likely due to two methodological issues. Namely sample size and the manner in which the variable depression was treated. Firstly, Park et al's. (2007) study had a larger sample size compared to our study (n= 9477 and n=86, respectively). Thus, the discrepancies between the present results and Park et al.'s (2007) might be reflective of the size difference between the two studies.

More significantly, the lack of measurement of an important variable such as depression by Park et al. (2007) might have contributed to the authors observing an association between SMC and elderly subjects without cognitive impairment. This would help to explain the high percentage of their sample reporting a memory complaint (57.3%). Given the reported associations between SMC and depression, it is possible that this percentage included subjects with undiagnosed depression.

9.5 Screening for cognitive impairment

One aim of the present study was to identify sensitive testing methods for early case detection. In the quest to achieve this, the present study was able to demonstrate a novel finding. After the initial analysis between subjects with and without SMC, all subjects were further screened for cognitive impairment using a well-validated and widely used verbal

memory test (Rey, 1964). It was observed that approximately one-quarter (n=12; 22%, Table 7.6, page 151) of the SMC group (n=54) demonstrated cognitive impairment as measured by performance 2SDs below the control group mean on delayed recall (Guarch et al., 2008). These subjects were subsequently re-classified as having aMCI.

Further analysis clearly showed that after the removal of these 12 subjects from the SMC group, the cognitive differences between subjects with SMC and without SMC was no longer apparent on neuropsychological assessment (Tables 7.8 and 7.17, pages 155 and 171). In fact, the means and SDs of both the control and SMC groups were almost identical on both the DRS and 7MS and cognitive domains. Whilst previous studies have identified subjects with SMC, they have not excluded those with SMC and concurrent cognitive impairment, (e.g. Dufoil et al. 2005 and Kim et al., 2006). A discussion of these concerns commences on page 225, Section 9.5.2.

Hypothesis 2: *There is in existence screening tests that are both sensitive and relatively easy to administer and can be used to potentially identify subjects with MCI.*

The present study was unable to identify sensitive screening to identify cognitive impairment in subjects with MCI.

9.5.1 Brief screening tests findings

There were discrepancies in identifying impairment based on standard thresholds for the 7MS and DRS (see Table 7.8, page 155). It is noteworthy

that on the DRS, seven subjects in the SMC group had DRS total scores below the threshold for impairment compared to none in the No SMC group. This highlights the sensitivity of the DRS as a screening tool for dementia. Similarly, on the 7MS total score, six subjects in the SMC group had 7MS total scores above the threshold for dementia compared to none in the No SMC group. Although SMC had good specificity (100%), it had unacceptably low sensitivity (< 15%).

Figure 7.3 (page 157) shows there was strong disagreement between the two screening tests for two SMC subjects. Two subjects in the aMCI group had abnormal scores on both tests (see filled stars quadrant 1).

The aMCI group had significantly lower global cognitive functioning compared to the SMC group on both the DRS and 7MS. At the level of each subtest, the aMCI group had significantly lower scores on DRS total score, memory, conceptualisation, enhanced cued recall and clock drawing compared to the other two groups.

9.5.2 Neurocognitive profile of impairment

The aMCI group could be differentiated from the control and SMC groups by significantly lower scores on tests of verbal learning, verbal recall, verbal ability, visual recall, visuo-motor speed and executive function (Table 7.17, Figure 7.4, pages 171-1172). Figure 7.4 shows that the aMCI group had greater deficits (-1SD below mean) on 4 of the 9 cognitive domains (IQ, verbal learning, verbal recall and visuomotor speed) compared to the other two groups.

A higher percentage of subjects with aMCI (92%) and SMC (38%) had multiple domain deficits compared to the control group (25%), (Table 7.19, page 180). The aMCI group had a high percentage of subjects with impairments on tests of verbal learning (83%) and verbal recall (92%). In comparison, 24% of the SMC group had impairments in verbal learning.

These findings are consistent with reports of lower global cognitive functioning and additional deficits beyond episodic memory in subjects with aMCI and those with early Alzheimer's disease (Archer et al., 2006; Bäckman et al., 2004; Ribero et al., 2006; Saxton et al., 2004). The present observation is in agreement with the findings of Archer et al. (2006). Archer et al. (2006) examined whether symptoms of memory impairment predict future cognitive impairment in 21 subjects with MCI, 37 subjects with symptoms of memory loss but no cognitive impairment (SNCI) and 33 healthy volunteers. Comparable to our study, the mean age of the three groups was (63.6 years) and all underwent a thorough neuropsychological assessment. These authors found that the MCI group could be distinguished from the SNCI and controls on tests of memory, at a group level, they also obtained lower scores on IQ, naming and executive function. The SNCI differed from the control group on tests of delayed recall, ROCFT (immediate and delayed recall), and Trail making B test.

Another study also found multiple cognitive deficits in subjects with MCI (Saxton et al., 2004). Saxton et al. (2004) investigated cognitive impairment in 693 non-demented subjects (mean age=76 years) prior to developing Alzheimer's disease over a mean interval of 7.4 years using a

standard neuropsychological assessment battery. After a median follow-up of 4.5 years, a total of 72 subjects were diagnosed with Alzheimer's disease. These authors reported that whilst performance on episodic memory was consistently identified, this was frequently accompanied by other deficits, such as semantic memory and executive function.

In so far as the results of the present study can be compared to previous studies, the present observation of inadequate screening for cognitive impairment has implications for studies that have used simple screening measures, such as the MMSE. This was apparent in many studies, especially in those studies that used subjects with cognitive impairment (Crowe et al., 2006; Kim et al., 2006). It was equally apparent in the diversity of cut-off scores to define cognitive impairment. One can question their results based on the limited sensitivity and specificity of these testing methods.

Some relevant literature examples of this are: Dufouil et al. (2005) examined whether SMC could predict future decline in 733 subjects (aged 59 to 71) with baseline MMSE scores of 27.6 $\pm$ 2.1, (range 18-30) and reported a positive association between the two. Clearly, with such a wide range, many of their subjects are likely to have had dementia at baseline.

Kim et al. (2006) also examined the association between SMC and cognitive decline in 686 subjects (mean age=71.0), that included 133 subjects with MMSE scores < 21 and reported a positive association. Once again, many subjects have dementia at the onset.

Snitz et al. (2008) examined the association between SMC and

memory function in 276 primary care outpatients (mean age=73.2) with MMSE scores >19 and also found a positive association.

Crowe et al. (2006) examined the association between SMC and future cognitive decline in 55 subjects with their own definition of aMCI (mean age=76 years) with mean MMSE scores of 26.1 and reported a positive association. Amnestic MCI was identified using a psychometric algorithm based on a composite memory score derived from three episodic memory tests (two verbal learning tests and one paragraph recall subtest). Subjects who scored $\leq 7^{th}$ percentile on the composite memory score and were not impaired on composite scores for reasoning or perceptual speed were considered to have aMCI. Whilst the present study used one verbal memory test and the presence of a memory complaint to classify subjects, Crowe et al. (2006) did not consider SMC to be a compulsory inclusion criterion. However, similar to our study, Crowe et al. (2006) did not collect functional performance data.

To complicate the issue, a wide range of cut-off scores to define cognitive impairment using the MMSE (e.g Dufoil et al., 2005; Geerlings et al., 1999; Jungwirth et al., 2008) has been used. Thus, allowing groups with different cognitive abilities to be formed and compared. For example, the "normal subjects" in the study by Geerlings as defined by an MMSE cut-off score of 26, would be considered to have "questionable impairment" according to the study of Jungwirth et al. (2008). Jungwirth used an MMSE cut-off score of $\geq$28 to define normal cognition. The implication of this for the study by Geerlings, would be that the observed differences may not be

valid given the likelihood that subjects with baseline MMSE scores between 26 and 28 may well not be "normal" either the differences would disappear or would be relatively weakened. Indeed, when Kim et al. (2006) excluded their patients with cognitive impairment (MMSE <19) the previous observed association between SMC and cognitive decline was weakened.

Furthermore, whilst the outcome of studies using patients with objective cognitive impairment or aMCI (e.g., Crowe et al., 2006; Kim et al., 2006) suggests they have some insight into their memory problems; they cannot draw conclusions regarding the role of SMC in subjects with no objective impairment. By definition, aMCI is a clinical condition that involves objective impairment and may or may not involve subjective impairment depending on the criteria used (e.g. Petersen versus Winblad).

Therefore, these findings do not provide further information on the role of SMC when no cognitive impairment is apparent. However, the question arises as to whether it is meaningful to include subjects with cognitive impairment to identify differences between subjects with and without SMC. The present study suggests that when cognitive impairment is removed from the equation SMC have limited prognostic value.

9.6 Other screening tests to identify cognitive impairment

The present study was able to identify a number of other sensitive neuropsychological tests that can be used to identify cognitive impairment in subjects with SMC.

9.6.1 Delayed verbal recall

The present study used Rey's (1964) verbal delayed recall test to categorize subjects with SMC as having aMCI. The observation of impairment on verbal memory in patients with an increased risk of future dementia due to their profile is consistent with a large body of evidence implicating impairment in delayed recall as a significant predictor of future Alzheimer's disease. (e.g., Andersson et al., 2006; Cargin et al., 2007 and 2008; Estevez-Gonzalez et al., 2003; Guarch et al., 2008; Saxton et al., 2004). Episodic memory is a highly sensitive cognitive test and its deterioration is characteristic of preclinical stages of a dementia syndrome of the Alzheimer's type (Bäckman et al., 2004; Perri et al., 2007).

Andersson et al. (2006) used the delayed recall test to identify subjects at high risk of developing Alzheimer's disease. These authors retrospectively assigned 224 subjects (mean age=61 years) to one of three memory groups, using their baseline results on the Delayed Recall. These authors found that 84% of the subjects in the severe impairment memory group (defined by a delayed recall score of < 6) had significant cognitive deficits in memory (and at least two non-memory domains). These included significant impairments in language, visuospatial function, and executive function and subsequently progressed to Alzheimer's disease at a high rate (64%) after an interval of 3 years.

9.6.2 Animal naming

The present study further identified animal naming as a simple and easy to use test for identifying cognitive impairment in subjects with SMC. Animal naming was part of the 7MS. According to Monsch et al. (1992), animal naming is a highly sensitive test capable of distinguishing between normal controls and patients with Alzheimer's disease. By using published thresholds (<14), the task with the best sensitivity and specificity was animal naming. In the present study, animal naming identified deficits in 36% of subjects with SMC compared to 50% of subjects with aMCI (Table 7.9, page 158).

Impairment on semantic memory, especially animal naming is increasingly being identified in subjects with an increased risk of Alzheimer's disease (Amieva et al., 2005; Hodges et al., 2006; Jorm et al., 2005b; Lehrner et al., 2005; Palmer et al., 2004). Category fluency is a highly sensitive test (Salmon et al., 2002) showing impairment in the pre-dementia phase of Alzheimer's disease (Raoux et al., 2008) and in the absence of other semantic deficits (Monsch et al., 1992). Support for the use of animal naming as a sensitive test is provided by Hodges et al. (2006). Hodges et al. (2006) examined the cognitive course of 10 patients with MCI from a memory clinic over a minimum period of 6 years. Hodges et al. (2006) also used detailed neuropsychological assessment to examine a wide array of cognitive domains. Despite the mean age difference between the study by Hodges et al. (2006) and the present study (72.8 and 63.1, respectively), these authors observed a consistent and early impairment on category

fluency (8 out of 10 patients) in the presence of episodic memory deficits within the first year of assessment. After an interval of 10 years, all the patients developed Alzheimer's disease and three were autopsy confirmed.

Sager et al. (2006) examined the usefulness of three brief screening tests (Animal Naming, Clock Drawing and the MMSE) in detecting dementia and mild cognitive impairment in 364 subjects (aged $\geq$ 50 years). This group of subjects consisted of 34 normal controls; 69 patients with MCI; 140 patients with Alzheimer's disease and 121 with other dementia syndromes from a memory clinic. By using the standard cut-off score of <24 on the MMSE, they were able to identify 60% of patients with dementia and 1% with MCI. However, by using the recommended cut-off score <14 words per minute (Monsch et al., 2006); on animal naming they identified 85% of patients with dementia with a low (12%) false positive rate. Similar to the present study, they also identified 54% of patients with MCI.

II. Follow-up assessment

9.7 Introduction

The present study employed a comprehensive neuropsychological test battery to examine in more detail the role of SMC on cognitive function over time in community-dwelling subjects, aged 50 to 79 years. When this study initially commenced in 1999, SMC were only beginning to be examined (e.g., Geerlings et al., 1999; Jonker et al., 1996; Schmand et al., 1997; Schofield et al., 1997; Tobiansky et al., 1995). Since this time, there has been a substantial increase in the number of longitudinal studies examining the role of SMC on cognitive function and Alzheimer's disease (Cargin et al., 2008;

Jungwirth et al., 2008). As mentioned previously, a longitudinal approach is invaluable as it provides further information regarding the stability of any relationship between SMC and cognitive function observed in cross-sectional studies. It is also valuable for identifying subjects in the very early stages of a dementia syndrome, such as Alzheimer's disease.

Fifty percent (50%) of the subjects returned for a follow-up test after an average interval of three years. Whilst this is considered to be a low follow-up response rate, these results would need to be replicated by a larger sample with a higher follow-up rate. This would provide more substantive evidence concerning the role of SMC in relation to cognitive function over time. Nevertheless, the author was interested in examining cognitive change over time in subjects with SMC in an attempt to identify early cases of cognitive impairment suggestive of Alzheimer's disease.

9.8 Subjective memory complaints

By analysing subjects with SMC who participated in both the initial and follow-up assessment, the present study was unable to demonstrate a significant relationship between SMC and cognitive function after an interval of 3 years. The low subject number and short follow-up interval meant that only relationships with large effect sizes could be identified.

The present observation of no significant relationship between SMC and cognitive functioning is not in accordance with results previously reported by others (e.g., Gallassi et al., 2008; Geerlings et al., 1999; van Oijen et al., 2007). Using a similar question and time interval, Geerlings et

al. reported an association between memory complaints and cognitive decline in subjects with normal baseline cognition. One of the major differences between these two studies, which likely explain the inconsistency between these two studies, was the sample size. The sample size in the present study was 43, while the sample size in the study by Geerlings et al. was 2169. It is likely that the current study's relatively small sample of subjects did not provide sufficient statistical power to demonstrate this association or the effect is of a small magnitude between memory complaints and cognitive decline or Alzheimer's disease among subjects.

However, whilst many studies support a relationship between SMC and cognitive decline (e.g., Jungwirth et al., 2008; van Oijen et al., 2007; Gallassi et al., 2008), several studies are discordant with these reports (e.g., Cargin et al., 2008; Mol et al., 2006). Mol et al. (2006) examined the association between SMC and cognitive function in 557 healthy subjects (mean age=67.7) with baseline MMSE scores >24. On baseline testing, these authors reported an association between SMC and lower scores on both the information processing speed task and delayed recall task. However, over a mean interval of six years and after controlling for baseline MMSE scores, SMC was no longer associated with change in cognitive function in subjects with and without SMC. Rather, these authors observed that SMC had stronger associations with symptoms of depression and anxiety than to cognitive decline.

The discrepant findings are likely due to the difference in sample size between the study by Mol et al. (2006) and the present study (n=557 and

n=46, respectively). However, the differences are also likely to be due to the different methods used to measure SMC. Although, Mol et al. (2006) used a single question to measure SMC, subjects that were not worried or hindered by their forgetfulness were excluded. This resulted in the exclusion of 78 subjects that may have developed cognitive decline at follow-up.

9.9 Cognitive change in subjects with SMC and aMCI

Hypothesis 3: *Subjects with SMC will demonstrate evidence of worsening cognitive function over a 3-year interval.*

9.9.1 Brief screening tests

The present study was able to show evidence of worsening cognitive function over time in subjects with aMCI on two brief screening tests (7MS and DRS; Tables 8.3 and 8.4, pages 190 and 192). Moreover, the aMCI group showed greater decline on the 7MS total score and two subtests; animal fluency and enhanced cued recall. Interestingly, compared to the aMCI group, the SMC group obtained significantly higher scores on the 7MS total score, verbal fluency as well as temporal orientation. The fluctuating course associated with the SMC group is a common finding (Glodzik-Sobanska et al., 2008) and a major cause for concern due to its inclusion in the criteria for MCI (Mitchell, 2008a and 2008b). The time frame for memory complaints to evolve into significant cognitive impairment has been estimated to take at least 7 years (Reisberg et al., 2008).

The present observation of decline on animal fluency and enhanced

cued recall in subjects with aMCI is consistent with the findings of Howieson et al. (2008). Howieson et al. (2008) examined the clinical and neuropsychological predictors of MCI and dementia in 156 cognitively intact, community dwelling older subjects (mean age=83 years). Mild cognitive impairment was defined as two consecutive observations with a CDR $\geq$ 0.5. Despite the difference in the mean follow-up interval between the two studies (7 years and 3 years, respectively), these authors found statistically significant cognitive loss at least 3 to 4 years prior the diagnosis of MCI on tests of verbal memory, animal fluency as well as visuospatial constructions. These findings are consistent with a large body of evidence implicating multiple cognitive domain deficits in the evolution towards Alzheimer's disease (Bäckman et al., 2004; Fleisher et al., 2007). It is possible that these impairments represent a stage of early cognitive decline suggestive of Alzheimer's disease but requires a large sample, sufficient follow-up interval to illustrate this change and a formal baseline assessment of dementia.

9.9.2 Neuropsychological tests

The present study did not find the predicted change in cognitive function over time in subjects with SMC and aMCI. The analysis of change over time examining cognitive domains showed that the majority of subjects (both SMC aMCI) either remained stable or improved their cognitive performance (Table 8.12, page 199). The SMC group had significantly higher scores on intellectual functioning, working memory, verbal learning, verbal recall and verbal ability. The aMCI group had significantly higher

scores on intellectual functioning and verbal learning. Although these changes are significant, closer inspection of the data shows the change was only .05 SD below the mean.

However, in interpreting these findings, one must keep in mind the low sample size and short follow-up interval of the present study. It is likely that these factors contributed to the present observation of no change in cognitive function over time. As larger studies using longer follow-up intervals have supported significant cognitive decline in subjects with SMC and aMCI (e.g., Gallassi et al., 2008).

Gallassi et al. (2008) examined the clinical and neuropsychological predictors of no cognitive impairment and MCI according to the criteria of Winblad et al. (2004) in 92 non-demented outpatients (mean age=67.4; SD=10.4). After an interval of 9 months, these authors found that self-reported SMC, measured with the Memory Assessment Clinic Questionnaire predicted MCI in 49 subjects with SMC. The high percentage (53%) of subjects who declined might be explained by the source of recruitment. The subjects in the Gallassi et al. (2008) study were recruited from a tertiary setting and were likely to be more impaired. Additionally, despite the differences in sample sizes between the present study and Gallassi et al. (2008) (n=43 and n=92, respectively) the two aMCI groups shared similar demographic features.

It is important to emphasize that although the subjects in the aMCI group in the present study did not decline on follow-up testing, they failed to show improvement across a range of neurocognitive tests. The lack of

improvement upon retesting has been noted by others as a diagnostically useful finding (Galvin et al., 2005). Galvin et al. (2005) identified histopathologic AD in one-third (34%) of their patients who did not have dementia at death and did not show improvement on tests of episodic and semantic memory upon retesting. These authors suggested that the cognitive impairment that preceded preclinical Alzheimer's disease is clinically indistinguishable from subjects without dementia, except for the observation of a lack of improvement upon retesting.

In reconciling this conflicting finding, it is important to remember that this may have occurred because of the small sample size. Another issue relevant to this study appears to be the fluctuating course frequently associated with SMC and that screening tests lack the sensitivity to capture this. This is evident as by the better performance of the SMC group on the 7MS compared to the aMCI group's decline in performance on this test. Essentially, a full neuropsychological evaluation is the current gold standard of cognitive performance and is more reliable compared to the results on the screening tests which produce more false positives and false negative results.

9.10 The role of age on SMC and cognitive functioning

A further interesting observation is shown in Figure 8.5 (page 206), which shows that age remains a strong predictor of cognitive functioning, especially for those over the age of 70 years, irrespective of cognitive status. However, closer inspection of Figure 8.5 clearly shows that subjects with

cognitive impairment (e.g., aMCI) have a steeper decline in cognitive function from the age of 70 onwards. Also, subjects with SMC aged between 60 and 65 years begin to show deficits in at least 2 cognitive domains. This suggests a potential point for early intervention by identifying individuals at risk of developing Alzheimer's disease at an earlier age.

The observation of a more rapid decline in cognitive function in older subjects with either SMC or aMCI is consistent with several studies (Crowe et al., 2006; Gallassi et al., 2008; Wang et al., 2004a). Crowe et al. (2006) examined the relationship between SMC and cognitive decline in subjects with baseline aMCI (mean age=74 years). In this study, SMC was not a compulsory inclusion criterion. However, subjects with baseline SMC had a statistically significant decline on MMSE scores.

9.11 The apolipoprotein ε4 (ApoE ε4) allele

Hypothesis 4: *Subjects with SMC and the ApoE e4 allele will show evidence of worsening cognitive function over time.*

The present study was unable support a role of the ApoE ε4 in cognitive change for carriers of the ApoE ε4 allele. Carriers of the ApoE ε4 allele did not have a larger magnitude of cognitive decline on follow-up assessment as demonstrated by the general stability of the groups (Figure 8.6, page 208). The analysis showed that ApoE ε4 status had no affect on the multiple regression and similar correlations were found between age and number of impaired domains and ApoE ε4 groups (Figure 8.6). In most cases performance improved or remained stable on retesting regardless of

ApoE ε4 genotype. However, this observation is limited by the small sample size (n=43). The ApoE ε4 allele is associated with a very small effect size and very large samples are required to find associations.

Whilst we were unable to show a significant effect of the ApoE ε4 allele on cognitive function, several studies using larger sample sizes provide support for a role of the ApoE ε4 on cognitive function (Caselli et al., 2004; Christensen et al., 2008; Estevez-Gonzalez et al., 2004; Fliesher et al., 2007).

Caselli et al. (2004) investigated memory loss in 180 cognitively normal community subjects (mean age=60 years) with ApoE ε4 allele prior to the onset of MCI. After an interval of 33-months, carriers of the ApoE ε4 had poorer performance on multiple measures of verbal memory tests including (total score on Auditory Verbal Learning Test (AVLT); delayed recall; and Selective Reminding Test (SRT), free and cued recall) compared to non-ApoE ε4 carriers. Additionally, these authors reported that carriers of the ApoE ε4 aged between 50 to 59 showed greater declines on the AVLT delayed recall, SRT free and cued recall, and Complex Figure Test. This study suggests that prior to the onset of MCI or dementia, ApoE ε4 carriers show a modest decline in memory skills commencing from the age of 50 onwards.

Similarly, Christensen et al. (2008) also reported that ApoE ε4 carriers have a greater vulnerability to cognitive decline in the presence of other risk factors at the age of 65-69 years. These authors showed that after an interval of 4-years, significant effects of the ApoE ε4 on cognitive decline

occurred on the MMSE and Symbol-Digit Modalities test, after controlling for risk factors, such as previous head injury or low education.

However, not all studies provide support for a role of the ApoE ε4 in cognitive function (Fliesher et al., 2007). Fliesher et al. (2007) examined predictors of Alzheimer's disease in 539 patients (aged between 55-90 years) with aMCI recruited from a clinical drug trial study. All patients received comprehensive assessment. Fliesher et al. (2007) observed that progression from aMCI to Alzheimer's disease was best predicted by a combination of ApoE status and cognitive domain testing (being delayed episodic recall, executive functioning and a composite measure of global cognition). These authors observed that the inclusion of the ApoE ε4 in their model did not enhance the prediction of Alzheimer's disease above that predicted by tests of memory and executive functioning.

9.12 Methodological limitations

Results from the present study must be considered in light of several important methodological limitations. Each of these is addressed below:

Experimental tests

Firstly, it is important to recognise that performance on each test and differences between groups might also be caused or attenuated by situational factors. It is likely that the experimental situation itself, particularly anxiety associated with neuropsychological assessment, produces stress in individuals, which may influence cognitive function. The

neuropsychological interview was rather demanding in nature and would have induced a certain degree of stress, possibly compromising subjects' performance. This issue would be more pertinent for the initial assessment due to unfamiliarity with the experimental situation.

Sample Size and follow-up response rate

The cross-sectional subject number was relatively small (n=86). Such a small sample size may result in subtle differences between groups being overlooked. The differences detected between the SMC and aMCI groups might have become statistically significant with larger study numbers.

The follow-up response rate was equally low (n=43). This limited the potential of addressing the important issue of whether SMC are associated with cognitive decline over time. Relatively smaller subject numbers may result in subtle differences between groups being lost. Differences detected between the SMC and aMCI groups might have become statistically significant with larger study numbers.

The time interval between testing may have contributed to the low follow-up response rate. It is likely that a yearly assessment would have increased the follow-up response rate. Thus, the small sample size and low follow-up rate limits the generalisation of these findings to other populations. Replication using a larger sample size and follow-up response rate (>85%) is required before more definitive conclusions can be drawn.

Amnestic Mild Cognitive Impairment (aMCI) classification

Another consideration for the implication of the present results was the classification of aMCI. The present classification of aMCI was based on a test of delayed recall (Rey, 1984), rather than a clinically based diagnosis. It was also based on the presence of a memory complaint by self-report, normal orientation, apparent adequate social functioning within the community and no evidence of longitudinal cognitive decline was collected. Also, no functional data were collected.

Whilst it is not unusual for different authors to modify aspects of the criteria (e.g., Crowe et al., 2006), in large scale studies it is important to collect this information before assigning a classification, such as aMCI (Winblad et al., 2004). Consequently, the results should be interpreted with caution.

To minimise the possibility that subjects had a dementia syndrome, exclusion criteria were applied. Based on the subjects' cognitive testing, there was evidence of mild cognitive impairment. The exclusion criteria for the study made it unlikely that subjects classified as having aMCI had a dementia syndrome.

Additionally, the term MCI could have been used to refer to the subjects with aMCI, however the candidate chose to use the term aMCI because of its association with progression to Alzheimer's disease (Guarch et al., 2008).

Medical History

Another feature that could possibly be confounding the present conclusion is that no medical illness data were collected (e.g., hypothyroidism, vitamin B_{12} deficiency), and there was limited coverage of past psychiatric history (e.g., delirium). It is important to exclude this information as SMC or cognitive impairment may be a consequence of an underlying medical or psychiatric illness. However, the aforementioned medical problems still remain a relatively rare cause of overall significant dementia level cognitive impairment. Additionally, subjects with delirium are usually acutely unwell and would be unlikely to present and attend for the lengthy (several hours) process of our neuropsychological assessment.

However, prior to entry into the study, the candidate made a reasonable attempt to exclude subjects whose complaints were likely to have been due to current medical, psychiatric or drug and alcohol issues.

It would have been ideal to have had a full psychogeriatric assessment (by a medical specialist) to exclude depressive syndromes, delirium and relevant medical illnesses on all subjects. However, this was logistically not possible for the present community-based study. Importantly since MCI is relatively new field of enquiry (having evolved over the past 10 years) it is unclear whether medical illness, in the absence of delirium, is a cause of cognitive impairment.

Selection bias

The participants in the present study were a volunteer sample who selected themselves for participation in response to an advertisement. The voluntary nature of the study sample may have resulted in recruiting subjects who were healthier than those in the general population. Thus, the study sample is not representative of the general population and this limits the generalization of the results.

Furthermore, subjects who returned for a follow-up test did not differ from subjects who did not return for a follow-up test (Table 8.1, page 187).

Practice effects

The importance of the practice effect is likely to be minimal given the somewhat lengthy interval between testing and re-testing.

Major Depression

Considering the age range of the sample (50 to 79 years), the decision to use two depression scales for geriatric populations was unfortunate. A more suitable self-rating scale of depression such as the Beck Depression Scale or Hospital and Anxiety Depression Scale would have been a better choice given the large number of middle-aged subjects. It is noteworthy that a high inter-correlation has been reported between the Geriatric Depression Scale and the Beck Depression Scale (Bass et al., 2008) and both are valid and reliable tools to screen for depression.

Subjective memory complaints

Firstly, instead of being spontaneously referred, the SMC was elicited by a flyer. This may have encouraged some subjects to complain, consequently influencing differences between complainers and non-complainers in the cognitive testing.

Whilst it is preferable to have corroborative evidence about short-term memory from a reliable informant (e.g., spouse) (Winblad et al., 2004), this was not possible in the present study as it did not include carers or family members.

It would have been of great interest to collect information on SMC at follow-up and not only on baseline assessment". Kim et al. (2006) identified that subjects with SMC at baseline and follow-up had a 4.8 times greater risk of dementia compared to a risk of 2.3 times in subjects who had SMC only at baseline. Kim et al. (2006) also found that dementia was not associated with new complaints at follow-up. Therefore, whilst SMC may persist or disappear at follow-up, this suggests that baseline memory complaints carry more weight in determining dementia, especially when present at both points. It also suggests that SMC that is no longer present at follow-up may have been related to anxiety. Nevertheless, collecting information on SMC at both baseline and follow-up is an important consideration for future studies.

A potentially confounding effect in the present study is the lack of measurement of traits such as stress, anxiety and personality factors. Research has shown that psychoaffective factors can influence the subject's perception of their memory and lead to an overestimation of cognitive

difficulties. Indeed, studies show that SMC are more related to factors such as depression than to cognitive impairment (Cargin et al. 2008). However, in contrast to some studies (Kumar et al., 2006), none of the aMCI subjects in the present had mild depressive symptoms based on their PAS or GDS scores". Nevertheless, the possibility remains that persons that are concerned about their memory to the extent they respond to an advertisement are likely to have an anxiety disorder. Thus, due to the lack of appropriate measurements the results need to be interpreted with caution.

The Mini- Mental State Examination

Considering the extensive nature of the assessment, the MMSE was considered redundant, because the majority of the questions within the MMSE were in the neuropsychological test battery. The decision not to include the MMSE was unfortunate, because this would have facilitated further comparison between studies using the MMSE and the two screening tools (7MS; DRS) in identifying cognitive impairment.

The apolipoprotein ε4 (ApoE ε4) allele

The lack of association between ApoE ε4 and change in global functioning between assessments may be attributed to several factors. Only one subject had a ε4/ε4 genotype which is associated with the largest effects of ApoE. A large sample size of over 1000 subjects would be required to recruit a sufficient number of ε4/ε4 carriers to demonstrate a

more rapid decline in cognitive functioning based on ApoE genotyping.

Alzheimer's disease

The present study set out to investigate the relationship between SMC and cognitive impairment; it did not set out to determine the aetiology of the cognitive impairment. Certainly, whilst the profile of impairment observed in subjects with aMCI was generally consistent with that observed in the literature, the conclusions are limited by the lack of sufficient medical, psychiatric and functional data. Thus, other causes for the cognitive impairment cannot be ruled out.

Moreover, Alzheimer's disease is the most common cause of substantive cognitive impairment in non-depressed community samples (Brookmeyer et al., 2007).

9.13 Clinical significance and future directions

The current findings have clinical, as well as research implications for early case detection using SMC. Firstly, the present findings suggest that in isolation, SMC are unlikely to be useful for identifying cases with significant cognitive impairment. This is particularly relevant for younger subjects under the age of 70 years. However, for subjects over the age of 70 years, SMC are likely to identify significant cases with neuropsychological assessment (such as animal fluency and delayed recall).

Secondly, it seems that a combination of SMC and neuropsychological assessment (especially cognitive domain tests, such as delayed recall and

animal fluency) is likely to be more effective in screening community subjects for dementia and identifying those who would benefit from further neuropsychological assessment. It is not economically feasible to provide frequent full neuropsychological evaluations to a large proportion of the population who complain about their memory without objective evidence of cognitive impairment. This approach can also be useful for monitoring at-risk individuals.

Therefore, based on the available evidence within the dissertation, the following information may be helpful to the clinician. Further neuropsychological investigation is warranted in patients with all the following characteristics: aged over 65 years, a memory complaint (preferably an informant, e.g., spouse or GP) and is currently residing within the community. The best tests to screen the individual would be the delayed recall (RAVLT) and the animal naming test. Poor performance on both of these tests as indicated by the cut-offs coupled with a memory complaint would warrant further investigation.

Thirdly, as dementia (and in particular Alzheimer's disease) is reaching epidemic proportions in Australia (Jorm, 2005), it is of interest to identify individuals in the earliest stage of dementia or when symptoms first appear to test potential disease modifying therapies (Cummings et al., 2007). This could provide crucial opportunities for early intervention and treatment of these individuals. It could also potentially reduce the significant costs associated with caring for patients with Alzheimer's disease.

Considering the complex array of factors that may be related to memory complaints, (e.g., depression, anxiety, personality), future research should identify ways of quantifying SMC that are free of psychological conditions. This could be achieved by developing questions that are sensitive to different underlying aetiologies.

Prevention is the best cure for Alzheimer's disease. In order to help identify those at the greatest risk of developing dementia, easy to administer tools (in particular animal fluency) that could be completed by a general practitioner within a few minutes would be a worthwhile. This could be done quite quickly in combination with the MMSE. Several recent studies (Scarmeas et al., 2006; Lautenschlager et al., 2008) have advocated the beneficial effects of diets and moderate exercise in improving cognitive function and potentially reducing the risk of developing dementia. These measures may have significant benefit in reducing the number and severity of AD cases within the community. In particular, the earlier identification of those at risk of AD or actual early cases of AD would likely represent a group who would be better treatment responders.

9.14 Final conclusions

Whilst the notion of a relationship between SMC and cognitive function seems intuitively appealing, there has been ongoing controversy regarding the precise role of SMC in cognitive function. The present study was a quantitative attempt to clarify this relationship. In pursuing this line of inquiry, this study has provided some valuable information regarding the

clinical utility of using SMC to identify individuals at risk of developing cognitive impairment suggestive of Alzheimer's disease within the community.

By addressing some of the methodological issues in previous studies (such as, the use of predominantly older subjects, limited cognitive testing), the present study demonstrated that SMC used in isolation is a poor predictor of cognitive function, especially in younger subjects (i.e., < 70 years).

The present study provides evidence that selected and relatively quick to administer formal neuropsychological assessment of cognitive function (in particular tests of animal fluency and delayed recall) can better identify those at risk of developing future Alzheimer's disease compared to current brief testing strategies (often only using the MMSE alone). This combination of cognitive domain testing and risk profile (e.g., age, SMC) could be used to identify individuals at risk of developing Alzheimer's disease at an earlier age, thus exposing a cohort with likely better treatment responsiveness.

Future (hopefully more efficacious) treatment strategies would be targeted at these individuals resulting in a major alleviation in the current substantial public health expense of Alzheimer's disease.

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Appendix

BRIEF TELEPHONE SCREENING INTERVIEW

1. Do you have a problem with your memory?
2. Are you over 50 years of age?
3. Do you have a family history of Alzheimer's disease?
4. Have you ever been hospitalised for a psychiatric illness? (e.g. depression)
5. Have you ever had a stroke?
6. Have you ever had an automobile accident?
7. Have you ever had a drug problem?
8. Have you ever had to go into detoxification?
    - how many drinks do you have a day?
    - have you ever blacked out?
    - has anyone ever told you that you have a drinking problem?

DEMOGRAPHIC INFORMATION

Questions	Response
1. What is your name?	
2. What year were you born in?	
3. How old are you?	
4. What country were you born in?	
5. Sex of subject	
6. Age when left school	
7. Years of education	
8. Highest level of education attained?	
9. Occupational background	
10. Do you have a family history of Alzheimer's disease?	
11. If yes to (10.) who?	
12. Are you currently taking any medication?	
If yes to (12.) what medication?	

STROKE SCALE

Have you ever had or been told that you had:

S1. *A stroke?*

No	0
Yes	1
Does not know	?

S2. *A series of mini-strokes or transient ischaemic attacks (or TIAs)?*

No	0
Yes	1
Does not know	?

Have you ever: (include present condition in recording responses)

S3. ... *had a <u>sudden</u> weakness on one side which got better?*

No	0
Yes	1
Does not know	?

S4. ... *had a <u>sudden</u> difficulty with speaking?*

No	0
Yes	1
Does not know	?

S5. ... *had a <u>sudden</u> severe difficulty with your vision?*

No	0
Yes	1
Does not know	?

S6. ... *had a <u>sudden</u> severe difficulty with your memory?*

No	0
Yes	1
Does not know	?

DEPRESSION SCALE (PAS)

Have you ever had or been told that you had:

D1. *In the last two weeks, have you been feeling depressed or sad at all?*

No	0
Depends on situation	0
Yes	1
Does not know	?

D2. *Have you had trouble sleeping over the past 2 weeks?*

No	0
Depends on situation	0
Yes	1
Does not know	?

D3. *In the past two weeks, have you been taking anything to help you sleep?*

No	0
Yes	1
Does not know	?

D4. *In the last two weeks, have you been worn out or had too little energy, even when you haven't been doing a lot?*

No	0
Yes	1
Does not know	?

D5. *In the last two weeks, have you talked or moved more slowly than is normal for you?*

No	0
Yes	1
Does not know	?

D6. *In the last two weeks, have you had to be moving some part of your body all the time – that is, you were so restless you couldn't sit still?*

No	0
Yes	1

Does not know ..... ?

D7. *In the past two weeks, how frequently have you felt lacking in self-confidence or felt inadequate?*

No 0

Depends on situation 0

Yes 1

Does not know ..... ?

Now I'd like to ask you about your thinking.

D8. *In the last two weeks, has your thinking been much slower than usual?*

No 0

Depends on situation 0

Yes 1

Does not know ..... ?

D9. *In the last two weeks, have you had trouble concentrating?*

No 0

Depends on situation 0

Yes 1

Does not know ..... ?

D10. *In the last two weeks, do your thoughts seem to get mixed up that you cannot get them sorted?*

No 0

Depends on situation 0

Yes 1

Does not know ..... ?

D11. *In the last two weeks, have you had difficulty making decisions?*

No 0

Depends on situation 0

Yes 1

Does not know ..... ?

As they get older, some people find their thoughts turning to death more than in earlier life.

D12. *In the last two weeks, have you felt as if you wanted to die?*

No 0

Depends on situation 0

Yes 1

Does not know ..... ?

GERIATRIC DEPRESSION SCALE (SHORT FORM)

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

Depression Score: /15

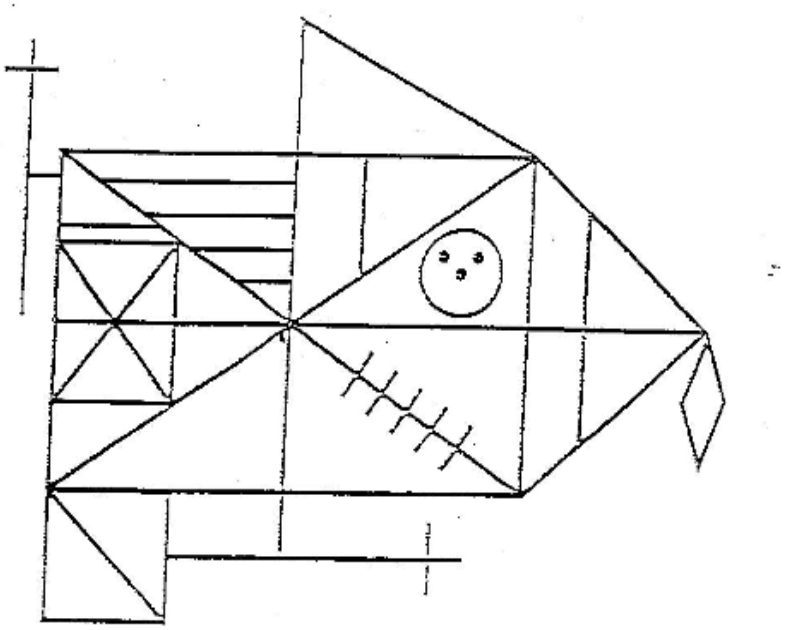
Code answers as Yes or No; Score one point for "No" to question 1, 5, 7, 11, and 13
Score one point for "Yes" to other questions.

3 ± 2 = normal

7 ± 3 = mildly depressed

12 ± 2 = very depressed

REY-OSTERRIETH COMPLEX FIGURE TEST



7 MINUTE SCREEN

ORIENTATION TEST	Correct Answer	Patient Response	**Scoring System**	**Score**
MONTH (Ask: What month us it now?)			5 points for each month off (max. score = 30)	
DATE (Ask: What is today's date?)			1 point for each date off (max. score = 15)	
YEAR (Ask: What year is it?)			10 points for each year off (max. score = 60)	
DAY OF THE WEEK (Ask: What day of the week is it?)			1 point for each day off (max. score = 3)	
TIME (Ask: What time is it now?)			5 points for each 30 minutes off (max. score = 5)	
				Score

Total (sum of all 5 scores; maximum = 113)

Insert the current month, date, year, day of the week, and time

If the patient does not respond or responds "I don't know", encourage him or her to guess.

If he or she will not guess, give the maximum score for that question

ENHANCED CUED TEST SCORE SHEET

MEMORY TEST SCORE SHEET

Delayed Recall

Category	Word	Uncued	Cued	Score
Piece of fruit	Grapes			
Animal	Tiger			
Body part	Foot			
Piece of furniture	Desk			
Tool	Screwdriver			
Article of clothing	Shoe			
Musical instrument	Guitar			
Type of vehicle	Motorcycle			
Toy	Top			
Vegetable	Tomato			
Insect	Spider			
Kitchen utensil	Pot			
Ship	Sailboat			
Part of a building	Door			
Bird	Eagle			
Weapon	Cannon			

Total Recall _____ +_____ = _____

Scoring Instructions

1. Total the number of uncued responses
2. Total the number of cued responses

The sum of the cued plus uncued responses is the score (maximum = 16)

CLOCK DRAWING

SAY: “I want you to draw the face of a clock with all the numbers on it. Make it large.”

After the patient has drawn the face of a clock,

SAY: “Now draw the hands, pointing at 20 minutes before 4 o’clock”

ANIMAL FLUENCY

SAY: "I will say a category name. Then I want you to give me as many words that fit in that category as quickly as you can. For instance, if I say vegetables, you might give me corn, spinach, lettuce, etc. Any questions"

SAY: "Begin when I name the category. The category is animals. Go ahead"

Allow 60 seconds for this test

Make a check mark [√] for each correct response in the lines below. Each check [√] = 1 point.

1. _____	16. _____	31. _____
2. _____	17. _____	32. _____
3. _____	18. _____	33. _____
4. _____	19. _____	34. _____
5. _____	20. _____	35. _____
6. _____	21. _____	36. _____
7. _____	22. _____	37. _____
8. _____	23. _____	38. _____
9. _____	24. _____	39. _____
10. _____	25. _____	40. _____
11. _____	26. _____	41. _____
12. _____	27. _____	42. _____
13. _____	28. _____	43. _____
14. _____	29. _____	44. _____
15. _____	30. _____	45. _____

Scoring: Record the number of the last line checked in the score box

Score

VERBAL FLUENCY

DIRECTIONS: I will say a letter of the alphabet. Then I want you to give me as many words that begin with that letter as quickly as you can. For instance, if I say 'B' you might give me 'bad', 'battle', 'bed'... I do not want you to give me words that are proper names such as 'Brisbane', 'Bob', or 'Brycreem' and no numbers. Also do not use the same word again with a different ending such as 'rain', 'rained', and 'raining'.

Any questions? (Pause)

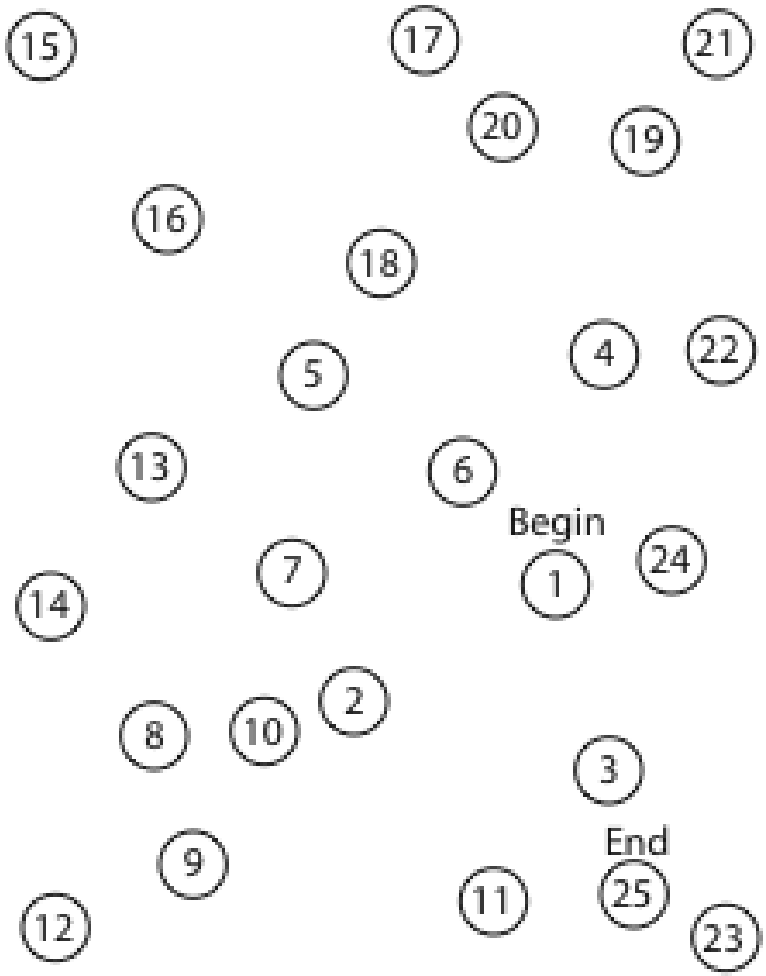
Begin when I say the first letter. The first letter is 'F'. Go ahead.

Allow 1 minute for each letter (F, A and S). Say **Fine** or **Good** after each 1 minute performance

F	A	S
Total:	Total:	Total:

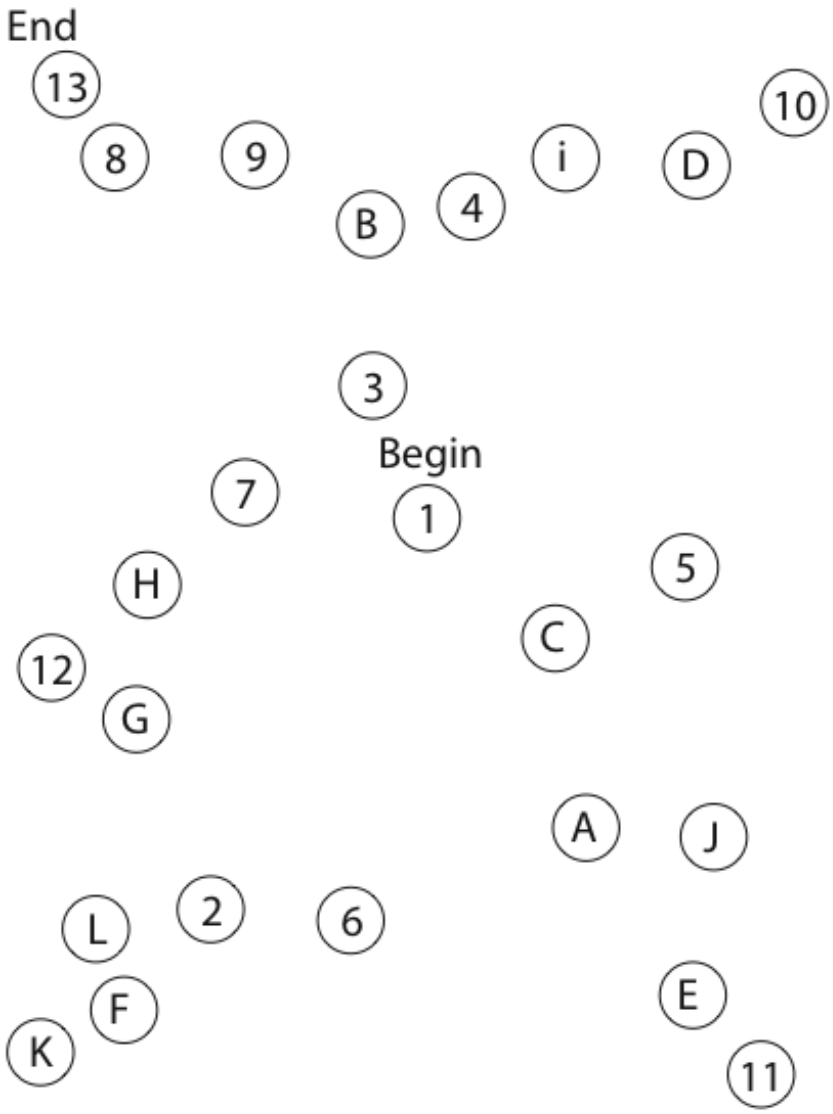
TRAIL-MAKING A TEST

Please connect the numbers in ascending order starting with number 1.



TRAIL-MAKING B TEST

Please connect the circles in the following order: start at one and then draw a direct line to the circle marked “A”; then draw a line to the circle marked “2”, then connect to B, as so forth until you reach the last circle marked 13.



MATTIS DEMENTIA RATING SCALE **DRS**

Scoring Form Steven Mattis

Name	**Age**	**Sex**	**Date**
Occupation	**Education**		
Diagnosis			

Scale	**Raw Score**	**Cut-off**	**SDAT Sample** **% ile** ***T*** **Score**
Attention			
Initiation/Perseveration			
Construction			
Conceptualization			
Memory			
DRS TOTAL SCORE			

Constitution and scores of the five subtests:

Attention subtest
- Digit span (forwards and backwards)
- Two-step commands
- One-step commands
- Imitation of commands

Initiation subtest
- Fluency for supermarket items
- Fluency for clothing items
- Verbal repetition (e.g. bee, key, gee)
- Double alternating movements
- Graphomotor (copy alternating figures)

Construction subtest
- Copy geometric designs

Conceptualization subtest
- Similarities
- Inductive reasoning
- Detection of different item
- Multiple choice similarities
- Create a sentence

Memory subtest
- Orientation (e.g. date, place)
- Counting of A's
- Counting randomly arranged A's
- Recall a sentence
- Recall a self-generated sentence
- Read a word list
- Verbal recognition
- Figure recognition
- Match figures

NATIONAL ADULT READING TEST (NART)

	Errors
Chord	
Ache	
Depot	
Aisle	
Bouquet	
Psalm	
Capon	
Deny	
Nausea	
Debt	
Courteous	
Rarefy	
Equivocal	
Naïve	
Catacomb	
Gaoled	
Thyme	
Heir	
Radix	
Assignate	
Hiatus	
Subtle	
Procreate	
Gist	
Gouge	

	Errors
Superfluous	
Simile	
Banal	
Quadruped	
Cellist	
Facade	
Zealot	
Drachm	
Aeon	
Placebo	
Abstemious	
Détente	
Idyll	
Puerperal	
Aver	
Gauche	
Topiary	
Leviathan	
Beatify	
Prelate	
Sidereal	
Demesne	
Syncope	
Labile	
Campanile	

MENTAL CONTROL (WMS-R)

1. Directions: Months Backwards (Time limit 76 seconds). Say, *I want to see how quickly you can remember the months of the year backwards from December to January, like this – December, November – all the way back to January.*

Repeat the directions if necessary, but give no aid during the examinee's effort.

Record the time in seconds

Dec Nov Oct Sept Aug Jul Jun
May Apr Mar Feb Jan _____ _____

Note: Months Backwards was used as a distracter task and was not scored.

2. Directions: Serial 7's (Time limit 76 seconds). Say, *Now I want you to subtract 7 from 100, and then subtract 7 from the answer you get, and keep subtracting 7 until I say stop.*

Repeat the directions if necessary, but give no aid during the examinee's effort.

Record the time in seconds

100 93 86 79 65 58 51 44 _____ _____
37 30 23 16 9 2

Scoring: Give 2 points if completed in time limit, and subtract one point for each error. Maximum 2, /Minimum 0

DIGIT SPAN (WAIS-R)

DIRECTIONS: (Digits Forward) Start with Item 1. Say,
I am going to say some numbers. Listen carefully, and when I am through say them right after me. The digits should be given at the rate of one per second. Let the pitch of voice drop on the last digit of each trial. Administer both trials of each item, even if the subject passes Trial 1.
Item 1 example 2-7-5

DIRECTIONS: (Digits Backward) Say,
Now I am going to say some more numbers, but this time when I stop I want you to say them backwards. For example, if I say 7-1-9, what would you say? (Pause for examinee) If the examinee responds correctly (9-1-7), say, That's right, and proceed to Trial 1 of Item 1. Say, Now listen to these numbers, and remember you are to say them backwards.

However, if the examinee fails the example, say, No, you would say 9-1-7. I said 7-1-9, so to say it backwards you would say 9-1-7. Now try these numbers. Remember, you are to say them backwards, 3-4-8. Give no help on this second example or any of the items that follow. Whether the examinee succeeds or fails with the second example (3-4-8), proceed to Trial 1 of Item 1.
*Discontinue after failure on both trials of any item

Forward (0,1,2)

	(0,1)		(0,1)	
1. 5-8-2	____	6-9-4	____	____
2. 6-4-3-9	____	7-2-8-6	____	____
3. 4-2-7-3-1	____	7-5-8-3-6	____	____
4. 6-1-9-4-7-3	____	3-9-2-4-8-7	____	____
5. 5-9-1-7-4-2-8	____	4-1-7-9-3-8-6	____	____
6. 5-8-1-9-2-6-4-7	____	3-8-2-9-5-1-7-4	____	____
7. 2-7-5-8-6-2-5-8-4	____	7-1-3-9-4-2-5-6-8	____	____

Forward Span ____ /9 **Total Forward ____ /14**

Backward (0,1,2)

	(0,1)		(0,1)	
1. 2-4	____	5-8	____	____
2. 6-2-9	____	4-1-5	____	____
3. 3-2-7-9	____	4-9-6-8	____	____
4. 1-5-2-8-6	____	6-1-8-4-3	____	____
5. 5-3-9-4-1-8	____	7-2-4-8-5-6	____	____
6. 8-1-2-9-3-6-5	____	4-7-3-9-1-2-8	____	____
7. 9-4-3-7-6-2-5-8	____	7-2-8-1-9-6-5-3	____	____

Forward Span ____ /9 **Total Forward ____ /14**

GRAND TOTAL ____/28

REY AUDITORY VERBAL LEARNING TEST

DIRECTIONS: For Trial 1, say I am going to read a list of words. Listen carefully, for when I stop, you are to say back as many words as you can remember. It doesn't matter in what order you repeat them. Just try to remember as many as you can. Read List 1 words at 1 second intervals (rate of 1 per second). Check off the words recalled, using numbers to keep tack of the patient's pattern of recall. No feedback should be given regarding the number of correct responses, repetitions or errors. If the patient asks if they have said a word before, examiner may tell them.

When the examinee indicates that he/she can recall no more words, the examiner rereads the list after giving a second set of instructions: Now I am going to read the same words again, and once again when I stop, I want you to tell me as many words as you can remember, including words you said the first time. It doesn't matter in what order you say them. Just say as many words as you can remember, whether or not you said them before.

The list is reread for trials 3-5, using trial 2 instructions each time. The examiner may praise the examinee as he or she recalls more words. On completion of trial 5, the examiner tells the examinee: Now I am going to read a second list of words. This time, again, you are to say back as many words of this second list as you can remember. Again, the order in which you say the words does not matter. Just try to remember as many words as you can. Examiner reads List 2.

Immediately following the reading and recall of List 2, without an additional presentation, subjects are asked to recall the words from the original list (List 1). After a 20 minute delay, the subject is again asked to recall the words from the original list (List 1). Immediately following this, the subject is given the Recognition page and is asked to identify as many of the list words as they can (by ticking boxes as indicated) and, if possible, the specific list of origin (1 or 2) (i.e., to write a 1 or 2 in the box next to the appropriate word).

List 1	Trial 1	Trial 2	Trial 3	Trial 4	Trial 5	List 2	List 2 Recall	List 1	Immed recall	20 Min Recall
DRUM						DESK		DRUM		
CURTAIN						RANGER		CURTAIN		
BELL						BIRD		BELL		
COFFEE						SHOE		COFFEE		
SCHOOL						STOVE		SCHOOL		
PARENT						MOUNTAIN		PARENT		
MOON						GLASSES		MOON		
GARDEN						TOWEL		GARDEN		
HAT						CLOUD		HAT		
FARMER						BOAT		FARMER		
NOSE						LAMB		NOSE		
TURKEY						GUN		TURKEY		
COLOUR						PENCIL		COLOUR		
HOUSE						CHURCH		HOUSE		
RIVER						FISH		RIVER		
Totals										

RECOGNITION TEST

	√ Tick if read to you	1 = List 1 2 = List 2		√ Tick if read to you	1 = List 1 2 = List 2
1 bell			26 gun		
2 window			27 crayon		
3 hat			28 church		
4 barn			29 turkey		
5 ranger			30 fountain		
6 nose			31 boat		
7 weather			32 hot		
8 school			33 parent		
9 hand			34 water		
10 pencil			35 farmer		
11 home			36 rose		
12 fish			37 cloud		
13 moon			38 house		
14 tree			39 stranger		
15 balloon			40 garden		
16 bird			41 glasses		
17 mountain			42 stocking		
18 coffee			43 shoe		
19 mouse			44 teacher		
20 river			45 stove		
21 towel			46 nest		
22 curtain			47 children		
23 flower			48 drum		
24 colour			49 toffee		
25 desk			50 lamb		

SIMILARITIES (WAIS-R)

DIRECTIONS: Start with Item 1. Say, **In what way are an ORANGE and a BANANA alike?** If the subject replies that they are both fruit, say, **Good** and proceed to the next item. If the subject gives a 1-point answer to Item 1, give an example of a 2-point response. For example, If the subject answers *"You eat them both"*, say **That's right, you do eat them both. Also, they are both fruit.** Then go onto the next item. If the subject fails to respond to Item 1 or gives an incorrect answer (a 0-point response), say, **They are both fruit, you eat them both,** and go onto the next item.

Item 2 and subsequent items should be phrased in the same way as the first item. For Item 2 say, **In what way are a DOG and a LION alike?** Give no further help on this or any subsequent item. However, if a response is unclear or ambiguous, say, **What do you mean? Or Tell me a little more,** or make a similar neutral inquiry.

Record, verbatim, the subject's response to each item in the appropriate space below.

Discontinue after 4 successive failures

1. Orange – Banana	
2. Dog – Lion	
3. Coat – Suit	
4. Boat – Car	
5. North – West	
6. Table – Chair	
7. Work – Play	

PRAXIS

DIRECTIONS: Tell the patient "I am going to ask you to do some things, try and do them as well as you can". If the patient fails to perform the command well, then show him or her how (imitate the action). If this fails, then give the patient the real object, where applicable (asterisks). Allow for variations in normal performances. Score 3 points for a good performance in the command column. Score 2 points for approximate performance or good performance on imitation only. Score 1 point for approximate performance on imitation or if performed with the actual object. If the patient uses a body part for an object, score 2 points (e.g., fingers used as a comb through the hair).

Examples: "Whistle" If the patient purses his or her lips and blows, but there is no sound, score 2 points for an approximate performance. If the patient declares that he or she cannot do it or purses his or her lips but does not blow, then demonstrate. If the patient then purses his or her lips and blows, score 1 point for approximate performance on imitation. If the patient fails to exhale then score (no points). "Sniff" If the patient grimaces or inhales through the mouth, score 1 point only. If performance improves on imitation, score 2 points. If the patient does it only with a flower, score 1 point only. If the patient rubs the flower on his or her nose, score 0 (no points)

	Command	**Imitated**	**With Object**
Upper Limb			
1 Make a fist			
2 Salute			
3 Wave goodbye			
4 Scratch your head			
5 Snap your fingers			
Facial			
6 Put out your tongue			
7 Close your eyes			
8 Whistle			
*9 Sniff a flower			
*10 Blow out a match			
Instrumental			
*11 Use a comb			
*12 Use toothbrush			
*13 Use a spoon to eat			
*14 Use a hammer			
*15 Use a key			
Complex			
16 Pretend to drive a car			
17 Knock at door and open it			
*18 Pretend to fold a paper			
19 Pretend to light a cigarette			
20 Pretend to play the piano			

BOSTON NAMING TEST

DIRECTIONS: Say, Now I am going to show you some pictures and I want you to say the name of each picture. For each picture ask: What is the name of this object? Or Can you name this? No semantic or phonetic cuing should be used. A non specific prompt can be used if the response is too general. For example, if the response to the "canoe" item is "boat" say, Is there another name for that? You may not ask, Isn't that a special kind of boat? If the test administrator uses a prompt after too general a response (i.e. "boat") only the specific response (i.e. "canoe") is counted correct.

General Instructions for All Subjects
The pictures are presented in order, allowing up to 20 seconds for response, unless the subject says he does not know the word before 20 seconds have gone by. If the answer is correct, score 1 in column (1) if they responded within 5 seconds and column (2) if it was >5 seconds but <20. Record verbatim any response other than the correct one. If their response is incorrect, score 0 in columns (1) or (2), and proceed with stimulus, letter and phonemic cueing, if appropriate, as outlined below.

Starting and Stopping points. Begin with item 1 for all subjects, and discontinue after 6 consecutive failures (Score>3)

Picture						
1. Bed ……..						
2. Tree ……..						
3. Pencil ……..						
4. House ……..						
5. Whistle ……..						
6. Scissors ……..						
.						
.						
55. Sphinx ……..						
56. Yoke ……..						
57. Trellis ……..						
58. Palette ……..						
59. Protractor ……						
60. abacus ……..						

Summary of Scores

1. Number of spontaneously correct responses ____ ____
2. Number of correct responses following a stimulus cue ____ ____
3. Number of times a stimulus cue was required ____ ____
4. Number of correct responses following phonemic cue ____ ____

TOTAL CORRECT (1+2) ____/60

VOLUNTEERS NEEDED FOR A STUDY ON AGEING AND ALZHEIMER'S DISEASE

Researchers at Concord and Royal Prince Alfred Hospital are conducting a study to identify early indicators for Alzheimer's disease (AD). Volunteers should be over 50 years of age with no history or current evidence of clinical depression or major psychiatric disorder, stroke, head injury or significant drug and alcohol problems. We are interested in recruiting people with or without memory difficulties, especially if they have a family history of Alzheimer's disease. Participants are asked to complete a number of simple memory tests and provide a small sample of blood. If you are interested in participating in the study please phone Concetta Tarantello on 9767-5106, 9515-5873 or (mobile 0404 498 653) during working hours.

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Telephone: (02) 9767 5106
Mobile: 0404 498 653

[on letterhead]

A RESEARCH STUDY INTO

COGNITIVE DECLINE IN NORMAL AGEING AND PRECLINICAL ALZHEIMER'S DISEASE: A COMMUNITY-BASED STUDY

INFORMATION FOR PARTICIPANTS

BACKGROUND INFORMATION

You are invited to participate in a research study about Alzheimer's disease (AD) and memory function. The aim of this study is to identify different patterns of memory capability in people aged over 50 years with and without mild memory complaints and in people with possible dementia seen by community mental health teams. A further aim is to examine the relationship between current memory ability and carriers of a particular gene (ApoE e-4 allele) thought to increase the chance of developing dementia later in life. The study is being conducted by Concetta Tarantello (PhD student), Dr. Glenn Hunt (Senior Research Fellow), and Dr. Richard White (Consultant Psychiatrist) in the Department of Psychological Medicine at Concord and Royal Prince Alfred Hospital.

WHAT DOES THE STUDY INVOLVE?

If you agree to participate in this study, you will be asked to provide a 5 ml blood sample drawn from a vein in your forearm, and to take part in a clinical assessment. The clinical assessment will involve a number of simple tests (mostly paper and pencil tests) examining all aspects of memory and will take about 1 to 2 hours to complete.

DISCOMFORT/RISKS

The collection of blood may involve some discomfort at the site of the needle puncture and the possibility of mild bruising afterwards. If this occurs, it

should go away within a couple of days. You may become tired during the clinical assessment. If this happens, you are welcome to ask for one or more short rest breaks.

BENEFIT

While we intend that this research study furthers medical knowledge and may improve treatment and assessment of Alzheimer's disease in the future, it may not be of direct benefit to you. Your blood sample will only be used for the purpose of this study (ApoE testing) and no portion will be stored for future use. You can obtain the results of the ApoE blood test but the results cannot be used to determine if you will develop dementia in later life, presently ApoE typing is of research interest only. If you would like more information on ApoE testing, we can give you a fact sheet of frequently asked questions or arrangements can be made for you to see a genetic counsellor if you want further advice.

PARTICIPATION AND CONFIDENTIALITY

Participation in this study is entirely voluntary, you are in no way obliged to participate and if you do participate you can withdraw at any time. Whatever your decision, please be assured that it will not affect your medical treatment, any present or future insurance policies or your relationship with medical staff (where applicable). All aspects of the study, including results, will be strictly confidential and only the investigators named above will have access to the information. A report of the study may be submitted for publication, but individual participants will not be identifiable. If you are currently being seen by a community health worker and you give your consent, a short summary of your current memory function may be placed in your health folder (community medical record), as it may be helpful to the people looking after you.

FURTHER INFORMATION

This information sheet is for you to keep. Concetta Tarantello will answer any further questions you may have about this study; you can contact her on 9767-5106 during working hours. This study has been approved by the Human Research Ethics Committee (RPAH and CRGH Zone) of the Central Sydney Area Health Service. Anyone with concerns or complaints about the conduct of the research study can contact the Secretaries of these committees on (02) 9515-6766 or 9767-6233. Alternatively, if you wish to speak with an independent person about any problems or queries about the way in which the study was conducted, contact the Concord Hospital Patient Representative on (02) 9767-7488.

Some answers to frequently asked questions about Alzheimer's disease and ApoE

What is my risk of developing Alzheimer's disease?

It is worth pointing out that we are *all* at some risk of developing Alzheimer's disease (dementia) provided that we live long enough. More people are likely to develop dementia over the next 20 years because more people are living into their 80's and 90's. Recent studies suggest that the prevalence of dementia in first-world populations doubles every five years between the ages of 65 and 85. Stated more clearly, the chance of developing dementia at the age of 65 is about 1.5% and by the age of 85 this increases to 13.6% and if you live to the mid-nineties the rate is around 30-40%.

What causes Alzheimer's disease?

Alzheimer's disease (dementia) is caused by the formation of tiny plaques in the brain over many years. The presence of these plaques (or tangles) interrupts the flow of information between different parts of the brain. This results in loss of function especially for remembering things. Progressively, the person becomes more and more forgetful to the point where they can no longer look after themselves. Presently, we do not know what causes dementia or why these plaques form in some people; it may be part of the normal ageing process. The majority of cases of Alzheimer's disease do not result from single gene mutations; it appears to be caused by a number of different genetic risk factors together with environmental factors. Recent research has identified one of the risk factors linked to Alzheimer's disease to be a gene called ApoE.

What is ApoE?

ApoE is short for apolipoprotein E. It is a protein derived from our DNA (genes) that has a role in fat metabolism and tissue repair. It is primarily synthesised (made) in the liver. There are three forms of ApoE known as apoE2, apoE3 and apoE4. Most of us know there are three different blood types-A, B and O. People differ in the type of ApoE they inherit just like people have different blood types.

A gene has two parts called alleles. We inherit one copy from our mother and one copy from our father. Together they form 2 copies (alleles) that determine our ApoE type. For example, if you inherited a copy of the ApoE e2 gene from your mother and an ApoE e3 allele from your father, your ApoE status would be ApoE (e2/e3). Since the ApoE alleles are different they are said to be heterozygous. If you inherited similar ApoE copies from each parent (for example, both e3 or both e4), this is said to be homozygous. Therefore, when you get your results they will be one of six possibilities. Either homozygous for which there are three types (e2/e2; e3/e3 or e4/e4) or heterozygous which there are also three types (e2/e3, e2/e4, or e3/e4). Research has shown that the majority of people will be carriers of the Apo e3 gene (e2/e3, e3/e3 or e3/e4). It is less common to be homozygous for the ApoE e2 (e2/e2) or the ApoE e4 (e4/e4) gene.

What is the association between ApoE and Alzheimer's disease?

In 1993, an important study was published showing that the frequency of ApoE e4 in people with Alzheimer's disease (namely 30-50%) was greater than the ApoE e4 frequency (namely 10-15%) in age-matched controls without dementia. This association showing that people with two copies of the ApoEe4 gene (homozygotes e4/e4) have higher rates of dementia than non-e4 carriers has been replicated several times in different racial groups. The consensus of opinion is that ApoE genotype determines 'when' rather

than ‘whether’ one develops dementia in later life. That is, carriers of the ApoE e4/e4 type develop dementia about 5 to 6 years earlier than non-e4 carriers.

Knowledge about your family history of dementia is of much greater importance than knowing your ApoE genotype in predicting who will develop Alzheimer’s disease. It seems that people with two copies of the ApoE e4 gene (e4/e4) have, on average, about a 50% chance of developing dementia by age 90 years (compared to the population average of 32%). Also, many people who are non-carriers of ApoE e4 gene will go on to develop dementia, so this test can not be used to rule-in or rule-out the likelihood of developing dementia in later life. In medical terms the test is said to have poor predictive value and should not be used as a diagnostic tool. *Thus, this test seems to have negligible diagnostic benefit so you should not be overly concerned about your test result.*

In conclusion

At the moment we do not how ApoE e4 and the apoE4 protein influence the pathophysiology (cause) of Alzheimer’s disease. The aim of this study is examine if there is an association between ApoE types, age and memory capability. Hopefully this study will shed some light on this subject. In conclusion, you should not be overly concerned about the type of ApoE you inherited from your parents. It is more important to look at your family pedigree to see if there are several members over many generations that developed Alzheimer’s disease at an early age (<55 years). If this is the case, you may want the advice of a genetic counsellor. We can help arrange an appointment for you, if you wish.