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**EXECUTIVE FUNCTION IN
HIGH FUNCTIONING INDIVIDUALS WITH
AGE-ASSOCIATED MEMORY IMPAIRMENT OR
ALZHEIMER'S DISEASE**

 Linda Vasudev

**Thesis presented to the School of Graduate Studies of the University of Ottawa in
partial fulfilment of the requirements for the degree of Doctor of Philosophy.**



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Abstract

The purpose of the study was to explore the possibility that age associated memory impairment (AAMI) may form part of a prodromal stage of Alzheimer's Disease (AD) through evidence of dysfunction beyond memory, involving also executive function. A sample of subjects meeting AAMI criteria least likely to show executive dysfunction was selected for study by specifying that all participants belonged to a "high functioning" group. As such, all subjects had completed 16 or more years of education. A total of 88 subjects were recruited for the study: 22 young control subjects (YC), 22 older control subjects (OC), 22 subjects with AAMI as specified by the NIMH Work Group criteria, and 22 subjects with mild to moderate probable AD according to NINCDS-ADRDA criteria. The young subjects were recruited to provide appropriate education-based norms for tests of recent memory required for AAMI inclusion criteria. Six executive function tests were used including: Controlled Oral Word Association (COWA), Colour Trails Test (CTT), Similarities subtest of the WAIS-R, Stroop Colour Word Test, Tower of Toronto (TOT), and the Wisconsin Card Sorting Test (WCST). Results indicated the AD group performed significantly worse than both the AAMI and OC groups on all six tests, providing evidence of test sensitivity to executive dysfunction in AD, and confirming the presence of executive function deficits early in the disease course. AAMI and OC groups only differed on the COWA and the TOT. However, when the AAMI subjects were compared to the OC subjects, independent of the AD group, significant differences were found on the COWA, TOT, two indices of the

WCST, and CT1. Profile analysis indicated the two groups were not statistically parallel, though examination of the pattern of executive function performance of the AAMI group revealed some similarities to that of the AD sample. It was concluded that AAMI is not merely a mild memory disorder, but that it fulfills to some degree, the criteria of probable AD, and as such, may be a prodromal stage in the development of AD. Current results are deemed particularly important in light of the most recent findings indicating that it is the earliest intervention with anti-dementia compounds which provides the most therapeutic benefit. Thus, the identification of individuals at the prodromal stage of dementia is imperative.

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Abbreviations

AAMI	Age Associated Memory Impairment
ACh	Acetylcholine
AChE	Acetylcholinesterase
AD	Alzheimer's Disease
ADL	Activities of Daily Living
ANOVA	Analysis of Variance
APOE	Apolipoprotein E
APP	Amyloid Precursor Protein
BDI	Beck Depression Inventory
CDR	Clinical Dementia Rating Scale
ChAT	Choline Acetyltransferase
COWA	Controlled Oral Word Association
CT	Computerized Tomography
CTT	Colour Trails Test
CT1	Colour Trails 1
CT2	Colour Trails 2
CVD	Cardiovascular Disease
df	Degrees of Freedom
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders 4 th Edition
EEG	Electroencephalogram
GDS	Global Deterioration Scale
HAM-D	Hamilton Depression Rating Scale
HSD	Honestly Significant Difference
IQ	Intelligence Quotient
LM	Logical Memory
MAC-Q	Memory Assessment Questionnaire
MAC-S	Memory Assessment Clinics Self-Rating
MANOVA	Multivariate Analysis of Variance
MMSE	Mini-Mental State Examination
MRI	Magnetic Resonance Imaging
NINCDS/ADRDA	National Institute of Neurological and Communicative Disorders and Stroke, and Alzheimer's Disease and Related Disorders Association
NIMH	National Institute of Mental Health
NFT	Neurofibrillary Tangles
OC	Older Control Subjects
PET	Positron Emission Tomography

PD	Parkinson's Disease
SD	Standard Deviation
SP	Senile Plaques
SPECT	Single Photon Emission Tomography
SPSS	Statistical Package for the Social Sciences
TOT	Tower of Toronto
VerbPA	Verbal Paired Associates (WMS-R)
VisPA	Visual Paired Associates (WMS-R)
WAIS-R	Wechsler Adult Intelligence Scale - Revised
WCST	Wisconsin Card Sorting Test
WHO	World Health Organization
WMS-R	Wechsler Memory Scale Revised
YC	Young Control Subjects

INTRODUCTION

Clinical conceptions of the nature and definition of age associated memory impairment (AAMI) and of the borders between this entity and degenerative dementing disorders such as Alzheimer's disease (AD) remain unclear. First introduced in 1986 (Crook et al.), AAMI describes a sample of individuals who, in the absence of dementia, exhibit both subjective and objective memory decline compared to that of a younger cohort. Several researchers are of the opinion that individuals with AAMI, though distinguishable from age matched peers who do not exhibit similar memory decline, are merely afflicted by a benign construct. Proponents of this view adhere to the opinion that AAMI will not progress to dementia and as such, individuals meeting AAMI criteria are not at any greater risk for the development of dementia than those in the general population. Conversely, other researchers feel AAMI is not a benign process, and that individuals with the disorder will eventually develop the full dementia syndrome. Though several studies have examined the relationship of AAMI to AD, it has yet to be definitively determined, if AAMI is a benign process, a risk factor, or a prodromal stage of AD.

As no reliable biological marker exists for either disorder, differential diagnosis of AAMI and early AD is based on clinical presentation, and is often difficult to establish with accuracy. This is due primarily to the fact that the cognitive impairment present in the early stages of AD can appear similar to that of AAMI rendering distinction between the two very difficult. Although cognitive impairment in AAMI and

AD is not easily distinguished on a purely clinical basis, its occurrence in the two disorders may be due to entirely distinct pathognomonic processes. Detection and accurate differential diagnosis of mildly impaired individuals is essential though, particularly when considering possible treatment. If it is determined that AAMI is in fact a prodromal stage of AD, then early intervention in the AAMI population may allow, at minimum, for a delay of the disease process, or ultimately, a prevention.

As a result, an extensive amount of research is currently being undertaken in an attempt to identify AD at its earliest stages. Much of this research is focussed on discovering potential risk factors, genetic factors, and biological markers. This research includes an examination of AAMI and its connection to AD. Research over the past decade has primarily focussed on an examination of the memory dysfunction involved in AAMI. Recently, however, examination of other cognitive areas has begun in an attempt to determine their possible roles. One particular domain which has received investigational attention is that of executive function. Generally considered a higher order cognitive system, executive function primarily serves as a control mechanism whose influence is evident across a number of cognitive processes. Deficits in executive functioning are a common characteristic of AD, yet they have not been well studied in individuals with AAMI. The study of executive function in the AAMI population is important as it will help to define the cognitive characteristics of the construct more clearly, and also aid in determining AAMI's relationship to AD.

Executive Function

Identification of a universally accepted definition for the term 'executive function' in the psychological literature proves to be an exhausting, and ultimately futile endeavour. Definitions of executive function and the role it plays in an overall conceptualization of human cognition differ depending on theoretical background, approach, and research strategy. For example, some researchers have developed a theory of cognition in which executive functioning coordinates two other central components, the cognitive and metacognitive level (Butterfield & Albertson, 1995). Others have incorporated executive function into specific models such as the 'IDEAL problem solver', with the acronym IDEAL used to symbolize components in problem solving (Bransford & Stein, 1993). Yet others have proposed a model of the development of planning, which incorporates several aspects of executive function (Scholnick & Friedman, 1993). Nevertheless, common among most definitions of executive function is that it is considered a mechanism by which performance is optimized in situations requiring the simultaneous operation of a number of different cognitive processes. Further, executive function is required when sequences of responses must be generated and scheduled and when novel plans of action must be formulated and carried out. Put differently, executive function is not about the extent of a person's previously acquired "knowledge base", but rather tests the extent to which individuals can inhibit habitual responses in favour of novel ones (Hays, Gifford, & Ruckstuhl, 1996). Various terms have been used to describe the specific cognitive processes involved in executive function such as self-regulation, set maintenance, goal

formation, planning and organizing, abstract reasoning and thinking, and decision making. However, the terms used to define executive function have themselves been criticized by several clinicians with regard to their vagueness.

In the literature, synonymous use is often found for the terms 'executive function' and 'frontal lobe function'. While it is true that executive functions are predominantly performed by the areas subserved by the frontal lobes, it is also true that the frontal lobes are responsible for more than is considered under the umbrella of the term executive function. In general, frontal lobe functions include a vast array of responsibilities such as planning, execution and control of movements, tone, gait and posture, regulation of affect and emotional responses, memory, speech and language, arousal, olfactory function, and personality. Frontal lobe function, if used in its most literal sense, refers to all functions subserved by the frontal lobes, whereas the term "executive function" would constitute a more narrow label, specifically relating to functions subserved by the prefrontal cortex.

One aspect of executive function that has received much attention in recent years is working memory. Initially introduced into the experimental psychology literature by Baddeley (1986, 1992), the term 'working memory' was intended to replace the existing concept of a passive short-term memory store and to emphasize, within a single model, both the temporary storage and the 'on-line' manipulation of information that occurs during a wide variety of cognitive activities (Owen, Sahakian & Robbins, 1998). Conceptualized as a three-part system, working memory consists of the central executive, and two slave systems: the phonological loop, and the

visuospatial sketch pad. The phonological loop (sometimes referred to as the articulatory loop) provides the means for a brief, verbatim storage and manipulation of verbal or speech-based information. It can be thought of as functioning like a short loop of recording tape that continuously stores a small amount of auditory information. The most commonly used measure of ability to store information in the phonological loop is the forward digit span task. Others include forward word span, sentence repetition, and nonword repetition. The second slave system, the visuospatial sketch pad, is responsible for generating and storing visual images.

The central executive in most basic terms is a controlling system. It is a limited capacity work space that can be devoted to a variety of processing activities. Some of the central executive's most fundamental tasks are to divide and allocate attentional resources, and to hold information while manipulating it. The functions of the central executive have been measured with tests such as the Consonant Trigrams Test, the Arithmetic subtest of the WAIS-R, or backwards digit span. As the central executive is viewed as a "controller", it fits into the broad definition of executive function. Further, considerable evidence from the study of patients with compromise to the frontal cortex (e.g., Owen, Morris, Sahakian, Polkey & Robbins, 1996), and from functional neuroimaging studies (e.g., Courtney, Ungerleider, Keil & Haxby, 1996; Gold, Berman, Randolph, Goldberg & Weinberger, 1996) has suggested that the lateral surface of the frontal lobe plays a critical role in certain aspects of working memory such as the central executive.

Measuring Executive Function

Measurement of executive function, or level of dysfunction, is an extremely challenging task. As executive function is not a unitary phenomenon, no single test is able to adequately assess the complexities of the construct. As a result, there are a number of tests that purport to measure various aspects of this domain. Clinicians who wish to assess an individual's level of executive functioning, therefore, must rely on a battery of tests in order to properly assess different aspects of executive function. The wide variety of assessment tools used to measure executive function points to its vague definition and lack of technical clarity. Although executive function tests vary widely, most involve an unusual circumstance where subjects are required to perform actions in which they do not activate well-established sources of behavioural regulation. Put differently, executive function is not invoked when responses are well-practised, smooth, or automatic. As such, tests of executive function arrange situations in which immediate and habitual sources of behavioural regulation *cannot* work (Hayes et al., 1996).

Though several measures are currently in use for the measurement of executive function, the ones presented in Table 1 are deemed a good representation of the different facets of the construct (detailed descriptions are provided in the method section). Further, these tests are generally well known in the psychological and neuropsychological literature, and have been included in several studies examining executive function.

Table 1

Tests of Executive Function Used in the Study

Name of Test	Comment
Colour Trails Test	Visual search, attention, mental flexibility
Controlled Oral Word Association	Verbal fluency
Similarities subtest WAIS-R	Verbal concept formation; abstraction
Stroop Colour-Word Test	Cognitive flexibility; divided attention
Tower of Toronto	Planning, goal formation, working memory
Wisconsin Card Sorting Test (WCST)	Ability to form abstract concepts, mental flexibility, set maintenance, perseveration

Executive function, much like other cognitive processes such as memory, is vulnerable to various factors. For example, such factors as age, head injury, or disease process can have a marked influence on successful completion of executive function tasks. With respect to age, executive function performance can be conceptualized roughly as a skewed bell shaped curve, with poorly developed skills early in life, reaching a maximum potential in adulthood, followed by a mild decline evident later in life. Converging evidence from the fields of neurology, neurophysiology, and neuropsychology indicates that executive functions are not fully developed until late adolescence (Eslinger, 1996). This view is supported by the theory that executive functions rely on the prior acquisition of elementary cognitive processes (e.g., sensation, perception, motor activation, attention, memory) which occur during infancy, childhood and early adolescence (Barkley, 1996; Borkowski &

Burke, 1996; Graham & Harris, 1996). As such it is believed that executive functioning is virtually absent among young children (Levin et al., 1991), emerging only later as assessed neuropsychologically (when successful completion of tasks of abstraction can be demonstrated), neurologically (indices of myelination), and neurophysiologically (electroencephalogram (EEG) studies indicating prefrontal region changes correlated with cognitive development). Several geriatric studies have indicated a mild decline of executive functioning as a function of increasing age (e.g., Brennan, Welsh & Fisher, 1997, Salthouse, Fristoe & Rhee, 1996). In addition, disease processes such as AD involve executive dysfunction (in addition to other cognitive deficits) often at very early stages. Thus, executive function appears to exhibit sensitivity to brain function, and as such its study is considered valid in gathering information across different populations. With respect to AAMI, by definition, the disorder exhibits a memory deficit similar in nature to that found in AD, thus establishing a potential link between the two processes. Thus, involvement of a second cognitive domain in the AAMI population such as executive function, which can be evident in the early stages of AD, may provide further evidence of a relationship between the two processes.

Optimal Aging

A discussion of the clinical characteristics of degenerative processes cannot be undertaken without first considering the changes in function that may occur as a result of normal, or as is currently termed, 'optimal aging' (additional terminology includes 'no cognitive impairment'; 'successful cognitive aging'). Optimal aging is defined as "aging

changes that occur in individuals free of overt diseases of the nervous system” (Katzman & Terry, 1983, p. 15). As more and more individuals are reaching older age free of disease, our concept of who is ‘old’ has also changed. There are numerous examples of artists, lawyers, musicians, physicians, politicians, and writers continuing productivity in their careers well into their 80's and 90's. Gerontologists have recognized this phenomenon by subdividing the elderly into the following categories: 65-75 ‘young old’, 75-85 ‘middle old’, or simply ‘old’, and 85+ ‘old old’, or ‘oldest old’ (Katzman & Terry, 1983).

Epidemiological estimates of the prevalence of normal aging can be derived from studies that assess prevalence of both AAMI and dementia (Laakso, 1996). Koivisto and colleagues (1995) reported the prevalence of cognitively normal aging at 37.5% for the age group 60-78. Similar rates have been reported at 32% (Ebly, Hogan & Parhad, 1995), and 44% (Sobel et al., 1995). Results of the Canadian Study on Health and Aging (1997) indicate that among Canadians 65 and older, 75.2% are estimated not to be cognitively impaired.

Early studies examining the cognitive abilities of brain damaged and non brain damaged individuals (Reitan, 1955) indicated that performance of non brain-damaged older adults were similar to brain damaged individuals. Specifically, tests that most clearly distinguished young and old subjects were also those that best distinguished between brain damaged and non brain damaged subjects (Reed & Reitan, 1963). Inspired by these findings, researchers began examining the pattern of cognitive performance of older adults. In response to the question “Does cognitive function

decline with normal aging?" globally the answer can be yes. More precisely, the consensus is that some functions deteriorate while others remain the same, or even improve. Briefly, intellectual performance as measured by non-timed tests of verbal abilities such as word knowledge, or general information reaches a peak at age 20 to 30, and is then generally maintained throughout life (Craik, 1990; LaRue, 1992). Conversely, cognitive functions related to speed of information processing, and those in which novel capabilities are required, typically reach a peak about age 20 and then decline slowly throughout life (Birren, Woods & Williams, 1980; Fozard, 1985; LaRue, 1992). Memory performance is differentially affected in the healthy elderly. The well known short-term/long-term dichotomy of memory, although now considered somewhat dated, is still useful for a general description of the changes in memory seen in optimal aging. In general, tasks assessing short-term memory show consistent age related changes, whereas tasks assessing retrieval from long term storage do not (e.g., Craik, 1977; Crook et al., 1986). More detailed memory systems have been described expanding on the short-term/long-term distinction. Specifically, immediate or primary memory (the initial stage of short term memory measured by digit span, or recall of 5 to 7 items), semantic memory (part of long term memory consisting of recollection of facts, rules), and procedural memory (also part of long term memory, can be described as 'knowing how', e.g., playing chess), have generally shown a relative sparing of function with age (e.g., Huppert, 1991; Kaszniak, Poone & Riege, 1986). Conversely, recent, or secondary memory (short term memory that is more complex than 5 to 7 items), episodic memory (memory dated in time and place; measured by free recall of supra

span lists, paired associates, and serial rate learning), and working memory (an expansion of short term memory; ability to hold information while simultaneously manipulating it) have shown a modest decline with age (e.g., Ardila & Rosselli, 1989; Poon, 1985).

Although generalizations of declining cognitive functioning relative to younger subjects have been well documented in the healthy elderly, some researchers have felt that 'these generalizations obscure the inter-individual variability' (Rediess & Caine, 1996, p. 112) and as such heterogeneity of cognitive aging is beginning to draw serious attention. Although measures of central tendency continue to support age-related declines in performance, some researchers have provided evidence that a significant number of older subjects fall outside this range, and are able to perform within the range of younger subjects, (Weintraub, Guinessey & Mesulam, 1994) For example, a study comparing the performance of under 35- to over 75-year-old physicians indicated the "top ten" scoring subjects in the over 75 group outperformed a large number of subjects in the under 35 group (Weintraub, Powell & Whitla , 1994). Additionally, individuals who have reached the category 'oldest old' have been reported as performing both cognitively and neuropathologically better than subjects 10 and 20 years their junior (Wernicke & Reichies, 1994). These findings of spared cognitive function up to and including the oldest old category has prompted a growing interest in examining characteristics of this population (e.g., educational and occupational history, lifestyle factors, medical history etc.).

Executive Function in Optimal Aging

A review of the literature examining executive function in the course of normal aging reveals a general consensus of a mild executive function decline with age (e.g., Brennan et al., 1997, Salthouse et al., 1996). Studies examining age differences on tests measuring 'crystallized' versus 'fluid' abilities have consistently found a decline in the latter, with sparing of function in the former. Fluid abilities have been described as "requiring manipulation of materials in novel ways, requiring new inferences, and relying on abstraction from the information given" (Parnetti et al., 1994). Based on this definition, fluid ability relies on executive functioning. Tasks of cognitive flexibility have also been found to undergo mild decline in normal elders (LaRue, 1992) as evidenced on the Wisconsin Card Sorting Test (WCST) and the Trail Making Test (TMT). In a recent examination of executive function skills in older adults, Brennan and associates (1997) compared the performance of young adults, young elderly (mean age=65 years), and older elderly individuals (mean age =75 years) on the Tower of Hanoi, a task of executive function involving planning, and working memory. Results indicated similar executive capacities among the young adult and young elderly participants in comparison with their older elderly counterparts on the simple 3-disk phase. However, on the more demanding 4-disk phase where problem complexity increased, young adults showed superior performance to those of both young elderly and older elderly subjects. According to the authors, these findings support the hypothesis that executive function capacity declines with increasing age. Similar results were found by Mejia and his colleagues (Mejia, Pineda, Alvarez & Ardila, 1998) who examined 60

older, healthy subjects on several measures including two executive function tests: the WCST and verbal fluency. Age was found to negatively correlate with the test scores, most significantly on semantic verbal fluency, indicating that as age increased, scores generally tended to decrease.

Some evidence has been gathered supporting the notion of sparing of executive functions with age (Salmoni, Richards & Persinger, 1996; Willis, Yeo, Thomas & Garry, 1988), and as such the association between the two variables remains somewhat unclear. It is safe to say that aging does not necessarily affect executive function, although in specific cases, it does. As a result, mild age-related executive function decline is generally accepted among clinicians in the field.

A current hypothesis that effectively encompasses the various behavioural observations in aging is the idea that some cognitive operations associated with the frontal lobes are particularly vulnerable to the effects of age (Van Gorp & Mahler, 1990). Several converging lines of evidence support this notion. For example, reductions in frontal lobe blood flow are noted with advanced age (Welsh-Bohmer & Hoffman, 1996). Further, neuropathological examination shows selective cell loss in the superior frontal, precentral and superior temporal gyri in the aged brain (Creasy & Rapoport, 1985; Haug et al. 1983). Further, frontal lobes undergo the earliest and most significant amount of cell loss during aging (Coffey et al., 1992; Cowell et al., 1994). The integration of neuropsychological and neuroanatomical evidence suggests that frontal regions are the last to develop during maturation, and in later life, the first to undergo involution (Hanninen & Soininen, 1997).

In summary, there is general consensus today among researchers in the field that as individuals age, a mild reduction in cognitive processes ensues particularly in the areas of certain memory abilities (predominantly short-term memory), executive function, and speed of information processing. Further, this decline occurs against a background of relatively spared verbal abilities and verbal intellectual function. However, many mediating variables appear to affect the rate and degree to which persons will experience decline in the above noted areas. Good overall health, high education, and high verbal IQ tend to reduce the discrepancy in scores between young and old persons. Additionally, conclusions are often influenced by the types of measurements used, the cognitive areas assessed, certain psychometric considerations (e.g., practice effects), and various personality and socioeconomic variables.

Alzheimer's Disease

Alzheimer's disease (AD) is a progressive dementing disorder which comprises approximately two-thirds of all dementia cases (Katzman & Jackson, 1991) making it the leading cause of dementia in older individuals (Villareal & Morris, 1998). The number of AD cases is expected to grow during the twenty-first century due to the increased number of individuals living beyond 65 years of age such that by the year 2021, more than half a million Canadians will be affected (Canadian Study of Health and Aging Work Group, 1994). Approximately 10% of individuals over the age of 65 years are diagnosed with AD (Testa, Brumback, Baik, Leech & Cannon, 1998), with an age-related prevalence ranging from 3% among individuals 65-74 years to 19% among

individuals 75-84 years, and 47% among individuals older than 85 years (Bachman et al., 1993).

Clinical Course

Deficits in recent memory are typically the earliest sign of AD (e.g., Linn et al., 1995). Besides memory loss, AD is characterized by neuropsychological deficits in language, learning, judgement, abstract thinking, visuospatial skills, and praxis. AD progresses by stages, from early, mild forgetfulness to severe dementia. AD may involve psychiatric features such as delusions, hallucinations, depression, and changes in personality and sleep patterns. Neurologically, AD may present with motor symptoms such as extrapyramidal signs, myoclonus, rigidity, or snout reflex. AD may also present in combination with other medical conditions such as cerebrovascular disease (AD and CVD together have been termed 'mixed dementia') thus rendering a more complicated diagnostic picture, and a more difficult case in terms of treatment and management. The duration of AD from time of diagnosis to death can be 20 years or more though the average length is thought to be in the range of 4 to 8 years (National Institute on Aging (NIA), 1998).

Numerous subgroups of AD have been proposed based on clinical heterogeneity, some of which include typical, early and late onset (presenile/senile), benign (slow progression), rapid progression, behavioural, myoclonic, extrapyramidal, sporadic, familial, and AD in trisomy 21 (Laakso, 1996). However, the existence of these subtypes is unclear and to date remains somewhat controversial, yet

identification of AD subtypes may have considerable impact on both the patient's response to treatment and evaluation of the disease progression.

Risk Factors for the Development of AD

Advancing age is the single most important risk factor for the development of AD (Jacobs & Schofield, 1998). Results of a collaborative study in Europe reported AD prevalence rates (per 100,000) of 15 for 50-59 age group, 340 for 60-69 age group, 2910 for 70-79 age group, 10740 for 80-89 age group, and 28040 for 90-94 age group (Rocca et al., 1991). In Helsinki, the prevalence of dementia at ages 75, 80, and 85 has been reported to reach 4.6%, 13.1%, and 23.3% respectively (Juva, Sulkava, Erkinjuntti, Valvanne, & Tolvis, 1993). An increase in dementia prevalence from 1.5% in individuals aged 65-69 years, to 22% in people aged 85-89 has been reported on the basis of a meta-analytic study (Jorm, Korten, & Henderson, 1987), indicating roughly a doubling of every 5 years. These rates have been confirmed by subsequent meta-analytic studies (Skoog, Nilsson, Palmertz, Andreasson & Svanborg, 1993). Somewhat higher rates have also been reported indicating by age 85 approximately half of all individuals exhibit symptoms of AD (Bachman et al., 1993, NIH, 1998). Conclusions from these studies are simply that the older a person is, the more likely he or she is to develop AD. Some researchers have even postulated that the disease is inevitable in those who live long enough, and as such is considered 'aging-related' (e.g., caused by the aging process itself) although this hypothesis has not been universally accepted. Alternatively, some investigators have suggested that the

incidence of AD may begin to level off in the very old (Mortimer, Schuman & French, 1981).

Individuals with less education are reported to have a higher prevalence of AD (Katzman, 1993; Korczyn et al. 1991). In contrast, individuals with high education appear to have a 4-to-5-year delay in the development of symptoms and a much slower course (Lopez & Becker, 1994). This finding has spurred much research into the investigation of 'protective' factors possibly related to lifestyle patterns in early adulthood. One theory that has gained considerable attention is that individuals with high premorbid intellectual or education level evidence a 'neural reserve' which acts as protection against dementia. Advanced education and occupational attainment has been postulated to provide a reserve that would allow an individual to cope longer before AD is clinically expressed. The well-known 'nun' study conducted by Snowdon et al. (1996) examined the writing style of 93 nuns who had 60 years earlier written autobiographies. At the time of the study 14 of the nuns had died. After brain autopsy, five of the nuns were found to exhibit Alzheimer tangles and plaques. Examination of the essays of those same 14 nuns revealed nine that were judged to be intellectually rich, packed with ideas, and grammatically complex, while the other five were considered idea-poor and grammatically simple. Although evaluators were blind to whose essay they had judged, the five considered poorly written belonged to the five nuns diagnosed with AD. Despite excitement over these findings and their implications, the study has since been criticized on several methodological grounds (e.g., subjectivity of evaluation, small sample size). Further, in the Framingham Study

(Cobb et al., 1995) and the Mayo Clinic Rochester Epidemiology Project (Beard et al., 1992), the incidence of AD was not affected by educational attainment. These findings suggest that even though an association between education and development of AD may be evident, no conclusions can as yet be drawn on the exact nature of the relationship.

Our understanding of genetic risk factors has undergone major advances over the past 5 years (Jacobs & Schofield, 1998). In brief, epidemiological studies have shown that family history of dementia and of Down's syndrome or mental retardation is a robust risk factor for development of AD. Estimates of cumulative risk in the first-degree relatives of probands with AD have ranged from 17 to 67% (Lautenschlager et al., 1996). Specifically, the risk for development of AD has been reported at five times greater in children of parents who both developed the disease. Investigation of AD susceptible genes led to the discovery of a strong association between the $\epsilon 4$ allele of the apolipoprotein E (ApoE) on chromosome 19 and a significant proportion of cases of late-onset AD (Corder et al., 1993; Poirer et al., 1991; Saunders, Strittmatter & Schmechel, 1993). The three alleles ($\epsilon 2$, $\epsilon 3$, $\epsilon 4$) of the ApoE gene are combined in the general population in six different genotypes, either heterozygous (ApoE 2/3, 4/3, 4/2), or homozygous (ApoE 2/2, 3/3, 4/4). ApoE $\epsilon 4$ is considered the first identified genetic susceptibility factor for late-onset familial AD (Strittmatter, Saunders & Schmechel, 1993) and late onset sporadic AD (Kuusisto et al., 1994; Saunders et al., 1993). It manifests in a dose-dependent manner in that the risk of AD increases with an increasing number of $\epsilon 4$ alleles (Corder et al., 1993). While the $\epsilon 4$ allele is

considered a risk factor for AD, the $\epsilon 2$ allele seems to have a protective effect. It has been reported that risk for AD in ApoE 2/2 individuals is about 20%, which increases to a 47% risk in ApoE 3/4 individuals, and a 95% risk at age 75 in individuals who are ApoE 4/4 (Corder et al., 1993; Roses et al., 1994). Further, mean age at onset has been shown to decrease from 84 to 64 years with increasing number of ApoE $\epsilon 4$ alleles (Abate, Ferrari-Ramondo, & Di Iorio, 1998). Though numerous reports have supported the association between ApoE $\epsilon 4$ and the increased risk of AD the predictive value of ApoE genotyping as a screening test is limited: about one half of AD patients do not have the $\epsilon 4$ allele, and many ApoE $\epsilon 4$ carriers do not develop dementia (Myers et al., 1996). In addition, the ApoE $\epsilon 4$ is not specific for AD as its presence has been associated with an increased risk of vascular dementia (Frisoni et al., 1994; Isoe et al., 1996; Myers et al., 1996), diffuse Lewy body disease (Arai et al., 1994), Parkinson's Disease (Helisami et al., 1996), and frontal dementia (Helisami et al., 1996). As such, it alone is not sufficient as a diagnostic tool. Further the risk associated with ApoE may lose its significance after a certain age and may no longer be a risk among the oldest old (Hyman et al., 1995; Sobel et al., 1995).

The relationship between gender and risk for AD is unclear (Jacobs & Schofield, 1998). Several studies have reported higher rates of AD among women (Zhang et al., 1990) whereas others have found no difference in the risk of AD by gender (Letenneur et al., 1994, Paykel et al., 1994). In general, conclusions are often offered that at all ages, women have an increased risk than men, and by age 93 the risk may be as high as 13%. However, since the risk for the development of AD increases with age,

women, who have a longer life expectancy than men, are disproportionately affected. Data related to race or ethnicity are scarce. One study worthy of mention was performed by Tang and colleagues (1998) who compared Caucasians with African Americans and Hispanics, all living in New York. It found that the latter populations were at increased risk for development of AD than the Caucasian population even in individuals without the ApoE ϵ 4 allele. The cumulative risk for getting AD before age 90 was 4 times higher among African Americans and 2 times higher among Hispanics. The implications of these results remain unclear.

History of head injury has been examined as a risk factor for AD. Early case studies revealed positive head injury history with loss of consciousness as nearly five times more common in AD cases than in hospital and community controls (Mortimer et al., 1983). Subsequent studies concurred with these findings, particularly if the trauma occurred within the 10 years preceding dementia onset (Mortimer et al., 1991). It is notable though that several studies failed to find an association between head injury and AD (Katzman et al., 1989; Williams, Annerggers, Kokmen, O'Brien, & Kurland, 1991). In a recent study, an association between head trauma and increased risk for AD was found in only carriers of the ApoE ϵ 4 allele (Mayeux et al., 1995), thus suggesting the association between the two variables may be modified by ApoE genotype.

Metals such as aluminum, zinc, and mercury such as found in fillings have been examined for their potential effect as risk factors. However, in most instances the association between these metals and the development of AD has been deemed

inconclusive or negative (Abate et al., 1998) and thus concern has, to a large extent, abated.

Depression has been identified as a risk factor for dementia. Evidence from a recent study (Devanand et al., 1996) found that among non demented elders, those depressed were nearly three times more likely to become demented over a 2.5 year follow up. Earlier research indicated that a history of medically treated depression was more common in AD patients than in healthy control subjects (Kokmen et al., 1991).

Oxidative damage as a result of free radicals (a molecule with one unpaired electron in its outer shell) has long been proposed as theory of aging, and may constitute a risk for development of AD. Evidence was found of a powerful oxidant called peroxyntirite in AD brain tissue, which was suspected of damaging neurons, while no evidence of marked presence of this agent was found in control subjects without AD (Smith et al., 1997). Free radicals can be damaging to the body because they are extremely reactive. As such, it has been suggested that their harmful effect can be neutralized through the use of anti-oxidants such as vitamin E, vitamin C, beta carotene, selenium, and ginkgo biloba. Several studies are currently underway investigating the role of free radicals, and the potential benefit of anti-oxidants in the process of AD.

Diagnosis of AD

Various clinical, biochemical, imaging, and genetic factors have consistently failed as diagnostic instruments, and as yet no marker for AD has been found. The

diagnostic process of AD, therefore, remains essentially a clinical one (Mohr, Dastoor & Claus, 1999). With the introduction of standardized clinical criteria (APA, 1994; McKhann et al., 1984) diagnostic accuracy rates of AD have been reported at 85% (Berg et al., 1998) to 90% (NIA, 1998) as confirmed later at autopsy. Although these rates are encouraging, the early, mild form of AD remains a diagnostic challenge. The National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS/ADRDA; McKhann et al., 1984) provides three levels of diagnostic confidence (see Appendix A).

According to these criteria, "probable" AD represents the most confident level of antemortem diagnosis and is diagnosed when subjects present with the typical course, including gradual onset between 40 and 90 (most will occur after age 65), deficits in two (or more) areas of cognition, the nature of which is progressive, and no disturbance of consciousness. Probable AD is supported by progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia). Impaired activities of daily living and altered patterns of behaviour, along with a family history of similar disorders also support the diagnosis. Finally, laboratory results of normal lumbar puncture, normal EEG, and evidence of cerebral atrophy on computerized tomography (CT) scan with progression documented by serial observation support the diagnosis. "Possible" AD is diagnosed when the patient presents with an atypical course of dementia or when there is a coexistent potentially dementing illness although AD is thought to be the primary cause of the progressive dementia. "Definite" AD is reserved for dementia cases when there is

confirmation either by biopsy or autopsy of the characteristic senile plaques and neurofibrillary tangles in the cortex.

NINCDS-ADRDA guidelines are compatible with the revised DSM-IV criteria (see Table 2). According to DSM-IV criteria, AD is diagnosed when there is a gradual progression of memory impairment and at least one other area of cognition both of which are considered a decline from previous function and sufficient to interfere with daily function. Both NINCDS/ADRDA and DSM-IV criteria apply in the absence of systemic disorders or other brain diseases that in and of themselves could account for the progressive deficits in memory and cognition.

Table 2

Clinical Diagnostic Criteria of AD

<i>NINCDS-ADRDA Criteria for Probable AD (McKhann et al., 1984)</i>	<i>DSM-IV Dementia of the Alzheimer's Type (APA, 1994)</i>
<p>Diagnostic Criteria for Probable AD include:</p> <ul style="list-style-type: none"> • Dementia established by clinical examination, documented by objective testing, and confirmed by neuropsychological tests • Deficits in two or more cognitive areas • Progressive worsening of memory and cognitive functioning • No disturbance in consciousness • Onset between 40 and 90 years of age • Absence of systemic disorders or other brain diseases that could account for the progressive deficits in memory and cognition <p>Diagnosis for Probable AD is supported by:</p> <ul style="list-style-type: none"> • Progressive deficits in language (aphasia), motor skills (apraxia) and perception (agnosia) • Impaired activities of daily living (ADL) and altered behaviour • Family history of similar disorders • Consistent laboratory results (e.g., cerebral atrophy on CT) 	<ul style="list-style-type: none"> • Development of multiple cognitive deficits manifested by both: <ol style="list-style-type: none"> 1. memory impairment and 2. at least one of the following: <ul style="list-style-type: none"> aphasia apraxia agnosia executive dysfunction • Cognitive deficits noted above each cause significant impairment in social or occupational functioning, and represent a decline from a previous level. • Course is characterized by gradual onset and continuing cognitive decline • Cognitive deficits not due to any other causes of dementia (medical, neurological, psychiatric), or better accounted for by other Axis I disorder

Adapted from Villareal & Morris (1998)

Based on the definition of AAMI, the memory deficits present are similar in nature to those found in AD. Further, diagnostic criteria of AAMI require several similar inclusion/exclusion qualifications of AD such as the gradual onset (as opposed to sudden onset as evident in vascular dementia), of cognitive impairment. Though impairment in AD is more pronounced and must substantially affect functioning, similar impairment is apparent in AAMI though to a lesser extent, as outlined by the requirement that deficits must be reflected in everyday living. Exclusion criteria are

essentially similar for the two disorders. With the above noted similarities in defining criteria, a potential link between the two processes is clear. Thus, involvement of a second cognitive domain in the AAMI population such as executive function, which is evident in early AD, may provide further evidence of a relationship between the two processes. Specifically, if involvement in more than one area of cognition is evident in AAMI, it would fulfill to some further degree the criteria for “possible” or even “probable” AD according to NINCDS-ADRDA criteria, and would also fulfill criterion 1 in the DSM-IV criteria. As such, AAMI may not be merely a mild memory disorder as previously conceptualized. Thus, the conception of AAMI as a benign construct would have to be revisited, perhaps as one which harbours a rather malignant course.

Preclinical Markers in Diagnosing Alzheimer’s Disease

Although to date no specific test or marker has been found that is sensitive to very early AD, progress has been encouraging, due to the fact that advances have occurred despite the fact that no cellular or universally accepted animal model for AD exists, thus making the disease inaccessible to most methods of experimental research (Mandelkow & Mandelkow, 1994).

Most recently (Solomon et al., 1998), a seven minute diagnostic screening test for AD has been developed for use in “real-world” primary care setting. The test is reported as 90 percent accurate in differentiating between individuals with “normal” memory loss associated with aging, and those with dementia characteristic of AD. The

screen is comprised of four components: orientation to time, enhanced cued recall, clock drawing, and verbal fluency. The utility of this test however, has yet to be thoroughly evaluated.

Another possible method for detecting AD before symptoms develop involves the use of single photon emission computed tomography (SPECT) scanning. Johnson and co-workers (1998) examined a large sample of individuals experiencing memory problems and were able to correctly identify 80 percent who would later go on to develop AD. This method however, is restricted in its application as the availability of SPECT scanning equipment is limited. These findings, though exciting, require replication and further study.

Magnetic resonance imaging (MRI) studies examining the size of various structures in the brain have revealed positive findings in the early diagnosing of AD. In particular, volumetric measurement of the hippocampus has been found to be quite sensitive. Convit et al (1997) report correctly discriminating between mild cognitive impairment and healthy individuals for 74 percent of cases studied. Similar findings were reported by Laakso (1996) who found hippocampal atrophy a highly sensitive indicator in early AD, but not significantly affected by age or AAMI. This tool was deemed useful by the authors in detecting, or rather excluding AD and differentiating it from benign memory impairment. Difficulty arises though as hippocampal atrophy is not unique to AD dementia (Laakso et al., 1996). Subjects with vascular dementia, Parkinson's Disease (PD) with dementia, and PD without dementia evidenced smaller hippocampal volumes compared to normal elderly control subjects in the above noted study. The overlap of

findings constitutes a potential limitation of this diagnostic tool.

When Alois Alzheimer first described AD in 1907 he observed what are today considered characteristic pathological features of the disease: the accumulation of senile plaques (SP) and neurofibrillary tangles (NFT) in the brain. These lesions are believed to be responsible for the significant degree of cell loss which has been universally found in the AD brain. Various regions of the brain are affected by cell loss, including the hippocampus, the lamina II of the entorhinalis, the basal forebrain nuclei, the locus ceruleus, and the cerebral cortex (Bondareff, 1995). NFT are made of submicroscopic paired helical filaments (PHF). Somewhat recently, PHF were shown to be composed mostly, if not exclusively, of tau protein (Harrington & Wischik, 1994). Tau is a microtubule-associated protein that normally stabilizes microtubules and promotes their assembly, however, it is thought that abnormal phosphorylation (hyperphosphorylation) of the tau protein is a feature of AD. Tangles are not unique to AD but are also found in progressive supranuclear palsy (PSP), encephalitis lethargica, post-encephalitic parkinsonism, cerebral trauma, and dementia pugilistica (Tomlinson, 1992). Like the NFT's, senile plaques contain PHF, although they also contain fibrils of β -amyloid. β -amyloid is an insoluble protein derived from a larger transmembrane amyloid precursor protein (APP) which is encoded for by a gene on chromosome 21 (Ashall & Goate, 1994; Muller-Hill & Beyreuther, 1989). Several varieties of Alzheimer plaques have now been identified including diffuse amyloid plaques (Gooch & Stennett, 1996), mature neuritic plaque, primitive plaque, and hypermature plaque (Testa et al., 1998).

The severity of cognitive deterioration observed in AD has been found to correspond to the extent of cell loss. In normal aging, cerebral neuronal loss can reach up to 30% by the age of 60 due to the wear and tear of normal life. However, this loss is substantially smaller than the 80% reduction necessary to produce clinical symptomatology in AD (Testa et al., 1998). The diagnosis of AD requires the demonstration of certain numbers of senile plaques, with or without neurofibrillary tangles. In other words, the presence of NFT is not required for the diagnosis to be made, simply the presence of age related density of the senile plaques is sufficient for a diagnosis of AD (Khachaturian, 1985; Mirra et al., 1991, 1993). However, certain studies have shown that the number of NFT may provide a better correlate of cognitive decline than β -amyloid pathology. For example, studies have shown that individuals in their 80's may have sufficient numbers of neocortical SP to support a diagnosis of AD, while their level of cognitive function does not support the diagnosis (Harrington, Mukaetova-Ladinska, Perry, Roth, & Wischik, 1995). These results further suggest that plentiful numbers of SP's are present for some time before the clinical symptoms of dementia appear. Support for this last proposition also arises in part from findings that persons with Down's syndrome develop the histological lesions of AD during young adulthood, whereas dementia does not begin until later years (Mann & Esiri, 1989; Motte & Williams, 1989).

The difficulty with biological markers is that they have been plagued by the finding of significant overlap in the data between patients with AD and healthy, non demented older individuals. Clinically normal elderly individuals may have significant numbers of

plaques and tangles. Consequently, neuropathological criteria must be supplemented with the requirement that the patient also have a clinical presentation consistent with AD.

Parallel to (or as a consequence of) the pathological features described above, various neurotransmitter systems are altered in AD. The cholinergic hypothesis of AD is well known as an explanation of the memory dysfunction of AD. Choline acetyltransferase (ChAT) activity in the hippocampal and limbic cortical areas is reduced by as much as 60-90% and is associated with a decrease of acetylcholine (ACh) synthesis, and reduced acetylcholinesterase activity (AChE) (Perry et al, 1978). While it is clear that acetylcholinesterase (AChE) is reduced in the cerebrospinal fluid of AD subjects, the variance of measured AChE activity among individuals with AD is large, resulting in a broad distribution of values that overlaps significantly with the distribution for normal aging (Eible, 1990). With respect to other neurotransmitters and enzymatic abnormalities found in AD (e.g., reduced somatostatin, serotonin), no test is available as of yet that is sufficiently sensitive or specific to be used in the early diagnosis of AD (Gertz, 1995).

Findings particularly promising in enhancing diagnostic reliability come from the study of genetics (for a review, see Plassman & Breitner, 1996). Early onset AD has been associated with several genetic mutations on chromosomes 1 (presenilin 2; Sherrington et al., 1995), 14 (presenilin 2; Rogaev et al., 1995), and 21 (β -amyloid precursor protein gene β -APP; Goate et al., 1991). The β -APP gene of chromosome 21 is thought to be responsible for only a few cases of early onset familial AD, and the

two located on 1 and 14 are likely responsible for the majority of early onset familial cases of AD (Sherrington et al., 1995). Genetic tests are available for the rare autosomal dominant forms of AD linked to chromosomes 14 and 21, though these tests are applicable in less than 1% of AD cases seen in clinical practice (Welsh-Bohmer & Ogrocki, 1998).

An increased risk factor for late-onset familial and late onset sporadic forms of AD is associated with the ApoE ϵ 4 allele on chromosome 19 (Strittmatter et al., 1993). It is reported that 60-75% of these AD cases carry at least one copy of the ϵ 4 form of the gene (Hyman et al., 1996), though other studies have indicated only about 45- 50% of these AD patients have the ϵ 4 allele. The ApoE gene is further modified by factors such as female sex, age, and ethnicity (Farrer et al., 1997; Palumbo et al., 1997). ApoE genotyping has been conceptualized as a new paradigm of genetic testing, and as such recent investigations examining sensitivity, specificity, and positive predictive value have been carried out. Results indicate the predictive value of the ϵ 4 allele for the diagnosis of familial AD was 97% and added to diagnostic confidence in over two-thirds of the AD patients assessed (Saunders et al., 1996; Welsh-Bohmer et al., 1997). A significant drawback in genetic markers is that causative mutations only account for fewer than 5% of all AD cases (Villareal & Morris, 1998). However, genetic information may prove useful in diagnostically challenging situations (e.g., atypical symptom presentation; very early disease) (Welsh-Bohmer & Ogrocki, 1998). As the full realization of the role(s) played by genetics remain to be identified, and the effect of environmental factors probably contribute to the heterogeneity that is observed within

this disorder, genetic markers as of yet are not considered a sufficient diagnostic marker for early AD (Marco, 1995).

Several other potential biological markers have been investigated in the study of AD including amyloid deposits in the skin (Joachim et al., 1989), dystrophic neurites in olfactory epithelium (Talamo et al., 1991), and pupil dilation in response to a dilute solution of tropicainamide (Scinto et al., 1994). These tests, however, have limited specificity and have not qualified as biological markers for AD.

Though several exciting advances have been made in the diagnostic sensitivity of early AD, to date, no single test is adequately able to distinguish very early AD from normal aging, or AAMI. Moreover, the clinical diagnostic utility of these advances remain unproven. Though it may eventually turn out that the combination of several tools such as the use of ApoE information, neuropsychological information, and neuroimaging changes hold promise for enhancing the accuracy of early diagnosis of AD, to date the most reliable and clinically proven diagnostic tool in the identification of AAMI, and early AD remains purely a clinical one.

Preclinical Cognitive Markers

It is well established that subtle cognitive impairment can be present for several years before the clinical diagnosis of probable AD is made (Linn et al., 1995). The period between disease onset and subsequent clinical diagnosis has been termed the "preclinical phase" of AD. Attempts to detect preclinical neuropsychological measures that will accurately distinguish early AD from healthy elderly controls have produced

varied results. One study observed that a group of very mild AD subjects had psychometric scores that overlapped both with those of samples of mild AD and with those of healthy controls (Storandt & Hill, 1989). The authors concluded that it was not possible to separate the groups cleanly based on either psychometric performance or clinical assessment of mental status.

Subsequent studies, however, have produced more positive findings with respect to early diagnosis of AD. For example, a recent longitudinal study examining normal elderly subjects and subjects with AD found that on two-year follow-up, 6 of the 50 normal elderly had become cognitively impaired (Flicker, Ferris, Reisberg, 1993a). The authors examined the baseline cognitive test data of these 6 subjects as potential psychometric predictors of dementia in the healthy elderly. Results indicated several of the memory tests, particularly measures of recall and recent memory, a language test, and a test of psychomotor speed and manipulation were able to discriminate at baseline between the 6 subjects who experienced a decline after 2 years compared to those who did not. As deficits in recent memory, language, and psychomotor speed are well documented in AD (Bondi et al., 1994; LaRue, 1992; Youngjohn, Larrabee, & Crook 1992), tests used in the above mentioned study assessing these areas were felt to be good predictors of ensuing dementia. These results have been replicated in a subsequent protocol (Morris et al., 1995) examining psychometric performance of very mild, or questionable AD (Clinical Dementia Rating (CDR) score of 0.5). The three measures that were most sensitive in distinguishing these subjects from controls were: a naming test, a measure of recent memory, and a measure of psychomotor speed.

These findings are congruent with earlier work suggesting that recent memory tests exhibited the best predictive value of dementia in addition to language and psychomotor speed (Flicker et al., 1993a).

Executive Function in Early AD

There is growing evidence, particularly from imaging studies (Chase, Burrows & Mohr, 1987; Grady et al., 1988), which suggests a considerable involvement of the frontal cortex in AD. Some researchers have proposed that AD subjects with greater frontal hypometabolism evident on positron emission tomography (PET) scanning constitute a subgroup of AD characterized by a relatively rapid clinical progression rate (Mann, Mohr, Gearing & Chase, 1992). However, until recently, it was still unclear whether executive dysfunction is integral to AD in the early phase, or if it is a feature more characteristic of the latter stages of the disease. Several recent studies have suggested that in addition to the pivotal role memory plays as a cognitive preclinical marker of AD, executive function may also be implicated in very early stages of the disease. In an attempt to ascertain preclinical cognitive markers for AD, a group of researchers followed a large sample of community dwelling subjects longitudinally and studied them for the development of AD (Katzman & Aronson, 1989). Results indicated that early problems on measures of mental status and verbal fluency (a measure of executive function) predated the subsequent diagnosis of AD by 2 to 5 years. Verbal fluency was also found to be an early manifestation of AD in a study examining cognitive performance between AD and Frontal Lobe Dementia (FLD) (Pasquier,

Lebert, Grymonprez & Petit, 1995). Although AD and FDL subjects had significantly lower verbal fluency scores than controls, no group differences were found on this task between the two patient groups.

In a longitudinal PET study of very mild AD subjects, researchers administered tests of executive function (Trail Making Test, Stroop Test, Porteus Maze Test, and Raven's Progressive Matrices), memory, language, and spatial function (Grady et al., 1988). Results indicated both impaired memory and executive function early in the course of the disease for some subjects, whereas in others normal executive function was observed when a memory deficit was clearly evident. For all subjects with impairments in executive function, dysfunction appeared prior to the onset of language and visuospatial deficits.

In an attempt to study executive function in patients with very early AD, Binetti and associates (1996) found that 7 of their 25 subjects showed an impairment in executive function as measured by the verbal fluency test, the Stroop test, the Wisconsin Card Sorting Test, and the release from proactive interference test. To examine whether the presence of executive dysfunction could be related to variables such as age, education, and duration of illness between the 7 subjects who evidenced executive impairments and the remaining 18 who did not, the two groups were compared. No significant differences between the groups were found. The authors concluded that executive dysfunction may be an early manifestation of AD.

In a recent study examining memory deficits in AD based on the concept of working memory (Becker, Lopez & Boller, 1994), researchers were able to identify two

subgroups of patients. The first had profound amnesic syndrome and normal executive functioning, and the second had a dysexecutive syndrome with normal secondary (or long term memory). A subsequent longitudinal analysis (Lopez & Becker, 1994) revealed that the pattern of decline of these groups differed, with the dysexecutive patients demonstrating a dramatic loss of secondary memory functions over a one year period, and a more rapid rate of decline as measured by the Mini Mental State Examination indicating that in this group, early executive functions preceded memory impairment.

Results of this study support earlier work conducted by Mann and colleagues (1992) who examined rate of disease progression and neuropsychological profile in AD. Results indicated that the two groups (divided on the basis of progression rates of symptoms) were indistinguishable on verbal or visuospatial function tasks, but the more rapidly deteriorating group had significantly greater impairment on executive function tasks (e.g., Word Fluency, Ego State Inventory, Mental Control).

In summary, in addition to impairments in memory, language, and psychomotor speed, executive dysfunction appears to be an early cognitive manifestation of the disease course. Thus, it is important to study executive function in a potential high risk group of AD dementia such as AAMI.

Age Associated Memory Impairment

The construct of AAMI was first proposed in 1986 by a National Institute of Mental Health (NIMH) Work Group on Aging and Memory which was convened to examine cognitive function in the elderly. An earlier concept had been proposed by Kral (1962)

who coined the term 'benign senescent forgetfulness', though this construct lacked precise definition. The NIMH work group coined the term AAMI "to describe the memory loss that may occur in healthy elderly individuals in the later decades of life" (Crook et al., 1986). The authors aimed to distinguish the sufferers from those who experienced no such loss and from those whose impairment is associated with other specific disease states (e.g., AD). To satisfy inclusion criteria, subjects must be over 50 years of age and have complaints of gradual onset of memory loss for everyday events, adequate intellectual function, and memory performance more than one standard deviation below the mean established for young adults on a standardized test of secondary (recent) memory. The diagnosis is excluded by any medical or neurological disorder, major psychiatric illness, or drug consumption that may be responsible for the cognitive changes present (Crook et al., 1986; see Table 7).

Prevalence rates of AAMI have produced inconsistent data. Some researchers have estimated that AAMI might affect most of the population over 50 years of age (McEntee & Crook, 1990). When strict criteria are not applied prevalence rates vary considerably. For example, when applying only memory test cut-off scores without any exclusion criteria, prevalence rates ranged from 39% for 50-59 age group to 85% for individuals over 80 years (Larrabee & Crook, 1994). Additionally, in the absence of assessment of subjective complaint, Smith and co-workers (1991) found prevalence rates of 77% to 98% for younger and older groups respectively. Based on these findings, it is easy to conclude the AAMI criteria are unreliable. However, adherence to the original criteria proposed produces significantly lower prevalence rates. For

example, in a large scale epidemiologic study (Koivisto et al., 1995), prevalence rates were reported at 38.4% when complete AAMI criteria were employed. These rates are in keeping with those reported by Lane and Snowdon (1989) at 34.9%.

Proposed Diagnostic Classifications

AAMI has generated a significant amount of controversy in the literature. As a result of dissatisfaction over the construct of AAMI and its criteria, several investigators have introduced new terms and definitions to categorize older individuals with cognitive decline falling short of dementia. However, instead of providing a clearer conceptualization, the vast assortment of diagnostic categories which now occupy the literature often results in significant confusion. Further, as each term provides unique requirements with respect to inclusion criteria, comparison of subject groups across research studies proves to be a difficult task. Currently, readers can find the following terminology in the literature: 'very mild cognitive decline' (Reisberg, Ferris, DeLeon & Crook, 1982), 'mild forgetfulness' (Reisberg et al., 1986), 'aging-associated cognitive decline' (Caine, 1993; WHO, 1992), 'mild cognitive impairment' (APA, 1987; Gomez de Caso, Rodriques-Artalejo, Claveria & Coria, 1994; WHO 1992), and 'cognitively impaired not demented' (Ebly, Hogan & Parhad, 1995; Graham et al., 1997). It has also been suggested (Blackford & LaRue, 1989) that AAMI be divided into 'late-life forgetfulness' and 'age-consistent memory impairment'. The DSM-IV has introduced in its section "Other conditions that may be a focus of clinical attention" the category for 'age-related cognitive decline', however specific diagnostic criteria are lacking. The

research criteria for 'mild cognitive disorder' (WHO, 1993), and 'mild neurocognitive disorder' (DSM-IV, 1994) have also been introduced, although these two diagnoses require the presence of a medical condition known to cause cerebral dysfunction and are not restricted to older subjects.

Criticisms of AAMI

While many studies have supported the theoretical construct of AAMI (Buschke & Grober, 1986, Lane & Snowdon, 1989; Youngjohn et al., 1992), numerous clinicians have called into doubt the usefulness of the AAMI diagnosis and suggested revisions of the defining criteria in order to enhance the reliability of the diagnosis (e.g., Blackford & LaRue, 1989; Caine, 1993). Criticism has ranged from conceptual challenges to methodological criticism, to what some authors (Crook, 1993) have described confused and generally irrelevant commentary (i.e., Rosen, 1990). The principal criticism of conceptual significance relates to the inclusion criteria requiring subjects to score at least one standard deviation below the mean established for *young adults* (rather than comparing their performance to age matched peers). The initial premise for requiring memory performance to be compared to younger adults is that it would more adequately capture the decline in performance than would comparison to an age matched group who may exhibit age related memory changes, albeit not as severe as that seen in AAMI.

Diagnostic rates of AAMI are reported by critics to differ depending on the memory test selected and the number of tests employed (e.g., Smith et al., 1991). Further,

critics argue, AAMI relies on classifying individuals as memory impaired based on the results of a single memory test rather than on a consistent pattern of memory deficit. As a result, the criteria have been said to be vulnerable to unreliability and may include a high number of false positives. As such AAMI has been considered too broad and over-inclusive an entity (Bamford & Caine, 1988; Levy, 1992). Some researchers (Hindmarch, 1993) have even suggested AAMI merits neither attention nor treatment because it is *too* prevalent. To this, one of the initial NIMH Work Group authors replied, "the logic behind this curious argument is not provided, but an inevitable consequence is that many disorders of later life should be neither acknowledged nor treated" (Crook, 1993, p. 99). As an analogous example, presbyopia is nearly a universal condition after the age of 50, nevertheless, it is certainly accepted as a condition that merits treatment. Granted, the prevalence rates of AAMI have varied considerably, though this may be due in part to investigators applying only partial criteria. As indicated by several studies (Koivisto et al., 1995; Lane & Snowdon, 1989; Reinikainen, 1990), strict adherence to the complete AAMI criteria produces more consistent prevalence rates as seen in Table 3.

Table 3

Prevalence of Age Associated Memory Impairment

<i>Criteria</i>	<i>% Meeting Criteria</i>
Subjective decline only	76.3%
Objective memory test decline only	31.9 - 78.4%
Subjective and objective decline	53.8%
Subjective and objective decline and exclusionary criteria	38.4%

From Larrabee (1996) Note: Mean age = 68.8, Data from Koivisto et al., (1995)

Additional concerns suggest that the AAMI criteria do not take into account individual differences in performance or any of a variety of conditions that can alter performance and result in the mistaken impression of memory deficits such as low education opportunities, age cohort effects, or test anxiety. Medical exclusion criteria have been described as too restrictive (Smith et al., 1991). In sum, basically all of the essential components of AAMI criteria have been criticized: subjective memory complaints, objective memory tests, intellectual capacity testing, and exclusionary criteria. Of note, however, the criteria initially proposed by the NIMH Work Group (Crook et al., 1986), were expected to undergo modification and revisions, and the authors felt one of the study's main purpose was to encourage research into the area of aging.

Possible Overlap Between AD and AAMI

The question of whether AAMI is completely independent of AD, or whether it is a risk factor, or even an early stage in the development of AD has yet to be fully determined. To further illustrate this point, the AAMI criteria themselves leave open the question of the progression of the condition. It has been proposed that AAMI might be an intermediary state in the continuum from normal aging to AD (Brayne & Calloway, 1988), should such a continuum exist. However, the condition has also been suggested to be rather stable (Hanninen et al., 1995). Longitudinal studies best address this question, as they are able to track the cognitive course of subjects with

AAMI to determine if they develop AD over time. Of note, however, is a serious limitation inherent in longitudinal research. Not only is it unclear if individuals with AAMI will progress to AD, but the length of time before dementia would present, should this be the case, is also unknown. Thus, the duration necessary for a meaningful longitudinal study is difficult to predict. As such, financial and practical concerns become significant issues. Nevertheless, results of one study indicated that elderly individuals with subjective perceptions of cognitive decline who failed to provide clear evidence of cognitive impairment upon clinical interview were not at a high risk for progressive cognitive decline over a subsequent 3- to 4-year interval (Flicker, Ferris, Reisberg, 1993b). However, it is important to note that subjective perceptions of cognitive decline have not consistently been shown to correlate highly with performance on psychometric tests. For example, a study examining the relationship of subjective memory complaint and dementia indicated that complaints correlated with depression rather than objective memory performance (McGlone et al., 1990). Although these results have been replicated elsewhere (e.g., Bolla, Lindgran & Bonaccorsy, 1991), a study controlling for the effects of depression, age, and intelligence concluded elderly people with subjective complaints performed worse on memory testing than did matched controls who did not present with complaints (Jonker, Lindeboom & Hooijher, 1995). Therefore, studies using subjects who present solely with subjective complaints (as did the Flicker et al., 1993 study), who do not fulfill the full AAMI criteria, and studies that do not control for level of depression must be interpreted with caution when they are being used to examine the relationship of AAMI

to AD.

A 2-year longitudinal study of AAMI (Ferrario et al., 1994) indicated that 12.5% (33/263) of their sample with a mean age of 73.2 years were affected by AAMI. Over the next two years, although the prevalence of subjects affected by AAMI rose to 15.5%, none of the subjects initially identified as AAMI progressed to AD. Subsequent longitudinal studies have indicated similar results. In their sample of 146 subjects aged 65 years or more, Snowdon and Lane (1994) found after 8-year follow-up of the initial 32 subjects identified as having AAMI, that only 2 were found to have developed definite dementia. An earlier study (Reisberg, Ferris, Franssen, Kluger & Borenstein, 1986) using 3.6-year mean longitudinal follow-up (range=2.78 to 5.12 years) indicated that individuals whose scores were at or below Global Deterioration Scale (GDS; Reisberg, Ferris, De Leon & Crook, 1982) Stage 4 had rather malignant prognoses, whereas virtually all subjects at GDS Stage 2 and most at GDS Stage 3 (GDS Stages 2 and 3 correspond to AAMI criteria) tended to remain relatively stable. It is important to note, however, that by the time individuals have reached stage 4 of the GDS, they are no longer at a level congruent with the criteria for AAMI. The results of this study therefore indicated the stability of AAMI, and the progressive decline of dementia. Results from a population-based follow-up study of AAMI evidenced only very slightly elevated incidence of dementia (Hanninen et al., 1995). Though results suggested AAMI is generally nonprogressive, the authors did acknowledge that the AAMI is a heterogeneous population including subjects with early dementia and subjects without genuine memory loss.

Conversely, many studies have indicated that AAMI is in fact a harbinger of AD, and that those who present with subjective memory complaints and meet AAMI criteria, will eventually develop frank dementia. For example, a 3-year follow-up study (Petersen, Smith, Tangalos, Kokmen & Ivnik, 1993) found that of their initial sample of 73 AAMI subjects (mean age of 77), 23% had evolved to a clinical diagnosis of probable AD by 18 months, and by 36 months, only 37% remained at their initial level of cognitive functioning. In a subsequent study, after a six-month interval, 6 out of 8 subjects initially fulfilling AAMI criteria progressed to dementia (O'Neill, Surmon & Wilcock, 1992). Similarly, in a study examining community dwelling subjects with minimal dementia, researchers (O'Connor et al., 1991) found that 12 out of 24 subjects progressed to definite dementia over a 2-year period. In a similar vein, Morris and co-workers (1995) reported that 68% of subjects at level 0.5 of the CDR (questionable dementia) who were followed longitudinally progressed to definite dementia. In addition, all subjects diagnosed at the CDR 0.5 stage who came to autopsy had histological AD. Finally, in their review of the literature, Ebly, Hogan and Parhad (1995) report "between 63% and 80% of individuals who are once identified as cognitively impaired will progress to dementia" (p. 617). However, it is not clear whether "cognitively impaired" would be similar to or further advanced than AAMI criteria indicate.

As of yet the question of AAMI and its relationship to AD, if any, has not been definitively answered. However, if the results of the studies linking AAMI to the development of AD reflect the actual course of progression, then AAMI may prove to

be an early cognitive marker for the development of AD. Before this conclusion can be made, however, more research into the precise relationship of AAMI and AD must be undertaken.

Executive Function in AAMI

Research on AAMI to date has concentrated primarily on the nature of memory dysfunction; the role executive function may play has not been extensively examined. However, as outlined above, several authors have suggested that many age-related cognitive changes are consequences of a decline in frontal lobe functions (Daigneault & Braun, 1993; Mittenberg, Seidenberg, O'Leary & DiGiulio, 1989). As such, interest into the possible involvement of executive function in AAMI has surfaced. A recent study (Hanninen et al., 1997) examined frontal lobe functions in AAMI using four neuropsychological tests: the modified WCST, Verbal Fluency, TMT, and the Stroop Test. Volumetric measurements of frontal lobes were investigated by MRI. Results indicated AAMI performed significantly worse than controls on three of the four frontal lobe tests (WCST, Stroop, and TMT), though the frontal lobe volumes did not differ between the groups. The neuropsychological results agreed with previous findings (Craik, Morris & Morris, 1990; Parkin & Walter, 1992), and authors suggest this might reflect the existence of a mild frontal lobe pathology in the AAMI population. Negative MRI findings were thought to be due to analysis of entire frontal lobe volumes rather than specific areas such as the lateral convexity. Further, the authors felt functional changes likely preceded structural changes, and thus functional MRI, PET, or SPECT

might prove to be better approaches in exploring neuropsychological and brain function interactions in AAMI.

To make the claim that AAMI is a prodromal stage of AD would result in significant repercussions. This is especially true considering the high prevalence rates of AAMI in a relatively young sample (50-60). To tell individuals in their fifth or sixth decade of life, many of whom may still be at the height of their career, that they exhibit the signs of an early stage of a debilitating disorder such as AD would no doubt cause widespread concern. On the other side of the coin, however, is that emerging early, 'first-line' treatments for AD should be employed with AAMI if such a relationship exists since this could allow at minimum for a delay of the disease or even ultimately a prevention. Nevertheless, interpretations into the nature of AAMI and its relationship to AD must proceed with extreme caution. To this end, in the current study, a group of high functioning individuals was selected. This population was chosen as they would be least likely to show executive function deficits. High functioning individuals have been shown to exhibit a high level of executive skills. This is made evident by normative data on several executive function tasks (e.g., Colour Trails Test, COWA) which provide different sets of norms based on education level. Specifically, an individual with grade 10 education would obtain a higher percentile than would an individual with more years of education, for an identical raw score. Support for the notion of well developed executive functions in high functioning individuals is also evident from the field of developmental psychology. Gifted children have an abundance of executive function skills (Sternberg & Davidson, 1986), whereas children

with developmental delay have relatively fewer resources in this area (Borkowski & Kurtz, 1987). Based on these findings, individuals in the general population with high education backgrounds or who have achieved a high level of employment, are thought to exhibit a higher degree of executive functioning. Due to the importance of the potential implications of the research question, a very conservative approach was chosen. As such, the standards were set very high to find positive results pertaining to executive function. Put differently, if executive function deficits can be demonstrated in this high functioning population, it follows that similar involvement in the general population can be shown with relatively greater ease.

Purpose of the Study

The purpose of the study was to examine the possibility that AAMI represents a prodromal stage of AD. By definition, AAMI involves a deficit in one area of cognition, namely, memory. Further, the nature of the memory impairment in AAMI is similar to that in early AD, consisting of a gradual decrease in secondary memory performance representing a decline from previous ability. Moreover, exclusion criteria of both entities are essentially similar according to DSM-IV and NINCDS/ADRDA criteria for probable AD, and NIMH criteria for AAMI. Together, these similarities have suggested a link between the two disorders. Given current AD criteria, an argument could be constructed that demonstrable deficits in at least two areas of cognition in AAMI would suggest the disorder fulfills to some further degree diagnostic criteria for probable AD. As such, findings of this nature would provide further evidence of a relationship between AAMI and AD and allow comment on the nature of this relationship to be

made.

Hypotheses

Hypothesis I. Performance of the AD group will be significantly poorer than both the AAMI and OC groups on all measures of executive function. Frontal involvement has been suggested to occur in early AD. Thus, AD subjects are expected to perform poorly on the executive measures chosen for the study. Documentation of the AD subjects' performance will establish a benchmark of sensitivity of executive function tests chosen to deficits in early AD.

Hypothesis II. Significant differences between the OC and AAMI subjects on executive function tests will be demonstrated. As it is proposed that AAMI may not be a benign construct, but rather a prodromal stage of AD, the AAMI group will fulfill to some degree the NINCDS-ADRDA criteria for probable AD by evidencing dysfunction in two areas of cognition: memory (by definition), and executive function.

Hypothesis III. It was predicted that the AAMI group will show a parallel profile of executive function performance as the AD group. As executive function is not a unitary phenomenon, AD subjects may perform better on some executive function tasks relative to their performance on others. As it is hypothesized that AAMI is an early form of AD, it is expected that as a group they will reveal a similar profile of strengths and weaknesses within the realm of executive function abilities. This was assessed using profile analysis, an extension of MANOVA, which assesses whether the profiles of groups differ on a set of measures.

METHOD

Subjects

Four groups of subjects were recruited for the study consisting of two clinical groups and two control groups. The two clinical groups included subjects who met AAMI criteria and a second who met criteria for probable AD. The two control groups included a sample of young healthy individuals (young controls; YC) and a sample of older healthy individuals (older controls; OC). All subjects included in the study were high functioning as defined by one of two possible criteria (Mohr et al., 1990). The first criterion was completion of 16 or more years of education. The second was supervisory or managerial experience during the subject's employment history in addition to at least 13 years of education (or completion of high school). The latter criterion was instituted as several potential subjects had attained a high level of functioning in their career, but had not completed post secondary education as is the more common trend today.

Inclusion/Exclusion Criteria

General exclusion criteria which pertained to all groups included the history or presence of any medical, neurological, metabolic, or psychological disorder that may involve or impair cognitive function beyond the appropriate diagnostic classifications (see Table 4 for complete listing).

Subjects were excluded from participation in the study if they responded positively to any one of the exclusion criteria. The first ten criteria were obtained through the self-

report of each subject, or in the case of the more severely cognitively

Table 4

Exclusion Criteria

-
- History of head injury with greater than 1 hour loss of consciousness followed by cognitive deficits,
 - History of seizures,
 - History of brain infection or inflammatory brain disease,
 - History of neurological disorder that could produce cognitive deterioration (i.e., Parkinson's disease, Pick's disease, Huntington's disease),
 - Diagnosis of multi-infarct dementia, cerebral infarction, or transient ischemic attacks,
 - Cardiac, pulmonary, vascular, metabolic, or hematologic condition of sufficient severity to adversely affect cognitive function,
 - History or presence of vitamin B12 deficiency that has not been stabilized,
 - Unable to discontinue psychotropic or other cognitively acting medication at least two weeks prior to the date of assessment,
 - Current diagnosis or history of alcohol or drug dependence,
 - Primary diagnosis according to DSM-IV criteria of any major psychiatric disorder
 - Current diagnosis of depression
-

impaired subjects, through their care giver. The last criterion was verified through the completion of a self-report measure of depression, the Beck Depression Inventory (BDI; Beck, 1987). Generally, individuals who scored above the cutoff point of 11 (Marsella, Sanborn, Kamboka, Shizuri, & Brennan, 1974; Beck, 1987) were not included in the study (see Table 5). Older controls obtained a mean score which fell well below this cutoff (BDI mean=2.78, with a maximum score of 10). AAMI and AD subjects also obtained mean scores well within the normal range on this measure (AAMI mean=4.27, AD mean=3.73). However one of the AAMI subjects and one of the AD subjects obtained a score of 11. These subjects were retained in the study, however, as individual analysis of their BDI profile revealed it was the contribution of certain

physical/somatic difficulties rather than cognitive/affective ones which elevated the overall score (i.e., neither of these subjects reported feelings of sadness, discouragement about the future, but rather, indicated such items as loss of sexual interest, increased concern over health).

General inclusion criteria for the four groups included appropriate age requirements, fulfilment of high functioning criteria, and a signed consent form (see Appendix B). Specifically, subjects were between the ages of 25-40 (YC), or above the age of 50 (for OC, AAMI, AD). The age criterion of 50 and above was chosen to correspond to AAMI criteria established by Crook and colleagues (1986). According to the AAMI criteria guidelines, no upper age level is specified. In the present study, there was no difference between the three older groups with respect to age level $F(2, 63) = 2.58$, $p > .08$. All subjects had completed 16 years of education, or had acted in a supervisory/managerial role during employment history (in addition to completion of 13 years of education). An analysis of variance indicated, as expected, the groups were comparable with respect to education level $F(2, 63) = 1.19$, $p > .31$. In addition, there were no group differences with respect to Vocabulary score between the YC, the OC and the AAMI subjects $F(2, 63) = .041$, $p > .90$. All subjects produced a signed consent form.

Young Control Subjects. Twenty-two YC subjects participated in the study (see Table 6). Of these, eight were female (36%) and fourteen were male (64%). Twenty (91%) were right handed and two were left handed (9%) as determined through questioning. Mean years of education for the group was 18.95, with a standard

deviation of 2.84. Mean age was 32.23, with a standard deviation of 4.44 years.

Table 5

Inclusion / Exclusion Criteria

<i>MEASURE</i>	GROUP			
	<i>YC</i>	<i>OC</i>	<i>AAMI</i>	<i>AD</i>
	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>	<i>Mean (SD)</i>
BDI	--	2.7 (3.4)	4.3 (3.6)	3.8 (4.0)
MMSE	--	28.8 (1.3)	28.2 (1.2)	22.8 (4.1)
MAC-Q	--	22.0 (3.9)	27.2 (2.0)	--
GDS	--	1.0 (0)	2.2 (0.4)	4.2 (0.4)
Vocabulary	58.3 (4.1)	59.2 (4.6)	59.0 (5.4)	37.9 (12.9)

Note. YC = Young Controls, OC = Older Controls, AAMI = Age Associated Memory Impairment, AD = Alzheimer's Disease, SD = Standard Deviation, BDI = Beck Depression Inventory, MMSE = Mini Mental State Examination, MAC-Q = Memory Assessment Questionnaire, GDS = Global Deterioration Scale.

Young control subjects were assessed in order to establish normative data for a high functioning population on the tests of recent memory (logical memory, verbal paired associates, and visual paired associates) used to assign subjects to the AAMI group. This was necessary as the normative data currently available for these measures do not pertain specifically to a high functioning group. Utilization of current normative data may therefore have resulted in a significant number of false negatives due to their lack of sensitivity for this population (potential AAMI subjects may have scored above the cutoff and thus not be included in the group). According to AAMI criteria established by Crook and colleagues (1986) performance on measures of recent memory of older adults is to be compared to young normals aged 20-29. However, due to the nature of the population in the current study, this age range would not have allowed sufficient

Table 6

Sample Characteristics

	YC*	OC*	AAMI*	AD*
Age				
Mean	32.23	65.32	66.18	71.82
SD	(4.44)	(11.11)	(10.26)	(9.49)
Education				
Mean	18.95	17.68	16.45	17.50
SD	(2.84)	(2.62)	(2.89)	(3.01)
Handedness				
Right	20	22	22	22
Left	2	0	0	0
Gender				
Male	14	16	11	14
Female	8	6	11	8

Note: YC=Young Controls, OC=Older Controls, AAMI=Age Associated Memory Impairment, AD=Alzheimer's Disease, SD=Standard Deviation.
*n=22 for each group.

time to permit the completion of 16 or more years of education. Therefore, the age range selected for the current study was from 25-40. The lower limit of 25 was selected in order to allow for completion of 16 years of education. The upper age limit of 40 was selected as research on normal aging has shown that memory changes may take place as early as the fourth decade (Stuart-Hamilton, 1991). Therefore, by establishing a cutoff of 40, the likelihood of obtaining subjects with mild cognitive changes was reduced.

Young control subjects completed three subtests of the WMS-R assessing recent memory: logical memory (LM) 1 and 2, verbal paired associates (VerbPA), and visual paired associates (VisPA), and the vocabulary subtest of the WAIS-R. On LM1,

subjects obtained a mean recall score of 15.64, with a standard deviation of 2.20. On LM2, they obtained a mean score of 15.23 with a standard deviation of 3.18. VerbPA had a mean score of 20.87 with a standard deviation of 3.07, and VisPA had a mean score of 16.78 with a standard deviation of 1.74. Therefore, to be included in the AAMI group, subjects (in addition to fulfilling other AAMI criteria) were required to score at or below 13 on LM1, 12 on LM2, 17 on VerbPA, or 15 on VisPA (see Table 7).

Table 7

Young Controls Tests of Recent Memory

TESTS OF RECENT MEMORY				
	LM1	LM2	VerbPA	VisPA
Mean	15.64	15.23	20.78	16.78
SD	2.20	3.18	3.07	1.74
-1 SD	13.44	12.05	17.71	15.04
Cutoff ^a	13.0	12.0	17.0	15.0

Note. LM1 & LM2= Logical Memory Stories 1 & 2, VerbPA = Verbal Paired Associates, VisPA Visual Paired Associates, SD = Standard Deviation.

^a Cutoff for inclusion into the AAMI group.

Older Control Subjects. Twenty-two OC subjects participated in the study. Of these, six (27%) were female, and 16 (73%) were male (see Table 6). All subjects were right handed. Mean level of education for the group was 17.68 years, with a standard deviation of 2.62 years. All subjects were over the age of 50 with a mean age of 65.32 and a standard deviation of 11.11 years.

Subjects were not to have evidenced significant subjective memory complaints in combination with a score on tests of recent memory below one standard deviation of the YC group. Memory complaint was assessed through a self-report measure of memory functioning, the Memory Assessment Questionnaire (MAC-Q). Guidelines for interpretation of the MAC-Q suggest scores above 25 indicate significant memory complaint. OC subjects generally scored below this cutoff (MAC-Q mean=21.87). However, six of the subjects obtained a score slightly above the cutoff. Therefore, the results of their tests of recent memory were examined. None of the six subjects' scores were one standard deviation below those of the YC group (in fact many scored above the mean of the YC group), and thus all six subjects were retained in the OC group. This is in keeping with documented procedures of the like in the literature (see Hanninen et al., 1997). On the MMSE, the mean score was 28.82 with a standard deviation of 1.27. This score is well within the normal range, indicating intact mental status.

Age Associated Memory Impairment. Twenty-two subjects were included in this group, of which eleven were male (50%) and eleven were female (50%). All of the subjects were right handed. Subjects had a mean age of 66.18, and a standard deviation of 10.26 years. The sample had a mean education level of 16.45, with a standard deviation of 2.89 years.

All subjects in this group satisfied AAMI criteria (summarized in Table 8). All subjects were above the age of 50. Each subject reported the subjective presence of

Table 8

Age Associated Memory Impairment Criteria**1. Inclusion Criteria**

- a. Males and females age 50 years and over
- b. Complaints of gradual memory loss reflected in everyday problems such as
 - difficulty remembering names of individuals following introduction,
 - misplacing objects,
 - difficulty remembering multiple items to be purchased or multiple tasks to be performed,
 - problems remembering telephone numbers or postal codes
 - difficulty recalling information quickly or following distraction
- c. Memory performance at least 1 SD below the mean for young adults on standardized test of secondary memory (recent memory) with adequate normative data
- d. Adequate intellectual function determined by scaled score of 9 or higher on vocabulary subtest of WAIS-R
- e. Absence of dementia as determined by an MMSE score of 24 or higher

2. Exclusion Criteria

- a. Evidence of delirium, confusion, or other disturbances of consciousness
- b. Neurological disorder producing cognitive deterioration
 - AD
 - PD
 - stroke
 - intracranial hemorrhage
 - local brain lesions including tumours
 - normal pressure hydrocephalus
- c. History of any infective or inflammatory brain disease including viral, fungal, or syphilitic etiologies
- d. Evidence of significant cerebral vascular pathology (Hachinski Ischemia Score greater than 4, or evidenced by neuroradiologic exam)
- e. History of repeated minor head injury or single injury resulting in a period of unconsciousness greater than 1 hour
- f. Current psychiatric diagnosis of depression, mania, or any major psychiatric disorder
- g. Current diagnosis of or history of alcohol or drug dependence
- h. Evidence of depression
- i. Any medical disorder that could produce cognitive deterioration including:
 - renal disease,
 - respiratory disease,
 - cardiac disease,
 - hepatic disease,
 - diabetes mellitus (unless well controlled)
 - endocrine disturbance,
 - metabolic disturbance,
 - hematologic disturbance, and
 - malignancy not in remission for more than 2 years
- j. Use of any psychotropic drug or any other drug that may significantly affect cognition during the month prior to psychometric testing

Crook et al., 1986

memory impairment as recorded by a score above 25 on a self-report measure of

memory, the MAC-Q (mean=27.23, range 25-31). Each subject also scored one standard deviation below YC subjects performance on tests of recent memory (see Table 7). On the MMSE, AAMI subjects obtained a mean score of 28.23 (SD 1.23) which was well above the cutoff of 23/30 recommended (Folstein et al., 1975).

However, given the fact that the cutoff score of 23 applies to a general population and not to one with a high level of functioning, in order to exclude the presence of dementia, scores on the MMSE were compared to those of the OC group. Performance was not significantly different between the groups $t = 1.55$ ($df=42$), $p > .13$. On the Vocabulary subtest of the WAIS-R, AAMI subjects obtained a mean score of 59.0 (SD= 5.42) which corresponds to a scaled score of 12. Although this score was well within the average range for the general population (AAMI criteria specifies a scaled score of 9 or above), it was compared to the YC and OC groups to ensure intact intellectual function for this high functioning group. One way ANOVA revealed it was not significantly different from the YC or OC groups $F(2, 63) = .041$, $p > .90$.

Alzheimer's Disease Subjects. Twenty-two subjects were included in this sample, fourteen of whom were male (64%) and eight of whom were female (36%). All subjects were right handed. Mean age for the group was 71.82 with a standard deviation of 9.49 years. Total years of education was 17.50 years with a standard deviation of 3.01.

All subjects in this group met criteria for probable Alzheimer's Disease (as defined by DSM-IV Criteria and/or NINCDS-ADRDA Criteria; see Table 2). Diagnosis was based on a complete evaluation (interview, medical history, physical, neurological, psychiatric,

and laboratory examinations). All subjects fell into the mild to moderate range (as defined by the Global Deterioration Scale and by the Mini-Mental State Examination) to ensure that the disease remained at a stage where comprehension of test instructions could be ensured.

Measures

The measures used in the study as dependent variables consisted of 6 tests of executive function including: the COWA, the CTT, the Similarities subtest of the WAIS-R, the Stroop Colour Word Test, the TOT, and the WCST. These tests generated a total of ten dependent variables. Subsequent measures that were used for inclusion/exclusion criteria consisted of: the Mini-Mental State Examination, the Global Deterioration Scale, the Memory Complaint Questionnaire, the Vocabulary subtest of the WAIS-R, and three subtests of the WMS-R including Logical Memory, Verbal Paired Associates and Visual Paired Associates. A summary of dependent variables and inclusion/exclusion measures is provided in Table 9.

Table 9

Test Administration by Group

	YC	OC	AAMI	AD
<u>Inclusion/Exclusion</u>				
LM	X		X	
VerbPA	X		X	
VisPA	X		X	
MMSE	X	X	X	X
MAC-Q		X	X	
BDI		X	X	X
GDS		X	X	X
<u>Dependent Variables</u>				
COWA •Total number words		X	X	X
Colour Trails •CT 1 •CT 2		X	X	X
Similarities •Total Score		X	X	X
Stroop Test •Stroop Colour •Stroop Colour Word		X	X	X
Tower of Toronto •Index score		X	X	X
WCST •Number of Categories •Errors •Perseverative Errors		X	X	X

Note. YC=Young Controls, OC=Older Controls, AAMI=Age Associated Memory Impairment, AD=Alzheimer's Disease, LM=Logical Memory, VerbPA=Verbal Paired Associates, VisPA=Visual Paired Associates, MMSE=Mini Mental State Examination, MAC-Q=Memory Assessment Questionnaire, BDI=Beck Depression Inventory, GDS=Global Deterioration Scale, COWA=Controlled Oral Word Association, WCST=Wisconsin Card Sorting Test.

• Dependent Variable

Dependent Variables

Controlled Oral Word Association (COWA). The COWA (Benton & Hamsher, 1983; Spreen & Strauss, 1991) is a measure of verbal association fluency. It has been reported to be highly sensitive to the effects of frontal lobe damage. Frontal lesions, regardless of side, have been found to lower COWA scores (Miceli, Caltagirone, & Gianotti, 1981), although lower word production has been reported more in patients with left frontal lesions compared to those on the right (Parks, Loewenstein, & Dodrill, 1988). Severe impairment has been reported for bilateral frontal lesions (Benton, 1968). PET studies have shown activated bilateral temporal and frontal areas when the COWA was administered to normal volunteers (Parks et al., 1988). Lower scores on verbal fluency tests have been documented in dementing processes such as AD (Murdoch, Chenery, Wilks, & Boyle, 1987), though some studies have not found reduced word fluency in AD patients but rather, found more intrusions, perseverations, and variation errors (Adams, cited in Spreen & Strauss, 1991).

Administration is as follows: subjects are asked to provide as many words possible beginning with a given letter (F, A, and S). The subjects are given 60 seconds for each letter. The examiner records the words verbatim, with the total score calculated by summing all three trials. Perseverative responses and intrusions (words not beginning with the given letter) are not included in the total score. Thus, one dependent variable is obtained from this measure: the total number of words generated across the three trials.

Inter-rater reliability has been reported at near perfect levels (Spreen & Strauss,

1991). Test-retest reliability with a sample of older subjects has been reported at .70 for one year retest span (Snow, Tierney, & Zorzitto, 1988), and .88 for between 19-42 day retest span (des Rosiers & Kavanagh, 1987). The COWA is not sensitive to gender effects (Zec, Andrise, & Vicari, 1990), nor is it sensitive to age in well-educated persons. However, in less-educated individuals, mean scores slide from a 50-54 year high (Spreeen & Strauss, 1991). The test shows education-effects with individuals who have obtained 13 or more years of schooling. These individuals score between 4-8 mean points higher than individuals with 12 or less years of schooling (Spreeen & Strauss, 1991).

Colour Trails Test (CTT). The CTT (D'Elia & Satz, 1996) is a test of speed for visual search, attention, mental flexibility, and motor function. With respect to its association with frontal lobe involvement, CT2 provides information on the ability of shifting course during an ongoing activity, and the ability to deal with more than one stimulus at a time. Electrophysiological measures that appear to be associated with fronto thalamic functioning (Lezak, 1995) have been shown to correlate highly with the CTT. This finding provides support to the association between the CTT and frontal activation (Segalowitz, Unsal, & Dywan, 1992). The CTT has also been found to be highly sensitive to the early stages of dementia, with CT1 alone contributing significantly to differentiating demented from control subjects (Storandt, Botwinick, & Danziger, 1986).

This test consists of two sections; CT1 and CT2. CT1 requires the subject to connect a series of numbers arranged randomly on a page in ascending order as quickly as he or she can. CT2 requires the subject to connect numbers in ascending

order while following a colour alternation rule (e.g., 1yellow, 2pink, 3yellow, etc.). The two scores obtained are the times in which the subject takes to complete each trial.

Normative data for adults up to 90 are available. Normative data also incorporate level of education attained. This test consists of two dependent variables: time to complete CT1 and time to complete CT2 (measured in seconds).

Reliability coefficients for six month intervals have been reported as high as .98 for CT1, and .67 for Trails 2 (Lezak, 1995). One-year retest reliability has been reported of .64 for CT1 and .72 for CT2 in 100 older subjects (Snow, Tierney, Zorzitto, Fisher & Reid, 1988). Construct validity for visual search was established by correlations ranging from .36 to .93 with an object finding test and a hidden pattern test obtained in 92 aphasic and non aphasic patients (Ehrenstein, Heister, & Cohen, 1982, cited in Spreen & Strauss, 1991). Additionally, CT1 has been found to distinguish between patients with early AD and matched normal controls (Storandt, Botwinick, & Danziger, 1984). However, CT2 is clearly the more sensitive part of the test with respect to indicating the presence of brain damage as it requires more information-processing ability than CT1.

Similarities. The Similarities subtest of the WAIS-R (Wechsler, 1981) is a measure of abstraction and reasoning, and has shown sensitivity to frontal lesions. Increased glucose metabolism is evident in the left temporal and frontal areas when normal subjects take the test (Chase, Fedio, & Foster, 1984). It is one of the best indicators of speech dominant hemisphere disease, and studies have shown that patients with left frontal lobe lesions had significantly lower Similarities scores than did those with

anterior lesions on the right (e.g., McFie, 1975). Lower scores on the Similarities subtest have also been associated with bilateral frontal lesions (Rao, 1990). Lower scores on this test have also been among the early predictors of abnormal cognitive decline in middle-aged persons (LaRue & Jarvik, 1987).

The Similarities subtest measures verbal concept formation by assessing the degree to which the subject is able to form higher abstract categories of two items. The subject is presented with two words (i.e., boat-automobile) and asked to describe one way in which the two items are most similar. The items begin with a relatively high degree of similarity, but progress to a more difficult level of abstraction (i.e., fly-tree). There are 14 word pairs in total, and each is assigned a score of 0, 1, or 2, with a maximum score of 28. Although gender effects are virtually absent, the test has shown high sensitivity to the effects of education, with higher scores produced with higher level of education (Kaufman, Kaufman-Packer, McLean, & Reynolds, 1991). This measure yields one dependent variable: the total score.

Test-retest reliability co-efficients have been reported at .77 for a sample of control subjects aged 75 and older after an interval of one to five months (Ryan, Paolo, & Brungardt, 1992). Brain damaged patients have produced reliability coefficients of .70 and .80 after retest intervals of up to nine years (Goldstein & Watson, 1989).

Stroop Colour Word Test. The Stroop (Trenerry, Crosson, DeBoe, & Leber, 1989) measures the ease with which a person can shift his or her perceptual set to conform to changing demands and suppress a habitual response in favour of an unusual one (Spreeen & Strauss, 1991). Considered a measure of cognitive flexibility, the Stroop has

shown sensitivity to patients with frontal lesions, although lower scores may be more pronounced with left-sided frontal damage (Holst & Villki, 1988; Perret, 1974). The test has also been shown to be sensitive to severity of dementia (Fisher, Freed, & Corkin, 1990; Koss, Ober, Delis, & Friedland, 1984).

There exist a number of different versions of the Stroop test, although all reportedly measure the same underlying construct. In the current study, subjects were given a sheet containing 112 words organized into rows, which were printed in four different colours of ink (red, blue, green and tan). Initially, subjects were required to read the words out loud as fast they could. A score out of 112 was recorded, with errors subtracted from the total score. Subjects were then presented with the second sheet, and were asked not to read each word, but report the colour of ink in which the word was printed. A total score out of 112 was recorded again with errors subtracted, with a maximum allotment of 120 seconds. The test yielded two dependent variables: Colour Score (number of words read) and Colour Word Score (number of words read).

Reliability of the Stroop scores is highly consistent across the different versions of the test. Test-retest reliability using one month follow up interval between test sessions yielded estimates of .83 and above for the different parts of the test (Spreen & Strauss, 1991). Practice effects do occur, as found with college students, with a 2 point improvement noted on second administration (Spreen & Strauss, 1991).

With respect to validity, the Stroop is reported as being fairly effective in distinguishing between normal controls and brain damaged subjects and between psychiatric and brain-damaged samples (Golden, 1976).

Tower of Toronto (TOT). The TOT (Saint-Cyr, Taylor, & Lang, 1988) is a measure of planning ability and working memory and is generally considered a measure of executive function. Parkinson disease patients, who exhibit frontal involvement through impairment in the fronto-subcortical pathways, have been shown to develop a solution plan slowly, taking and learning an inefficient path to the solution (Lezak, 1995). However, its use with frontal lobe patients has not been extensively documented. Nevertheless, the use of similar measures (Tower of Hanoi) to assess executive function skills has indicated frontal involvement (i.e., Brennan et al., 1997). Age effects have also been documented, with older adults performing less well than their younger counterparts (Brennan et al., 1997).

The subject is provided with a wooden board with three pegs. On the farthest left peg are four disks in the order black, red, yellow, and white from bottom to top. The goal of the test is to move the disks so that they end up on the farthest right peg in the same colour order in which they began. Subjects must follow two rules: they must only move one disk at a time, and they may never place a darker disk on top of a lighter one. Subjects are told to take as long as they may require, with the goal being to complete the task in as few moves as possible (15 moves is the lowest; the test is discontinued after 50 moves). The examiner counts the number of moves, the number of colour errors, and the number of two disk errors, each time correcting subjects when a rule has been violated. Five trials are administered and after a break of 1 ½ hours five further trials are administered, for a total of 10 trials. A total index score is obtained (calculated as the number of trials under 18 minus the number of trials over 30 plus 10)

with scores below 9 considered impaired, although normative data on the test is not available. The test consists of one dependent variable: the Index Score.

Wisconsin Card Sorting Test (WCST). The WCST (Berg, 1948; Grant & Berg, 1948; Heaton, 1981) is a measure designed to assess the ability to form abstract concepts, and shift and maintain the set. The test has shown sensitivity to frontal lobe damage. For example, Parkinson's disease patients, whose pathological involvement lies primarily in the basal ganglia and the afferent connections to the pre frontal region, consistently perform poorly on the WCST (Cronin-Golomb, 1990). In earlier studies, Milner (1963, 1964) found clear differences between patients with dorsolateral frontal excisions and those with orbitofrontal and posterior lesions. Adults with damage to the dorsolateral prefrontal cortex were able to deduce the first criterion of sorting but were impaired when the experimenter changed the criterion.

The test is begun by placing four stimulus cards in front of the subject which contain a red triangle, two green stars, three yellow triangles, and four blue circles. The subject is then handed two packs of 64 response cards, varying in colour, form, and number, similar to the designs on the stimulus cards. The subject is instructed to match each of the response cards in the decks to one of the four stimulus cards. The subject is not told how to match the cards, only whether each response is right or wrong. Once the subject has made 10 consecutive matches to colour, without warning, the sorting principle is changed to form. Once 10 correct responses have been made, it then changes to number. This procedure continues until the subject has completed the 6 categories or until all of the cards have been used. A number of different indices can

be obtained from the test. For the present study, three dependent variables were utilized including: number of categories completed, number of error, and number of perseverative errors. These indices were chosen due to their high sensitivity to level of impairment.

Information regarding test-retest, split-half, or other forms of reliability is unavailable. This may be due in part to the fact that the test is not easily re-administered, as once the principle of sorting is known, re-administration does not yield new information other than the degree to which practice effects have occurred. Early investigations using the WCST found substantial age differences (e.g., Heaton, 1981) although more recently these have been found to be inconsequential before the seventh decade (e.g., Boone, Miller, & Lesser, 1990). Study results of very healthy and well-educated elderly volunteers (Haaland, Vranes, Goodwin, & Garry, 1987) found relatively small age decrements compared to results from college undergraduates. Subjects ranging in age from 64 to 69 actually performed slightly better than the young adults. An old-old subgroup (aged 80 to 87) only produced statistically significant decrements on two measures (number of categories attained, and total errors). Therefore, the WCST is a particularly useful test for well-educated individuals when there is a question of frontal lobe deficit.

Inclusion/Exclusion Measures

The following measures were used for inclusion and exclusion purposes and for assignment to the groups (see Table 9).

The Mini-Mental State Examination (MMSE). The MMSE (Folstein et al., 1975) is a

screening instrument used for determining the presence and degree of cognitive impairment. The MMSE takes 5-10 minutes to administer. It contains 10 orientation questions, immediate and delayed recall of three words, measures of attention and calculation, several simple language items, and a single visuographic item. Errors are summed and subtracted from a maximum score of 30 points. Preliminary data collected on 206 hospitalized patients with varied diagnoses (i.e., dementia syndromes, affective disorder, schizophrenia) led to the recommendation that a cutoff score of 23 be used to raise the question of cognitive impairment. However, when used with healthy, well-educated older adults the MMSE is often insensitive to mild impairment. For example, in older patients with mild dementia of the Alzheimer type who are otherwise healthy and well educated, 15% to 33% can be expected to score 24 or higher (Galasko et al., 1990). Based on this research, raising cutoff scores for clinical screening to 28 for people between the ages of 50 and 79 and a score of 26 for 80- to 89-year-olds with a minimum of 12 years of education has been suggested (Bleecker, Bolla-Wilson, Kawas, & Agnew, 1988).

Test-retest reliability was assessed at 24 hour and 28 day retest. Correlation coefficients were found to be .88 and .98 respectively (Folstein et al., 1975). Subsequent studies have found the MMSE has acceptable sensitivity and specificity when used with general adult populations (Foreman, 1989). However, as Folstein emphasized (Folstein, Anthony, Parhad, Duffy, & Gruenberg, 1985) the MMSE is inadequate with respect to diagnostic parameters; instead, a lower than expected score suggests the need for further assessment.

Global Deterioration Scale (GDS). The GDS (Reisberg et al., 1982) was developed to differentiate the characteristics of normal aging, AAMI, and primary degenerative dementia, particularly AD. It is divided into seven clinically identifiable and ratable stages ranging from one (no cognitive decline), to seven (very severe cognitive decline). The GDS in the current study was used as an aid to diagnostic parameters and group assignment. All of the older healthy control subjects fell into stage 1; AAMI subjects fell into either GDS stages 2 or 3, and the AD subjects fell into either stage 4 or 5 as these stages correspond to normal, AAMI, and AD respectively. Stages 6 and 7 represent a very severe progression of dementia, and patients in the current study who fell into this category were excluded.

In a retrospective analysis of the relationship between the GDS scores and independent psychometric assessments of patients with very mild to moderately severe cognitive decline, the GDS correlated significantly with 13 of 19 cognitive items in the Inventory of Psychic and Somatic Complaints in the Elderly (Reisberg, Ferris, & Schneck, 1981), and with 25 of 26 commonly used psychometric measures (Reisberg et al., 1982) indicating adequate convergent validity. In an examination of the relationship of the GDS to anatomical brain changes as visualized on CT scans and metabolic changes as determined by PET scans in patients with AD, significant correlations of .62 and .69 respectively were found (De Leon, Ferris, & George, 1980; Ferris, De Leon, & Wolf, 1980).

Memory Complaint Questionnaire (MAC-Q). The MAC-Q (Crook, Feher, & Larrabee, 1992) is a standardized self-report memory questionnaire designed to assess age-

related memory complaint. The MAC-Q is brief (six questions), but generates a score (range 7-35) that quantifies the presence and degree of memory complaint in the elderly, with higher scores indicating greater complaint. The first five items reflect specific situations which the elderly frequently report problematic with respect to age associated memory decline. These items are rated on a 5 point Likert scale. The sixth item is a global item pertaining to overall memory decline, and is given more weight in the scoring system than the other five items. The format of the MAC-Q targets age-related changes in that the subject is asked to rate current abilities compared to past abilities. The authors suggest a cutoff score of 25 or above represents "age-associated memory decline" since such a score would require several item ratings falling in the "somewhat poorer than now" category (Crook et al., 1992).

Test-retest reliability has been assessed at 12 week follow up, with total MAC-Q score obtaining a reliability coefficient of .67, with reliability of the six individual items of .46, .78, .65, .63, .52, and .71 for items 1-6 respectively (Crook et al., 1992). Internal consistency of the MAC-Q was assessed with Cronbach's alpha (.57, $p < .001$; Crook, et al., 1992). Concurrent validity of the MAC-Q was supported by a moderate but significant correlation ($r = .41$, $p < .001$) with a lengthy, well-validated memory questionnaire (Memory Assessment Clinics-Self-Rating; MAC-S; Crook & Larrabee, 1990). It should be noted that the MAC-Q was chosen in the present study over the MAC-S because the latter queries the subject about current memory ability, whereas the former asks about memory decline. Due to several studies claiming that self-report of poor memory is more closely related to dysphoric mood than to actual memory, a

multiple regression analysis was conducted with the MAC-Q and the Hamilton Depression Rating Scale (HAM-D; Hamilton, 1967). Overall, HAM-D scores did not predict MAC-Q scores indicating that memory complaint is not strongly related to affective status in subjects meeting the criteria for AAMI.

Vocabulary subtest of the WAIS-R. The WAIS-R (Wechsler, 1981) provides a measure of general intellectual function. It is composed of 11 subtests - six verbal and five performance-oriented tasks which yield a Verbal IQ, Performance IQ, and a Full Scale IQ. Vocabulary, one of the six verbal subtests, is a measure of word knowledge, and is considered a good indicator of overall level of intellectual function. The Vocabulary subtest consists of 35 words which are presented to the subject. The examiner begins with the word "Winter", and asks the subject what the word means. The examiner records the subjects' response, and assigns a score of 0, 1, or 2. This continues for the remaining words, or until five consecutive scores of 0 have been given, at which time the test is discontinued. The maximum score is 70. The subtest provides a measure of word knowledge and is highly correlated with level of verbal intellectual functioning. This subtest was administered to the groups to provide an overall measure of level of intellectual functioning as outlined by AAMI criteria guidelines (Crook et al., 1986).

Logical Memory & Paired Associates (WMS-R subtests). The WMS-R (Wechsler, 1987) is a diagnostic and screening device used for appraisal of major dimensions of memory functioning. It consists of nine subtests including: information/orientation, mental control, figural memory, logical memory, visual paired associates, verbal paired

associates, visual reproduction, digit span, and visual memory scan. In the current study, three of the subtests were used for inclusion into the AAMI group: logical memory, verbal paired associates, and visual paired associates. Young controls were administered these tests in order to establish a comparative index of functioning in a highly educated sample. Their scores were then used as cutoff points for inclusion into the AAMI group.

Procedure

Recruitment

The AAMI and AD groups were collected through the Memory Disorders Clinic at the Sisters of Charity Hospital, Elizabeth Bruyere Centre, various nursing and retirement homes in the Ottawa and surrounding area, the Alzheimer's Disease Society through their newsletter, and community and recreational facilities (i.e., curling club, Lions club etc). Of those who were obtained through the Hospital, names of individuals seen in the clinic for diagnostic assessment of dementia were obtained and later contacted by telephone. Others simply responded by telephone to advertisements placed in the community. Control subjects were recruited primarily through advertisements placed in local papers, church bulletins, grocery stores, and recreational centres. Additional control subjects included spouses or relatives of the AAMI or AD subjects.

Assessment

Subjects were underwent a brief screening (to ensure no major exclusion criteria were present), and if suitable, a testing session was then arranged. Subjects were given their choice of location for assessment, and all subjects preferred to be tested at

their own place of residence. Once suitability for the study was established, subjects read and signed the consent form. It was necessary for three of the AD subjects to have consent signed by their substitute. The proper notarized documentation authorizing the substitute was reviewed by the examiner. All testing was conducted by the same examiner. Tests were administered in the same order for each subject: TOT initial trials, CTT, COWA, Stroop Colour Word Test, Similarities, WCST, TOT final trials.

Statistical Analysis

Data was analysed using the Statistical Package for the Social Sciences (SPSS). Group differences on measures of executive functioning were examined using multivariate analysis of variance (MANOVA). Chi-square analysis was employed for categorical variables. Profile analysis was conducted to compare the profiles of the set of executive function measures in the AAMI and AD samples.

RESULTS

Evaluation of Assumptions

Prior to analysis, screening was undertaken to ensure the assumptions of multivariate analysis were achieved. Variables were examined by group to identify outliers (both univariate and multivariate), normality, linearity, homogeneity of variance-covariance matrices, and multicollinearity and singularity. It should be noted that throughout, all results have been rounded to two decimal places.

Missing Data. Examination of the data indicated there were no missing data points evident for any of the groups. The sample sizes were equal for all groups (YC=22,

OC=22, AAMI=22 & AD=22).

Outliers. Univariate outliers were examined visually through SPSS descriptives, boxplot subcommand, and their distance from the mean was subsequently calculated. Scores which exceeded three standard deviations from the mean were considered outliers. Values which are considered outliers generally are treated by one of three methods: modification, transformation, or deletion of the data as outlined in Tabachnick and Fidell (1996). For the current study, modification of the data was undertaken as transformation of the data may lead to difficulty with interpretation. Deletion of the case was considered unfavourable as the n's for each group were relatively small. Thus, univariate outliers were reduced to three standard deviations from their mean. This method is generally considered acceptable provided no more than five percent of the data is modified. The ratio of the number of variables modified to the total number of variables in the present study was calculated at below 4.90%, thus satisfying the suggested guidelines. Once this was completed, the data were re-examined, with no further outliers identified.

Multivariate outliers were analysed through SPSS regression, residuals subcommand. No multivariate outliers were found using Mahalanobis' distance (27.75; $df=9$) corresponding to a probability value of $p<.001$ as outlined in the chi square tables (values above 27.87 are considered multivariate outliers).

Normality. Normality of the data was examined through analysis of skewness (symmetry of the distribution) values obtained through the SPSS descriptives command for each group. Of the ten variables, two were non-normally distributed. The first,

Stroop Colour score, evidenced significant ceiling effects, with a mean at the upper limit of the test and no variability (mean=112, SD=0) in both the OC and AAMI group. This finding, however, is not surprising considering the subjects were merely required to read a list of words; a skill which evidences little compromise until severe intellectual deterioration is evident. Thus, in the expected absence of variance, the Stroop Colour score was excluded from further analysis. The second variable, the WCST number of categories, was not deemed to be continuous (it can only have a value of 0-6), and thus was analysed using the chi square design. The number of variables analysed using MANOVA was thus reduced from 10 to 8. As a result, the overall power level of the study, which was initially calculated at .70 ought to have increased. Of the remaining eight variables, skewness values fell well within the recommended ± 3.0 range.

Linearity. This assumption was assessed through a review of selected pairwise bivariate scatterplots. The plots did not show evidence of a marked departure from linearity.

Homogeneity of Variance-Covariance Matrices. Box's M, a test of homogeneity of variance was significant $F(72,11058) = 243.47, p > .001$. However, there are several factors to consider in this case. First, the sample sizes in the present study are equal. According to Tabachnick and Fidell (1996), if this is the case then the significance of Box's M can be disregarded. Further, Box's M is a notoriously sensitive test and in the worst of cases, heteroscedasticity (the failure of homogeneity) will not severely affect the analysis. In other words, MANOVA tends to be quite robust to violation of this assumption.

Multicollinearity and Singularity. Correlations among the DV's were examined through MANOVA correlation matrices. Intercorrelations generally fell in the moderate range (between 4 to 6) and none exceeded the value of $r = .90$. Examination of the within-cell determinants of the correlation matrices indicated none approached zero (Log (determinant) = 26.86, 30.37, & 39.79 for Cells 1, 2, and 3 respectively; Log (determinant) of the pooled correlation matrix = 36.20). Thus, there was no indication of singularity or multicollinearity.

Summary. Evaluation of assumptions revealed sporadic univariate outliers which were modified to within three standard deviations. No multivariate outliers were identified. Examination of normality revealed two variables which were non-normally distributed (Stroop Colour score, and WCST number of categories). The former was not further analysed, and the latter was analysed by chi-square. Homogeneity of variance-covariance was somewhat problematic, however, based on the equal sample sizes, and the robustness of MANOVA to this assumption, no further action was taken. Linearity, multicollinearity, and singularity assumptions were met.

Data Analysis

In order to determine if the three groups differed on measures of executive functioning, a between-subjects multivariate analysis of variance (MANOVA) was conducted. The overall results indicated a significant main effect of Group as revealed by Wilks Lambda $F(16, 112) = 7.02$ $p < .001$. Both Pillais and Hotellings tests were significant as well ($F(16, 114) = 5.39$ $p < .001$; $F(16, 110) = 8.84$ $p < .001$ respectively). Multivariate effect size (η) was in the moderate range; Hotellings $\eta = .563$. To

determine where the differences occurred, univariate F-tests (ANOVAS) were conducted on the dependent variables (see Table 10). To control for experiment-wise error, the alpha level was adjusted to account for the fact that eight tests, rather than one, were being analysed ($.05/8 = <.006$). To discover which groups differed, Tukey's HSD (Honestly Significant Difference) post hoc analysis was conducted on each of the variables.

Table 10

Univariate Analysis and Effect Size of the Eight Dependent Variables

<i>Variable</i>	<i>df</i>	<i>Univariate F</i>	<i>Eta Square η</i>
COWA	2, 63	18.50*	.37
CT1	"	19.58*	.38
CT2	"	17.05*	.35
Similarities	"	23.16*	.42
StroopCW	"	56.68*	.64
Tower of Toronto	"	13.69*	.30
WCST Err	"	20.44*	.39
WCST Per	"	16.76*	.34

Note. COWA=Controlled Oral Word Association, CT1=Colour Trails 1, CT2=Colour Trails 2, WCST Err=Wisconsin Card Sorting Test number of errors, WCST Per=Wisconsin Card Sorting Test number of perseverative errors.

* significant at the $p <.001$ level.

Controlled Oral Word Association. A one-way ANOVA revealed a significant effect, indicating the groups differed in their performance level on this measure $F(2, 63) = 18.50, p < .001, \eta = .37$. To determine which groups differed on this variable, the post hoc analysis Tukey's HSD was performed. The AD group significantly differed from

both the AAMI and OC group. Also, the AAMI and OC groups were significantly different (see Table 11).

Table 11

Scores on Measures of Executive Function

	OC	AAMI	AD
	Mean (SD)	Mean (SD)	Mean (SD)
COWA	45.73 (10.55)	36.50** (7.76)	22.82* (17.39)
CT1	39.18 (13.08)	56.04 (23.07)	99.54* (50.86)
CT2	87.32 (28.24)	103.00 (30.10)	181.59* (90.41)
Similarities	22.91 (2.33)	20.95 (2.98)	14.41* (6.49)
StroopCW Score	96.64 (17.13)	85.09 (19.49)	39.18* (19.97)
Tower of Toronto	12.04 (3.77)	8.86** (3.12)	5.27* (5.59)
WCST Errors	11.68 (4.20)	21.13 (9.95)	44.62* (28.56)
WCST Per Err	6.73 (2.73)	11.36 (5.83)	26.18* (19.10)

Note. OC=Older Controls, AAMI=Age Associated Memory Impairment, AD=Alzheimer's Disease, SD=Standard Deviation, COWA=Controlled Oral Word Association, CT1=Colour Trails 1, CT2=Colour Trails 2, WCST=Wisconsin Card Sorting Test, WCST Per Err=Wisconsin Card Sorting Test Perseverative Errors.

*AD differed from both AAMI and AD at $p < .05$, **AAMI differed from OC at $p < .05$.

Colour Trails Test. Univariate F was significant for both parts of this test (CT1 and CT2) indicating an effect by Group $F(2, 63) = 19.58, p < .000, \eta = .38$, and $F(2, 63) = 17.05, p < .001, \eta = .35$ respectively. On both CT1 and CT2, Tukey's HSD test indicated

the AD group differed from the AAMI and the OC. No differences were evident between the AAMI and OC subjects on either part of the test.

Similarities. With respect to this variable, a significant effect of Group was found $F(2, 63) = 23.16, p < .001, \eta = .42$. Post hoc analysis revealed group differences between the AD and AAMI groups and the AD and OC groups. The AAMI and OC groups did not differ on this measure.

Stroop Colour Word Test. With respect to the StroopCW Score, univariate F-tests revealed a significant group effect $F(2, 63) = 56.86, p < .001, \eta = .64$. Again, Tukey's post hoc analysis revealed that the AD group differed from both the AAMI and the OC, however there was no significant difference in performance between the AAMI and OC groups.

Tower of Toronto. A significant univariate analysis was evident as revealed by $F(2, 63) = 13.69, p < .001, \eta = .30$. Tukey's HSD test indicated the AD group was significantly different from both the AAMI and the OC group. A significant difference was also found between the AAMI and the OC group.

Wisconsin Card Sorting Test. Univariate F revealed a significant group effect for both the number of errors and the number of perseverative errors $F(2, 63) = 20.44, p < .001, \eta = .39$, and $F(2, 63) = 16.76, p < .001, \eta = .34$ respectively. As revealed by post hoc analysis, the AD group differed from the AAMI and the OC groups on both variables of the test. No differences between the AAMI and the OC groups were found on either variable.

Chi-square analysis

As noted above, one of the dependent variables was considered categorical in nature, and thus was analysed using the Chi-square test for independence. The variable, WCST number of categories completed, can only have a value of 0 to 6. An examination of assumptions for the chi-square test was undertaken to ensure violations were not present. The assumption of Independence of observations states that each observed frequency is generated by a different subject. In the present study, this assumption was met as each score was produced by one subject. The second assumption indicates that the expected frequency of each cell should not be less than 5. If so, the chi-square statistic may be distorted. In order to meet this assumption, the variable was collapsed to form two levels: WCST number of categories completed values 0 to 5 were collapsed to form the first level, and WCST number of categories completed value of 6 formed the second level. As a result, all the cells had an expected frequency size greater than 5 and thus, the second assumption was met.

A 2x3 chi square was analysed (see Table 12). The null hypothesis states that the separate populations all have the same proportions (same shape). Results were significant for overall effect as indicated by $\chi^2(2, n=66) = 28.38, p < .001$. As for group differences, qualitative examination of the data indicates the AD group accounting for most of the contribution to each cell, as their observed frequencies differ greatly from expected frequencies for each cell.

Table 12

Chi-square analysis of WCST Number of Categories Completed

# of Categories		OC	AAMI	AD
0 - 5	Observed	0	2	14
	Expected	5.3	5.3	5.3
	Adj. Residual	-3.2	-2.0	5.3
6	Observed	22	20	8
	Expected	16.7	16.7	16.7
	Adj. Residual	3.2	2.0	-5.3

Note. OC=Older Controls, AAMI=Age Associated Memory Impairment, AD=Alzheimer's Disease.

Summary

Multivariate analysis revealed an overall significant main effect for group, and thus the null hypothesis was rejected. Univariate F-tests revealed all eight dependent variables were significant at the $p < .001$ level. With respect to group differences, Tukey's HSD post hoc analysis revealed that the AD group performed significantly worse than both the AAMI and the OC groups on all eight variables. However, the AAMI and OC groups differed only on the TOT and the COWA test. The Chi-square analysis was significant and revealed overall group differences for the WCST number of categories, although the AD group reveals the greatest amount of contribution to observed-expected cell differentiation.

Re-Analysis of the Data

A second analysis was conducted using only the OC and AAMI groups on the eight

dependent variables. This was undertaken as the AD subjects evidenced marked floor effects on several of the variables, and as a result their extreme scores accounted for most of the differences found between the groups. As past literature had indicated differences in executive function scores between the AAMI and control populations, the above noted findings were surprising. Therefore, a second MANOVA was run excluding the AD sample obtained in this study. An overall significant multivariate effect for Group was found $F(1, 42) = 4.28, p < .001, \eta^2 = .495$. Thus, examination of the Univariate F's was undertaken to determine which of the DV's were significant. As seen in Table 13, five of the eight variables were significant using the appropriate Bonferroni correction ($.05/8 = .006$) including COWA, CT1, TOT, WCST number of errors, and WCST number of perseverative errors. Strength of association (effect size; η^2) ranged from 7 to 28 percent and is also presented in Table 13.

Table 13

Univariate Analysis of Eight Dependent Variables for OC and AAMI

DV	df	F	Significance of F	ETA Square
COWA	1, 42	10.92	.002*	.206
CT1	"	8.89	.005*	.174
CT2	"	3.17	.082	.070
Similarities	"	5.87	.020	.122
StroopCW Score	"	4.35	.043	.093
Tower of Toronto	"	9.29	.004*	.181
WCST Errors	"	16.85	.000*	.286
WCST Per Errors	"	11.42	.002*	.213

Note. DV = dependent variable, df = degrees of freedom, COWA = controlled oral word association, CT = colour trails, CW = colour word, WCST = Wisconsin card sorting test.
*groups significantly different at $p < .05$ (Bonferroni correction applied)

Profile Analysis

A profile analysis was performed on the eight dependent variables: COWA, CT1, CT2, Similarities, StroopCW, TOT, and WCST number of errors and number of perseverative errors. The grouping variable was subject group (AAMI or probable AD). All raw scores were converted to standardized scores relative to the OC group, the means of which are represented in Table 14. This procedure was conducted to ensure commensurability of the scores as outlined in Tabachnick and Fidell (1996). Using Wilks' criterion, the profiles, seen in Figure 1, did not deviate significantly from parallelism ($F(7, 36) = 7.14, p < .001$). The levels test indicated reliable differences between the groups $F(1, 42) = 7.42, p < .01$. The graph in Figure 1 has been arranged

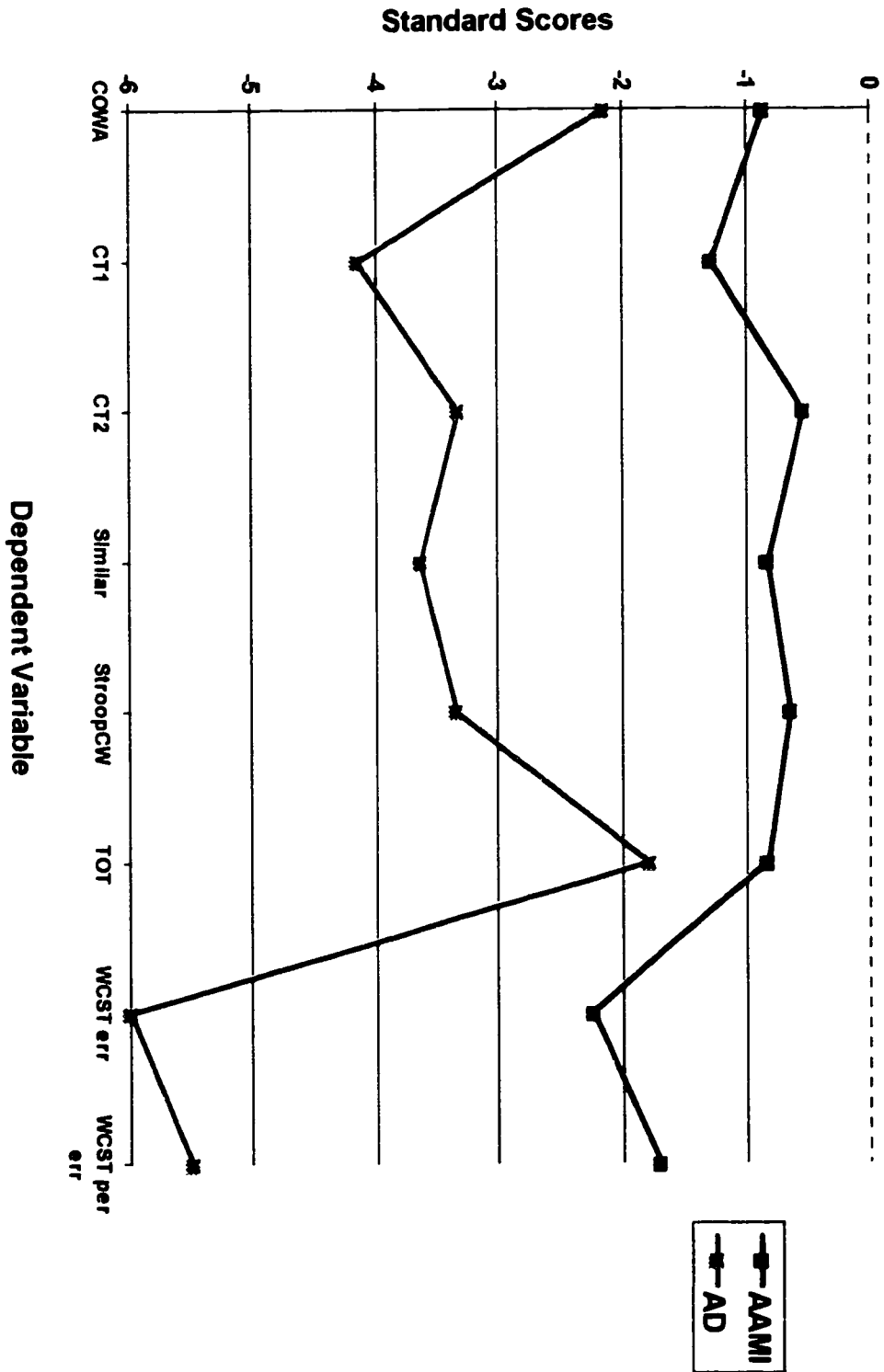


Figure 1 Profile of AAMI and AD Executive Function Performance:

to represent the negative performance of the groups (i.e., Colour Trails scores for AAMI and AD are actually higher than OC as this variable is measured in 'time to complete', however they have been reversed to indicate negative performance).

Table 14

AAMI and AD Standardized Scores

DV	AAMI	AD
	Mean	Mean
COWA	-.87	-2.17
CT1	1.29	4.61
CT2	.56	3.34
Similarities	-.84	-3.65
StroopCW Score	-.67	-3.35
Tower of Toronto	-.84	-1.79
WCST Errors	2.25	7.84
WCST Per Err	1.70	7.12

Note. DV=Dependent Variable, AAMI=Age Associated Memory Impairment, AD=Alzheimer's Disease, COWA=Controlled Oral Word Association, CT1=Colour Trails 1, CT2=Colour Trails 2, WCST=Wisconsin Card Sorting Test, WCST Per Err=Wisconsin Card Sorting Test Perseverative Errors.

Summary

A MANOVA between the three groups (OC, AAMI, and AD) indicated an overall significant main effect. All Univariate F's were significant indicating all DV's were contributing to the overall group difference. Post hoc analysis revealed the AD group differed significantly from the OC and AAMI on all DV's, although the OC and AAMI only differed on two (COWA and TOT). Thus, MANOVA was run on the OC and AAMI groups, excluding the AD group, and again a significant main effect for group was

found. Examination of the univariate F's revealed significant differences between the OC and AAMI on five of the DV's. A profile analysis conducted on the set of dependent variables indicated the groups did not differ significantly from parallelism. The levels test was significant, indicating the AAMI group, on average, scored higher than the AD group, and support the findings obtained from the MANOVA.

DISCUSSION

The concept of AAMI has primarily been viewed as a mild memory disorder whose relation to AD was unclear. The current study, however, demonstrated mild AAMI impairment on several measures of executive function compared to an age and education matched group. These measures were also found to be impaired in a sample of mild to moderate AD subjects. These findings are important for a number of reasons. First, the nature of the cognitive characteristics of AAMI have been more clearly defined, and appear to include involvement of more than just memory deficits as was previously believed. Second, the presence of AAMI executive function decline similar in pattern to that of AD, allows us to make an important link between the two disorders. As such, comment on AAMI as a prodromal stage of AD can be rendered.

Discussion of Hypotheses

Hypothesis 1. *Performance of the AD group will be significantly poorer than both the AAMI and OC groups on all measures of executive function.* The AD group's performance on tests of executive function revealed two findings. First, their performance on all tests of executive function was impaired. This finding established the sensitivity of the tests to AD impairment. Though several of the executive function tests employed in the study have previously shown sensitivity to AD impairment (e.g., COWA), others had not been well studied in the AD population (e.g., TOT). Moreover, given the level of functioning of the sample used in the current study, it was important to document that the measures showed sensitivity to a *high functioning* AD group. Based on the results obtained from the AD subjects' performance, it can be concluded

that the six dependent measures used in the study are sensitive to the impairment evident in the AD population.

The second finding was that the AD group's performance was significantly worse than both the OC and AAMI groups on all executive function measures. This finding was expected and confirms the hypothesis that executive function deficits could be documented in a mild to moderate AD sample. This hypothesis was based on a growing body of evidence indicating early involvement of the frontal cortex in AD. Alzheimer's disease has been traditionally conceptualized as a disorder involving the temporal/parietal area, as evidenced by significant impairment in memory and learning, which are cognitive abilities predominantly subserved by these regions. While executive dysfunction is a well accepted part of the disease process, the timing of the clinical manifestation in the course of the disease is less well established. While several studies substantiated the notion of very early executive deficits (Binetti et al., 1996; Katzman & Aronson, 1989; Pasquier et al., 1995), others obtained mixed results (Becker et al., 1994; Grady et al., 1988). When results of these studies were analysed further, evidence began to emerge of the possibility of a subgroup of AD individuals who present with very early executive difficulties, sometimes even prior to the onset of language or visuospatial deficits (Grady et al., 1988). While it is possible that a sample of particularly 'frontal' subgroup of AD subjects participated in the current study, it is more likely that any executive function differences in the sample was due more to the respective stage of the disease rather than sub-grouping. This assumption is based on an examination of the distributions of scores on the dependent variables, which showed

essentially a normal distribution. Had the sample consisted predominantly of a frontal subgroup, the distributions would have been non-normal, or positively skewed. The fact that the AD group evidenced variance among the scores on the variable suggests heterogeneity of executive function performance. Thus, the findings obtained from an undifferentiated sample of mild to moderate AD subjects, indicate that as a group, executive deficits are evident. These results are in keeping with findings of similar studies suggesting impairment across measures of executive functioning early in the disease course (Bondi, Monsch, Butters, Salmon, & Paulsen, 1993; Lafleche & Albert, 1995; Morris & Fulling, 1988; Pasquier et al., 1995).

Hypothesis II. *Significant differences between the OC and AAMI subjects on measures of executive function can be demonstrated.* Results from the initial analysis, which included all three groups, indicated that the AAMI group only differed from the OC group on two of the nine dependent variables. On initial examination, this finding appeared to support the notion of only minimal executive function involvement in AAMI, particularly considering the fact that the two variables which evidenced significant differences also relied to some extent on aspects of memory functioning (TOT is a test of planning which relies on working memory; COWA is a verbal fluency test dependent also upon intact word retrieval). However, it could also be argued the mere fact that executive differences were found at all in this supposedly mild 'memory' disorder is suggestive of a pathogenetically more morbid disease process. Thus, the results merited further examination.

Though a number of possible explanations could account for the lack of executive

function differences between the AAMI and the OC groups (e.g., not enough power to detect differences), one issue in particular warranted specific attention. The AD group exhibited significant floor effects on several of the tests. That is, many of the tests proved to be difficult for several of the AD subjects. For example, on the TOT, almost half of the AD subjects obtained an Index score of 0. A score of this nature indicates that on all ten trials, the maximum number of moves was required to complete the test, and in some instances completion of the test was never reached (the test is discontinued after 50 trials regardless if the subject is near completion). Compared to the OC and AAMI subjects, who between them did not produce one Index score of 0, the TOT is clearly an extremely difficult test for some of the AD subjects. Similar effects were seen on the Stroop Test (Colour Word score only), and to a somewhat lesser extent, the WCST. Although these floor effects may complicate data interpretation, they also provide useful clinical information as to the appropriateness of tests for an AD population. As a result of these significant floor effects, the means of the AD group on all of the variables were so different from the OC and AAMI groups that potential differences between these latter two were washed out. As such, potential differences between the OC and AAMI samples may not have been found.

This presumption appeared to be substantiated when analysis of the AAMI and OC groups (excluding the AD group) was undertaken. Group differences were evident on five of the nine variables including COWA, CT1, TOT, WCST number of errors, and WCST number of perseverative errors. Thus, when the very impaired performance of the AD group was removed from the analysis, differences on several tests emerged

between the AAMI and OC groups. These findings are in keeping with studies indicating frontal involvement in AAMI (Hanninen et al., 1997) and age-related memory loss (Craik et al., 1990; Parkin & Lawrence, 1994; Parkin & Walter, 1992). With respect to the COWA, in the current study, this test was able to distinguish between the OC and AAMI groups even when the AD group was included in the analysis. The same was true of the TOT. From this it can be presumed that these tests appear to be sensitive to differences in OC and AAMI. Though the TOT has not been examined in many studies, the COWA has been included in several studies examining early cognitive impairment in the elderly. A number of studies have indicated that verbal fluency is one of the earliest detectable areas of cognitive involvement in the development of AD (Binetti et al., 1996; Mann et al., 1992; Pasquier et al., 1995). The results of the current study, thus, are in agreement with these findings. One study in particular is worth noting as it employed an AAMI sample. In their examination of executive function in AAMI, Hanninen et al., (1997) did not find a significant difference between AAMI and controls on the verbal fluency test. Though no explanations were put forth by the authors, one possible reason may be that they used a Finnish version of the test. As no study examining the comparability of the test across languages has been published, language differences may have had an effect on the performance of the group.

With respect to the WCST, the number of errors and number of perseverative errors differed significantly between the OC and AAMI groups. This is in keeping with previous studies (Hanninen et al., 1997) and suggests mild difficulty in the area of

mental flexibility. Although no significant difference in the number of categories completed between the AAMI and OC groups was found, the AAMI group took significantly longer (in terms of number of cards) to complete the same number of categories as did the OC group. In other words, even though the AAMI were able to complete the required 6 categories (and thus did not appear different from the OC) they made more mistakes (both errors and perseverative errors) than did their OC counterparts, resulting in an overall greater number of cards played. As such, perhaps a better discriminative question to ask when using the WCST with questionably impaired elderly individuals is 'How many cards are required to achieve 6 categories?', rather than 'Were six categories achieved?' The answer to the former question may provide the clinician with more appropriate information with respect to their patients' subtle executive function difficulties. However, further study examining test validation of this idea would be required before its implementation into clinical use. The performance of the AAMI group suggests a mild difficulty with cognitive flexibility and perseveration (difficulty switching from a habitual response to a novel response). Cognitive rigidity and tendency for perseveration are considered indications of frontal lobe pathology (Stuss & Benson, 1986) and have been well documented in AD.

The CTT, as performed in the current study, revealed different findings for the two parts of the test. CT1, a measure of psychomotor speed and attention was able to differentiate the OC from the AAMI subjects. The CT1 has been reported to be a sensitive indicator of very early impairment (Morris & Fulling, 1988) and also has been found to distinguish between early AD and matched normal controls (Storandt et al.,

1984). Thus, current findings are congruent with those in the literature. The CT2, however, did not differentiate the OC and AAMI subjects. This is somewhat surprising as CT2 is thought to be the more sensitive part of the test. CT2 requires more information processing, and consequently, more reliance on executive function abilities. Why it did not reach significance is unclear. Perhaps the AAMI group evidences a relative sparing of function underlying the ability to perform CT2. However, previous decline in performance on this tests has been documented in the AAMI population (Hanninen et al., 1997). Thus, this hypothesis is not congruent with past findings. Further, CT2 relies on ability to shift set - an ability also found in the WCST which was impaired in the AAMI sample in this study. Thus, although there was a trend suggestive of AAMI involvement on this measure (based on the difference in mean scores), the number of subjects in each group may have been too small to allow this difference to reach significance.

The Stroop CW test, and the Similarities subtest did not differentiate the OC from the AAMI sample. The negative findings on the Stroop tests is contrary to those of Hanninen and group (1997). The Similarities subtest has not yet been studied in the AAMI population. The Stroop, measuring ability to inhibit cognitive interference, was quite impaired in the AD sample (test norms place the AD performance below the first percentile). Based on current results this cognitive ability appears spared in the AAMI sample obtained for the study. Though the Similarities subtest differentiated the AD group from the OC and AAMI, the performance of the AD group is not considered impaired using the WAIS-R normative data (their mean score falls in the average

range). Thus, the AAMI group appeared to perform well on measures of ability to inhibit cognitive interference and verbal concept formation, and even the AD group can be said to have performed well on the latter. The lack of significant findings on these measures may be a result of the high level of functioning of the groups. First off, the normative data noted above do not take into account level of education. As such the performance compared to normative data quoted above may be artificially inflated. Adequate education based normative data would better address this possibility. A second possibility is that the abilities measured by the tests may well be preserved in a specific population of high functioning individuals. Clearly the ability to form verbal concepts is very well developed in highly educated individuals. Finlayson, Johnson and Reitan (1977) compared the relationship of level of education to neuropsychological measures in brain-damaged and non-brain-damaged individuals. Their results indicated University-educated brain-damaged individuals performed significantly better on several WAIS-R subtests than did a sample of non-brain-damaged high-school graduates. One of those tasks included the Similarities subtest. Thus, the level of functioning of the groups may exert a protective effect on their performance, particularly evident on tasks strongly correlated to educational attainment such as verbal concept formation. Though the pattern of spared versus impaired abilities across executive function abilities makes conceptual sense in the population employed in the study, it is important to note that the findings may differ from the performance of a general population.

An examination of the effect size in the first analysis between all three groups

indicated two of the variables accounted for a moderate amount of variance: the similarities subtest (about half) and the StroopCW score (about two thirds). It appeared on initial examination these tests might be important in discriminating between the groups and thus potentially useful as sensitive diagnostic tools. However, as noted above, closer examination during the second analysis between the OC and AAMI samples revealed that these were two of the three variables that failed to reach significance. Further, they accounted for only minimal amount of variance between the two groups (approximately ten percent). Thus, it can be surmised that it was the poor performance of the AD group (particularly on the Stroop Colour Word test) compared to the relatively well intact performances of the other two groups that was contributing to the impressive effect size. As such, the Similarities subtest and the Stroop Colour Word test can be considered good discriminative tools between clear AD and control populations, but lack sensitivity between the AAMI and OC populations.

In summary, significant differences between the OC and AAMI subjects could be demonstrated on several, but not all, of the executive function measures used in the study. The lack of findings may be due to several factors. Some of these factors may include inadequate power to detect differences, poor performance of the OC subjects on those particular measures, intact performance of the AAMI subjects on those measures, or perhaps the nature of the population studied allowed preservation of the abilities underlying the successful completion of the measures. If AAMI is indeed not a benign entity but rather the early stage of AD, then another possibility for the lack of findings in the current study, may be simply that given more time, deficits on these

measures will be evident.

Hypothesis III. *It is predicted that the AAMI group will show a parallel profile of executive function performance as the AD group.* This part of the study addressed the issue of the pattern of group performance on the various measures of executive function. The positive finding on the levels test was expected and is in keeping with the results of the MANOVA indicating significant group differences between the AAMI and the AD samples. Though the overall profiles were not deemed statistically parallel at this point in time, there were several similarities in noted in the two profiles. The COWA and the TOT were performed more poorly in the AAMI group, relative to performance of the other variables, than they were in the AD group. Put differently, the AD subjects, as a group, performed best on the COWA and the TOT. Conversely, this was not the case with the AAMI group. It is interesting to note that these two variables were also the only ones that were significantly different between the OC and AAMI in the first analysis of all three groups together. As such, these two measures are likely good indicators of AAMI dysfunction, and may provide good discriminative power with questionable AAMI. Except for the COWA and TOT, the pattern of performance of the AAMI group was similar to that of the AD group. Thus, the most difficult aspect for both groups was that seen on the WCST, characterized by poor set-shifting, perseveration, and difficulty with abstraction, followed by slowed psychomotor speed on the CT1, and so on. A similar pattern has also been reported in the two groups on tasks assessing memory function. For example, the earliest aspect of memory to be affected in AD is that of recent memory; a pattern also seen in AAMI (Crook et al., 1986).

The inferior performance of AAMI subjects on a frontal lobe test battery in the current study might reflect the existence of a mild frontal lobe pathology in this group. In their MRI study, Soininen and co-workers (1994) found that AAMI subjects evidenced mild structural abnormalities in the temporal lobe. In a subsequent study, these researchers later obtained results which suggested frontal involvement in AAMI on the basis of neurophysiological findings (Soininen et al., 1995). Based on the latter results, this group went on to examine the frontal lobes of individuals with AAMI by means of MRI volumetric analysis (Hanninen et al., 1997). Results indicated no major structural abnormalities in the frontal lobes of AAMI subjects by either MRI volumetric analysis or visual analysis of the MRI's. Correlations between the psychometric performance of the AAMI group on four tests of executive function and MRI volumetric measures were subtle. However, the authors felt that the lack of correlation may be in part due to the fact that they analysed the whole frontal lobe volumes, and not more specifically the volumes of the lateral convexity of the frontal lobe. Moreover, they felt functional changes likely preceded structural changes in age-related brain pathology. As such, they indicated potential future use of functional MRI, PET, or SPECT studies for examining neuropsychological and brain function interactions in the AAMI population. As of yet the notion of frontal lobe pathology in AAMI has not been definitively documented. The results of the current study provide neuropsychological evidence of frontal involvement in AAMI. Thus, the recommendations of functional imaging studies put forth by Hanninen et al., is considered a useful and valid step in the study of individuals with AAMI.

The Cognitive Continuum

The concept of a cognitive continuum suggests that dementia, particularly AD, is a direct consequence of the normal aging process alone. Thus, normal aging, AAMI, and AD are not thought of as discrete categories, but rather, lie on a continuum from normalcy to pathology. As such, this theory holds that individuals who live long enough will eventually develop the full dementia syndrome (Smith et al., 1996). Support for the notion of cognitive continuum has been gained from several converging fields including neuropsychology, neuroimaging, and neuropathology (Brody, 1982; Dickson et al., 1991; Parnetti et al., 1996). Several authors have rejected the concept of a cognitive continuum. Rather, these researchers suggest dementia is partly due to normal aging but that the deficits are increased by additional, unrelated disease, or by the acceleration of normal aging due to other factors. Still others propose that AD is a specific disease process, unrelated to normal aging (Berg, 1985).

The debate continues whether AAMI could be seen as an intermediate phase in a continuum from normal aging to Alzheimer's disease, or whether it is merely a benign process perhaps reflecting an increased variability of cognitive performance in the elderly population. Studies to date have thus far produced varied results. Some studies have shown that AAMI is relatively stable and does not necessarily deteriorate to a dementia state (Hanninen et al., 1995; Howard, 1993; Nielsen, Lolk & Kragh-Sorensen, 1998). There is, however, other evidence that this population manifests the progressive mental deterioration characteristic of AD dementia and as such may be an early form of the disease process (Brayne & Calloway, 1988; Flicker et al., 1993; Smith

et al., 1996). Thus, the question remains 'Is AAMI an early stage of AD'? The results of the current study provide supporting evidence. Examination of the criteria for probable AD (NINCDS/ADRDA; McKhan et al., 1984) indicates, in addition to other criteria, the requirement of deficits in two or more areas of cognition. AAMI fulfills half of that criterion through the memory decline evidenced by all individuals in the population. Based on results of this study, individuals with AAMI also show decline in a second area of cognition, namely, executive function. To this end, it can be argued that the AAMI group fulfills to some degree the criteria for probable AD. Though the definitive resolution of the question whether AAMI is a prodromal stage of AD may require additional research efforts, the current study indicates AAMI can no longer be considered just a mild memory disorder. Additional areas of cognition have yet to be examined in the AAMI population. If involvement is indeed evident in other areas of cognition (e.g., visuospatial function) as well, it would indicate the disorder is one with multiple cognitive involvement, providing support to the notion that AAMI is not benign, but rather an early, though mild form of AD.

Longitudinal studies examining the course of AAMI over time are useful in providing information with respect to the question of AAMI's relationship to AD. The basic premise is this: compare the rate of individuals with AAMI who progress to dementia to the rate of individuals in the general population (without a diagnosis of AAMI) who develop dementia over the same time frame. If the rate is greater in the former group, then the presence of AAMI would appear to be a strong predictor of who will develop AD, and as such may represent an early form of the disease. Several studies that have

suggested AAMI may be an early form of dementia have indicated significant rates of conversion to AD (up to 75%) (O'Neill et al., 1992). Similarly, individuals diagnosed with mild cognitive impairment (MCI), a disorder similar to AAMI, have evidenced high conversion rates to full dementia syndromes (55% by 5 year follow up) (Smith et al., 1996). Subsequent studies on individuals with MCI found that 45 percent of individuals diagnosed developed AD by three year follow-up (10-15% of MCI subjects per year). By contrast, only one percent of healthy individuals over the age 65 are reportedly diagnosed with AD each year (NIA, 1998). Morris and colleagues (1991) have demonstrated that all 10 of their mildly demented subjects (CDR = 0.5; corresponds to the level of AAMI impairment) at autopsy evidenced sufficient neurofibrillary tangles and senile plaques to warrant a diagnosis of AD. Though these results and other similar findings suggest individuals with mild cognitive impairment such as AAMI may actually have an early form of dementia, caution should be taken before this conclusion can be made. Certainly, conversion rates have varied widely depending on the study in review. Several longitudinal studies have failed to show AAMI conversion to dementia, but rather, indicate the stability of the disorder over time. Though these findings may reveal AAMI is not a prodromal form of AD, several other possibilities may account for their conclusions. The lack of findings may be due in part to differing diagnosis at baseline, which makes comparison across studies rather difficult. Also, the uncertainty of the length of time one exhibits AAMI symptoms before demonstrating signs of AD dementia is extremely unclear. Perhaps the studies that failed to show an AAMI progression to

AD merely did not wait long enough. Clearly, the study examining Catholic nuns (Snowdon et al., 1996) suggests the prodromal phase may last for decades before the symptoms of full dementia begin to manifest. Some individuals may fulfill criteria of AAMI for years without ever progressing to full dementia. Support for a long prodromal phase of AD is suggested through autopsy studies of individuals age 20-100 that showed the neurofibrillary tangles and neurophil threads found in AD developed over approximately five decades (Ohm et al., 1995). In all likelihood, many individuals with AAMI may die of other conditions before the full dementia syndrome is expressed. It is likely that a host of environmental, biological, and/or psychosocial risk factors play a role in the timing of the manifestation of the dementia syndrome. However, the current study suggests that the presence of AAMI indicates the eventual development of AD, though the time at which this occurs remains unclear.

Whatever the eventual answer is to this question, the results of the current study demonstrate that at very least, the concept of AAMI can no longer be viewed as that of a mild memory disorder, but must be viewed as a disorder with involvement in two areas of cognition which can be distinguished from healthy, education matched, peers.

Importance of Study Findings

AAMI may be an early form of AD. Although the value of treating AAMI itself is currently unclear, there is a widespread consensus that it would be of great importance to delay and ideally to prevent the progression of incipient AD to frank dementia. Given that prevention is generally preferred to treatment, the AAMI population would have the greatest potential to benefit from preventive and restorative therapy. Neurochemical

replacement therapy has recently emerged as a useful treatment strategy of AD. However, as specific neurochemical deficits have not been identified in the AAMI population, therapy has focussed on the use of nootropics, which do not rectify specific biochemical defects. Since AAMI is by definition not a disabling condition, the benefits of any putative treatment must be high and the treatment must be very safe in order to have a reasonable risk benefit ratio. Nootropics improve cognition and have essentially no side effects (Giron & Koller, 1998). They are typically regarded as 'metabolic enhancers' although many have cholinergic activity (Sarter, 1991). Piracetam, an agent in the nootropic category, has been studied in the AAMI population. Though results were generally disappointing, some benefit was seen when combined with memory training (Israel, Melac, Milinkevitch & Dubos, 1994; Israel, Myslinski & Kozarevic, 1998). Non-prescription agents such as the anti-oxidants Vitamin E are also gaining attention in the treatment of AAMI, and clinical trials have begun examining their potential effects.

Finally, the significance of the current study findings also lies in the identification of potential responsibilities of primary health professionals who are dealing directly with individuals with AAMI. The results of this study suggests that patients meeting criteria for AAMI should undergo a regular medical follow-up to chart progression of cognitive symptoms. Proper monitoring of symptoms and rate of decline is of utmost importance when considering factors such as driving ability, and occupational quality control (i.e., several occupations rely exclusively on intact executive functioning and memory ability). One interesting approach has been proposed by Blusztajn (1994) to help

identify the cognitive course of individuals at risk for the development of AD. This approach would entail the use of psychometric tools capable of detecting subtle declines in cognition. The author suggests that the measures be adapted to consist of a self-administered computerized test that an individual would undergo every 6 months. Further suggestions include the notion that the computerized test could be connected via the Internet to a central database. As such, individuals need not visit a clinic or hospital, but may provide test data through their home-based computer. This would allow for a large number of individuals to be effectively monitored, as this method would reduce the time demands for health professionals to administer cognitive tests to individual subjects. To be effective, a large longitudinal study with healthy volunteers would be followed over time. It should be noted, this approach has been successful in studies on breast cancer in nurses and on the effects of aspirin on the development of coronary heart disease in physicians (cited in Blusztajn, 1994).

Limitations of Study

As with many studies using clinical samples which are difficult to obtain, the sample size in the current study was relatively small. Further, as a group of individuals with a very high level of education was examined, the amount to which generalizations of the results can be made to the population in general may be limited. However, it can be argued that the fact executive function involvement was detected at all in this group, who characteristically exhibit very well developed executive skills, indicate the same involvement should be demonstrable in the general population.

The tests of executive function used in the current study were chosen for their

validity and reliability, and for their documented relationship to frontal lobe functioning. While this relationship has been documented through various investigative measures (SPECT; PET) some authors argue that the 'regional specificity' of the tests is not completely understood (Hanninen et al., 1997). Several studies have suggested associations of the tests with other brain regions than the frontal lobes (Anderson, Damasio, Jones, & Tranel, 1991; Corcoran, 1993; Strauss, Hunter & Wada, 1993; Reitan & Wolfson, 1995; Vilkki & Holst, 1994). For example, the TOT has received criticism (Tranel, Anderson, & Benton, 1995) on the grounds that it requires such an extensive integrated set of spatial and sequential elements that it typically occupies a factor all its own within executive function boundaries (Levin et al., 1991). Based on their results, the authors felt the test was poor in specificity as the number of subordinate cognitive processes involved increased the number of interpretations of failures other than executive function per se. Thus, though the tests for the most part are sensitive to executive functioning, there may be the possibility that other cognitive domains were assessed in combination.

Though depression was controlled for in the current study, no measure of anxiety was administered. Previous studies have suggested that anxiety, which is well documented as exerting potential negative affects on cognitive functioning, may be a factor for the AAMI group in particular. While it is unlikely to play a significant selective role relative to the AD and OC populations, future studies may be designed to assess the level of anxiety in their AAMI samples.

The sample of AD subjects that was used for the current study was an

undifferentiated sample, thus, no identification of possible sub-groups was undertaken. As a result, the AD group may represent a rather heterogenous sample. Scores on some of the tests were quite varied, which may be in part accounted for by the presence of subgroups, though disease severity may also have played a role. Similarly, sub-grouping the AD sample based on age at onset may also have produced different results. Past research has suggested early and late onset AD exhibit different clinical signs and symptoms. Specifically, investigators have suggested that focal symptoms such as aphasia, agnosia, and apraxia are more frequent and more severe in early-onset AD, whereas late-onset AD may be characterized by generalized cognitive decline and confusion (Blennow et al., 1991). The decision in the current study to sample an undifferentiated AD group was based in the fact that the concept of subgrouping in AD, though an important area of study, is not yet not fully or definitively developed.

Another possible limitation of the current study is that non-AD subjects may have been included in the AD sample. While there is no complete certainty, without brain tissue biopsy, how many of the patients in the group actually suffered from AD, accuracy rates of clinical diagnoses are usually at approximately 85 to 90% (Mohr et al., 1999). Thus, the chance of a non-AD subject participating in the study was minimal. Another limitation may be co-morbidity rates which indicate that combined vascular and AD pathologies coexist in as many as 27.5% of dementia patients (Mirra et al., 1991) and diffuse Lewy body disease in as many as 20% (Kosaka, 1990; Hansen et al., 1990). While some brain infarctions have not been found to cause AD dementia

in and of themselves, they may contribute to a more severe cognitive impairment (Pantoni & Garcia, 1995). This hypothesis is congruent with findings of Snowdon and colleagues (1997) which indicated subjects who evidenced infarction in certain brain regions had more clinical symptoms of dementia than could be explained by the number of plaques and tangles in the cerebral cortex.

With respect to potential limitations of the AAMI criteria itself, several opponents have argued that the exclusion criteria may be too restrictive. As part of the Canadian Study of Health and Aging, Ebly et al (1997) indicated 25% of seniors who resided in the community had functional impairments, 25% had a psychiatric condition, 10% a neurological condition exclusive of dementia, and up to 80% had a chronic medical condition. As such, the authors caution that 'any proposed instrument designed to describe cognitive impairment in the elderly must recognize and accept the medical complexity of seniors' (Ebly et al., 1997; p. 618). In the current study, the collection of an otherwise healthy sample of AD and AAMI subjects proved rather difficult, often times due to medical history which, based on exclusion criteria, eliminated the subject from study. To this end, several researchers have argued that the exclusion criteria of AAMI (or any other classification instrument designed to describe cognitive impairment in the elderly) should be more lenient, allowing inclusion of individuals whose medical condition may not affect their memory performance (Blackford & LaRue, 1989). Of particular difficulty, though, is the determination, if certain medical conditions may have an impact on cognitive performance. While there is evidence that physical health status such as presence of diabetes (Zelenski, Crimming, Reynolds, & Seeman, 1998),

hypertension (Zhu, Viitanen, Guo, Winblad, & Fratiglioni, 1998) cardiovascular disease (Breteler, Claus, Grobbee, & Hofman, 1994), obesity, or history of smoking (Kilander, Nyman, Boberg, & Lithell, 1997) to name a few, may exert some effect on cognition, the relationship is not always conclusive (Steen, Berg, & Steen, 1998; van Boxtel et al., 1998). Uncertainty remains with respect to the nature and extent of cognitive impairment, the permanence of the impairment, and whether each individual is affected in the same way (e.g., Zelinski et al., 1998). As the AAMI criteria currently dictate, if an individual meets inclusion criteria of AAMI, but presents with a history of renal disease, he or she is no longer eligible for diagnosis of AAMI. As such, several individuals may be excluded from study, and may not be eligible for potential treatment. If the purpose of the AAMI exclusion criteria are meant solely to define a 'pure' group of individuals free of any other conditions who may be followed over time for research purposes, then the exclusion criteria as it stands may not pose significant problems. If, however, the criteria are intended to describe a population of individuals living in the community and in institutions, then there may be serious limitations.

Future Directions

While the current study provided information with respect to the nature of AAMI, further research is needed. Selecting a group of individuals with AAMI who evidence known risk factors for AD such as the ApoE ϵ 4 allele, or positive family history, and following them over time continues to be an important research strategy.

Currently, individuals with AAMI, who constitute a high risk group for development of dementia, must evidence memory impairment to be included into research studies.

However, based on current results, it is apparent this group may also have impairment in areas other than memory. The question of order of presentation of impairments has not yet been addressed. Should executive dysfunction (or possibly other areas of cognition not yet studied, e.g., visuospatial abilities) manifest prior to memory decline, then an entire group of individuals who may be at risk would not even be identified for study. That is, limitation to identification based on memory problems may exclude individuals who have acquired intellectual defects that would be important to identify and document. Thus, research examining other areas of cognitive function would be an important area of further study.

Conclusions

The current study examined executive function in a sample of AAMI subjects, healthy subjects, and subjects with probable AD. The results obtained allow for several conclusions to be made. The first set of conclusions pertains to the measures employed in the study. The six executive function tests used can be considered sensitive to AD impairment in a group of high functioning individuals. The TOT, the StroopCW, and the WCST are difficult tests for some individuals with AD. Thus, tools such as the modified WCST (Nelson, 1976) may be more appropriate with this population as they may be simpler, and considerably less stressful for the AD patient. Previous study has shown sensitivity of modified versions of the WCST to the AD population (Bondi et al., 1993). The Similarities subtest of the WAIS-R and the Stroop CW are sensitive in discriminating between AD and healthy adults, but lack sensitivity distinguishing AAMI from OC. Two tests that did display good sensitivity between the

AAMI and OC groups were the TOT and COWA. As such, these tests should be included in any neuropsychological test battery with older adults when there is question in differentiating healthy individuals and those with AAMI.

The second set of conclusions pertains to the nature of AAMI and its relationship to AD. First off, individuals with mild to moderate AD evidence impairment across a number of executive function measures. Further, the fact that the study was able to provide such clear evidence in a population least likely to show executive involvement indicates executive dysfunction is indeed present early in the disease course. Second, individuals with AAMI evidence impairment on several executive function measures compared to age and education matched control subjects. Further, their pattern of executive functioning shows some similarities to that of the AD group. As such, not only are the same memory systems affected in the two disorders, but similar executive systems appear affected as well. Based on involvement of two cognitive domains similar to those found in AD, AAMI fulfils to some degree the diagnostic criteria of probable AD. Thus, AAMI must be considered more than a mild memory disorder. The study suggests that indeed AAMI is more morbid than was previously believed and may well be a prodromal stage of AD.

These results are important particularly considering new evidence has that has emerged from the field of psychopharmacology. At the 1999 meeting of the International Psychogeriatric Association (August, 1999), data were presented on the long term treatment effects of a cholinesterase inhibitor, rivastigmine (Exelon) (Anand, Messina, Hartman, Graham, & Cicin-Sain, 1999) which were most encouraging.

Results from long-term extensions of the placebo-controlled studies indicated that after two years of treatment on the drug, the cognitive decline in AD patients was less than that noted in subjects receiving placebo for six months. Thus, the results indicated at minimum, an 18-month delay in the progression of cognitive symptoms as a direct result of the drug effect. Conclusions from this study are that the therapeutic effects can be maximised by initiating treatment as early as possible, and by continuing treatment as long as feasible. Thus, the evidence provided in the current study indicating that AAMI may be a prodromal stage of AD is important and timely. With the importance of the identification of AD as early as possible, the current study raises the possibility that such an early identification may be the diagnosis of AAMI.

In conclusion, this investigation provides considerable evidence that AAMI is likely a prodromal stage of AD. As such, individuals meeting AAMI criteria should at very least undergo regular assessment to monitor progression of cognitive decline. Moreover, though, is the importance that AAMI may represent a very early form of AD, and that individuals meeting criteria for AAMI, should be identified in order to implement treatment strategies which will delay progression to and evolution of dementia symptoms as long as possible.

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APPENDIX A

**CRITERIA FOR CLINICAL DIAGNOSIS OF ALZHEIMER'S DISEASE
ESTABLISHED BY:
NATIONAL INSTITUTE OF NEUROLOGICAL AND COMMUNICATIVE DISORDERS
AND STROKE AND THE ALZHEIMER'S DISEASE AND RELATED DISORDERS
ASSOCIATION (NINCDS-ADRDA)**

The criteria for the clinical diagnosis of PROBABLE Alzheimer's disease include:

- ▶ Dementia established status by clinical examination and documented by the Mini-Mental Test, Blessed Dementia Scale, or some similar examination, and confirmed by neuropsychological tests;
- ▶ Deficits in two or more areas of cognition;
- ▶ Progressive worsening of memory and other cognitive functions;
- ▶ No disturbance of consciousness;
- ▶ Onset between the ages 40 and 90; most after age 65;
- ▶ Absence of systemic disorders or other brain diseases that in an of themselves could account for the progressive deficits in memory and cognition.

The diagnosis of PROBABLE Alzheimer's disease is supported by:

- ▶ Progressive deterioration of specific cognitive functions such as language (aphasia), motor skills (apraxia), and perception (agnosia);
- ▶ Impaired activities of daily living and altered patterns of behaviour;
- ▶ Family history of similar disorders, particularly if confirmed neuropathologically;
- ▶ Laboratory results of normal lumbar puncture, normal pattern or nonspecific changes

in EEG, such as increased slow-wave activity, and evidence of cerebral atrophy on CT scan with progression documented by serial observation.

Other clinical features consistent with the diagnosis of PROBABLE Alzheimer's disease after exclusion of causes of dementia other than Alzheimer's disease, include:

- ▶ Plateaus in the course of progression of the illness;
- ▶ Associated symptoms of depression, insomnia, incontinence, delusions, illusions, hallucinations, catastrophic verbal, emotional, or physical outbursts, sexual disorders and weight loss;
- ▶ Other neurological abnormalities in some patients, especially with more advanced disease and including motor signs such as increased muscle tone, myoclonus, or gait disorder;
- ▶ Seizures in advanced disease;
- ▶ CT normal for age.

Features that make the diagnosis of PROBABLE Alzheimer's disease uncertain or unlikely include:

- ▶ Sudden, apoplectic onset;
- ▶ Focal neurological findings such as hemiparesis, sensory loss, visual field deficits, and incoordination early in the course of the illness,
- ▶ Seizures or gait disturbances at the onset or very early in the course of the illness

Clinical diagnosis of POSSIBLE Alzheimer's disease:

- ▶ May be made on the basis of the dementia syndrome, in the absence of other neurologic, psychiatric, or systemic disorders sufficient to cause dementia, and in the presence of variations in the onset, in the presentation, or in the clinical course;
- ▶ May be made in the presence of a second systemic or brain disorder sufficient to produce dementia, which is not considered to be the cause of the dementia;
- ▶ Should be used in research studies when a single, gradually progressive severe cognitive deficit is identified in the absence of other identifiable cause.

Criteria for diagnosis of DEFINITE Alzheimer's disease are:

- ▶ The clinical criteria for probable Alzheimer's disease and
- ▶ Histopathologic evidence from a biopsy or autopsy

Classification of Alzheimer's disease for research purposes should specify features that may differentiate subtypes of the disorder, such as:

- ▶ Familial occurrence;
- ▶ Onset before the age of 65;
- ▶ Presence of trisomy-21;
- ▶ Coexistence of other relevant conditions such as Parkinson's disease.

APPENDIX B

CONSENT FORM

***EXECUTIVE FUNCTION IN HIGH FUNCTIONING
INDIVIDUALS WITH AGE-ASSOCIATED MEMORY IMPAIRMENT
OR ALZHEIMER'S DISEASE***

I, _____, am interested in participating in this study on executive function in older adults conducted by Linda Vasudev, Ph.D. student, and Dr. Erich Mohr, Professor of Medicine and Psychology at the University of Ottawa. The purpose of this study is to better understand the cognitive functioning of persons with Age Associated Memory Impairment and those with early Alzheimer's Disease.

I understand that my participation will be on a voluntary basis.

I understand that my participation will consist of a one hour session. This session has been arranged for _____. I understand that I am able to cancel or reschedule this time should it be required. During this time, I will be required to complete such tasks as: answer general knowledge questions, solve various puzzles, or generate various word lists.

The information I provide will remain strictly confidential. Individual test results will be distinguished solely by identification number, and my name will therefore not appear on published material.

I understand that I am free to withdraw from the study at any moment or refuse to participate without penalty.

I also have been informed that the only foreseeable risks or discomforts to myself may be a mild level of fatigue at the end of the session.

Should I desire, I will be informed in writing the overall results of the study to be made available upon completion of the study. I understand that individual summaries of test performance may be made available only after I have signed a release emphasizing that information was collected in a research context only and should not be interpreted to have clinical relevance.

Please retain a copy of this form for your personal file. If you require further information, please feel free to contact either of the following persons:

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Signature of Participant

Signature of Investigator

Witness or Substitute

Date