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**The Central Executive System of Working Memory and Primary Memory Deficits
in Patients with Probable Alzheimer's Disease**

**Dissertation
Submitted to the School of Graduate Studies
of the University of Ottawa**

In partial fulfillment of the requirements for the degree of Doctor of Philosophy

**Robbie D. Curwin
Ottawa, Ontario
2000**



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ABSTRACT

Alzheimer's disease is an insidious neurodegenerative disorder characterized by gradual and progressive deterioration in intellect, cognitive skills, personality, and functional independence. There is significant heterogeneity of symptom presentation in the early stages of Alzheimer's disease, however, memory impairment is universal. Both secondary and primary memory systems are consistently reported in the literature to be affected by the disease. Primary memory is considered a limited capacity system characterized by a rapid rate of forgetting. Historically, primary memory was thought to be a unitary system necessary for the transfer of information into secondary memory and underlying a range of cognitive functions such as reasoning and language comprehension. However, research over the past decade has suggested an important role of a deficient putative central executive system in working memory as fundamental to the deficits in primary memory demonstrated by patients diagnosed with Alzheimer's disease. Working memory is defined by two primary memory storage systems, the phonological loop, and the visuospatial sketchpad, controlled and organized by a central executive system. Research with respect to working memory in patients diagnosed with Alzheimer's disease has shown the phonological loop and visuospatial sketchpad to remain unaffected by the disease process during the mild stages of the disorder. Thus, deficits in primary memory were ascribed to a faulty central executive system. However, few, if any, empirical studies directly relating deficient primary memory with executive system dysfunction are available.

The goal of this dissertation is aimed at providing empirical validation that executive system dysfunction underlies the primary memory disturbance in a sample of patients diagnosed with probable Alzheimer's disease within the mild stages of dementia. Performance on measures of primary such as Digit Span and the Consonant Trigrams Test were compared amongst patients identified with a possible executive system disturbance, patients assumed to have executive functions relatively intact, and normal controls. Furthermore, Alzheimer's disease patients and normal controls were compared on the Random Generation Task, assumed to be the prototypical measure of central executive functioning in working memory.

The data supports the hypothesis that executive system disturbance may explain the difficulties that Alzheimer's patients have on measures of primary memory. Those patients identified with a putative executive system disturbance performed significantly worse on all measures of primary memory compared to those Alzheimer's patients assumed to have a relatively intact executive system. Furthermore, those Alzheimer's patients identified as having no executive dysfunction performed similarly to normal controls on measures of primary memory, thus further supporting the role of executive system disturbance in deficient primary memory functioning. Performance on the Random Generation Task also followed a similar pattern in that those patients with an assumed executive system disturbance performed significantly worse than those patients with a relatively intact executive system and normal controls. The current findings are discussed in the context of the working memory model proposed by Baddeley and Hitch in 1974.

INTRODUCTION

Alzheimer's disease (AD) is a neurological condition characterized by specific neuropathological changes within the cerebrum. Clinically, AD is distinguished by progressive memory, intellectual, behavioral, and functional decline of insidious onset (Papolla & Røbakis, 1995; Cummings & Khachaturian, 1996; Sloane, 1998). There is great symptom heterogeneity in the behavioral presentation of AD, particularly during the initial stages of disease progression (Grondon & Rosser, 1998). Differential involvement of language, visuospatial, and executive system functioning is not uncommon in early AD leading some researchers to reason that possible subtypes of AD may exist. However, memory deterioration is universal (Grondon & Rosser, 1998; Sloane, 1998).

The memory disturbance typical of AD universally reflects involvement of the secondary memory system. Secondary memory refers to an unlimited capacity storage system whereby memories are retained and retrieved for longer durations. Primary memory, on the other hand, refers to a limited capacity storage system with a much quicker rate of forgetting whereby memories quickly decay unless rehearsed and stored into the secondary memory system (Morris & Baddeley, 1988). Although primary memory is frequently affected in AD as the disease progresses, it is not equally affected during the early stages of the disease. A dissociation between the secondary and primary memory systems in early AD has been demonstrated in several investigations (Becker, 1988; Morris & Kopelman, 1986; Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986; Baddeley, Della Sala, & Spinnler, 1991; Becker, Bajulaiye & Smith, 1992) whereby primary memory may be relatively intact compared to secondary memory.

At one time primary memory was thought to be a unitary system and critical for the transfer of information into a more permanent store, and necessary for higher cognitive functions such as reasoning, planning, and language comprehension. However, the available data on both normal and patient populations did not support the unitary nature of the primary memory system. Thus evolved the concept of a tripartite working memory system as it more parsimoniously explained the available data. Working memory, often described as a cognitive function involved in briefly holding and manipulating information in consciousness, includes at least two independent primary memory stores. These primary memory systems are largely phonological and visuospatial in nature. In addition, working memory includes a putative central executive system (CES),

which is purported to be a system of attentional control (Baddeley & Hitch, 1974; Baddeley, 1998). The CES is thought to be one of the more important but least understood components of working memory (Baddeley, 1986; 1998; Towes, 1998). Nevertheless, dysfunction of the working memory system, particularly the CES, is thought by several researchers to be deficient in some AD patients within the mild stage of the disease compared to normal elderly controls. A deficient working memory is assumed by several investigators to underlie difficulties in reasoning, new learning, and language comprehension, (Morris & Kopelman, 1986; Becker, 1988; Baddeley, Della Sala, & Spinnler, 1991; Brugger, Monsch, Salmon, & Butters, 1996; Kemper 1997; Kempler, Almor, Tyler, Andersen, & MacDonald; 1998; Baddeley 1998; Collete, Van der Linden, Bechet, Belleville & Salmon, 1998; Wagner, 1999).

In those AD patients, within the mild stages of the disease, demonstrating a primary memory disturbance, it is a dysfunction of the CES that is thought to underlie the disturbance (Kopelman, 1985; Morris & Kopelman, 1986; Baddeley et al., 1986; Morris & Baddeley, 1988; Baddeley, 1998). Assessment of phonological short term storage in AD research has consistently found it to be intact (Morris, 1987; Baddeley, Bressi et al., 1991; Belleville, Perez & Malenfant, 1996), thus poor performance by some AD subjects on standard measures of primary memory such as digit span and the consonant trigrams test have been interpreted to reflect a faulty putative CES in working memory. However, in these studies, primary memory disturbance has not been directly related to difficulties in executive system functioning.

The goal of this dissertation is to investigate the nature of primary memory deficits in probable AD. Given that a central executive system disturbance is thought to underlie primary memory difficulties in some AD patients, then those patients demonstrating executive system difficulties should also demonstrate primary memory problems relative to AD patients without an executive system disturbance and normal elderly controls. To put this goal into context, a comprehensive review of the literature on AD, including the neuropathological and neurochemical correlates of the disease, clinical features, and AD memory research will be presented. Following this, a detailed elaboration of the working memory model (Baddeley & Hitch, 1974) and the research of this model as it is applied to probable AD will be presented concluding with the present study's objectives.

LITERATURE REVIEW

Neuropathology of Alzheimer's Disease

The brain regions that are thought to be most sensitive to the neuropathological changes associated with AD include medial temporal structures such as the amygdaloid complex, uncus, hippocampus, parahippocampal region, and entorhinal cortex (Kohler, Black, Sindén, et al., 1998; Brun & Englund, 1981). The posterior cingulate gyrus, superior parietal lobule, inferior and middle temporal gyrus, and inferior parietal lobule also show a predilection for neuropathological changes whereas sensorimotor, calcarine, and anterior cingulate areas of the neocortex usually remain unaffected until the very late stages of the disease (Brun & Englund, 1981).

Macroscopic neuropathological changes typically associated with AD include generalized cortical atrophy characterized by narrowed gyri, widened sulci and enlarged ventricles (Jack, 1998; Lishman, 1978). Specific atrophy in the hippocampal and entorhinal cortex are also reported early in the disease with even greater atrophy in these areas evident in the moderate to severe stages of AD (Frisoni, Laakso, Beltramello, Geroldi, Bianchetti, Soininen, & Trabucchi, 1999). Microscopic neuropathological changes include the neurofibrillary tangle and neuritic plaque (Jack, 1998; Mohr, Mann & Chase, 1990; McKhann et al., 1984). Decreased density of synapses and dendritic spines as well as cell death of selectively vulnerable neuronal populations including the nucleus basalis of Meynert in the forebrain, the nucleus raphe dorsalis in the midbrain, and the locus coeruleus at the anterior pontine level, are also identified as common neuropathological markers (Jack, 1998; Berg & Morris, 1990).

The neurofibrillary tangle is an intraneuronal structure that often displaces the nucleus and distorts the cell body and is associated with a number of abnormal proteins found in AD patients but not in the cognitively healthy elderly (Katzman & Jackson, 1991). Neurofibrillary tangles are most predominant in the hippocampal area, particularly the CA1 and subiculum, and amygdala but also occur throughout the brain sparing the primary motor and sensory regions (Terry & Davies, 1980; Kemper, 1984). In the very early stages of AD, neurofibrillary changes are thought to begin focally in the entorhinal cortex spreading with disease progression to the hippocampus and related medial temporal lobe and limbic areas and then to higher order association cortices (Jack, 1998). Neuronal loss and neurofibrillary tangles in the entorhinal cortex and hippocampus are presumed to

be the pathological correlates of the significant memory loss typical in AD (Growden & Rosser, 1998). Neurofibrillary tangles are also observed in normal aging but are rarely demonstrated within the cortex of intact elderly persons at autopsy and tend to be confined to the hippocampal region in normal aging. Furthermore, neurofibrillary tangles tend to be significantly more numerous within the brains of individuals suffering from AD than age-matched normal controls (Yamamoto & Hirano, 1985).

Neuritic plaques are extracellular and are composed of degenerating presynaptic neuronal terminals and reactive glia and macrophages with a central core of abnormal protein, amyloid (Arendt, Bigl, Tennstedt, & Arendt, 1985). All areas of the cerebral cortex show evidence of neuritic plaques, particularly the parietal lobe (Roth, 1978) and the amygdala, other limbic structures, and the corpus striatum (Herzog & Kemper, 1980). Although the neuritic plaque and the neurofibrillary tangle are often seen in other disorders and in normal aging, it is the combination of plaques and tangles and the frequency and density with which they occur in AD that make them neuropathological markers for the disease (Jack, 1998; McMenemey, 1970).

Both the neurofibrillary tangle and the neuritic plaque are widespread throughout the neocortex increasing in density from primary motor and sensory cortices to secondary association cortices. The highest density is found in multimodal association and limbic cortices (Kemper, 1984). Both are found in the amygdala and the hippocampus. Neurofibrillary tangles are found more abundantly than plaques in the nucleus basalis of Meynert and the large neurons of the pontine tegmentum (Candy, Perry, Perry, Irving, Blessed, Fairbairn & Tomlinson, 1983). Neurofibrillary tangles are rare in the neocortex and basal forebrain of the healthy elderly (Kemper, 1984).

Single photon emission tomography (SPECT) has been used to investigate regional metabolic abnormalities in AD. Reduced metabolism in the anterior and posterior cingulate gyrus, entorhinal and hippocampal cortices, and anterior thalamus has been identified in the preclinical stages of AD with greater involvement observed in the temporoparietal regions with disease progression (Johnson, Jones, Holman, Becker, Spiers, Satlin, & Albert, 1998; Kennedy, 1998). Frontal lobe pathology at one time was thought to be affected relatively late in the progression of the disease (Brun & Englund, 1981), however, recent studies have

reported abnormalities in prefrontal cortex even in the early stages of the disease (Johnson et al., 1998; Teipel, Hampel, Alexander, Schapiro, Horwitz, Teichberg, Daley, Hippious, Moller, & Rapoport, 1998; Frisoni et al., 1999).

Leukoaraiosis or white matter pathology has also been observed in certain AD subjects and associated with greater cognitive impairment (Amar, Bucks, Lewis, Scott & Wilcock, 1996). Leukoaraiosis is often associated with cerebral vascular disease and thus it is possible that such findings in AD reflect simply the superimposition of cerebral vascular disease on AD. However, not all AD subjects with leukoaraiosis go on to develop cerebral vascular disease, thus leading some investigators to conclude that a subset of probable AD patients might have white matter pathology as a direct result of AD (Amar et al., 1996). Atrophy of the corpus callosum, particularly in the rostrum and splenium, has also been associated with AD (Teipel et al., 1998). Other neuropathological changes seen in AD include granulovacuolar degeneration of the large pyramidal neurons and Hirano bodies, which are rod shaped neuronal inclusions, in the hippocampus (Heston et al., 1981). Amyloid deposits, a microscopic protein composed of fine fibrils, is also demonstrated within the walls of small intracortical blood vessels (Heston, Mastri, Anderson, & White, 1981) and thought to be critical in the pathogenesis of neuritic plaques (Sloane, 1998).

Attempts to associate the presence and density of senile plaques and neurofibrillary tangles with cognitive deficits and dementia severity has met with conflicting results. Severity of dementia has been associated with neurofibrillary tangles and senile plaques in association cortices and the hippocampus (Constantinidis, 1978; Katzman & Jackson, 1991) and associative visual agnosia has been related to neurofibrillary tangles in the occipitotemporal association areas (Giannakopoulos, Gold, Duc, Michel, Hof, & Bouras, 1999). Although density of neurofibrillary tangles have been more clearly associated with cognitive difficulty, several studies have failed to demonstrate an association between senile plaques and dementia severity or focal cognitive abnormality in AD (Giannakopoulos, Hof, Michel, Guimon, & Bouras, 1997; Giannakopoulos et al., 1999).

Neurochemical Changes

Neurochemical changes in the cerebrum are also frequently observed in AD. The primary neurochemical abnormality in AD is depletion of acetylcholine (ACh) as measured by reductions in synthetic and degrading enzymes, choline acetyltransferase (ChAT) and acetylcholinesterase (AChE), respectively (Kuhl,

Koepppe, Minoshima, Snyder, Ficaró, Foster, Frey, & Kilbourn, 1999; Reed & Jagust, 1999). Significant reductions of acetylcholine has been reported in the frontal cortex and hippocampus (Barner & Gray, 1998) and as much as 60 to 90 percent decreases in ChAT activity has been demonstrated post mortem (Kuhl et al., 1999). However, these percentages are often obtained when the patient has come to autopsy reflecting ChAT reductions within the severe stages of dementia. It has been suggested that perhaps only 30 to 40 percent reductions of ChAT or AChE are typical in the earlier stages of the disease (Kuhl et al. 1999; Reed & Jagust, 1999). ACh deficiency in AD is thought to be due to loss of cholinergic neurons in the Nucleus Basalis of Meynert, however, postsynaptic cholinergic receptors are reported to remain relatively intact in the early course of the disease (Terry & Katzman, 1983; Barner & Gray, 1998).

The amount of acetylcholine deficiency has been reported to be different depending on age of onset of AD. In younger subjects with the disease (age of onset approximately 65 years), acetylcholine has been found to be decreased over the entire neocortex including the frontal lobes whereas in older subjects (age of onset around 80 years), acetylcholine deficiency was found to be predominately restricted to the temporal lobes including limbic structures such as the amygdala and hippocampus (Rossor, Iversen, Reynolds, Mountjoy, & Roth, 1984). APOE-4 mutation has also been associated with a greater reduction in cholinergic activity compared to probable AD patients without the mutation (Gauthier, 1999). ACh synthesis is inversely related to both cognitive impairment and mean plaque count (Perry, Tomlinson, Blessed, Bergmann, Gibson, & Perry, 1978).

Although a cholinergic deficiency is characteristic of AD, it is not a disease of a single neurotransmitter but a more complex disorder with multiple neurotransmitter and neuropeptide deficiencies (Feldman & Gracon, 1996; Davies & Terry, 1981; Peabody, Davis, & Berger, 1986). Neuronal degeneration in the locus coeruleus and the dorsal raphe nuclei are sometimes demonstrated in AD (Bondareff, Mountjoy, & Roth, 1982; Yamamoto & Hirano, 1988). Noradrenaline, somatostatin, and γ -aminobutyric acid have also been reported to be deficient in some AD patients, particularly those with earlier age of onset (Rossor et al., 1984; Adolfsson, Gottfries, & Roos, 1979; Francis, Palmer, & Sims, 1985). Somatostatin concentrations have been found to be lower in parietal association areas and correlated with decreased cholinesterase activity in AD. Furthermore, somatostatin like immunoreactivity has been found to be present in plaque containing neurons and neurofibrillary tangles leading some investigators to suggest that somatostatin

containing neurons may be an important site of damage in AD and may be associated with damage to the cholinergic system (Johannessen, Mohs, Lawlor, & Altstiel, 1995). Dopamine and serotonin have also been found to be deficient in some cases (Gottfries, Bartfai, Carlsson, Eckernas, & Svennerholm, 1986). The presence of deficiencies in dopamine and serotonin has been associated with greater severity of dementia and earlier death (Selkoe & Kosik, 1984).

Neurotransmitter Replacement Therapies. The importance of acetylcholine (ACh) in human memory has been acknowledged for years and given the consistent findings of ACh depletion in AD, attempts at ACh replacement as a therapy to ameliorate cognitive functioning in probable AD have proliferated (Reed & Jagust, 1999; Barner & Gray, 1998; Crimson, 1994). However, the failure of acetylcholine precursors (e.g., lecithin and choline) to facilitate the synthesis of acetylcholine presynaptically have been reported in probable AD (Gauthier, 1999; Forette & Boller, 1998). On the other hand, the development of pharmacological agents that inhibit the degradation of acetylcholine within the synapse have shown therapeutic promise in AD. Currently, two cholinesterase inhibitors are available for use in the clinical treatment of AD in the United States, tacrine, and donepezil, with the latter also approved in Canada (Sloane, 1998; Barner & Gray, 1998; Gauthier, 1999). The effects of tacrine and donepezil are considered modest and patients who respond well to the drugs are reported to return to a level of functioning that was present six to twelve months before commencement of medication (Sloane, 1998). Tacrine has been demonstrated to delay nursing home placement (Small, Rabins, Barry, Buckholtz, DeKosky, & Ferris, 1997).

The first large scale study of an AChE inhibitor involved tacrine (Gauthier, 1999). However, tacrine has a short half life necessitating dosage requirements up to four times daily, thus, decreasing the likelihood of compliance (Gauthier, 1999). Because of adverse gastrointestinal side effects associated with tacrine use, gradual upward titration to a maximally therapeutic dose of between 120 and 160 mg is required (Gauthier, 1999). Beneficial effects of tacrine use are documented and patients who were able to tolerate the maximum therapeutic dose tended to remain out of long term care institutions longer than those patients able to tolerate only small doses of tacrine (Knopman, Schneider, & Davis, 1996). Multicenter clinical trials of tacrine have been conducted in a variety of countries including Canada. These studies typically utilize a double blind, placebo controlled, randomized methodological format with a variety of safety and efficacy outcome measures (Gauthier, 1999). With respect to tacrine, improved performance by probable AD

patients compared to age matched controls on placebo have been demonstrated within 12 to 24 weeks on most efficacy outcome measures such as psychometric tests, functional measures, family ratings, and clinician's ratings (Davis, Thal, & Gamzu, 1992; Forette, Bert, Breuil, & Boller, 1992, Forette, Hoover, Gracon, Rotrou, & Hervy, 1995). Beneficial effects associated with tacrine are reported in approximately 26 to 55 percent of patients who can tolerate the medication (Schneider & Forette, 1996). However, liver toxicity, gastrointestinal side effects, and daily multiple dosage regimen have been cited as major limitations in its clinical use (Forette, Bert, Breuil, & Boller, 1992, Forette, Hoover, Gracon, Rotrou, & Hervy, 1995; Gauthier, 1999).

Donepezil, the only pharmacological agent for the symptomatic relief from AD currently available clinically in Canada, is a selective cholinesterase inhibitor thought to be most efficacious in some AD patients within the mild to moderate stages of disease (Barner & Gary, 1998; Gauthier, 1999). By preventing the metabolism of ACh, increased concentrations of ACh remain in brain synapses, which allows for increased post synaptic stimulation of muscarinic receptors (Barner & Gray, 1998). Donepezil is highly selective as an inhibitory agent to the enzyme that breaks down ACh in the brain but does not appear to have an effect on peripheral ACh activity, thus causing less peripheral cholinomimetic adverse reactions such as gastrointestinal distress (Barner & Gary, 1998; Coyle, Price, & DeLong, 1983). This is in contrast to tacrine which inhibits cholinesterases both centrally and peripherally (Sugimoto, Iimura, Yamanishi, & Yamatsu, 1995).

Donepezil has been investigated in multicenter clinical trials throughout North America and Europe following a randomized, double blind, and placebo controlled methodological format (Barner & Gray, 1998). Donepezil has been shown to produce few side effects with the most common adverse reactions such as nausea, diarrhea, insomnia, and vomiting reported (Barner & Gray, 1998). Donepezil has also been demonstrated to be most efficacious in some patients within the mild to moderate stage of AD with improvements in cognition and behavior reported based on psychometric testing and clinician ratings (Rogers, Doody, Mohs, & Friedhoff, 1996). After a six week washout period, patients treated with donepezil deteriorated cognitively, performing similarly on psychometric tests to age matched AD patients included in the placebo experimental group, who never received donepezil. Given that the two groups (AD patients on placebo and donepezil) performed similarly on psychometric tests and obtained similar clinician ratings at baseline, the return to similar cognitive and

daily functioning (as determined by tests and clinical ratings) of the donepezil treated patients compared to patients on placebo after a washout period was suggested to support the assumption that donepezil serves as a treatment for the symptoms of AD, rather than treating the underlying disease process (Barner & Gray, 1998; Rogers & Friedhoff, 1996).

Other cholinesterase inhibitors such as eptastigmine, metrifonate and rivastigmine are in the late stages of clinical trials and show promise as an efficacious treatment for AD (Sloane, 1998; Cummings, Cyrus, Bieber, Mas, Orazem, & Gulanski, 1998). Multicenter clinical trials of eptastigmine have demonstrated that it is a centrally acting cholinesterase inhibitor with a longer mechanism of action (Imbimbo, Martelli, Troetel, Lucchelli, Lucca, & Thal, 1999; Brufani, Marta, & Pomponi, 1986; Brufani, Castellano, & Marta, 1987; Rupniak, Tye, Brazell, Heald, Iversen, & Pagella, 1992). Early clinical trials of eptastigmine have shown that it is well tolerated and can improve cognitive efficiency in probable AD patients (Sramek, Block, Reines, Sawin, Barchowsky, & Cutler, 1995; Canal & Imbimbo, 1996). However, in these earlier studies, the dosage of eptastigmine utilized only improved performance on cognitive tests, failing to demonstrate improvement in functioning as assessed by clinical ratings and measures of daily functioning. In a study investigating whether probable AD patients would benefit further with 20mg of eptastigmine (taken 3 times daily) compared to 15mg (taken 3 times daily) and placebo, significant improvements in clinical ratings, performance on cognitive tests, and caregiver accounts of increased daily functioning were reported (Imbibo et al., 1999). Although side effects of eptastigmine were reported as minor and non-significant, the potential for increased haematological toxicity as a result of eptastigmine ingestion was demonstrated suggesting limited clinical utility overall (Imbibo et al., 1999).

Metrifonate has also been demonstrated to be as efficacious as tacrine and donepezil in clinical trial studies, however, with less side effects than tacrine (Cummings, Cyrus, Bieber, Mas, Orazem, & Gulanski, 1998; Knopman, 1998; Morris, Cyrus, Orazem, Mas, Bieber, Ruzicka, & Gulanski, 1998). There appears to be a dose dependent response with respect to performance on efficacy measures such as psychometric tests, global clinical ratings, mood and behavior rating scales, and measures of daily activities, with higher doses demonstrating greater improvement (Morris et al., 1998). Metrifonate is considered to be long acting and thus requires a once daily dosage schedule. Treatment effects were observed as early as two weeks following administration of metrifonate with adequate safety

and tolerability demonstrated (Morris et al., 1998). Adverse events were considered mild and transient and generally occurred during initiation of treatment and waned thereafter (Morris et al., 1998). Metrifonate is considered the longest acting AChE inhibitor and although the drug is well tolerated, reversible muscular weakness of the arms and legs has been reported (Schmidt & Heinig, 1998; Gauthier, 1999).

Rivastigmine, for which Canadian approval is pending, requires a dose titration period of several weeks prior to attainment of a therapeutic dosage (Gauthier, 1999). It has been suggested that twice daily dosages of between 3 and 6mg are required for greater gastrointestinal tolerability (Gauthier, 1999). Improvement on psychometric tests of cognitive functioning, global clinical ratings, and activities of daily living have been demonstrated in clinical trials (Corey-Bloom, Anand, & Veach, 1998; Rosler, Anand, Cicin-Sain, et al., 1999).

In addition to cholinesterase inhibitors, several nonspecific drug therapies have demonstrated promise as a treatment for AD (Sloane, 1998). Estrogen replacement therapy in women has been suggested to have a protective effect with the risk of developing AD reported to be lower depending on dosage and duration of use (Tang, Jacobs, Stern, Marder, Schofield, & Gurland, 1996; Paganini-Hill & Henderson, 1996; Kawas, Resnick, Morrison, Brookmeyer, Corrada, & Zonderman, 1997). Nonsteroidal anti-inflammatory drugs (NSAIDs) such as aspirin and ibuprofen have also been suggested to decrease the incidence of dementia presumably as a result of reduction in inflammation associated with AD (Stewart, Kawas, Corrada, & Metter, 1997; Rozzini, Ferrucci, Losonczy, Havlik, & Guralnik, 1996). However, NSAIDs use is not routinely recommended as a treatment for AD because of their high potential for gastrointestinal and renal toxicity (Sloane, 1998). Vitamin E and Gingko Biloba extract have also been studied as a treatment for AD with few side effects thus far reported and the potential that these agents may retard the progression of the symptomatology of the disease has been suggested (Sano, Ernesto, Thomas, Klauber, Schafer, & Grundman, 1997; Le Bars, Katz, Berman, Itil, Freedman, & Schatzberg, 1997).

Clearly, research investigations aimed at symptomatic relief from AD have focused on ACh replacement therapies. However, as stated above, AD is a complex disease affecting several neurotransmitter systems. Nevertheless, research investigations into the pharmacological replacement of noradrenaline, somatostatin, y-aminobutric acid, serotonin, and dopamine have not demonstrated any significant success (Bruno et. al., 1986).

Attempts thus far to replace or replenish diminishing neurochemicals (i.e., acetylcholine) in individuals with probable AD have only met with modest success. Several reasons are suggested for this lack of significant symptomalogical improvement in probable AD (Knopman, 1998). First, most clinical trials in AD tend to be monotherapeutic in nature. In other words, only one neurotransmitter system is targeted at any given time. Given that several neurotransmitter systems are implicated in the pathophysiology of AD, significant symptomatic improvement might occur were several neurotransmitter systems targeted simultaneously in future clinical trials.

Second, a criticism regarding the ecological validity of the efficacy measures utilized in clinical trials has been raised (Knopman, 1998; Feldman & Gracon, 1996). Although improvement on psychometric tests of cognition and global clinical ratings are often observed within the typical six month time frame of most clinical trials, how these improvements relate to the milestones of AD such as reduced activities of daily living, decreased independence, loss of competence, and eventual nursing home placement, are not always obvious. The primary care practitioner is likely to assess his or her AD patient in the context of these milestones (Sloane, 1998; Knopman, 1998; Feldman & Gracon, 1996). Thus, current pharmacological treatments in clinical use or under experimental investigation need to demonstrate a retardation of the development of these milestones for most general practitioners to observe a degree of efficacy with respect to AD drug treatments.

Finally, it has been argued that the typical six month period for most double-blind, placebo controlled, randomized clinical trials of anti-dementia drugs is not sufficient enough to ascertain the utility of such agents during the long term (Knopman, 1998). As such, the efficacy of current cholinesterase inhibitors past a six month time frame have not been empirically validated (Sloane, 1998).

It has been argued that the future of clinical trials with respect to the development of anti-AD agents will need to target the underlying pathophysiological mechanisms of the disease and not just symptomatic relief (Feldman & Gracon, 1996; Sloane, 1998). Thus, an important component of future AD research will be to identify those patients considered to be in the pre-clinical stages of the disease. The rational behind this is that pharmacological agents that are developed to treat the underlying pathophysiology of AD will be most

successful prior to the cascade of pathophysiological events as the disease progresses (Knopman, 1998). Thus, the retardation of disease progression should also retard AD symptomatology and hence, prolong functional independence.

In summary, AD is associated with characteristic neuropathological and neurochemical changes. Neuronal degeneration within the cortical association areas and particularly the hippocampal and surrounding structures are most characteristic of the disease, however, the spread, density, and degree of neuronal loss can vary between individual patients afflicted with AD. Furthermore, the neurochemical abnormalities associated with AD may also vary between afflicted patients. Given the diverse nature of the neuropathological and neurochemical changes associated with AD, it is no surprise that the clinical features of the disease also reflect great heterogeneity.

Clinical Features of AD

Alzheimer's Disease (AD) is an insidious neurodegenerative disorder that results in progressive intellectual, behavioral, personality, and functional deterioration (Papolla & Robakis, 1995; Cummings & Khachaturian, 1996; Sloane, 1998). It is considered one of the most common neurological disorders and the most frequent cause of dementia in North America and Europe (Grondon & Rosser 1998). AD is estimated to cause more than one half of all cases of dementia in elderly persons 65 years of age or older (Moss & Albert, 1992; Gurland & Cross, 1986; Sloane, 1998). Because the prevalence of AD increases significantly with age and there is a current trend towards an extended life span in our population, it is not surprising that diagnosis of AD is on the rise (Moss & Albert, 1992). AD patients survive many years after diagnosis and given the significant deterioration in independence and functioning characteristic of the disease, it has become one of the most pressing and critical health concerns of the past decade (Mohr, Claus, Mann, & Chase, 1991; Erkinjuntti, Ostbye, Steenhuis & Hachinski, 1997; Grondon & Rosser, 1998).

The most salient clinical characteristic of AD is an insidious progressive dementia with memory impairment thought to be the first and most pervasive among a number of cognitive manifestations (Grondon & Rosser, 1998; Petersen, Smith, Invnik, Kokmen, & Tangalos, 1994). The definition of dementia lends itself to broad interpretations but is generally accepted to reflect deterioration in intellectual and personality functioning with deficits in memory often most prominent (Lezak, 1995; Mohr, Dastoor, & Claus, 1999). Dementias may be

classified by the assumed neural systems involved and include cortical, subcortical, axial, and mixed dementias (Joynt & Shoulson, 1985). Cortical dementias such as AD are characterized by loss of cortical functions and often manifests, in addition to memory impairment, with perceptual (agnosia), language (dysnomia, dysphasia), and skilled movement (apraxia) dysfunction. Subcortical dementias such as Parkinson's Disease are usually classified by symptoms of apathy and mental slowing in the absence of perceptual, language, and apraxic difficulties. Axial dementias involve damage to midline cerebral structures such as the thalamus and the hypothalamus and often result in a severe anterograde amnesia with a less severe retrograde amnesia observed and possible dysfunction in other cognitive domains as well. Korsakoff syndrome has been cited as the prototypical axial dementia, however, controversy exists as to whether this disease truly represents a dementing syndrome, as often memory impairment is the sole cognitive deficit (Joynt & Shoulson, 1985). Vascular dementia often manifests itself in multifaceted cognitive decline as a result from cerebrovascular injury (Chui, 1998). The clinical presentation can be quite varied depending on the brain sites involved and often manifests features of both cortical (e.g., aphasia, agnosia) and subcortical dysfunction (e.g., bradykinesia, bradyphrenia). Although AD is generally classified as a cortical dementia, in some cases signs of both cortical and subcortical dysfunction may be evident (Bowler, Eliasziw, Steenhuis, Munoz, Fry, Merskey, & Hachinski, 1997).

The earliest signs of AD are generally a failing recent memory, with disturbances in language (e.g., word finding difficulties, loss of verbal spontaneity, and intrusion errors in speech), diminished visuospatial skills, intellectual deterioration and disorientation to time also frequently evident (Fuld, Katzman, Davies, & Terry, 1982; Reid et al., 1996; Becker, Boller, Lopez, Saxton, & McGonigle, 1994; Sloane, 1998; McCracken, 1999). The particular manifestation of these signs is variable in the early stages of the disease. As AD progresses, marked memory, language, and visuospatial impairment is characteristic. Patients may also display an inability to recognize common objects (agnosia) and have great difficulty executing skilled movements (apraxia). Disease progression may also result in the accentuation of premorbid personality traits, marked apathy, loss of insight, and distractibility. Eventually, in the severe stages of the disease, patients may become mute and bedridden. The average duration of the disease is approximately 10 years from onset of mild memory difficulties to the need for 24-hour supervision, total dependency and eventual death (Sloane, 1998).

Diagnostic Criteria and Differential Diagnosis of AD. The diagnosis of AD remains problematic because no adequate biological markers are currently available (Cummings & Khachaturian, 1996; Mayeux, Saunders, Shea, et al., 1998; Ferrario, Molaschi, Villa, Varetto, Bogetto, & Nuzzi, 1998; Sloane, 1998). At present, a definitive diagnosis of AD can only be made through biopsy or autopsy demonstrating the neurofibrillary tangles and neuritic plaques characteristic of the disease (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984). Thus, only a diagnosis of probable AD can be made for the living patient based on medical history, clinical examination, evidence of progressive cognitive decline, and absence of other medical conditions which could account for the presenting symptoms (McKhann et al., 1984; Sloane, 1998).

There are three sets of criteria utilized most frequently in the diagnosis of AD in the living patient, including those criteria delineated by the International Classification of Diseases, tenth edition (ICD-10; World Health Organization, 1992), the Diagnostic and Statistical Manual of Mental Disorders-fourth edition (DSM-IV; American Psychiatric Association, 1994), and the National Institute of Neurological and Communicative Disorders and Stroke-Alzheimer's and Related Disorders Association (NINCDS-ADRDA; McKhann et al., 1984).

The ICD-10 criteria define dementia characterized by deterioration in memory, thinking, and reasoning sufficient enough to impair personal activities of daily living (World Health Organization, 1992). The criteria for diagnosis of AD includes the presence of dementia with insidious onset and slow deterioration, absence of clinical or laboratory evidence of systemic illness or brain disease that could cause dementia, and absence of sudden onset of neurological signs suggestive of focal brain dysfunction (World Health Organization, 1992).

The most frequently utilized diagnostic classification systems involve both DSM-IV and NINCDS-ADRDA criteria. Both the DSM-IV and NINCDS-ADRDA diagnostic systems are similar in many respects regarding the defining features of AD. Both systems require the presence of memory impairment and at least one or more other cognitive disturbances. Furthermore, the clinical course must be demonstrated to be of a gradual onset (between the ages of 40 and 90) and characterized by continuing cognitive decline. The dementia must be shown not to be related to other neurological, psychiatric, metabolic, endocrine disorders, or delirium (American Psychiatric Association, 1994; McKhann et al., 1984).

Slight differences exist, however, between the DSM-IV and NINCDS-ADRDA criteria in the diagnosis of AD. The DSM-IV criteria specifies that in addition to memory difficulties, disturbance in at least one of the following cognitive domains must be demonstrated including language, skilled motor movement, object recognition, and executive system functioning. NINCDS-ADRDA criteria differs from DSM-IV criteria in which deficits in language, motor skills, and perception are factors which support the diagnosis of AD but are not required criteria. Impairment in social and occupational functioning as well as activities of daily living is required from the DSM-IV perspective and a decline from a previous level of functioning must be demonstrated. NINCDS-ADRDA criteria states that impaired activities of daily living are also supportive of AD but not necessary for diagnosis. Furthermore, NINCDS-ADRDA criteria stipulates that altered behavior, family history of AD, normal cerebrospinal fluid studies, normal or non-specific changes on electroencephalogram (EEG) studies, and evidence of progressive cerebral atrophy as determined with neuroradiological instruments are also considered supportive features in the diagnosis of AD (McKhann et al., 1984). Focal neurological signs, abrupt onset, and presence of seizures or gait disturbance early in the disease are considered incompatible with the diagnosis of AD from the perspective of NINCDS-ADRDA criteria.

The description above delineates the criteria utilized in the diagnosis of probable AD, however, NINCDS-ADRDA criteria also allow for the diagnosis of definite and possible AD. Definite AD is diagnosed when the patient has met the clinical criteria for probable AD while living and demonstrates evidence of characteristic histopathological changes, such as neurofibrillary tangles and neuritic plaques, upon autopsy (McKhann et al., 1984). Possible AD is characterized by the presence of cognitive deterioration in the absence of other neurological, psychiatric, or systemic disorders sufficient to cause dementia but whose course or presentation may be atypical. For example, possible AD may be diagnosed when the presence of a second systemic or brain disease is sufficient to cause the dementia observed, but not thought to produce it. Furthermore, possible AD may be diagnosed when a single, gradually progressive severe cognitive deficit is demonstrated in the absence of other identifiable etiologies (McKhann et al., 1984).

The three major diagnostic systems of AD reviewed above, DSM-IV, NINCDS-ADRDA, and ICD-10, all have similar features in defining AD. For example, all require the presence of a dementia syndrome, that memory loss be a major feature of the clinical presentation, impairment in at least one other non-

memory cognitive domain, absence of delirium as an explanation for the intellectual decline, gradual progressive course, and the absence of systemic illness or other brain disease that might account for the clinical picture (Cummings & Khachaturian, 1996). Nevertheless, prevalence rates of dementia in the general population vary depending on the set of criteria used for diagnosis (Erkinjuntti et al., 1997). Prevalence refers to the total number of cases of a disease or disorder in a specified population at a given point in time. When ICD-10 criteria are used (World Health Organization, 1992), dementia prevalence is reported at 3.1 percent whereas a 13.7 percent prevalence rate is reported with DSM-IV criteria (American Psychiatric Association, 1994). The factors assumed to cause the most disagreement in diagnosis between the DSM and ICD systems were remote memory, executive functioning, social activities, and duration of symptoms with the ICD-10 system requiring more of these factors to be present within the symptom profile for a diagnosis of dementia to be made. The Canadian Study of Health and Aging (1994), a multicenter study conducted in communities and institutions in ten Canadian provinces, reported prevalence rates for dementia at 8 percent in persons 65 years or older increasing to 34.5 percent in persons 85 years of age or older. With respect to AD, prevalence rates of 5.1 percent in the general population and up to 25 percent of those 85 years of age and older were reported (Canadian Study of Health and Aging, 1994).

The diagnosis of AD has also been attempted on biological grounds. The $\epsilon 4$ allele of the gene encoding apolipoprotein (APOE-4) has been demonstrated to be significantly associated with both familial and sporadic Alzheimer's Disease (Saunders, Strittmatter, & Schmechel, 1993; Poirier, Davignon, Bouthillier, Kogan, Bertrand, & Gauthier, 1993; Mayeux, Stern, & Ottman, 1993). Recently, attempts to identify the utility of APOE-4 in the diagnosis of AD has been undertaken with equivocal results demonstrated (Slooter, Breteler, Ott, Van Broeckhoven, & van Duijn, 1996; Mayeux, Saunders, Shea, et al., 1998). In a study of 1833 demented individuals with a variety of etiologies, diagnosis of AD based solely on the presence of APOE-4 was compared to definitive diagnosis of AD upon autopsy. In general, diagnosis based on APOE-4 was not thought to contain enough sensitivity (identifying a disorder when it is there) at 65 percent compared to 93 percent based on clinical diagnosis conforming to NINCDS-ADRDA criteria. Furthermore, specificity rates (exclusion of false positive diagnosis) were thought to be low at 68 percent when diagnosis was made based on the presence of the APOE-4 allele alone (Mayeux et al., 1998).

Videopupillography, which is the measurement of pupillary dilation, has also been studied as a diagnostic tool in AD following the administration of the cholinergic antagonist, tropicamide (Scinto, Daffner, & Dressler, 1994; Ferrario, Molaschi, Villa, Varetto, Bogetto, & Nuzzi, 1998). Although pupillary dilation in response to tropicamide was observed to be greater in AD than in normal elderly controls (Scinto et al., 1994), this was not replicated in a more recent study, leading to the conclusion that videopupillography does not distinguish between AD patients and controls, and therefore, is not a useful diagnostic tool (Ferrario et al., 1998).

Thus, biological markers of AD have met with equivocal results with respect to their utility as a diagnostic tool for the disease and do not demonstrate adequate sensitivity and specificity in clinical or research settings. The clinical criteria delineated by the DSM-IV, NINCDS-ADRDA, and ICD-10 classification systems are still the best diagnostic tools currently available and account for approximately 90 percent accuracy in the hands of a good clinician (Mayeux et al., 1998). However, diagnostic precision of AD is likely to be increased when the clinician entertains other neurodegenerative disorders as part of the differential diagnosis. Although DSM-IV, NINCDS-ADRDA, and ICD-10 diagnostic classification systems rule out the presence of systemic illness and other brain disorders in the differential diagnosis of AD, diagnosis of AD is still complicated by other neurodegenerative disorders that may or may not have biological markers indicating their presence and can manifest similarly in clinical presentation as probable AD, particularly in the early stages of disease progression (Cummings & Khachaturian, 1996). Dementia, the defining clinical feature of AD, may arise from several possible etiologies or pathologies, many of which remain incompletely understood. As such, it has been recommended that the differential diagnosis of probable AD should always include other disorders such as Lewy body disease, Pick's disease, focal brain atrophies, and vascular dementia (Cummings & Khachaturian, 1996).

Lewy body disease is characterized by fluctuating cognitive impairment affecting both memory and other higher cortical functions and episodic confusion (McKeith, Perry, Fairburn, Jabeen, & Perry, 1992). The presence of either visual or auditory hallucinations or mild spontaneous extrapyramidal features are also required for diagnosis. These clinical features must persist over a period of weeks or months (unlike delirium) and the absence of underlying physical illness and past history of confirmed stroke or evidence of cerebral ischemic changes must be demonstrated (McKeith et al., 1992).

Pick's disease is a fronto-temporal dementia that may have clinical features similar to AD and clinicians unfamiliar with the characteristics which discriminate between the two disorders may misdiagnose Pick's disease as AD (Cummings & Khachaturian, 1996). Criteria for the diagnosis of Pick's disease are offered by the ICD-10 classification system and include progressive dementia, a predominance of frontal lobe features with euphoria, emotional blunting, coarsening of social behavior, disinhibition, and apathy or restlessness (World Health Organization, 1992). In Pick's disease, behavioral manifestations often precede frank memory problems and frontal lobe features are more marked than temporal and parietal features, unlike AD (World Health Organization, 1992).

Focal cerebral atrophies also need to be considered in the differential diagnosis of AD (Cummings & Khachaturian, 1996). Typically, focal cerebral atrophy manifests in gradual progressive neuropsychological impairments largely confined to one single intellectual or cognitive domain (Cummings & Khachaturian, 1996). Examples include primary progressive aphasia, progressive visuospatial deficits, progressive amusia and aprosodia, and progressive apraxia (Abe, Yorifuji, Tanabe, & Yanagihara, 1994; Casselli, Jack, Petersen, Wahner, & Yanagihara, 1992; Confavreux, Croisile, Garassus, Aimard, & Trillet, 1992; Weintraub, Rubin, & Mesulan, 1990).

Finally, the presence of a vascular dementia must be considered when diagnosing AD (Cummings & Khachaturian, 1996). Diagnostic systems such as ICD-10, DSM-IV, and NINCDS contain differing inclusion criteria for the diagnosis of vascular dementia and thus, depending on the criteria utilized, vascular dementia may be misdiagnosed as AD (Cummings & Khachaturian, 1996). For example, DSM-IV criteria stipulate that vascular dementia is characterized by the presence of a dementia similar to AD in conjunction with focal neurological signs and symptoms or laboratory evidence of cerebrovascular disease (American Psychiatric Association, 1994). However, abrupt onset and stepwise disease progression, typically associated with vascular dementia, is not required diagnostic criteria and neither is neuroradiological imaging if focal neurological signs are present (American Psychiatric Association, 1994). The ICD-10 criteria for vascular dementia incorporate the presence of abrupt onset, uneven disease progression, and neuroradiological abnormalities in addition to focal neurological signs and uneven impairment in cognitive functions (World Health Organization, 1992). Perhaps the NINCDS criteria are the most comprehensive with respect to inclusionary criteria for the diagnosis of vascular dementia (Cummings &

Khachaturian, 1996). NINCDS criteria stipulate the presence of memory impairment, deterioration in two or more cognitive domains, decline from previous level of functioning, abrupt onset and stepwise deterioration, onset of dementia within three months of stroke, laboratory evidence of cerebrovascular disease, computerized tomography demonstrating evidence of neuropathology consistent with cerebrovascular disease, and absence of delirium as an explanation for intellectual decline. The presence of aphasia, agnosia, apraxia, or executive dysfunction (typical criteria for AD diagnosis) and focal neurological signs and symptoms are not necessary for the diagnosis (Roman, Tatemichi, & Erkinjuntti, 1993).

An important issue to consider in the differential diagnosis of AD is the potential for comorbid pathology. Comorbidity of AD with vascular ischemic lesions has been described on both pathophysiological and clinical grounds, and manifests in features consistent with cortical and subcortical involvement (Bowler, Eliasziw, Steenhuis, Munoz, Fry, Merskey, & Hachinski, 1997). Comorbid AD with cerebral vascular lesions is identified histopathologically by the typical neurofibrillary tangles and neuritic plaques characteristic of AD mixed with evidence of stroke and/or ischemic lesions. Comorbid AD with vascular features can also be differentiated on clinical grounds from either 'pure' AD or 'pure' vascular dementia based on the presence of localizing neurological signs and evidence of a gradual progression of cognitive impairment (Bowler et al., 1997). The dementia of AD often does not manifest in localizing neurological signs and is gradually progressive in nature whereas vascular dementia often displays localized neurological signs with a stepwise progression of cognitive deterioration (Bowler et al., 1997).

The diagnosis of probable AD is easier during the moderate to severe stages of the disease, as by then the characteristic clinical features such as severe memory impairment, agnosia, aphasia, and apraxia are likely to be present (Morris & Baddeley, 1988). However, during the very mild and mild stages of the disease, diminished memory functioning and mild word finding difficulties may be the only apparent symptoms. Thus, it may be difficult to differentiate the presence of a mild dementia from normal aging, particularly the elderly with limited education, as the latter may also manifest in occasional difficulties in word finding and recalling parts of past episodes (Kral, 1978; Gurland, 1981; Morris & Baddeley, 1988). Nevertheless, neuropsychological assessment has proved useful in disentangling those individuals who have a bona fide dementing syndrome from the normal

elderly (Lezak, 1995). The NINCDS-ADRDA task force responsible for the development of diagnostic criteria for AD have recommended the routine use of neuropsychological assessment to facilitate diagnosis of AD (McKhann et al., 1984).

Neuropsychological Assessment of AD. Neuropsychological assessment has proved to be an essential aid, not only in the differential diagnosis of early probable AD from depression, other psychiatric disorders, and treatable neurological disorders (Lezak, 1995; Mohr et al., 1999), but also for different stages of patient management, documentation of functional changes over time, and clinical trials research geared towards the development of effective treatment strategies (Mohr et al., 1999). Although a significant increase in knowledge regarding both the cognitive and behavioral correlates as well as the biological processes of AD has occurred within the last 10 years (Khachaturian, 1998), the diagnostic process still remains a clinical endeavour (Mohr et al., 1999). Thus, the neuropsychological assessment of patients suspected of having AD necessitates a thorough understanding of the pathophysiology of AD, a comprehensive understanding of the clinical features of the disease, and thorough knowledge of the neuropsychological correlates of AD (Mohr et al., 1999). Neuropsychological assessment, as an aid to diagnosis of probable AD takes on even greater relevance in the context of symptomatic pharmacological treatment for the illness (Knopman & Morris, 1997). Neuropsychological assessment may aid in the identification of AD sub-classification thus facilitating the answers to questions of which patients may show the most benefit from drug treatment (Richard, Helbecque, Neuman, Guez, Levy, & Amouyel, 1997; Mohr et al., 1999). Furthermore, neuropsychological assessment may be sensitive as an aid to early diagnosis of AD which may become critical as treatments become available that prevent or retard disease progression (Mohr et. al., 1999).

There are a number of caveats in the neuropsychological examination of the elderly suspected of having a dementing illness that may affect the reliability and validity of test results (Mohr et. al., 1999). First, the measures used must demonstrate adequate domain and construct validity. Because the symptom presentation in AD is heterogenous, an adequate breadth of cognitive domains must be assessed to capture the nature of the cognitive disorder. For example, the Mini Mental Status Examination (MMSE; Folstein, Folstein, & McHugh, 1975), although widely used in the assessment of AD, does not capture adequately disturbances in focal cognitive functions such as aphasia or executive functions

(Mohr et al., 1999). Second, the elderly are often treated with a combination of medications that may have an effect on cognitive functions, and the clinician must take this into account when interpreting test results (Mohr et al., 1999). Third, adequate sensory (e.g., hearing, vision, tactile) and motor capabilities must be ascertained as deficiencies in these areas may confound proper interpretation of neuropsychological test data regarding higher cognitive functions (Mohr et al., 1999). Finally, the demented elderly are prone to fatigue which could further aggravate cognitive deficits. Thus, to mitigate against fatigue as a confound in the interpretation of neuropsychological test results, it is suggested that assessment of functions occur in brief intervals of one hour or less (Mohr et al., 1999; Cole & Dastoor, 1980; Cole & Dastoor, 1996).

The neuropsychologist must also ensure patient cooperation, ease, and rapport in order to elicit the necessary clinical information and obtain valid test results (Cole & Dastoor, 1980; Mohr et al., 1999). Optimum performance is best obtained in an opportunistic manner and the neuropsychologist must be adequately flexible to allow the patient to relay their concerns and provide an account of their earlier achievements while at the same time gathering essential information necessary for the diagnostic process (Mohr et al., 1999). Performance levels by probable AD patients on neuropsychological measures often fluctuate as a function of differing levels of arousal due to the time of day, familiarity with the testing environment, and familiarity with the examiner. Optimum cognitive performance may manifest for brief intervals only, and examination of AD patients demands an awareness of these intervals (Mohr et al., 1999). To elicit optimal performance, the neuropsychologist should take appropriate opportunities to push the patients cognitive ability to the limit, interspersed between less demanding tasks in which the patient is likely to succeed (Mohr et al., 1999).

The cognitive domains that must be assessed in the neuropsychological evaluation of AD include general intellectual ability (Lezak, 1995; Mohr et al., 1999) as well as attention, language skills, memory, praxis, gnosis, visuospatial and constructional abilities, calculation, abstraction, and judgment (Mohr et al., 1999). The pattern of intellectual functioning in early AD reflects preserved abilities on standard measures of overlearned material such as fund of knowledge, vocabulary, and social judgment and reasoning as assessed by the Information, Vocabulary and Comprehension subtests of the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981). Passive auditory attention (e.g., digits forward of the WAIS-R Digit Span subtest) is also usually preserved in AD, however, effortful attention

(e.g., digits backward of the WAIS-R Digit Span subtest) is frequently impaired. Tests of intellectual ability that are unfamiliar, abstract, and time dependant are usually performed the most poorly. Thus, performance on WAIS-R subtests such as Block Design and Digit Symbol are usually most affected by the disease (Lezak, 1995).

The earliest measurable cognitive changes in AD using neuropsychological testing involves explicit memory of both verbal and visual material (Mohr et. al., 1999). Thus, a comprehensive assessment of memory functions is required in patients suspected of having AD. Examination of several aspects of memory should be conducted including encoding, storage and retrieval processes, as well as immediate and delayed recall capabilities (Mohr et al., 1999; Kohler, Black, Sinden, Szekely, Kidron, Parker, Foster, Moscovitch, Wincour, Szalai, & Bronskill, 1998). In the differential diagnosis of AD from depression, both encoding and retrieval tend to be affected in AD whereas only retrieval impairments are characteristic of depression (Mohr, Feldman & Gauthier, 1995). Furthermore, delayed recall tends to distinguish early AD patients from normal controls greater than immediate recall or recognition memory (Welsh, Butters, Hughes, Hohs & Heyman, 1991; Locascio, Growdon & Corkin, 1995).

In addition to intellectual and memory assessment, the neuropsychological assessment should focus on examination of language skills through confrontation naming tasks and verbal fluency tests. Visuospatial construction should also be assessed with such tests that require copy of simple and complex geometric stimuli. In addition, executive system abilities, such as planning, reasoning, and abstract thinking should be carefully evaluated, as they may show deterioration in the early stages of the disease (Mohr et. al, 1999; Moss & Albert, 1992). Serial testing of these cognitive functions may be necessary, particularly in the early stages of AD, to document progression of cognitive deterioration, which is required for the diagnosis of AD to be made. Furthermore, cognitive functions may deteriorate at different rates necessitating repeat testing of a wide range of cognitive functions over time. Such detailed and repeated testing will provide important information regarding rate of progression of the disease and issues of patient management (Mohr et. al., 1999).

Putative Subgroups in AD. There is a wide variety of putative demographic, pathological, neurochemical, and neuropsychological markers in AD reflecting the heterogenous nature of the disease (Mohr, Mann, & Chase, 1990). This heterogeneity has led some researchers to investigate the possibility of subtypes

within the general rubric of AD (Mohr, Mann, & Chase, 1990; Martin et al., 1986; Jorm, 1985). Demographic variables, such as age at onset, have been used to support the notion of at least two distinct subgroups. At one time, the term 'Alzheimer's disease' was originally used as a descriptor for dementia in patients with onset of symptoms before the age of 65 years whereas senile dementia was used when the onset of symptoms occurred after 65 years of age (Blennow, Wallin, & Gottfries, 1994). However, since the 1960's, early and late onset AD have been assumed to reflect a single, homogenous entity, largely as a result of similar neuropathological findings (e.g., neurofibrillary tangles and neuritic plaques) at autopsy in both conditions (Katzman, 1986; Martin et al., 1986). Nevertheless, symptom presentation, neurochemical deficits, and neuropathological changes have been reported to be different between the two conditions with greater severity observed in early onset AD (Burns, Tune, Steele & Folstein, 1989; Roth, 1986; Reid, Broe, Creasey, Grayson, McCusker, Bennett, Longley, & Sulway, 1996; Heston, Mastri, Anderson, & White, 1981), leading some researchers to question whether early and late onset AD are the same disorder (Gottfries, Blennow, Regland & Wallin, 1990). Temporoparietal symptoms such as aphasia, apraxia, and agnosia are thought to occur more frequently and severely in early onset compared to late onset AD (Blennow, Wallin, & Gottfries, 1991) whereas confusional symptoms are thought to occur more frequently in late onset compared to early onset AD (Blennow, Wallin & Gottfries, 1990). Other investigators have shown that early onset AD might be associated with a shorter life expectancy, rapid cognitive decline, higher frequency of language impairment, widespread neurochemical abnormalities, and a greater density of neurohistological lesions (Raskind, Carta, & Bravi, 1995).

Differences in neuropathological changes between early and late onset AD have also been reported. For example, the degree of neuronal loss and density of neurofibrillary tangles as well as neuritic plaques have been reported to be greater in early onset than in late onset AD (Hansen, DeTeresa, Davies & Terry, 1988). In addition, several studies have demonstrated that the presence of leukoaraiosis in AD patients is associated with a later rather than earlier onset of symptoms (Blennow, Wallin, Uhlemann & Gottfries, 1991; Scheltens, Barkhof, Valk, Algra, Gerritsen van der Hoop, Nauta & Wolters, 1991). Furthermore, an earlier age of onset in AD has been associated with greater focal metabolic deficits, particularly in the right temporoparietal area (Kennedy, 1998; Ichimiya et al., 1994).

Other investigators have failed to find age associated differences in symptom

presentation and progression of AD (Harvey & Rossor, 1995). Indeed, it has been argued that the differing clinical picture between the two age groups simply reflects differing stages of the disease and not distinct subgroups per se (Mohr, Mann, & Chase, 1990; Joynt & Shoulson, 1985). However, in at least one study, where duration of illness was statistically controlled, an earlier age of onset of AD was associated with significantly greater impairment than later age of onset in certain cognitive functions including attention span, working memory, graphomotor functions, praxis, and executive functioning (Reid et al., 1996).

Subgrouping has also been attempted on anatomical grounds with some AD patients showing more frontal involvement than others as ascertained by positron emission tomography (PET) and single photon emission tomography (SPECT) studies (Chase, Burrows, & Mohr, 1987). In a review of a series of positron emission tomography (PET) studies in AD (Kennedy, 1998), most patients displayed a significant reduction in cerebral glucose bilaterally in the parietal and temporal regions. However, a subset of patients were identified with a predominantly unilateral hypometabolism and others with additional cerebral glucose reductions in frontal association areas (Kennedy, 1998).

Neuropsychological profiles have also been employed towards the goal of subgrouping. Certain AD patients, in addition to memory deficits, have been identified with a predominant visuoconstruction deficit and others with language disturbance (DeLeon, Potegal, & Gurland, 1984; Kirshner, Webb, Kelly & Wells, 1984) and others with a profound dysexecutive syndrome (Becker, 1994). In a factor analytical study of 407 AD patients in the very mild and mild stages of the disease, different profiles of focal deficits including mental control, memory, and visuospatial skills were identified (Kanne, Balota, Storandt, McKeel, & Morris, 1998). Furthermore, these areas of focal deficits were associated with greater focal density of neuritic plaques in brain regions assumed to underlie their function (e.g., mental control-frontal; memory-temporal; visuospatial, temporoparietal) as ascertained through autopsy on a subset of study participants. Distinct syndromes based on differing memory patterns in AD have also been reported (Becker, 1988; Becker, 1994; Baddeley, Della Sala, & Spinnler, 1991). In these studies, a subset of AD patients demonstrated a predominant amnesic disturbance in the context of relatively normal primary or working memory, yet other patients were more profoundly compromised with respect to working memory relative to secondary memory. Furthermore, a differential rate of decline was observed in the two subgroups with the working memory disordered patients tending to show a greater

rate of decline in secondary memory over time (Becker, 1994).

It is tempting to relate the variety of cognitive and cerebral metabolic profiles described above to distinct subgroups in AD, however, the issue of true subtypes is one of continuing scientific debate. Nevertheless, the review of the literature above attests to the heterogeneous nature of the clinical manifestations in probable AD. Despite this heterogeneity in symptom presentation, memory impairment is consistently observed in all stages of probable AD.

Overview of Memory Research in Alzheimer's Disease

AD is the most common cause of dementia in the elderly with memory impairment as a core clinical feature of the disease, beginning even in the earliest stages of progression. Thus, more memory research has been conducted on AD than perhaps any other illness (Brandt & Rich, 1995). Episodic memory deficits reflecting compromise in both primary and secondary memory processes is clearly demonstrated in AD memory research (Brandt & Rich, 1995; Morris & Baddeley, 1988; Morris & Kopelman, 1986; Kopelman, 1985). This often manifests in diminished ability to recall recent and remote events (i.e, conversations, current events, where objects have been recently placed, telephone numbers, etc.). Episodic memory is clinically assessed with word list learning, story recall, and recall of visuospatial stimuli. Semantic memory is also frequently affected during the course of AD and manifests in difficulty finding words during conversational speech and diminished ability to recall factual information such as names of places or people (Libon, Bogdanoff, Cloud, Skalina, Giovannetti, Gitlin, & Bonavita, 1998; Brandt & Rich, 1995; Heindel, 1994). Despite these significant difficulties in memory functioning, some aspects of learning and memory remain relatively unaffected by AD. For example, such patients retain well ingrained habits and skills such as dressing and grooming, until later stages of the disease, and are shown to be able to learn new motor skills (Carlesimo, Mauri, Graceffa, Fadda, Loasses, Lorusso, & Caltagirone, 1998; Libon et al., 1998; Morris & Kopelman, 1986).

This pattern of preserved and deficient ability in certain aspects of memory functioning in AD is thought to reflect differential involvement of at least two distinct memory systems, a declarative and a procedural memory system (Libon et al., 1998; Brandt & Rich, 1995). The declarative memory system is directly accessible to conscious recollection and is involved in the acquisition of facts and events and can be assessed with conventional tests of recall and recognition

(Squire, 1992). Procedural memory, on the other hand, operates without conscious awareness and can be assessed with a wide variety of techniques including priming, classical conditioning, and motor skill learning (Heindel, 1994; Brandt & Rich, 1995; Libon et al., 1998; Squire, 1992). Although the declarative memory system is consistently demonstrated to be deficient in AD (Kohler et al., 1998; Kanne et al., 1998; Carlesimo, Mauri, Graceffa, Fada, Loasses, Lorusso, & Caltagirone, 1998; Reid et al., 1996; Heindel, 1994), certain aspects of the procedural memory system are considered compromised whereas others remain relatively intact (Libon et al., 1998; Brandt & Rich, 1995; Heindel, 1994). For example, the priming effect is often demonstrated as deficient in AD with motor skill learning, such as maintaining contact between a stylus and a square of light on a rotating circle, thought to remain unaffected (Brandt & Rich, 1995; Libon et al., 1998).

Procedural Memory

Priming Effect in AD Research. Generally, priming refers to a wide variety of phenomena in which the presentation of a stimulus influences subsequent processing of either the same or similar stimuli (Brandt & Rich, 1995; Heindel, 1994). For example, in verbal priming tasks, a list of words may be presented prior to a word completion task. Subjects may be required to read the list of words or make a statement about the word's likeability to ensure proper attention to the priming stimuli. Word completion tasks often involve the presentation of a few letters of a word (e.g., per) and the subject is asked to complete the word (e.g., per could become perfect, perennial). The priming effect refers to the phenomena whereby subjects tend to use previously presented words during word completion tasks (Brandt & Rich, 1995; Morris & Kopelman, 1986).

A reduced priming effect has been demonstrated in probable AD compared to the normal healthy elderly and patients with predominant subcortical disease such as Parkinson's and Huntington's disease (Bondi & Kasniak, 1991; Keane, Gabrieli, Fennema, Growdon, & Corkin, 1991). In these studies, AD patients tended to respond less to primed stimuli on word completion tasks compared to normal age matched control subjects. However, the priming effect in AD subjects was not observed to be abolished, rather diminished compared to control subjects. Reduced priming phenomena on word completion tasks in probable AD has been replicated in other studies as well (Brandt & Rich, 1995; Heindel, 1994).

In contrast to this, Moscovitch (1982) demonstrated an intact priming effect with AD subjects when they were required to make a lexical decision. Subjects were asked to determine whether a string of letters constituted a word or not. AD patients were more likely to make accurate lexical decisions when the string of letters constituted a word presented earlier in the priming condition. Furthermore, perceptual priming has also been observed to be intact in AD subjects (Keane et al., 1991; Brandt & Rich, 1995). In these studies, pictures or drawings of objects are presented to subjects like word lists are in semantic priming paradigms. Subsequently, subjects are asked to identify incomplete line drawings and AD patients displayed a normal priming effect when compared to healthy normal controls. In other words, AD patients benefited from the prior exposure of drawings or objects in subsequent recall (Keane et al., 1991).

It has been argued that the poor performance on verbal priming paradigms, particularly word stem completion tasks, reflects a compromise in semantic memory as opposed to a true deficiency to benefit from priming per se. (Heindel, 1994; Daum et al., 1996). It appears that when semantic demands are high on these priming tasks, AD patients tend to perform poorly. Conversely, priming effects appear normal or near normal when less demands are made on the semantic memory system (Daume et al., 1996). This may explain why preserved priming phenomena is observed in perceptual and lexical priming tasks, as these depend less on an intact semantic network for correct responses during testing (Daum et al., 1996). If this were to be true, then the memory system involved in priming may not be affected by the disease process in AD. However, this issue is still one of scientific debate.

Procedural Learning. This aspect of procedural memory is usually assessed with motor skill learning tasks (Heindel, Salmon, Shults, Walicke, & Butters, 1990; Knopman & Nissen, 1987). In a recent study (Libon et al., 1998), a dissociation between AD and Ischaemic Vascular Dementia (IVD) patients was demonstrated with respect to declarative and procedural learning using the California Verbal Learning Test (Delis et al., 1991) and a pursuit rotor task (Martin, Heyes, Salazar, Law, & Wisllian, 1993). The general procedure of the pursuit rotor task requires subjects to maintain contact between a stylus and a square of light on a rotating circle. AD patients demonstrated intact learning ability during the pursuit rotor task compared to IVD patients whereas the opposite profile was elicited for verbal learning. Visuomotor procedural learning was also demonstrated intact in AD

during a modified digit symbol test from the Wechsler Adult Intelligence Scale (Carlesimo et al., 1998). In this test, subjects were required to perform two versions of the test, one day apart. Different symbols were associated with the numbers in the two test conditions. Procedural learning was ascertained by the measure of reduced time in performing the second task. AD subjects performed comparably to normal healthy elderly controls and even better than very old controls on this task.

Given the impressive body of evidence supporting normal procedural memory in AD (Heindel et al., 1990; Knopman & Nissen, 1987; Libon et al., 1998; Carlesimo et al., 1998), it has been proposed that brain regions involved in this aspect of memory functioning are spared from the pathological processes in AD, during at least the mild to moderate stages of the disease (Carlesimo et al., 1998; Libon et al., 1998). However, the neuroanatomical substrate underlying procedural memory is poorly understood at the present time (Libon et al., 1998). Nevertheless, it has been argued that subcortical structures such as the caudate nucleus of the basal ganglia and their connections with the frontal lobe may mediate procedural learning. Patients with Parkinson's disease or Huntington's disease are known to have neuropathological changes in basal ganglia structures. Furthermore, they tend to perform poorly on motor skill learning tasks. AD patients, on the other hand, tend not to demonstrate pathological changes within basal ganglia structures, at least in the early stages since later on in the disease extrapyramidal disorders are increasingly common, and often do well on motor skill learning tasks. This double dissociation has thus led some authors to suggest that the basal ganglia and its connections to the frontal lobes might serve as the neuroanatomic pathway for procedural learning (Granholm, Bartzokis, Asarnow, & Marder, 1993; Sabe, Jason, Juejati, Leiguarda & Starkstein, 1995). Other authors have proposed that cerebellar structures may also be involved in procedural learning (Carlesimo et al., 1998).

Declarative Memory

Semantic Memory in AD Research. Semantic memory refers to a person's general fund of knowledge including the meanings and representations of words, concepts, and facts that are not dependent on contextual or temporal cues for retrieval (Salmon & Chan, 1994; Hodges, 1994; Morris & Kopelman, 1986). It

can be considered an aspect of declarative memory because one's general fund of knowledge is acquired through experience and didactic training, thus, it can be assumed that some degree of awareness occurs during acquisition.

The most common clinical manifestation of semantic memory impairment in AD is a diminished word finding ability in which the patient encounters difficulty naming common objects or in producing an appropriate word during speech (Salmon & Chan, 1994; Abeysinghe, Bayles, & Trosset, 1990). However, word finding difficulties may also represent an aphasic disorder which is common in AD (Kirshner, 1994). Compared with language changes in normal aging, studies of patients with AD using standard aphasia test batteries have consistently demonstrated impairment of language, although marked variability between individual patients is reported (Cummings, Benson, Hill & Read, 1985; Murdoch, Chenery, Wilks & Boyle, 1987; Faber-Langendoen, Morris, Knesevich, LaBarge, Miller & Berg, 1988). The pattern of language in patients afflicted with AD is characterized as fluent yet deficient in content with word finding difficulties, circumlocutions, and a paucity of abstract content reported (Kirshner, 1994). Receptive vocabulary and auditory comprehension remain relatively intact, but comprehension of complex material becomes deficient with progression of the disease (Kirshner, 1994). Reading comprehension and writing are thought to be more sensitive to the effects of AD than auditory comprehension (Horner, Heyman, Dawson & Rogers, 1988).

AD patients in the early stages of the disease often exhibit the language profile of anomic aphasia (Kirshner, 1994). As the disease progresses, the language impairment displayed by AD patients resembles more that of a transcortical sensory aphasia (Cummings et al., 1985). An anomic aphasia is characterized predominantly by word finding difficulties, and sometimes is the only significant language disturbance (Benson, 1993). Individuals with an anomic aphasia will have a fluent verbal output, little or no paraphasia, relatively normal ability to comprehend, and excellent ability to repeat words or sentences (Benson, 1993). A transcortical sensory aphasia is characterized by fluent yet paraphasic output, significant disturbance of comprehension, but intact repetition. Naming, reading, and writing are usually seriously compromised (Benson, 1993). The pathology of the anomic and transcortical sensory aphasias is thought to spare the perisylvian cortical area, and hence the individual's ability to demonstrate relative normal capacity to repeat words or sentences (Benson, 1993). Rarely is a non-fluent aphasia and transcortical motor aphasia encountered in AD (Kirshner, 1994).

Non-fluent and transcortical motor aphasia are predominantly characterized by the paucity, if not absence, of verbal output and inability to repeat sentences or words (Benson, 1993).

The question of whether the language disturbances in AD reflect an aphasic disorder or a semantic memory problem is one of scholarly discussion (Kertesz, 1994). At the present time, it is not known whether the language disorders in AD represent compromised symbolic processing, characteristic of aphasic disturbances, or deterioration of a semantic network, which is considered a deterioration of a form of memory. Indeed, the presence of intact language skills in the context of impoverished memory has been reported in AD and thought to support the idea that language disturbances in AD are a result of aphasia (Kertesz, 1994). Nevertheless, consistent with the theme of the current discussion regarding memory dysfunction in AD, the following is a review of the literature in support of a semantic memory difficulty in AD.

Most of the evidence for impaired semantic memory in AD comes from neuropsychological tests of confrontation naming or verbal fluency (Brandt & Rich, 1995). In confrontation naming tasks, patients are asked to name drawings of common objects. In verbal fluency tasks, patients are asked to name as many words as possible, within a time constraint, of either letters of the alphabet (e.g., F. A. S.) or of specific categories (e.g., animals, plants). AD patients consistently perform poorly on these tasks, particularly in category fluency, even in the early stages of disease, compared to normal healthy elderly controls (Crossley, D'Arcy, & Rawson, 1997; Daum, Riesch, Sartori, & Birbaumer, 1996; Laiacina, Barbarotto, & Capitani, 1998; Heindel, 1994; Salmon & Chan, 1994).

Semantic knowledge is thought to be organized as a complex network of conceptual categories (Daum et al., 1996; Heindel, 1994; Salmon & Chan, 1994). Specific items or exemplars are thought to be placed within these categories based on their associated and distinguishing attributes. For example, dog and cat would be categorized as animals because they share similar features such as domesticity, have fur, are alive, etc. They would not be categorized as tools because of distinguishing features such as animate and inanimate. It is thought that there is a hierarchical organization of associative and distinguishing features of exemplar attributes within categories from the more abstract to the concrete (Heindel, 1994; Salmon & Chan, 1994). Another model of the organization of semantic memory suggests three levels of the representations of objects and concepts (Daum et al., 1996). First there is a structural descriptive level which contains information

regarding the sensory properties of a concept. Second, a semantic representation level includes functional and associative information. Third, the level of phonological representation includes the names that refer to the objects in question. These levels are thought to interact during information processing.

The main impetus in AD research on semantic memory has been to elucidate the nature of the semantic memory deficit. Two major hypotheses have been proposed, namely that the semantic memory difficulties in AD reflect a functional deficit or a structural deficit (Heindel, 1994; Salmon & Chan, 1994; Daum et al., 1996; Crossley, D'Arcy, & Rawson, 1997). The functional deficit hypothesis proposes that AD patients have impaired access to an otherwise intact semantic network (Nebes & Brady, 1988). In other words, AD patients are unable to retrieve semantic information although such information remains intact within the network. The structural deficit hypothesis assumes that it is a degradation in the organization of the semantic network that underlies the semantic memory deficits in AD (Heindel, 1994; Salmon & Chan, 1994). Much of the research conducted on semantic memory in AD appears to support the structural degradation hypothesis based on error analyses in confrontation naming studies and verbal fluency studies in AD (Crossley, D'Arcy, & Rawson, 1997; Daum et al., 1996; Laiacona, Barbarotto, & Capitani, 1998).

The structural degradation hypothesis in AD assumes a weakening of the strongly related associations and distinguishing attributes of exemplars within conceptual categories in the semantic network. This is thought to occur as a result of degeneration of neocortical association areas presumed to store these representations (Butters, Salmon, & Heindel, 1990; Squire, 1987). It has been suggested that degradation of associations and distinguishing attributes of exemplars follow a hierarchical process. In other words, abstract attributes are more vulnerable to the effects of the disease process in AD than concrete attributes (Heindel, 1994; Salmon & Chan, 1994). Similarly, the sensory properties of exemplars in the semantic network are thought to remain relatively unaffected whereas functional and associative information regarding exemplars has been shown to be compromised in AD (Daum et al., 1996).

Support for the hypothesis regarding the structural degradation of the semantic network in AD has been demonstrated largely through studies examining the performance of patients with probable AD on verbal fluency and confrontation naming tasks (Crossley, D'Arcy, & Rawson, 1997; Heindel, 1994; Salmon & Chan, 1994). In these studies, AD patients were required to generate, within a time

constraint, as many words as possible that begin with a given letter (e.g., FAS) and as many words as possible from a given category (e.g., animals). Patients with probable AD demonstrated a consistent and significant difficulty generating words from specific categories compared to letters of the alphabet (Crossley et al., 1997). Furthermore, probable AD patients tend to respond with superordinate categories on the supermarket verbal fluency task which requires subjects to name as many items as they can in a supermarket (Salmon & Chan, 1994). Analyses of their responses indicated a tendency to respond with superordinant category names (e.g., meat) instead of specific exemplars (e.g., ham). Thus, it appears that probable AD patients have difficulty with specific category representations within the semantic network.

Error analyses of AD patients responses on confrontation naming tasks has also lent support to the structural degradation hypothesis (Daum et al., 1996; Laiacona, Barbarotto, & Capitani, 1998; Heindel, 1994; Salmon & Chan, 1994). As was demonstrated in the verbal fluency studies described above, the errors by probable AD patients on confrontation naming tasks are also characteristic of naming superordinant categories (e.g., animal for dog) or semantically related items (e.g., dog for wolf). Thus, given the types of errors observed during semantic memory tasks, and their consistency over a wide range of tests, it has been argued that a degradation of the semantic memory network occurs in AD as opposed to a retrieval deficit (Heindel, 1994; Salmon & Chan, 1994). If a retrieval deficit were to be true, then AD patients would demonstrate as much difficulty in letter fluency as category fluency and would also have equal difficulty in generating superordinate category names in addition to specific exemplars.

Nevertheless, it has also been argued that a perceptual disorder may underlie the errors made by AD patients in semantic memory tasks (Daum et al., 1996; Laiacona, Barbarotto, & Capitani, 1998). As many confrontation naming tasks involve perceptual processes prior to access to semantic information, it has been stated that perceptual disorders in AD may underlie deficits in confrontation naming (Daum et al., 1996). However, this was not borne out in studies in which perceptual factors were covaried in statistical analyses (Laiacona, Barbarotto, & Capitani, 1998).

Further still, it has been argued that semantic memory deficits may reflect reduced cortical tone due to abnormalities in the locus coeruleus (Heindel, 1994). In other words, AD patients, due to lowered arousal of the cerebral cortex, may not

be investing the same amount of attention towards the semantic memory task relative to normal controls, thus explaining the difficulties observed. However, this question still remains one of scientific debate.

One final point concerning semantic memory impairment has to do with gender issues. It has been suggested that male and female AD patients may show differential degradation of the semantic memory system with respect to certain categories involved. For example, category dissociation was observed in one study in which male AD patients tended to make more errors in categories of animate objects whereas female AD patients made more errors within categories of inanimate items (Laicon, Barbarotti, & Capitani, 1998).

Thus, in summary, it appears that AD patients demonstrate a degradation or breakdown in the organization and structure of the semantic network. Although it is still not certain which role retrieval and arousal may play in part or in whole in the semantic memory difficulties observed in AD, they cannot be entirely ruled out as factors in the overall underlying deficit in semantic memory. This is because many of the tasks designed to assess semantic memory require several cognitive components for efficient performance including retrieval, attention, and working memory in which AD patients could conceivably have difficulties (Hodges, 1994). Additionally, gender may play a role in the nature of the semantic memory difficulty in AD. Thus, although the types of errors made by AD patients on semantic memory tests consistently support a degradation in the semantic network, it is likely that retrieval problems, attentional difficulties and diminished working memory all play a role in semantic memory deterioration in AD.

Episodic Memory. Episodic memory refers to memory of personally experienced events such as what one did a previous weekend (Cermak, 1984; Wagner, 1999). As opposed to semantic memory, contextual and temporal cues are characteristic of the retrieval process in episodic memory (Salmon & Chan, 1994). Thus, episodic memory has an autobiographical referent as it can be dated and it records the spatial context of the learning experience (Brandt & Rich, 1995). Episodic memory is also characterized by an awareness of the learning experience and strongly influenced by the degree of attention and organization utilized during learning (Baddeley, 1995).

Episodic memory is significantly disrupted in AD and is considered a cardinal symptom of the dementia syndrome typical of such patients (Brandt & Rich, 1995). Most clinical tests of memory, such as word list learning, story recall,

and visual stimuli recall, are measures of episodic memory (Brandt & Rich, 1995). AD patients consistently perform poorly on these neuropsychological measures (Kohler, Black, Sinden, Szekely, Kidron, Parker, Foster, Moscovitch, Wincour, Szalai, & Bronskill, 1998; Carlesimo et al., 1998) and such tests are often used to aid in the differential diagnosis of AD (Lezak, 1995; Mohr et al., 1999). Delayed recall has been suggested to be the most sensitive measure of episodic memory in differentiating AD patients from normal controls and other patient groups (Brandt & Rich, 1995; Kohler et al., 1998) whereas recognition memory has been reported to be superior in differentiating AD patients from those with cerebral vascular disease (Libon et al., 1998). Recognition memory and word finding difficulties are purported to be more sensitive than delayed recall in discriminating between mild and moderate AD groups (Brandt & Rich, 1995).

Episodic memory is thought to be comprised of two distinct systems, namely, secondary or long term memory and primary or short term memory (Baddeley, Della Sala, & Spinnler, 1991; Brandt & Rich, 1995). It has been proposed that primary and secondary memory deficits in AD reflect impairment of two independent memory systems (Becker, 1988; Morris & Kopelman, 1986; Baddeley, Logie, Bressi, Della Sala, & Spinnler, 1986; Baddeley, Della Sala, & Spinnler, 1991; Becker, Bajulaye, & Smith, 1992). A pattern of dissociation between primary memory and secondary memory has been reported in patients with AD (Becker, 1988; 1994). Patients in the mild stage of the disease have been identified to exhibit a predominant primary memory difficulty with secondary memory relatively intact (Becker, 1988; 1994; Morris & Kopelman, 1986). In contrast, other patients have demonstrated a significant secondary memory difficulty with primary memory relatively unaffected (Baddeley, Della Sala, & Spinnler, 1991). However, as the disease progresses, this dissociation disappears with most patients displaying disorders in both primary and secondary memory (Becker, 1994).

Secondary memory refers to an organism's ability to store information (Lezak, 1995). The process of storing information may occur quickly or continue for considerable lengths of time with much of the information in long term storage appearing to be organized on the basis of meaning (Squire, 1987). Secondary memory is thought to be limitless in its storage capacity (Brandt & Rich, 1995). Long term memory storage likely involves a number of processes that occur at the cellular level (Mayes, 1988). Such processes include neurochemical alterations in the neuron, neurochemical alterations of the synapse, changes in the amount of

neurotransmitter released or taken-up at the synaptic juncture, elaboration of dendritic spines, and increased connections with other cells (Bailey & Kandel, 1985; Mayes, 1988; Petit & Markus, 1987). It has been suggested that there is not a single storage site for long term memories; rather such memory involves neuronal contributions from many cortical and subcortical regions (Squire, 1987). Thus, given the diffuse nature of the pathophysiology of AD, it is not surprising that such patients, even in the early stages of disease progression, display significant deficits in long term memory.

Assessment of secondary memory impairments in AD involves measures of word list learning as well as recall of meaningful and non-meaningful verbal and visual information (Lezak, 1995). Impairment in secondary memory, as assessed by such measures, has been consistently demonstrated to be related to dysfunction of the medial temporal lobes, particularly the hippocampus (Wilson, Bacon, Fox, & Kaszniak, 1993; Baddeley & Wilson, 1988; Constantinidis, 1978). The degree of hippocampal and parahippocampal atrophy in AD has been strongly associated with poor performance on delayed recall of both word list learning and story recall tests as well as delayed visual recall tests (Kohler et al., 1998; Libon et al., 1998).

Primary memory, also termed short term memory, refers to memory for events or material lasting for approximately 30 seconds (Morris & Baddeley, 1987). It is considered to temporarily hold information retained from the registration process and necessary to transfer information into a more permanent long term store (Squire, 1987). The information in primary memory is thought to be maintained in reverberating neural circuits (Shepherd & Koch, 1990). Reverberating neural circuits is conceptualized as self-contained neural networks that sustain a nerve impulse by channelling it repeatedly through the same network. If not converted into a more stable biochemical organization necessary for long term storage, the electrochemical activity that reflects the primary memory trace is assumed to spontaneously dissipate and the memory not retained (Shepherd & Koch, 1990).

The mechanisms which underlie primary memory are considered complex, nevertheless, there is broad agreement as to the limited capacity nature of primary memory (Crowder, 1982; Morris & Baddeley, 1987; Wagner, 1999). That is, only a limited amount of material can be remembered for short periods relative to the greater capacity of long-term or secondary memory (Morris & Baddeley, 1987). In addition, primary memory is characterized by a rapid rate of forgetting over short periods of time when subjects are distracted by a subsidiary task. Thus, primary

memory is thought to rely on continuous attention, not only during encoding, but also during recall and retention (Morris & Baddeley, 1987; Wagner, 1999). Impairment in primary memory is characterized by deficits in short term retention and is often assessed using three different paradigms such as recall of the most recently presented words in a list (recency in free recall), retention of strings of numbers, letters, or words (memory span), and the retention of infraspans strings of letters while engaging in a distracter task (Brown-Peterson technique) (Kopelman, 1985).

When a list of approximately 15 items is presented to a subject that has to be immediately recalled in any order, the last few items tend to be most likely recalled. The recall of these last few items is termed the recency effect (Morris, 1994). It is thought that due to the relatively short period of time passed from the presentation of the most recent items of a word list and their subsequent recall, that secondary memory influences in recall are minimal (Kopelman, 1985). However, there is argument as to when secondary memory influences recall of the most recent words in a list because cut-off scores for recency items are varied and considered arbitrary (Kopelman, 1985). For example, scoring only the last 3 to 5 items in a word list has been reported to reflect the recency effect (Miller, 1973). Alternatively, assessment of the recency effect has been determined by scoring those items within seven or fewer intervening items between presentation and recall (Tulving & Colotla, 1970). Nevertheless, the recency effect has been contrasted to the primacy effect (ie. the tendency to recall the first few words of a word list and thought to reflect long term storage) in normal and amnesic patients (Kopelman, 1985; Morris, 1994). Neurologically intact subjects tend to retain both the primacy and recency effect whereas amnesic patients retain a recency effect but demonstrate a negligible primacy effect (Kopelman, 1985).

The cognitive explanation for the recency effect has remained controversial (Morris, 1994). One theory proposes that with orally presented material, the recency effect represents a trace or sensory residue that can be accessed at recall (Crowder, 1982). The recency effect has also been interpreted to reflect a retrieval strategy in which the last items are accessed first (Baddeley, 1986). This retrieval strategy is assumed to be automatic and not found to be easily disrupted by concurrent attentionally demanding activities (Baddeley, 1986).

Memory span refers to the recall of a string of items from memory immediately in serial order (Miller, 1956). Memory span may involve the recall of numbers, letters, meaningful or nonsensical words, or objects (Lezak, 1995).

In clinical situations, memory span is routinely assessed with the digit span procedure from the Wechsler Intelligence Scales (Wechsler, 1981). It involves repeating digits both in serial and reverse order of increasing length and is thought to be a measure of primary memory because performance depends on the immediate recall of digits and very little, if any, long term learning of digit sequences occurs (Kopelman, 1985). The standardized administration and scoring of the Wechsler Digit Span test treats the forward and reversed digit span procedure as if they were measuring the same mental process (Lezak, 1995). Although correlations between forward and reversed digit span are high in most normal control subjects (Kaplan, Fein, Morris & Delis, 1991), this correlation is reported to be reduced in some studies of brain damage (Black, 1986; Sullivan, Sagar & Gabrieli, 1989). A difference score of three or greater between forward and reversed digit span length is considered to be indicative of brain dysfunction (Lezak, 1995). Although both digits forward and digits backward require the retention of information in primary memory, the two procedures also entail different mental operations. For example, digits forwards is thought to be closely related to the mental operation of efficiency of attention whereas reversed digit span is thought to involve the mental processes of auditory tracking and manipulation of information (Lezak, 1995; Kaufman, McLean & Reynolds, 1991).

The Brown-Peterson technique, considered a measure of short term forgetting within the primary memory system, involves the presentation of nonsense words that are required to be held in memory while engaging in an interference task, such as counting backwards. The use of nonsense words are thought to mitigate against the influence of semantic processing on recall. Rates of forgetting are assessed during interference times of various lengths, the most commonly employed include 3, 9, 18, and 36 second interference delays (Peterson & Peterson, 1959). The purpose of the interference task is to prevent rehearsal of material being held in primary memory and thus is thought to be a direct measure of the rate of forgetting, or decay, from the primary memory system (Peterson & Peterson, 1959; Morris, 1994). The Consonant Trigrams Test, which requires the subject to retain three consonants in memory while counting backwards by threes during three different time delays (e.g., 3, 9, and 18 seconds) is considered the clinical analogue of the Brown-Peterson paradigm (Franzen, 1989; Lezak, 1995). The three letter combinations are largely without semantic meaning and thus are similar to the original paradigm utilizing nonsense words (Franzen, 1989).

Rapid forgetting as assessed by the Brown-Peterson technique has been associated with frontal lobe dysfunction (Stuss, Kaplan, Benson, Weir, Chirilli & Sarazin, 1982; Kapur, 1988; Leng & Parkin, 1989). For example, the Consonant Trigrams Test was the only test out of several measures of learning and memory that was sensitive to orbitofrontal leucotomy in schizophrenic patients (Stuss et al., 1982). Huntington's patients, who are considered to have predominant neuropathology involving frontal-subcortical structures are also particularly impaired on the Consonant Trigrams Test (Butters, Sax, Montgomery & Tarlow, 1978; Myers, 1983). Nevertheless, it has been argued that performance on the Consonant Trigrams Test is related more to cortical atrophy rather than to specific dysfunction of the frontal lobes (Kopelman, 1994). Significant correlations between CT scan measures of cortical atrophy and performance on both the verbal Brown-Peterson technique and the non-verbal analogue, the Corsi block retention test, have been reported with left cortical atrophy being related to poor performance on the verbal Brown-Peterson procedure and right cortical atrophy being related to poor performance on the Corsi block retention test (Kopelman, 1985a; 1991).

In addition to the association of performance on the Consonant Trigrams test to both frontal lobe pathology and cortical atrophy, poor performance has also been demonstrated to be associated with degree of excision of the left hippocampus in epileptic patients (Milner, 1972). Although these patients were found to have a verbal memory defect prior to operative procedures to excise the hippocampus, the degree of severity of dysfunction on the Consonant Trigrams test was clearly associated with the degree of hippocampus removed with those patients in which the hippocampus was spared performing similarly to normal controls (Milner, 1972). Given that the hippocampus and related structures are thought to be critical in secondary memory processes, it would appear that performance on the Consonant Trigrams test may be dependent to some degree on secondary memory processes.

Additional support for the role of secondary memory in performance on the Consonant Trigrams test is demonstrated in studies of patients with Korsakoff's syndrome, a disorder characterized mainly by a severe anterograde amnesia (Kopelman, 1994). Severe impairment on various versions of the Consonant Trigrams test was found in Korsakoff patients compared to both normal and non-Korsakoff alcoholic controls (Butters & Cermak, 1974; 1980). This was found to be in contrast with studies showing a dissociation in other amnesic patients in which performance on most measures of primary memory including recency in free

recall, memory span, and the Brown-Peterson technique were found to be intact with severe impairment on measures of secondary memory and learning demonstrated (Baddeley & Warrington, 1970). It has been argued, however, that the diencephalic lesions typical of Korsakoff's disease and implicated in the severe anterograde amnesia that characterizes the disorder may not be the crucial factor involved in the poor performance demonstrated by these patients on the Consonant Trigrams test (Kopelman, 1985a). A great deal of variation has been demonstrated by Korsakoff patients on their performance on the Consonant Trigrams test with some patients performing similar to normal controls and others displaying a significant deficiency. Furthermore, performance on the Consonant Trigrams test by Korsakoff's patients was reported to be related more to the degree of concomitant cortical atrophy (Kopelman, 1991a). Thus, it has been argued that in some amnesic patients, performance on the Consonant Trigrams test may not necessarily reflect secondary memory dysfunction but rather a short-term memory impairment superimposed on a secondary memory defect (Warrington, 1982; Kopelman, 1985; 1991). Although the Milner (1972) study demonstrating an association between the degree of impairment on the Consonant Trigrams test and degree of hippocampal removal in epileptic patients is less easily explained by a short term memory impairment, there was no data concerning cortical atrophy in this patient group. Furthermore, significant connections between hippocampal structures and the neocortex have been reported (Kopelman, 1994) which might explain the findings of the Milner (1972) study. Given the research findings that performance on the Consonant Trigrams test is related to cortical atrophy, it can be assumed that performance on this measure is related predominantly to neocortical functioning. Thus, disruptions between hippocampal and neocortical connections may have some detrimental effect on performance on the Consonant Trigrams test. This assumption, of course, would have to be borne out with empirical investigations.

Even given the difficulties in interpretation of the studies on the Consonant Trigrams test described above, it has been routinely utilized as a measure of rapid forgetting (Kopelman, 1985a; 1991; Lezak, 1995). However, research has demonstrated that difficulties on the Consonant Trigrams test may not reflect rapid forgetting past the three second delay data point (Kinsbourne & Wood, 1975; Kopelman, 1991; 1994). Thus, even in patients where impairment on the Consonant Trigrams test has been demonstrated, the relative curve of the slope between patients and normal controls have been reported to be similar after the

three second delay data point. The only divergence in slopes was found between the zero and three second delay (Kinsbourne & Wood, 1975; Kopelman, 1991). Even in Alzheimer's patients in which a relatively severe impairment on the Consonant Trigrams test is observed relative to Korsakoff patients and particularly normal controls, the slope of the curve past the three second delay has been reported to be similar to normal controls with the divergence in slope between AD patients and normal controls occurring only between the zero and three second delays (Kopelman, 1991b; 1992a; 1992b). This has been interpreted as reflecting diminished encoding, retrieval, or an encoding-retrieval interaction rather than accelerated forgetting (Kopelman, 1994). However, as has been aptly argued, accelerated forgetting between the zero and three second delay in Alzheimer's and Korsakoff patients cannot be entirely ruled out (Kopelman, 1994). However, it would be unlikely that accelerated forgetting would be observed only within the three second delay interference condition on the Consonant Trigrams test with rate of forgetting similar between normal controls and patient groups after the three second interference trial. Thus, it has been reported that the most parsimonious explanation for the divergent slopes between the zero and three second delay interference conditions of the Brown-Peterson procedure is one of encoding, retrieval, or an encoding-retrieval interaction (Kopelman, 1994).

Performance by AD patients in the mild stages of the disease on tests of primary memory such as recency in free recall, memory span, and the Brown-Peterson procedure is varied. Little or no impairment is demonstrated with respect to recency in free recall (Martin, Brouwers, Cox, & Fedio, 1985; Kopelman, 1985; Miller, 1971), whereas mild to moderate memory impairment is observed on memory span (Corkin, 1982; Kopelman, 1985; Morris, 1986) in some patients, and moderate to severe impairment is reported on the Brown-Peterson paradigm (Corkin, 1982; Kopelman, 1985; Morris, 1986) in some patients. This variation in performance by AD patients on measures of primary memory has been interpreted to reflect varying amounts of central executive system resources within working memory required for each task (Kopelman, 1985b; Morris & Kopelman, 1986; Morris & Baddeley, 1988; Baddeley, 1998). Thus, it is assumed by these investigators that executive system dysfunction rather than primary memory storage difficulties is the predominant factor in poor performance on most measures of primary memory in certain AD patients.

Working Memory

The psychological construct of memory is typically divided into three structural components: a sensory register which holds modality specific sensory information for very brief periods of time; a short term store which holds transferred sensory information for longer, albeit still brief, periods of time; a long term store which has limitless capacity where information from the short term store is transferred and stored indefinitely. Historically, short term memory was conceptualized as a unitary system in which information decays within a period of 30 seconds unless rehearsed. With rehearsal, a limited amount of information can be maintained within the short term memory store (Atkinson & Shiffrin, 1968). According to this model, short term memory was thought necessary for manipulation of information, learning, long term memory storage, reasoning, and comprehension.

The concept of a unitary short term memory system, however, could not account for much of the research data gathered from cognitive psychology and neuropsychology (Baddeley & Hitch, 1974). Studies were conducted with normal subjects manipulating the limited capacity of the short term memory store by requiring participants to engage in a distracter task. Based on the assumption that short term memory was a unitary and limited capacity system, it was assumed that engaging in a distracter task while performing tests such as digit span should use up the resources in the system, thereby significantly impairing performance. Consistently, results of such studies showed that memory span was not reduced to the level expected given the assumed limited capacity and unitary nature of such a system (Baddeley & Hitch, 1974; Baddeley, 1986; Baddeley, 1998).

A particularly useful neuropsychological research technique, double dissociation, has also been instrumental in refuting the concept of a unitary short term memory system. Double dissociation is a concept which asserts that if two behaviours are performed by one system, damage to that system should produce deficits in both behaviours (Teuber, 1955). However, if there exists a subject who demonstrates impairment in the first behavior but not on the second whereas another subject demonstrates a deficit on the second behavior and not the first, the two behaviours are assumed to be performed by two different systems, thus doubly dissociated (Shuron, 1997). The concept of double dissociation is also utilized in clinical practice to identify the critical neuropsychological disorder underlying poor performance on complex tasks (Lezak, 1997). Most cognitive tests reflect two or more different functions. However, in the individual case, only one of these

functions may be impaired. To facilitate delineation of the compromised function, examination comparing the performances on different tests which each measure just one or two of the several functions in question is conducted. Failure on one or two of the different tests while normal performance is observed on others will indicate which functions are normal and which ones are impaired and underlying the deficit on complex cognitive tests (Lezak, 1997)

Neuropsychological studies on patients with relatively circumscribed short term memory deficits showed that learning, reasoning, and comprehension were often intact, a finding inconsistent with a unitary short term memory system necessary for these cognitive functions (Shallice & Vallar, 1990). Furthermore, based on lesion studies, patients were identified who had intact long term memory yet impaired short term memory and vice versa (Shallice & Vallar, 1990). In other words, subjects performing complex cognitive activities (e.g., reasoning, learning, long term memory) assumed to be dependent on a unitary short term memory system demonstrated a dissociation of these various cognitive operations from short term memory processes. These findings were incompatible with the conceptualization of a unitary short term memory system being necessary to carry out these complex cognitive activities. If such a unitary system was indeed critical, then patients with short term memory deficits should also display diminished long term memory functioning, learning, and reasoning.

Thus, the construct of a unitary short term system is inadequate to explain the available data. If such a system were indeed unitary and necessary to transfer information into long term storage and important in supporting other cognitive functions such as reasoning, comprehension, and learning, then damage to this system should dramatically interfere with these other cognitive functions. The findings reported above demonstrating intact long term memory and comprehension in patients with a short term memory deficit clearly did not support a unitary short term memory system. However, the concept of a system that allows for the brief storage of material still appeared to be useful in understanding the operations of various cognitive activities but needed to be reconceptualized. Thus, theorizing about short term memory has evolved from a unitary system to a tripartite working memory system largely based on the work of Baddeley and Hitch (1974) and Baddeley (1986; 1998).

According to the present conceptualization, working memory can be defined as a system responsible for the short term maintenance and manipulation of information necessary for the execution of such complex cognitive functions as

learning, comprehension, and reasoning (Baddeley, 1992, 1998; Wagner, 1999; Belleville, Peretz, & Malenfant, 1996). It is thought that working memory requires the cooperation among various brain regions, with the precise brain region depending on whether the task entails remembering objects, locations, or words (Wickelgren, 1997). Working memory may also be construed as a system of activated traces which are the output of domain-specific processors and domain-free controlled attention (Kane, Conway, & Engle, 1999). The domain-specific processors may correspond to the phonological loop and visuospatial sketchpad of working memory whereas the domain-free controlled attentional system appears to correspond to the central executive system.

It has been suggested that working memory is comprised of three separate components, a central executive system (CES) which is the central tenet of the model, a phonological loop (sometimes referred to as the articulatory loop), and a visuospatial sketchpad (Ashcraft, 1989; Baddeley, 1992; 1998). The CES is assumed to be an attentional control system that allocates the various resources necessary to keep information in short term memory while simultaneously manipulating that information. The phonological loop and visuospatial sketchpad reflect short term verbal and visuospatial memory respectively and are thought to be controlled and coordinated by the CES. However, they can operate independently in terms of their own processing and storage mechanisms but rely on the CES when task demands exceed their processing capacities (Morris & Baddeley, 1988; Baddeley, 1990a; 1998). For example, if a task is relatively simple it may not depend on resources mediated by the CES and be executed independently by the phonological loop or visuospatial sketchpad. Storage of a few (2 to 3) simple phonological items (e.g., digits) or visual items (e.g., colours) are thought to reflect the independent storage and processing capacities of the phonological loop and visuospatial scratchpad respectively (Ashcraft, 1989). When tasks become more complex (e.g., the retention of phonological or visual items while performing a reasoning task), the storage and processing capacities of these subsystems become taxed and additional resources from the CES are required (Ashcraft, 1989). This new tripartite model was able to account for the data because it was assumed that patients with a relatively circumscribed short term memory impairment, as assessed with the digit span procedure, were thought to have a deficient phonological store whereas the visuospatial sketchpad and central executive were still intact, thereby learning and everyday cognition might not be affected (Baddeley, 1992, 1998; Belleville, Peretz, & Malenfant, 1996).

Phonological Loop. This component of working memory is auditory verbal in nature and thought to be comprised of a phonological short term memory store and an articulatory or subvocal rehearsal control process that serves to maintain phonological items in the store (Vallar & Baddeley, 1984; Baddeley, 1986, 1992, 1998). It has been reported to correlate with digit span, a conventional measure of primary memory (Baddeley, 1998). Without the process of subvocal rehearsal, items that are registered within the phonological store would fade quickly from memory. Auditory verbal information is assumed to gain direct access to the phonological store whereas visually presented items can gain access to the store only via the articulatory rehearsal process. Only visual items that can be transformed into phonological units (e.g., visually presented lists of digits) can utilize the articulatory loop and hence be stored in phonological short term memory (Baddeley, 1986, 1998). There is a wide range of laboratory phenomena that are thought to reflect the nature of the phonological loop and used to assess the integrity of this component of working memory. These phenomena include the similarity effect, irrelevant speech sounds effect, word length effect, and articulatory suppression (Baddeley, 1992; 1998). The first two are thought to reflect the nature of the phonological store whereas the latter two are thought to characterized the articulatory subvocal rehearsal process.

The phonological similarity effect is observed when similar sounding items (e.g., B C G) are presented for immediate recall. Memory span is reduced for similar rather than dissimilar sounding items. This finding is interpreted as reflecting the phonological based nature of the auditory verbal short term store (Vallar & Baddeley, 1984; Baddeley, 1992). Similar sounding items have fewer distinctive characteristics and are more likely susceptible to trace decay (Baddeley, 1966; Conrad & Hull, 1964).

Memory span may also be reduced with the presentation of irrelevant speech sounds during memory span tasks. Known as the irrelevant speech effect, it is thought to occur because such material is assumed to gain direct access to the phonological store disrupting the memory trace and leading to impaired performance on memory span tasks (Salame & Baddeley, 1982; Vallar & Baddeley, 1984; Baddeley, 1986). However, it has been argued that irrelevant speech may interfere with the mechanism of storing serial order as opposed to directly disrupting the phonological memory trace (Jones & Macken, 1995).

The word length effect is observed when memory span is reduced for longer than shorter words (Vallar & Baddeley, 1984). The crucial factor here is the temporal duration to pronounce the word and not the syllables per se (Baddeley, 1986). The word length effect is thought to occur because rehearsal occurs in real time, the longer it takes to rehearse a list of words, the more likely a decay of these items in the phonological store. Shorter sounding words can be rehearsed more quickly and therefore more efficiently retained within the phonological store.

Memory span is also reduced when subjects are required to repeatedly articulate some word or sound (e.g., the) during memory span tasks (Baddeley, 1992). This phenomenon is known as articulatory suppression and memory span is thought to be reduced because the articulation of irrelevant material is thought to reduce or suppress the control process of subvocal rehearsal which is assumed to maintain phonological items in short term memory. Without rehearsal, items in the phonological short term store decay much quicker resulting in shorter spans. During conditions of articulatory suppression with orally presented material, the word length effect is abolished yet the effects of phonological similarity and irrelevant speech remain intact. This has been taken to support the assumptions that phonological similarity and irrelevant speech reflect the nature of a passive phonological short term store whereas the word length effect reflects the nature of the articulatory rehearsal process (Vallar & Baddeley, 1984). Furthermore, phonological similarity, irrelevant speech, and the word length effect are all abolished during articulatory suppression with visually presented words supporting the assumption that visually presented items gain access to the phonological store via subvocal rehearsal.

These phenomena have been observed in a wide variety of experimental settings with normal subjects and patients with neuropsychological deficits (e.g., Vallar & Baddeley, 1984; Baddeley, 1986; Shallice & Vallar, 1990). It is thought that patients with a short term memory deficit who demonstrate normal reasoning, learning, and comprehension likely have a specific dysfunction of the phonological loop in working memory with the visuospatial scratchpad and the central executive systems remaining intact. Evidence is forthcoming from functional imaging studies that the phonological memory store might be located within Wernike's area and the articulatory rehearsal process related to Broca's area (Paulesu, Frith, & Frackowiak, 1993).

Visuospatial Sketchpad. This component of working memory is also assumed to be comprised of a brief store and control processes for the short term retention of both spatial information, such as the location of an object, and information about an object's visual appearance (Baddeley, 1986, 1998; Ploner, Gaymard, Rivaud, Agid, & Pierrot-Deseilligny, 1998; Logie, 1986; Farmer, Berman, & Fletcher, 1986; Baddeley & Lieberman, 1980). However, the nature of the visuospatial sketchpad is not as well understood as the phonological loop and the wide range of phenomena that characterizes phonological memory are not yet discovered for the visuospatial sketchpad (Baddeley, 1992; 1998).

Evidence for the independence of the phonological and visuospatial short term memory systems was provided by Farmer, Berman and Fletcher (1986). In their series of studies, concurrent verbal articulation and spatial tracking disrupted independently performance on verbal and spatial reasoning tasks respectively. They further stated that the results of their studies support the notion that these short term memory systems operate independently of central processing as either of the concurrent tasks would have disrupted performance on verbal or spatial reasoning if central processing played a key role. Functional imaging has also supported the independence of the phonological and visuospatial short term memory systems (Smith, Jonides, & Koeppel, 1996)

Presentation of both concurrent visual and spatial material has been shown to disrupt memory performance (Baddeley, 1998). Performance on a verbal paired associates task was impaired with concurrent presentation of visual and spatial information when subjects were required to use a visuospatial mnemonic to facilitate learning, whereas performance remained normal during rote rehearsal (Baddeley & Lieberman, 1980). Logie (1986) showed that subjects' memory span for visual information was disrupted with the concurrent presentation of patterns and patches of colour. Furthermore, Baddeley and Lieberman (1980) discovered that concurrent visuospatial tracking disrupted the memory performance of subjects utilizing a visual imagery mnemonic. This disruption was independent of visual input, attesting to the spatial nature of the sketchpad. Subjects who were blindfolded were asked to track a moving sound source while attempting to learn a list of words using an imagery mnemonic. Concurrent spatial tracking disrupted performance whereas those subjects who learned the list by rote rehearsal performed normally.

Based on the studies above, Baddeley (1992) proposed that the visuospatial sketchpad has independent visual and spatial components and Farah (1988) argues for the anatomical and functional distinction between these components with the former localized to parietal structures and the latter to the occipital lobes. Other research as well has provided support for the dissociation of spatial and object working memory (Tresch, Sinnamon & Eamon, 1993; Quinn & McConnell, 1996). Essentially, this research demonstrated that visual but not spatial aspects of memory can be disrupted by a visual distracter task whereas spatial memory can be disrupted by a spatial tapping task leaving visual memory unaffected.

Central Executive System. The CES is perhaps the most important component of working memory (Baddeley, 1992, 1998; Kane, Conway, & Engle, 1999; Towse, 1998). It is thought to be a modality free, limited capacity attentional control system responsible for the selection, planning, and control of the various processes involved in storage and serves a general role in processing (Ashcraft, 1989; Kane et al., 1999; Towse, 1998; Van der Linden, Coyette, & Seron, 1992; Baddeley, 1992). Therefore, the CES is thought to be necessary for many cognitive functions such as reasoning, comprehension, planning, and learning and remembering (Baddeley, 1992, 1998; Kemper, 1997; Kempler et al., 1998; Wagner, 1999; Wickelgren, 1997). An important feature of the CES in the working memory model is the assumption that it coordinates and regulates the activities of the phonological loop and the visuospatial sketchpad and integrates information from these systems with long term memory (Baddeley, 1992, 1998; Towes, 1998; Van Der Linden, Coyette, & Seron, 1992).

Baddeley (1986; 1998) proposed to use the Norman and Shallice (1986) model of attentional control to characterize the operation of the CES. According to the Norman and Shallice model, action is controlled at two levels. First, action may involve the operation of existing automatic and routine schemata. Many environmental demands or tasks can be carried out via routine schemata that can run themselves off automatically. Second, a supervisory attentional system (SAS) can override the automatic schemata potentials. Such a system requires conscious deliberate attentional activity and would be necessary to take control in novel situations where automatic schemata may be nonadaptive. Norman & Shallice (1986) argued that the frontal lobes may be the anatomic site for the operation of the SAS. With frontal dysfunction and SAS impairment, patients get locked into existing schemata and behave perseveratively, even when such behavior is

maladaptive. Conversely, SAS dysfunction may characterize patients whose attention is captured by any available salient stimulus because control of attention is impaired.

Within the working memory framework, the construct of the SAS has been used to explain the existing data on random generation, thought to be a prototypical experimental measure of CES functioning (Baddeley, 1986; 1992; Baddeley, Emslie, Kolodny, & Duncan, 1998; Towes, 1998). In random generation, a subject is asked to produce a random string of units (e.g., from the alphabet). Most subjects are able to complete this task if required to do it slowly. However, when subjects are asked to quickly randomly generate letters of the alphabet, stereotyped responding and common acronyms are produced (e.g., rst, usa). This is thought to occur because the SAS, limited in capacity, must override the prepotent tendency to respond with overlearned and automatic schemas, such as in either reciting the alphabet in sequence or in using common acronyms. In addition, the SAS must provide attentional resources to allow for novel responding, such as in the generation of a retrieval strategy necessary for random output.

Although the construct of the SAS has proved helpful in understanding the nature of the CES, this very important component of working memory is still little understood. It is likely not a unitary system and dysfunction of the CES may result in differing behavioral symptoms (Baddeley, 1986; 1998; Kane et al., 1999; Towes, 1998). At present, CES dysfunction is thought to present with at least two differing symptom pictures. First, damage to the CES may show up in a global reduction of processing capacity. Second, deficits in the control or planning component of executive functioning might be observed. CES dysfunction in frontal lobe patients is thought to reflect deficits in control and planning functions, in the elderly it is thought to reflect damage in processing capacity, whereas in AD, it is thought to reflect damage to both aspects (Van Der Linden, Coyette, & Seron, 1992).

Assessment of working memory capacity requires evaluation of the various components that comprise it (Baddeley, 1992; 1998). Phonological similarity, word length effect, irrelevant speech, and articulatory suppression are routinely used to assess the integrity of the phonological loop. There is little in the way of measurement for the visuospatial sketchpad as phenomena such as found for the phonological loop has, of yet, been unidentified. Presently, tasks that assess short term retention of visuospatial material (e.g., visual tapping test of the Wechsler Memory Scale-Revised) appear to be useful (Van der Linden, Coyette, & Seron, 1992). However, the degree to which the CES plays a role in this test has not been

ascertained, and poor performance cannot be solely explained based on dysfunctional visuospatial short term memory. The CES is routinely investigated in experimental settings with divided attention tasks (e.g., random generation of the alphabet). There are a variety of paradigms utilized (e.g., Baddeley, 1986; Becker, 1988; Van Der Linden, Coyette, & Seron, 1992; Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991; Kane et al., 1999; Towse, 1998) and most require the execution of two tasks simultaneously.

Distinction Between Working Memory and Primary Memory. The distinction between working memory and primary memory is often confusing in the literature because both concepts share similar characteristic features. The concept of working memory evolved from primary memory and both are characterized by limited capacity storage, relatively quick decay of material, and the maintenance of attentional resources during tasks that assess them (Wilson, Bacon & Fox, 1983; Becker, 1988; Morris & Baddeley, 1988). However, it can be argued that the two concepts are distinct and such a distinction might be heuristically useful. Primary memory may be conceptualized as part of the working memory system that involves the operations of short term storage of phonological or visuospatial information with or without the aid of a putative CES. Given that primary memory systems are not necessarily dependent on CES functioning, they can be characterized as independent cognitive systems (Morris & Baddeley, 1988; Kopelman, 1994; Morris, 1994).

Working memory, on the other hand, can be conceptualized as the operation of the whole system, the interaction of CES resources with the independent primary memory storage mechanisms (Morris & Baddeley, 1988). The heuristic value in differentiating working memory from primary memory may be best demonstrated by the cognitive deficits that will arise given the specific component of working memory affected by neurological disease or trauma. Relatively circumscribed deficits in phonological short term memory, with CES resources intact, will likely result in a different symptom profile than would be observed should the CES be deficient. As described above, patients with circumscribed deficits in phonological short term storage (e.g., a primary memory system) often results in a specific cognitive deficit in which phonological items decay quicker from the phonological primary memory store compared to individuals without such an impairment (Shallice & Vallar, 1990). Furthermore, patients identified with a circumscribed primary memory deficit often retain their ability to engage in other cognitive

functions such as reasoning, language comprehension, and long term storage at normal levels (Shallice & Vallar, 1990). A working memory deficit, on the other hand, may be present in the context of normal storage processes in primary memory. However, the control of attentional resources required to manipulate and coordinate the information retained in the various primary memory systems may be deficient resulting in diminished capacity, for example, to reason and comprehend complex linguistic information (Morris, 1994; Kopelman, 1994; Kemper, 1997; Kempler, Almor, Tyler, Andersen & MacDonald, 1998; Almor, Kempler, MacDonald, Andersen & Tyler, 1999; Wagner, 1999). Thus, working memory can be differentiated from primary memory by the predominance of executive system dysfunction relative to primary memory storage deficiencies and by the constellation of cognitive symptoms that might arise. However, it is conceivable that both CES and primary memory storage dysfunction may co-occur in certain neurological diseases thus reflecting impairment in both working memory and primary memory. With respect to Alzheimer's disease, it is thought by several investigators that the phonological and perhaps the visuospatial primary memory storage systems remain relatively intact during the early stages of the disease whereas the attentional component of the CES in working memory is deficient (Baddeley et al., 1986; Morris, 1987; Baddeley & Bressi et al., 1991; Belleville, Perez & Malenfant, 1996).

Working Memory and Alzheimer's Disease

Several studies have investigated CES dysfunction in AD patients and have found it to be deficient compared to age matched elderly controls (Brugger, Monsch, Salmon, & Butters; 1996; Collette, Van der Linden, Bechet, Belleville & Salmon, 1998; Hodges & Baddeley, 1995; Belleville, Peretz, & Malenfant, 1996; Baddeley & Della Sala et al., 1991; Baddeley et al., 1986; Morris & Kopelman, 1986). In addition, CES functioning is thought to decline with the progression of the disease (Baddeley, Bressi, Della Sala, Logie, & Spinnler, 1991). The criticism that AD patients may be unduly penalized because of a limited general processing capacity which is highly taxed by more difficult tasks (such as the dual task paradigm), that are typically used to assess CES functioning, is not supported in the literature (Baddeley & Bressi et al., 1991; Belleville, Peretz & Malenfant, 1996). If these assertions were granted, AD patients would show greater performance decrements, relative to normal controls, when single task difficulty is increased. However, AD patients performed similar to controls when a sorting by category

task was made more difficult by increasing the number of categories by which to sort (Baddeley & Bressi et al., 1991). Furthermore, a CES hypothesis would propose that a specific impairment be seen (e.g., impairment specifically on dual task paradigms). Indeed, when simultaneous performance on two tasks is required, AD patients show decrements in performance relative to normal elderly controls, even when the level of difficulty on each task independently was adjusted so that performance levels were equal between the two groups. Thus, it was the combination of the two tasks that proved difficult for AD patients (Baddeley et al., 1986; Baddeley & Bressi et al., 1991). Indeed, the working memory model has generated a significant interest in AD research recently and has been suggested to underlie deficits in autobiographical memory, metalinguistic judgments, and sentence comprehension (Kempler, Almor, Tyler, Andersen, & MacDonald, 1998; Kemper, 1997; Reid et al., 1996) as well as learning and long term remembering (Wagner, 1999). It is precisely this, a defective working memory that is thought by several researchers (Becker, 1988; Baddeley, Della Sala, & Spinnler, 1991; Carlesimo et al., 1998; Kemper, 1997; Kempler, Almor, Tyler, Andersen, & MacDonald, 1998; Baddeley, 1998; Wagner, 1999) to underlie many of the cognitive difficulties in AD including new learning, reasoning, and comprehension.

It is a dysfunction of the CES that is also thought to be responsible for the primary memory disturbance observed in AD (Kopelman, 1985; Morris & Kopelman, 1986; Baddeley et al., 1986; Morris & Baddeley, 1988; Baddeley, 1990b, 1998; Baddeley & Bressi et al., 1991). AD patients, certainly as the disease progresses, often do poorly on measures of short term memory such as the Digit Span procedure and the Consonant Trigrams Test (Kopelman, 1985; Morris & Kopelman; Lezak, 1995). Because investigations of the phonological loop and the visuospatial scratchpad in AD have shown these systems to remain generally intact (Baddeley & Bressi et al., 1991; Belleville, Perez & Malenfant, 1996; Morris, 1987), it is assumed that deficits in central executive allocation of attentional resources is the underlying problem in performance of AD patients on short term memory tasks (Morris 1987a; Morris 1987b; Baddeley, 1990a; Baddeley, 1990b). Furthermore, executive system difficulties are often observed in certain AD patients even in the early stages of the disease (Reid et al., 1996; Moss & Albert, 1992). Because the limited capacity of the CES is assumed to be further compromised by the disease process in AD, it cannot simultaneously allocate resources to the necessary processing and storage mechanisms required in some primary memory tasks (Morris & Baddeley, 1988; Baddeley, 1998). Thus, the

deficits in primary memory in AD are assumed to reflect impoverished central executive resources and not storage capacity per se. The Digit Span test and the Consonant Trigrams test are routinely used in clinical settings. Therefore, taken together, these tests may be sensitive indices of the effects of CES dysfunction on cognition in AD.

Nevertheless, the research to date on primary and working memory difficulties in AD utilizing the Digit Span test and the Consonant Trigrams test have assumed that central executive difficulties underlie the poor performance by AD patients on these measures. This is largely due to observations of intact phonological and visuospatial short term storage, thus leaving only the CES as an explanatory factor underlying the poor performance by AD patients on measures of primary memory. However, empirical validation of the role of executive system processes in performance by AD patients on primary memory tasks is somewhat lacking.

STUDY OBJECTIVES

The working memory model may have general importance in understanding the disease process in AD for various reasons. First, working memory may support a variety of cognitive activities such as reasoning, comprehension, and new learning. Thus, an understanding of working memory difficulties may elucidate the nature of diminished reasoning, comprehension, and new learning in AD and other disorders. Second, given that working memory capacity is assumed to underlie many complex cognitive abilities, the identification of probable AD patients with a working memory deficit might have importance with respect to current drug treatments and future clinical trials. For example, several authors have suggested that a deficient CES in working memory may reflect a subtype of probable AD (Baddeley et al., 1991; Becker, 1994). Patients demonstrating a working memory difficulty might not show as great a treatment effect in clinical trials research than patients who do not exhibit diminished working memory capacity, particularly if the pharmacological compounds under investigation have a negligible affect on working memory. Thus, a treatment effect may be obscured when AD patients with a working memory deficiency are included in the overall efficacy analyses in clinical trials investigations. AD Patients with problematic working memory, therefore, may serve as an indicator regarding which patients will or will not respond to certain pharmacological treatments. The identification of probable AD subgroups that may not respond to pharmacological treatment is regarded as an

increasingly important component in clinical trials research (Mohr et al., 1999). Third, given the assumed importance of working memory in complex cognitive activities, future pharmacological compounds might be investigated that target specifically a working memory deficit. If such an endeavour proves to be successful, than improvement in several areas of cognitive functioning might be demonstrated. However, in order for these general goals to be attained, valid measures of working memory must be identified.

Much of the research reviewed above lends support to executive system dysfunction rather than predominantly mnemonic problems as contributing to working memory difficulties in probable AD. Furthermore, it is thought that executive system dysfunction within working memory contributes significantly to the poor performance of many probable AD patients on tests of other cognitive ability areas such as primary memory, learning, and reasoning. However, experimental measures (e.g., dual task paradigms; random generation) with no known validity have often been utilized when investigating the nature of the working memory deficit in probable AD (Baddeley et al., 1991).

The main purpose of this study is to investigate the role of executive system disturbance in primary memory functioning in probable AD patients within the mild stage of the disease. Given the research reviewed above, certain AD patients should show a disturbance in executive system functioning whereas others will not. Given this to be true, it is hypothesized that those probable AD patients identified with an executive disturbance will perform more poorly on measures of primary memory than those patients identified as not having an executive disorder. Furthermore, probable AD patients not exhibiting an executive disturbance should perform comparably to normal elderly controls on measures of primary memory, given the hypothesized role of the CES in primary memory functioning. Tests used routinely in clinical practice to assess the cognitive domains under consideration in this thesis will be employed to investigate the research questions.

METHODOLOGY

Participants

The participants in this study were patients recently diagnosed as fulfilling the NINCDS-ADRDA criteria for probable Alzheimer's disease. They were recruited from the Memory Disorders Clinic at the Elizabeth Bruyere Hospital waiting for inclusion into one of the various experimental pharmacological clinical trials conducted at the center. Diagnosis was made by a neurologist and followed

both DSM-IV (American Psychiatric Association, 1994) and NINCDS-ADRDA (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984) criteria. All patients participating in this study were contacted and tested prior to their inclusion in experimental therapeutic research and thus were not under the effects of experimental pharmacological agents that may have an effect on their cognitive functioning. Any patients who had other neurological disorders (e.g., Parkinson's Disease), or were under pharmacological treatment with known psychoactive effects, had a history of substance abuse, previous history of head injury with loss of consciousness, or significant depression were excluded from study. These exclusion criteria are routinely utilized in clinical trials research with AD patients as these factors tend to impact negatively with respect to performance on cognitive measures (Mohr et al., 1999). Thus, to avoid the potential of additional cognitive dysfunction other than the disease process in AD, only those patients who met these exclusion criteria were considered for the current study. Appendix three contains a complete list of inclusion and exclusion criteria for the sample of probable AD patients participating in this study.

In all, thirty one patients diagnosed with AD met exclusion and inclusion criteria. Of these 31 patients, two found the testing stressful and withdrew from the study. Thus, complete data on 29 patients with probable Alzheimer's disease was yielded for analysis. The Mattis Dementia Rating Scale (MDRS; Mattis, 1988) was administered to facilitate grouping the probable AD patients into those with a predominant executive disturbance and those without. Factor analytical analysis of the MDRS demonstrated that the Conceptualization subscale could be considered a greater overall measure of executive system ability than any other subtest that comprises the MDRS (Colantino, Becker, & Huff, 1993). According to the MDRS manual (Mattis, 1988), the recommended cut-off score for the conceptualization subscale falls at 32. Thus, those patients who scored at or above 32 were included within the non-executive group and those falling below 32 were grouped as having a predominant executive disorder yielding 12 subjects grouped as non-executive and 17 subjects as executive. Further justification for the use of the MDRS conceptualization subscale as a measure differentiating AD patients as either having an executive system disorder or not can be found below in the discussion of the MDRS under the heading of accession criteria. The Mini Mental State Examination (MMSE; Folstein, Folstein & McHugh, 1975) was conducted on the 29 probable AD patients to as a means to gather data on the overall severity of cognitive impairment. The MMSE is often used to classify the severity of

dementia in AD with scores between 18 and 24 assumed to reflect mild cognitive impairment and scores lower than 18 thought to reflect moderate to severe cognitive impairment (Tombaugh & McIntyre, 1992).

The sample of control subjects included in this study were volunteer friends or relatives of patients as well as community dwelling volunteers. Patients and control subjects were matched with respect to age but not education. Control subjects who had a history of psychiatric difficulties, significant current depression, neurological disorder, history of head trauma with loss of consciousness, history of substance abuse, and being treated with pharmacological agents with known psychoactive effects were excluded from the study, as these factors may have an influence on cognitive functioning. Complete inclusion and exclusion criterion for control subjects are found in Appendix Four. Recruitment yielded 15 control subjects who met the inclusion and exclusion criteria and their data are included in the analyses.

Measures

A). Accession Criteria:

1). Mattis Dementia Rating Scale (MDRS). This scale was developed to quantify the mental status of patients suffering from dementia (Mattis, 1976). The subtests include measures of attention, construction, verbal and nonverbal immediate memory, and various executive functions such as initiation, conceptualization, verbal fluency, and perseverative tendency. The MDRS is relatively simple to administer and takes approximately 10 to 15 minutes to administer to the healthy elderly and 20 to 30 minutes for demented patients.

Reliability studies of the MDRS show high test-retest reliability coefficients of .90 or greater (Coblentz, Mattis, Zingesser, Kasoff, Wisniewski, & Katzman, 1973) and split half reliability coefficients of .90 (Gardner, Oliver-Munoz, Fisher, & Empting, 1981). Validity studies show that the MDRS is sensitive in differentiating brain damaged patients from normal elderly subjects (Montgomery, 1982) and is particularly sensitive to the behavioral changes that characterize senile dementia of the Alzheimer's type (Lezak, 1983).

Although the MDRS is related to the MMSE as an overall measure of gross cognitive functioning, this test examines cognition in much greater depth and detail (Mattis, 1976). Particularly germane to this study is the inclusion of a measure of executive function found in the MDRS but not on the MMSE. A study investigating the factor structure of the Mattis Dementia Rating Scale in a sample

of patients diagnosed with Alzheimer's Disease identified three factors underlying performance on the total MDRS (Colantino, Becker, & Huff, 1993). These factors were identified as visuospatial construction, memory, and conceptualization (Colantino, Becker, & Huff, 1993). All of the items that comprise the Conceptualization subtest of the MDRS loaded on one factor and given the item content of the subscale, the authors of this study reasoned that the MDRS Conceptualization subtest was likely related to executive system functioning (Colantino, Becker, & Huff, 1993). A confirmatory factor analytical study has replicated these findings in a sample of mildly demented AD patients (Woodard, Salthouse, Godsall, & Green, 1996).

The conceptualization subscale of the MDRS assesses both verbal and non-verbal abstraction and conceptual ability (Mattis, 1988). It requires the identification of similarities and differences amongst various verbal and non-verbal stimuli and elicits priming inductive reasoning. Although the MDRS subscale has not been empirically investigated to correlate with standard clinical measures of executive system functioning such as the Wisconsin Card Sorting Test, both measures are considered to assess abstract thinking. Abstract thinking is accepted by many clinicians and researchers to be a component of executive system functioning. Some correlational investigations of the MDRS Conceptualization subtest have found significant relationships between performance on it and verbal fluency, WAIS-R Similarities, WMS-R Mental Control, and WMS-R Digit Span (Woodard et al., 1996; Marson, Dymek, Duke, & Harrell, 1997). Although these measures are not necessarily considered pure measures of executive system functioning, they are often considered to have a significant executive component. Thus, some psychometric support for the use of the MDRS Conceptualization Subscale appears evident. However, further correlational analyses with better accepted tests of executive system functioning would add to the psychometric validity of the MDRS Conceptualization subtests as a measure of executive system functioning.

Given that the MDRS Conceptualization subscale places little demand in the way of memory functioning (as all items are left in view during task administration), that item content (e.g. similarities; differences) is similar to task requirements of other more accepted measures of executive system functioning, the strong loading of the MDRS Conceptualization subtests items on a single factor, and the fact that the MDRS avoids potential floor effects, the use of MDRS Conceptualization subtest was considered to be conceptually sound as a measure of

executive system functioning in mild AD patients. In addition, other research has utilized the Conceptualization subscale of the MDRS as a measure of executive system functioning in Alzheimer's disease (Chen, Sultzer, Hinkin, Mahler, & Cummings, 1998). Although other routinely used tests of executive functioning are available, such as the Stroop and Wisconsin Card Sorting Tests, studies have indicated that AD patients tend to exhibit a floor effect on these measures (Chen et al., 1998). The MDRS Conceptualization subtest was thus utilized to group the overall probable AD sample into those assumed to have an executive disturbance and those assumed not to have a predominant executive disturbance. The recommended cut-off score of 32 as published in the manual (Mattis, 1988) was used as the criteria in grouping the probable AD sample.

2). Mini Mental State Examination (MMSE). The MMSE (Folstein, Folstein, & McHugh, 1975) is a widely used clinical measure designed to assess cognitive impairment and to help document dementia. It serves as one of the tests recommended by the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association (NINCDS-ADRDA) to document the clinical diagnosis of probable AD (Tombaugh & McIntyre, 1992).

The MMSE consists of a number of questions that measure orientation to time and place, registration and recall of three words, language, visuospatial construction, and attention\concentration. It yields a maximum score of 30 and takes approximately 5 to 10 minutes to administer (Tombaugh & McIntyre, 1992). The MMSE is often used to classify the severity of dementia in AD (mild, moderate, severe) based on degree of cognitive impairment as reflected in scores (18-24 = mild cognitive impairment and 0-17 = severe cognitive impairment).

Reliability studies have shown the MMSE to possess adequate internal consistency and test-retest reliability (Foreman, 1987; Folstein, Folstein, & McHugh, 1975). Alpha levels for internal consistency ranged from (.68) to (.96) with the highest alpha level obtained in a medical population. Test-retest reliability coefficients ranged from (.89) to (.99) in a mixed population of medical patients.

The validity of the MMSE was demonstrated in a series of studies examining the sensitivity and specificity of the test in identifying dementia (Folstein, Folstein, & McHugh, 1975; Foreman, 1987). The sensitivity of the MMSE refers to its ability to correctly identify those patients who have been classified as cognitively impaired by some other standard. Specificity refers to the identification of those

individuals who have been previously classified as cognitively intact. Sensitivity percentages ranged from 82 to 100 percent and specificity percentages ranged from 80 to 100 percent (Tombaugh & McIntyre, 1992). Overall, these studies suggest that the psychometric properties of the MMSE make it a useful tool in clinical settings.

3). Geriatric Depression Scale. This scale is used to measure depression specifically in the elderly and consists of 30 yes/no questions designed for self administration (Yesavage, Brink, Rose, Lum, Huang, Adey, & Leirer, 1983). The Geriatric Depression Scale (GDS) deliberately omits items thought to be inappropriate for elderly subjects such as guilt, sexuality, and suicide. Factor analytical studies revealed a major factor of dysphoria, and minor factors of worry, dread, obsessive thought, apathy, and withdrawal (Parmalee, Lawton, & Katz, 1989). Internal consistency of the scale has been reported at .94, split half reliability at .94, and test-retest reliability after one week at .85 (Koenig, Meador, Cohen, & Blazer, 1988). Concurrent validity correlations were reported at .73 with the Beck Depression Inventory (Hyer & Blount, 1984), .84 with the Zung Depression Scale, and .83 with the Hamilton Depression Rating Scale (Yesavage, Brink, Rose, & Adey, 1986).

The GDS is to be used for subjects over 55 years of age and has shown satisfactory discrimination between demented patients with and without depression (Snowdon & Donnelly, 1986). Based on the following cut off scores, 0-9 = normal; 10-19 = mild depression; 20-30 = severe depression, 84 percent sensitivity and 95 percent specificity ratings were reported (Yesavage et al., 1983).

B). Outcome Measures:

1). Digit Span. Digit span is the immediate recall of digits in both forward and reverse conditions after auditory presentation. The forward condition of digit span is thought to reflect operation of a short term phonological store and rehearsal processes (Shallice & Vallar, 1990). As digit load is increased, patients with probable AD perform increasingly poorly (Kopelman, 1985). It is assumed that resources of the CES are required for proper recall of increasing strings of digits in probable AD (Ashcraft, 1989). The digit backwards procedure of the digit span test requires subjects to repeat strings of digits in reverse order. It is thought to

require the resources of CES functioning because strings of digits must be held in memory while manipulated so that they can be orally reproduced in reverse order (Fisk & Warr, 1996). Thus, digit span may be a sensitive measure of CES dysfunction.

2). Consonant Trigrams Test. This is a test of rate of forgetting from primary memory (Kopelman, 1985) and is the standardized clinical analogue to the Brown-Peterson paradigm (1959). The procedure requires subjects to retain orally presented consonant trigrams (e.g., three consonants of the alphabet) while performing an interpolated distracter task (counting backwards by threes). Intervals between presentation of the trigrams and recall are varied (from 3 to 18 seconds). Subjects are then required to verbally provide the earlier presented trigrams. It is assumed that the CES must allocate different resources necessary to rehearse and maintain verbal trigrams in short term storage while subjects simultaneously perform the distracter task. Because the nature of this test requires division of attentional resources, it might be the relatively most sensitive measure of CES dysfunction in AD currently available as a widely established neuropsychological tool.

3). Random Generation. Baddeley (1998) asserts that random generation of the alphabet is a direct measure of CES functioning according to the model of attentional control espoused by Norman and Shallice (1986). The degree of randomness of output is considered to be an indication of the integrity of CES functioning. According to procedures developed by Baddeley (1966; 1986), subjects will be required to randomly generate letters of the alphabet as quickly as possible until they generate 50 responses. The production of stereotypical alphabetic sequences (e.g., a-b), familiar acronyms (e.g., usa), and repetition of alphabetic digrams (e.g., 'ru' repeated throughout the sequence) is thought to reflect the integrity of the CES. Probable AD patients have demonstrated a greater tendency to make stereotypical errors in random output and quantification of such has been utilized as a measure of non-random generation (Brugger et al., 1996). Thus, a quantitative index can be computed by adding the number of these various productions with a higher score reflecting a greater degree of non-random output. A potential caveat that is inherent in this type of task involves whether or not a sequence of letters is truly random but represents a personal or less familiar acronym. To reduce this potential bias, randomness of output was judged by two

separate raters thus providing an index of interrater reliability. A practice trial of 20 responses was conducted initially to ascertain that the subjects understand the task. As the random generation task is largely experimental in nature, its validity as a measure of executive functioning has not been clearly ascertained.

Study Procedure and Design

The study protocol was approved by the ethics committees of both the University of Ottawa and the Elizabeth Bruyere Health Sciences Center. All study participants (both probable AD and normal controls) were contacted in person by the principal investigator (RC) during a visit to the Memory Disorders Clinic at the Elizabeth Bruyere Hospital. A brief description of the study protocol was provided and for those who expressed interest contact was made at a later date at which time informed consent was obtained and the study protocol conducted. For all the probable AD subjects, a significant other was present during informed consent and required to sign informed consent forms in addition to the patient's signature. The requirement of the significant other's signature on the informed consent forms was required by the Ethics Committee of the Elizabeth Bruyere Hospital to ensure that patients had the opportunity to discuss their concerns regarding the study with a significant other. A brief unstructured interview was then conducted to gather demographic information such as age, education, work history, race, and gender, and to ascertain that inclusion and exclusion criteria were met. In the case of probable AD patients, a significant other was present during this interview to ensure adequacy of the information provided. Afterwards, the GDS and the MMSE were administered to rule out significant depression and severe dementia respectively. Subjects (both probable AD and normal controls) scoring 10 or higher on the GDS were excluded from further study. No patients with probable AD or control subjects scored higher than 10 on the GDS. Any probable AD patients scoring less than 18 on the MMSE were also excluded from further study, however, there were no patients with probable AD who scored below 18 on the MMSE within the current sample under study.

All neuropsychological testing was completed in one session and all subjects were tested alone. The administration of all neuropsychological tests followed the same procedure and sequence for every subject. The random generation task was administered first. Subjects were asked to orally generate as randomly as possible letters from the alphabet. They were initially given 10 practice trials to ensure adequate understanding of the test instructions. Following this, they were required

to generate randomly the alphabet for 50 responses without further instruction. Following this, the MDRS was administered following the standard administration protocol as published in the manual (Mattis, 1988). The Consonant Trigrams Test was then administered. Both patients and normal controls were instructed that this was a test to try and do two things at once. They were asked to try to hold three consonants in memory while counting backwards by threes. All trials of the Consonant Trigrams Test were administered orally by the examiner and subjects were requested to produce the consonants at the end of each trial verbally. Five sequential trials involving no interference ('0' second trials) were administered first. After administration of these five 'no interference' trials, five trials each involving 3, 9, and 18 second interference delays were administered according to standard procedure (Lezak, 1995, p. 432). According to standard procedure, administration of the different interference/delay trials is variably interspersed throughout the test. Following administration of the Consonant Trigrams Test, the digit span procedure was administered according to the standard administration format as described in the Wechsler Adult Intelligence Scale-Revised manual (Wechsler, 1981).

Scoring for the random generation task included one raw score for every stereotyped alphabet sequence (e.g., a-b), familiar acronym (e.g., usa), and repeated digram (e.g., r-u repeated twice or more). A total raw score was then computed by adding all scores derived from stereotyped alphabet sequences, familiar acronyms, and repeated digrams and expressed as a percentage of non-random output from the total responses obtained in each individual subject. The higher the percentage score, the greater degree of non-random output inferred. Scoring for the MDRS, consonant trigrams test, and digit span procedure followed standard instructions (Mattis, 1988; Lezak, 1995; Wechsler, 1981). Based on demographic data obtained, an index of premorbid intelligence (Barona Index) was computed for all subjects. The Barona Index takes into account level of education, type of occupation, residence (urban or rural), and gender in the determination of estimated premorbid intelligence (Spreeen & Strauss, 1991). It is assumed to be a better index of premorbid intelligence in dementia because of its reliance on demographic as opposed to cognitive variables for estimates of intelligence (Spreeen & Strauss, 1991). All tests were scored and all data were entered by the principal investigator (RC).

The data were analyzed using the Statistical Package for the Social Sciences (SPSS) for Windows, Standard Version (Release 6.1, 1994). A series of one-way analysis of covariance (ANCOVA) was conducted on the dependent variables including digit span forward, digit span backwards, the consonant trigrams test, and the random generation test to test the main hypothesis. ANCOVA was utilized to statistically remove the effects of differing educational levels in the sample in the overall analyses. All post-hoc comparisons were performed with the least significant difference (LSD) test (at significance level .050) to correct for possible Type I error. Results were considered significant at $p = .05$.

RESULTS

Descriptive Statistics. Within the probable AD sample, 12 subjects were classified as not having an executive disorder and 17 were classified as having an executive disorder based on their scores on the conceptualization subtest of the Mattis Dementia Rating Scale. Of the 12 probable AD subjects identified as not having an executive disorder, 6 (50 %) were male and 6 (50 %) were female. Of the 17 probable AD subjects identified as having an executive dysfunction, 8 (47 %) were male and 9 (53 %) were female (Please see summary table 1). Fifteen aged matched volunteers constituted the control group. Of these 15 subjects, 6 (40%) were male and 9 (60%) were female (Please see summary table 1).

The three groups, probable AD with executive disturbance, probable AD without executive disturbance, and normal controls, were matched with respect to age but not matched with respect to education and estimate of premorbid intelligence. Therefore, a MANCOVA, with groups (AD-executive; AD-nonexecutive; normal controls) as the independent variables and number of years of education and the Barona Index (estimate of premorbid intelligence) as the dependent variables, was conducted to determine whether significant differences existed amongst the groups. The results of the MANCOVA indicated a significant multivariate effect for both education ($F(2, 41) = 8.73, p < .01$) and the Barona Index ($F(2, 41) = 6.68, p < .01$). Post-hoc comparisons utilising the Tukey-HSD (with significance level at .050) to control for type 1 error revealed that the probable AD patients without an executive disorder, demonstrated as a group, higher levels of education and premorbid intelligence than either the probable AD patients with an executive disorder or normal controls. There were no differences between normal controls or probable AD patients with an executive disturbance concerning level of education obtained or premorbid intelligence. Given this, all

subsequent analyses included scores on the Barona Index as a covariate to control for differences in estimated premorbid intelligence. Summary table 1 contains the means and standard deviations of the three groups on age, education, and estimates of premorbid intelligence.

Table 1

Demographic Data on Probable AD Patients With an Executive Disorder, Probable AD Patients Without an Executive Disorder, and Normal Controls

Demographic Variables	Non-exec N = 12	Executive N = 17	Normal Controls N = 15
<u>Gender</u>			
Males	6 (50%)	8 (47%)	6 (40%)
Females	6 (50%)	9 (53%)	9 (60%)
<u>Age</u>			
Mean	73.5	71.6	71.5
SD	5.8	4.9	2.8
<u>Education</u>			
Mean	15.0	11.8	11.2
SD	2.4	2.2	2.8
<u>Barona Index</u>			
Mean	114.0	105.1	104.1
SD	7.5	7.1	8.1

Inferential Statistics. Results of evaluations of assumptions of normality, homogeneity of variance-covariance matrices, linearity, and multicollinearity were satisfactory for the analysis conducted.

The first ANCOVA conducted included the groups of probable AD with executive dysfunction, probable AD without executive dysfunction, and normal controls as the independent variable whereas the scores on the digit forwards component of the Wechsler Adult Intelligence Scale-Revised (WAIS-R) digit span subtest served as the dependent variable. An overall significant effect was demonstrated by the analysis ($F = 7.996$, $p < .001$). Post hoc analysis (LSD test; alpha at .05) revealed that those probable AD patients identified as having an executive disorder performed worse than those patients without an executive disorder ($P < .001$) and normal elderly controls ($p < .001$). There was no significant difference on the digit span forward procedure between those patients identified as not having an executive disorder and normal controls. Table two displays the means and standard deviations of both groups of probable AD patients and the normal elderly controls on the digit span forward procedure of the WAIS-R digit span subtest. Figure one represents the performance of all three groups on the digit span forward procedure.

Table 2

Means and Standard Deviations on Digit Span Forward for Probable AD Patients with an Executive Disorder, Probable AD Patients Without an Executive Disorder, and Normal Controls

Variable	Executive N = 17	Non-executive N = 12	Controls N = 15
<u>Digit Span Forward</u>			
Mean	5.5	8.0	7.9
Standard Deviation	1.8	2.3	1.4

The second ANCOVA conducted included the groups of probable AD with executive dysfunction, probable AD without executive dysfunction, and normal controls as the independent variable whereas the scores on the digit backwards component of the WAIS-R digit span subtest served as the dependent variable. An overall significant effect was demonstrated by the analysis ($F = 8.118$, $p < .001$). Post hoc analysis (LSD test; alpha at .05) revealed that those probable AD patients identified as having an executive disorder performed worse than those patients without an executive disorder ($P < .009$) and normal elderly controls ($p < .000$). There was no significant difference on the digit span forward procedure between those patients identified as not having an executive disorder and normal controls. Table three displays the means and standard deviations of both groups of probable AD patients and the normal elderly controls on the digit span backward procedure of the WAIS-R digit span subtest.

Table 3

Means and Standard Deviations on Digit Span Backward for Probable AD Patients with an Executive Disorder, Probable AD Patients Without an Executive Disorder, and Normal Controls

Variable	Executive N = 17	Non-executive N = 12	Controls N = 15
<u>Digit Span Backward</u>			
Mean	4.3	6.4	7.1
Standard Deviation	1.7	2.9	1.3

The third analysis was concerned with performance amongst those patients identified with an executive disorder, those patients without an executive disorder, and normal elderly controls with respect to performance on the consonant trigrams test. Given the controversy in the literature whether performance on the consonant trigrams test involves rapid forgetting or initial encoding, the slopes of the curves were analyzed by investigating the difference scores between the 0 and 3 second delays, 3 and 9 second delays, and 9 and 18 second delays. Thus a series of ANCOVA's were conducted with group inclusion (e.g., AD patients with an executive disorder; AD patients without an executive disorder; normal elderly controls) as the independent variable and the difference scores between 0 and 3 seconds, 3 and 9 second, and 9 and 18 second data points as the dependent variables.

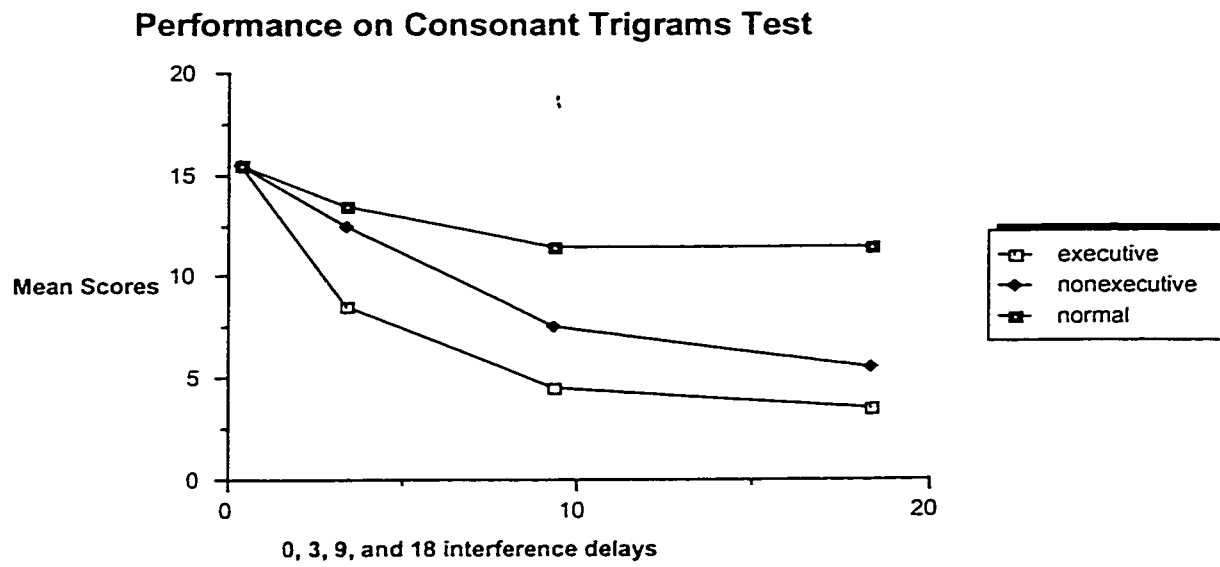
With respect to the difference score between the 0 and 3 second delay, an overall significant effect was demonstrated by a one-way ANCOVA ($F = 18.059$, $p < .000$). Post hoc analysis (LSD test; alpha at .05) revealed that those probable AD patients identified as having an executive disorder performed worse than those patients without an executive disorder ($P < .000$) and normal elderly controls ($p < .000$). There was no significant difference between those patients identified as not having an executive disorder and normal elderly controls with respect to the 0 second and 3 second difference score on the consonant trigrams test. With respect to the difference score between the 3 and 9 second delay, there was no overall significant effect demonstrated by a one-way ANCOVA ($F = 2.286$; $p = .12$). In addition, no significant effects were demonstrated by a one-way ANCOVA for the difference scores obtained between the 9 and 18 second delays ($F = 1.173$; $p = .32$). Table four contains the means and standard deviations for the three difference scores on the consonant trigrams test obtained for all groups included in the analysis. Figure one displays the slope of the curves on the consonant trigrams test for all three groups.

Table 4

Means and Standard Deviations on Consonant Trigrams Test
 Difference Scores for Probable AD Patients with an Executive
 Disorder, Probable AD Patients Without an Executive Disorder, and
 Normal Controls

Variable	Executive N = 17	Non-executive N = 12	Controls N = 15
<u>0 and 3 second difference score</u>			
Mean	6.9	3.5	2.1
Standard Deviation	2.5	2.5	1.7
<u>3 and 9 second difference score</u>			
Mean	4.5	4.8	2.3
Standard deviation	3.1	3.9	2.8
<u>9 and 18 second difference score</u>			
Mean	.18	1.5	-.33
Standard deviation	2.8	3.3	2.2

FIGURE ONE



With respect to performance on the random generation task, a fifth ANCOVA was conducted with group inclusion (probable AD with executive dysfunction, probable AD without executive dysfunction, and normal controls) as the independent variable and scores on the random generation task serving as the dependent variable. An overall significant effect was demonstrated by the analysis ($F = 11.822, p < .000$). Post hoc analysis (LSD test; alpha at .05) revealed that those probable AD patients identified as having an executive disorder performed worse than those patients without an executive disorder ($P < .023$) and normal elderly controls ($p < .000$). There was also a slight significant difference between those patients identified as not having an executive disorder and normal controls ($P < .033$). Table five summarizes the means and standard deviations of both groups of probable AD patients and the normal elderly controls on the random generation task.

Table 5

Means and Standard Deviations on Random Generation for Probable AD Patients with an Executive Disorder, Probable AD Patients Without an Executive Disorder, and Normal Controls

Variable	Executive N = 17	Non-executive N = 12	Controls N = 15
<u>Random Generation</u>			
Mean	39.1	28.3	17.9
Standard Deviation	14.4	13.5	7.3

To determine that differences in performance by the probable AD patients identified as having an executive disorder was not due to their overall level of severity of cognitive dysfunction or due to differences in degree of memory impairment, two separate ANCOVA's were conducted with group inclusion (probable AD with executive dysfunction; probable AD without executive dysfunction; normal control) as the independent variable and scores on the MMSE as the dependent variable in the first analysis and scores on the Memory subtest of the Mattis Dementia Rating Scale as the dependent variable on the second analysis. With respect to the analysis concerning the MMSE, an overall significant effect was obtained ($F = 22.077$; $P < .000$). Post hoc analysis (LSD test; alpha at .05) revealed no significant differences between those probable AD patients identified as having an executive dysfunction and those identified as not having an executive dysfunction ($P = .532$). However, as expected, both groups of AD patients performed worse on the MMSE than normal controls ($P < .000$ for both groups compared to normal controls). An overall significant effect was also obtained with respect to performance on the Memory subtest of the Mattis Dementia Rating Scale ($F = 74.267$; $P < .000$). Post hoc analysis (LSD test; alpha at .05) revealed no significant differences between those probable AD patients identified as having an executive dysfunction and those identified as not having an executive dysfunction ($P = .593$). Again, as expected, both probable AD groups performed significantly worse than normal controls on the Mattis Dementia Rating Scale Memory subtest ($P < .000$ for both groups compared to normal controls). Table six contains the means and standard deviations for all three groups with respect to performance on the MMSE and Memory subtest of the Mattis Dementia Rating Scale. Figures two and three graphically display the performance of both groups of probable AD patients and normal controls on the MMSE and Mattis Dementia Rating Scale Memory subtest respectively.

Table 6

Means and Standard Deviations on the MMSE and MDRS Memory Subscale for Probable AD Patients with an Executive Disorder, Probable AD Patients Without an Executive Disorder, and Normal Controls

Variable	Executive N = 17	Non-executive N = 12	Controls N = 15
<u>MMSE</u>			
Mean	23.0	23.6	28.4
Standard Deviation	2.4	3.3	1.5
<u>MDRS MEMORY</u>			
Mean	12.5	13.1	24.4
Standard deviation	3.7	3.5	1.1

FIGURE TWO

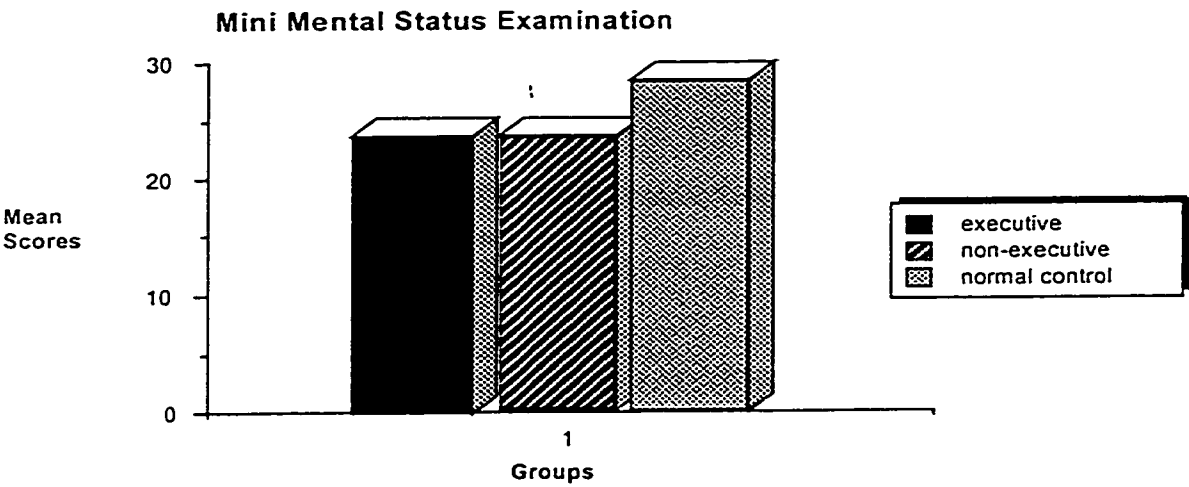
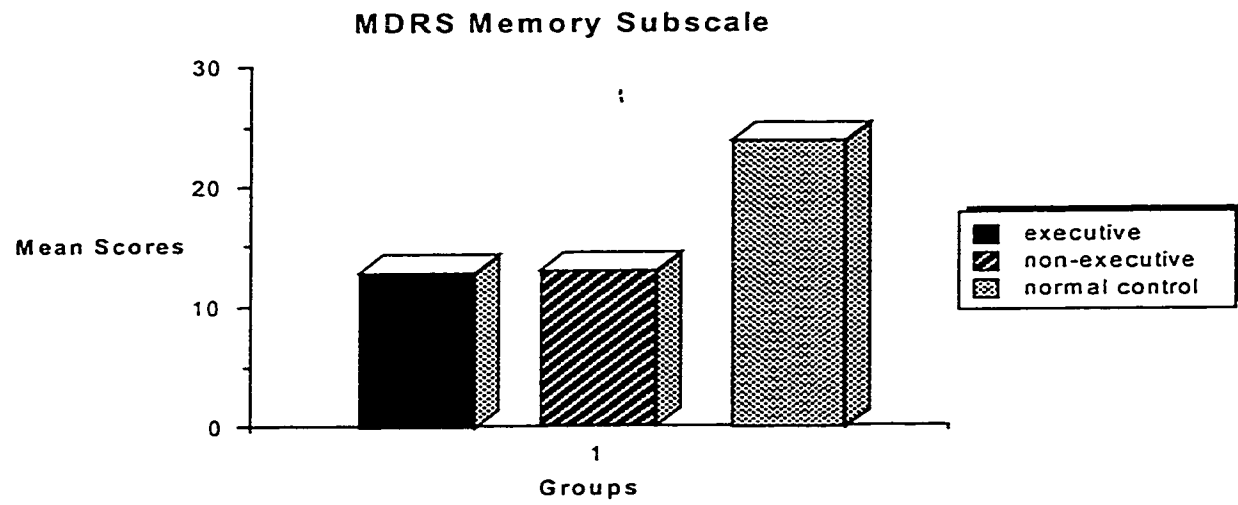


FIGURE THREE



DISCUSSION

The results of the present study provide empirical support for the hypothesis that executive system dysfunction underlies the deficit in primary memory, as measured by the digit span procedure from the Wechsler Adult Intelligence Scale-Revised (WAIS-R; Wechsler, 1981) and the consonant trigrams test, in patients diagnosed with probable AD. Statistical analyses revealed that those probable AD patients identified as having an executive disorder, as determined from the Conceptualization subscale of the Mattis Dementia Rating Scale, performed significantly worse on digits forward and backward of the Wechsler digit span procedure. Furthermore, there were no significant differences between those probable AD patients without an executive disorder and normal elderly controls, further supporting the executive nature of the disturbance on digit span in Alzheimer's patients.

Some interesting findings were also demonstrated with respect to performance on the consonant trigrams test. Although probable AD patients performed worse than normal controls in terms of absolute scores on the consonant trigrams test, there was no significant difference in degree of forgetting amongst all three groups (those probable AD patients with and without an executive disorder and normal controls) past the three second interference delay. Only those probable AD patients with an executive system disorder displayed a divergent slope between the zero and three second data points. This finding is consistent with that reported in the literature concerning the performance of AD patients on the consonant trigrams test (e.g., Kopelman, 1994). Thus, it does not appear that the primary memory deficits in probable AD reflect an abnormal rate of forgetting from the primary memory system. Rather, the data suggests that executive system difficulties underlie primary memory deficits in probable AD, as inferred from performance on digit span and the consonant trigrams test.

With respect to performance on the random generation task, considered the prototypical experimental measure of CES functioning (Baddeley, 1998), significant differences were also obtained between those probable AD patients identified as having an executive disorder and those identified as not having an executive disorder. Thus, when the data is considered together, some degree of construct validity has been obtained that the consonant trigrams test and the WAIS-R digit span procedure are measures of working memory where executive system resources are employed in the service of short term or primary mnemonic functions in patients diagnosed with probable AD.

The random generation task also differentiated those probable AD patients without an executive disorder and normal elderly controls. This finding may be a function of a possible secondary memory component to the random generation task. For example, within this study subjects were required to randomly generate letters of the alphabet until 50 responses were obtained, often taking between two to five minutes to complete the task. Repeated alphabetic digrams (e.g., either stereotypical responses such as a-b; familiar acronyms such as u-s; non-stereotypical responses such as r-a repeated twice or more) calculated as part of the overall score of non-randomness, may reflect memory decay rather than executive dysfunction because probable AD subjects may have forgotten that they had previously provided these digrams. Thus, cognitive processes other than the CES may play a role in random generation procedures.

Although the results of the current study appear to support an executive disturbance underlying performance difficulties on primary memory tasks, alternate explanations may be entertained. It is conceivable that the two groups of probable AD patients utilized in this study differed in their global information processing capacity. Thus, those patients identified with an executive disturbance may have had a relatively greater diminished processing capacity than those patients without an executive disturbance, resulting in the observed greater impairment on measures of digit span, consonant trigrams, and random generation. However, if such a difference in processing capacity existed between the two probable AD groups, then this difference should have been evident with greater performance difficulty obtained by the probable AD group identified as having an executive disorder on measures of global cognitive functioning, such as the MMSE. The data in this current study demonstrates that no significant difference was obtained between the two probable AD groups with respect to performance on the MMSE and the Mattis Dementia Rating Scale memory subtest. Thus, a greater diminished processing capacity does not appear to be the most parsimonious explanation for the findings in the current study.

It is also conceivable that language disturbances could explain the results obtained within the current study. A language assessment was not conducted on the probable AD patients utilized in this study. Thus, those patients identified as having an executive dysfunction may have had a greater degree of language impairment resulting in greater performance decrements on the measures digit span, consonant trigrams, and random generation. However, the Mattis Dementia Rating Scale Conceptualization subtest, utilized to differentiate the probable AD

sample into those with and without an executive disorder, employs both verbal and non-verbal stimulus items. Therefore, it cannot be construed strictly as a language test and likely would not have differentiated the groups of probable AD patients based solely on language functioning. Furthermore, the consonant trigrams test and the digit span procedure are not heavily dependent on semantic content, thus reliance on language skills could be considered minimal with respect to performance on these measures.

Another explanation for the current results is that those AD patients identified as having an executive disorder may have had phonological short term storage deficits rather than executive system difficulties, thus explaining their greater performance decrements on measures of digit span and the consonant trigrams test. Although several studies indicate that the phonological and visuospatial short term storage mechanisms remain intact in AD, a recent study has argued the contrary (Collette et al., 1998). Investigations specific to phonological short term storage deficits, such as word length and phonological similarity effects, were not conducted in this study. However, if phonological short term storage deficits were the underlying mechanism involved in those probable AD patients exhibiting a possible executive system disturbance, than a greater degree of forgetting from the primary memory system should have been observed on the consonant trigrams test. The data in the current study demonstrates no significant differences in terms of rate of forgetting between both probable AD groups and normal controls with respect to performance on the consonant trigrams test. Thus, an abnormal rate of forgetting from the primary memory system does not appear to be the most parsimonious explanation for the findings observed in this study.

Finally, it is conceivable that the group of AD patients demonstrating a putative executive system disorder were misdiagnosed and may include patients with a frontal-temporal dementia. Given that no biological markers allow for a definitive diagnosis of AD and that early AD may be difficult to differentially diagnose amongst other dementias, the significant findings demonstrated within this study may reflect a different disease process rather than a subgroup of AD patients exhibiting a working memory deficiency.

Limits of Current Study.

The interpretation of the current study's findings are limited by several issues. The first concerns the validity of the conceptualization subtests of the Mattis Dementia Rating Scale (MDRS) as a measure of executive system ability. Although there is some preliminary support that the conceptualization subtest of the MDRS measures in part executive system abilities (Colantino, Becker & Huff, 1993), further studies are needed to show greater psychometric and convergent validity with more traditionally accepted measures of executive system functioning. Nevertheless, the items that comprise the MDRS conceptualization subtest, such as similarities and differences, are thought to measure executive abilities by some researchers and more appropriate in Alzheimer's disease research because of possible floor effects on the more typical tests of executive system functioning such as the Wisconsin Card Sorting Test (e.g., Chen et al., 1998).

Another limitation of this study relates to the extrapolation of the current findings to Alzheimer's disease. AD is definitively diagnosed only upon confirmatory evidence of characteristic histopathological changes such as amyloid deposits, neurofibrillary tangles, and neuritic plaques (McKhann et al., 1984). Thus, diagnosis of probable AD in the sample utilized within this study relied on behavioral and clinical criteria as delineated by DSM-IV (American Psychiatric Association, 1994) and NINCDS-ADRDA (McKhann et al., 1984) diagnostic systems. Although diagnosis of probable AD by the DSM-IV and NINCDS-ADRDA systems generally results in high sensitivity rates, the specificity of diagnosis is not as robust (Mayeux, 1998). Therefore, it is possible that disease processes other than AD are represented in the sample under study. The extrapolation of the current findings that CES dysfunction underlies primary memory performance and that validated clinical neuropsychological measures of primary memory such as the WAIS-R digit span procedure and the consonant trigrams test evaluate working memory dysfunction in probable AD is necessarily constrained by limitations imposed by the diagnostic process.

A further limitation in the current study is the relatively few numbers of subjects included in the samples under study, thus limiting extrapolation of the current findings to the general population of probable AD patients with a putative executive system disturbance. Although, preliminary support is obtained concerning that executive system dysfunction may underlie primary memory disturbances in probable AD, further cross validation studies would be desirable.

Future Implications

The WAIS-R digit span procedure and the consonant trigrams test appear to be measures of the CES in working memory in probable AD. Thus, these measures may be applied in future research aimed at identifying the role that working memory plays in other cognitive functions such as reasoning, comprehension, and new learning. Furthermore, these measures may be useful in functional neuroimaging studies investigating the anatomical correlates of working memory. Recent research utilizing positron emission tomography (PET) and functional magnetic resonance imaging (fMRI) has identified the frontal cortex as an important anatomical site in the mediation of working memory tasks (Smith & Jonides, 1999). Storage of verbal material in working memory has been shown to activate not only left posterior parietal cortex but also Broca's area and left hemisphere supplementary and premotor regions (Smith, Jonides, Marshuetz & Koeppel, 1998). The activation of frontal cortex in verbal storage operations in working memory was assumed to reflect the rehearsal and preparation of speech (Smith & Jonides, 1999). In addition, executive processes involved in the regulation and manipulation of the contents of working memory were associated with activation in prefrontal cortex (Smith & Jonides, 1999). Thus, digit span and the consonant trigrams test might be employed in future neuroimaging studies interested in identifying the anatomical correlates of working memory.

Perhaps the greatest utility of the working memory model might be in experimental pharmacological therapeutic investigations in probable AD. Given that pharmacological agents could be identified which have the potential to improve working memory in probable AD, it could be assumed that concomitant improvement in reasoning, comprehension, and new learning could occur as well, given the putative importance of working memory in these cognitive domains. Subsequently, this might extend the quality of life of many probable AD patients increasing the time period of their functional independence for some time. In a recent study, the acute effects of corticosteroids affected, positively affected to a greater degree, working memory capacity rather than declarative memory in a small sample of young men (Lupien, Gillin, & Hauger, 1999). The authors reported a dose dependent response curve in which lower doses of corticosteroids decreased working memory performance whereas higher doses increased working memory capacity (Lupien et al., 1999). This study, although not directly related to the treatment of patients diagnosed with probable AD, sheds interesting light into possible investigations of corticosteroids in the amelioration of working memory

deficits in probable AD. Thus, digit span and the consonant trigrams test might be utilized to assess the efficacy of corticosteroids on working memory ability in probable AD.

The tests of primary memory employed in this study are routinely utilized in clinical neuropsychological assessments. Thus, given the findings of the current study, they may prove useful as indices of working memory in other patient populations such as head injury, Parkinson's disease, or Huntington's disease, to name a few. However, research regarding the validity of the consonant trigrams test and the digit span procedure as tests of CES dysfunction in working memory would need to be carried out specifically in these patient populations in order to determine their validity with respect to these disorders.

In summary, a possible impairment in CES capacity of working memory has been demonstrated in patients diagnosed with probable AD within the current study, consistent with the large body of literature already amassed on the subject. This putative disturbance in CES functioning also appears to underlie the difficulties that AD patients have on measures of primary memory. Although the current study provides preliminary support for executive system abilities in primary memory in AD, further research utilizing more accepted measures of executive system functioning would provide greater support for the findings obtained within this study.

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Appendix One

Subject Recruitment Script

Hi, my name is Robert Curwin. I am a research assistant here at the Memory Disorders Clinic and I am a Ph.D. student at the University of Ottawa. I was wondering if I may be able to take a couple of minutes of your time to discuss my thesis research and to see if you would be interested in participating. If you feel hesitant about this and would rather not talk to me regarding my thesis, I completely understand and will not take up any more of your time. If you don't mind talking with me, it will only take about five minutes.

I am interested in studying individuals both with memory difficulties and those without to look at various aspects of the memory system. This is for my Ph.D. thesis at the university of Ottawa. I will want to do some testing involving memorization of some words, pictures, and numbers. I will also ask you some questions regarding your mood, where you live, your age, occupation, and some questions regarding your health. If you agree to participate in my study, the questions and testing will all be done in one session that will take between one hour and one hour and a half to complete. We could conduct the session here at the Elizabeth Bruyere center, or if you feel more comfortable doing this at your home, I would be willing to go there. Some of the memory testing might be a bit difficult and cause some mild anxiety and some of the questions you might not want to answer. Please be assured that you always have the right to discontinue or refuse to answer any questions you feel uncomfortable about. Also, you have the right to refuse to participate in any way with this study without any risks to your ongoing treatment here at the Memory Disorders Clinic.

Appendix Two

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Short term memory problems in Alzheimer's disease

Primary Researchers: Mr. Robert Curwin, Ph.D. Candidate; Dr. Erich Mohr; Dr. Jonathan Willmer

Before you consent to participate in this study involving research, you must understand several general principles that apply to all who take part in our studies

- a) Taking part in this study is entirely voluntary and you may refuse to answer certain questions.
- b) You may withdraw from the study at any time without penalty or loss of any benefits to which you are otherwise entitled
- c) All of the information collected on you will be kept strictly confidential and anonymity assured.
- d) You will not be paid for taking part in this study.
- e) There are two copies of this consent form, one of which you keep for your records

Purpose of the Study: For my Ph.D. thesis project, I am interested in studying different types of memory problems associated with Alzheimer's Disease. Some of these memory problems may be identified early in the disease. It is important to understand the nature of these memory problems and to develop sensitive tests so that they may be detected early. The purpose of this study is to provide greater knowledge regarding a specific type of memory problem in Alzheimer's Disease, that of short term memory. In addition, this study will attempt to identify tests that will be sensitive to detecting these kinds of memory problems.

Study Plan: If you agree to participate in this study, you will come to the memory disorders clinic of the Elizabeth Bruyère Hospital for one visit. If you prefer, the session can be conducted within your home. This visit will last approximately one hour and a half. During your visit you will be asked to complete a few tests. In these tests you will do some tasks such as remembering numbers and letters. You will also be required to do a little reading and answer a few simple questions. In addition, questions regarding your mood, age, education, and work history will be asked.

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Short term memory problems in Alzheimer's disease

Primary Researchers: Mr. Robert Curwin, Ph.D. Candidate; Dr. Erich Mohr; Dr. Jonathan Willmer

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RISKS AND BENEFITS

Risks: You will not receive any treatments or undergo any medical procedures which might involve any risk to your health. You may find the memory testing mildly stressful and the appointments may cause some inconvenience to you. Participation in this study will not help your memory. You will not derive any personal benefit from participating, but your involvement may indirectly benefit others in the future.

CONFIDENTIALITY

All of the information that is gathered on you will be kept strictly confidential. Only the primary researchers will have access to this information. All of the information gathered on you will be locked in Mr. Robert Curwin's personal filing cabinet. Anonymity is also assured. Your name will not be included on any forms, questionnaires, or tests that you complete. At the outset of testing, you will be assigned a study number and this number will be used to identify you. Again, only the primary researchers will have access to that number. When results of this study are reported you will not be identified by name.

PROBLEMS OR QUESTIONS

Should any problems or questions arise as a result of this study, please do not hesitate to contact any of the primary researchers involved. We'd be more than happy to answer questions for you. Dr. Mohr, Dr. Willmer, or Mr. Robert Curwin can be reached at the Memory Disorders Clinic at 562-6328.

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

Short term memory problems in Alzheimer's disease

Primary Researchers: Mr. Robert Curwin, Ph.D. Candidate; Dr. Erich Mohr; Dr. Jonathan Willmer

COMPLETE APPROPRIATE ITEM BELOW, A OR B;

A. Patient's Consent.

I have read the explanation and have had the opportunity to discuss it and to ask questions. I consent to take part in this study.

Name of Patient

Signature of Patient

Date

B. Spouse/Guardian's Permission.

I have read the explanation of this study and have had the opportunity to discuss it and to ask questions. I consent to my ward's participation in this study

Name of Spouse/Guardian

Signature of Spouse/Guardian

Date

Name of Investigator

Signature of Investigator

Date

Name of Witness

Signature of Witness

Date

Appendix Three

PATIENT INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

1. Diagnosis of Alzheimer's Disease, based on DSM-IV (American Psychiatric Association, 1994) and NINCDS-ADRDA (McKhann, Drachman, Folstein, Katzman, Price, & Stadlan, 1984) criteria for probable Alzheimer's disease.

Patient Exclusion criteria.

1. History or current clinical evidence of stroke, normal pressure hydrocephalus, subdural haematoma, intracranial mass lesion, current seizure disorder, significant head trauma within 5 years of dementia diagnosis that resulted in unconsciousness and hospitalization, or dementia with an onset immediately following heart surgery or cardiac arrest.
2. A diagnosis of Parkinson's Disease, Pick's Disease, Huntington's Disease, or Creutzfeldt-Jakob's Disease.
3. Evidence of systemic infection, or current cognitive impairment due to pharmacological agents.
4. Current evidence or history of substance use disorder within past 2 years.
5. Clinically significant depression as determined by the Geriatric Depression Scale (score > 10).
6. Non stable use of antidepressant medication with known anticholinergic effects (e.g., tricyclic compounds).
7. Routine use of antipsychotics.
8. Visual or auditory deficits.
9. Mini Mental State Examination (MMSE) scores lower than 18.
10. 55 years of age or young

Appendix Four

CONTROL SUBJECTS INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria

1. Healthy elderly subject with no known diagnosis of Alzheimer's Disease matched to the AD patient group with respect to age and education.

Exclusion criteria.

1. History or current clinical evidence of stroke, normal pressure hydrocephalus, subdural haematoma, intracranial mass lesion, current seizure disorder, significant head trauma within 5 years of dementia diagnosis that resulted in unconsciousness and hospitalization, or dementia with an onset immediately following heart surgery or cardiac arrest.
2. Parkinson's Disease, Pick's Disease, Huntington's Disease, or Creutzfeldt-Jakob's Disease.
3. Evidence of systemic infection, or current cognitive impairment due to pharmacological treatments.
4. Current evidence or history of substance use disorder within last 2 years.
5. Clinically significant depression as determined by the Geriatric Depression Scale (score > 10).
6. Self report of memory disturbance.
7. Non stable use of antidepressant medication with known anticholinergic effects (e.g., tricyclic compounds).
8. Routine use of antipsychotics.
9. Visual or auditory deficits.
10. 55 years of age or younger