UNIVERSITY OF CALIFORNIA, SAN DIEGO
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Qualitative Memory Changes in Alzheimer's Disease

A dissertation submitted in partial satisfaction of the
requirements for the degree Doctor of Philosophy

in

Clinical Psychology

by

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The Dissertation of Theresa Lee Demadura is approved, and it is acceptable in quality and form for publication on microfilm and electronically:

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Curriculum Vitae

Education:

1999 - 2014 University of California, San Diego/San Diego State University
Joint Doctoral Program in Clinical Psychology
Specialty Track: Neuropsychology

1999 - 2000 Predoctoral Internship, Clinical Psychology, Portland VA Medical Center

1979 - 1989 Bachelor of Arts Degree in Psychology, University of California, Santa Barbara

Awards and Honors

Recipient of San Diego Fellowship 1993, 1994
Minority Supplemental Grant 1997-1999

Professional Experience

Current Position:

2007-2014 Portland Veteran's Medical Center
Neuropsychology Department
Psychometrist
Supervisor, Daniel Storzbach, Ph.D

Currently employed as a psychometrist at the Portland VA Medical Center, Neuropsychology Department. My job duties included the administration and scoring of neuropsychological tests, psychological measures, behavioral rating scales, behavioral observations to multiple clinical populations that have been referred to the Neuropsychology department for consultation on cognitive and psychological diagnoses. Assessments that are conducted include a structured clinical interview, administrations of personality and mood questionnaires, administration of standardized tests that assess areas of speech-language, memory, executive functioning, processing speed, and motor functioning. In addition, I am responsible for scheduling consult referrals to the neuropsychology department for assessment, group treatment, and research participants.

2001 –2007 Research Assistant
End of Life Care Research Program
Portland VA Medical Center
Research PI Dr. Linda Ganzini
Supervisor: Dr. Elizabeth Goy

Conducted research on the effectiveness of methylphenidate on mood in palliative care patients and the incidence and treatment of mood in renal dialysis patients. Research also includes the incidence of mental health disorders and delirium in VA Hospice Care patients. Responsibilities include project management, clinical study coordination and organization, IRB administration, interviewing patients and assessing for delirium, psychological assessment, depression, and PTSD. Also involved in data

base management, data analyses and administering grant submissions. Software packages used: Microsoft excel, word, & access. Statistical package used: SPSS.

2000 – 2001 Research Assistant, Psychology Department
Portland VA Medical Center & OHS
Research PI's Dan Storzbach, Ph.D. & Keith Campbell, Ph.D.
Involved in fMRI research on the effects of PTSD on hippocampal structures. In addition, I have also collaborated on research on early prediction of AD using MRI. Responsibilities included subject recruitment, literature searches, and administering grant submissions.

May - July 2000 Mental Health Clinic Rotation
David Shaw, Ph.D.
Assessment and therapeutic treatment of individual, couples and families in a VA Medical Center outpatient setting. The emphasis on training was with the use of interpersonal and cognitive behavioral treatment interventions

Jan. - May 2000 Neuropsychology Rotation
Supervisor: Dan Storzbach, Ph.D.
Neuropsychological assessment of an adult medical population in both outpatient and inpatient settings. Responsibilities included neuropsychological evaluations, report writing and feedback to staff, patients and their families. Didactics include neuropsychological seminars, journal clubs, neurology and grand rounds at Oregon Health Science University.

July-Dec 1999 Portland Veteran's Affairs Medical Center
Geropsychology Rotation
Supervisors: Gina Ortola, Ph.D.
Linda Gonzales, Ph.D.
Training in the psychological assessment and therapeutic treatment of a geriatric population in an outpatient setting. The geropsychology rotation included maintenance of a clinical load, psychological assessments, and weekly assessments in a multidisciplinary geriatric assessment clinic. Responsibilities included both neuropsychological and psychological evaluation, treatment planning and implementation, leading and devising a psycho educational group, and co-leading a recreational group for demented patients. Didactics included weekly seminars on the neuropsychological and psychological assessment of adults and monthly journal club meeting in geropsychiatry.

1993-1999 Graduate Research Assistant, Neuropsychological Research Lab
UCSD and VA, Medical Center, La Jolla
Advisor: Dean C. Delis, Ph.D.
Involved in research on the executive dysfunction in Parkinson's Disease, Asymmetrical Cognitive Profiles in Alzheimer's Disease (AD), and executive dysfunction in at-risk(positive family history and APOE-E4 allele) AD patients, Visual

attention in Parkinson's Disease, at risk for Alzheimer's Disease and Alzheimer's Disease patients. Collaborated on research experiments on sustaining visual attention in Parkinson's Disease, and Child Traumatic Head Injury. Responsibilities included data collection, training research assistants, data analysis and manuscript preparation.

1989-1993 Staff Research Associate
UCSD and VA Medical Center
Supervisor: Arne Ostegaard
Supervisor: Dean C. Delis

Longitudinal testing of studies investigating visuospatial dysfunction, visual attention, priming, and asymmetric cognitive profiles of Alzheimer's, Korsakoff's, Parkinson's, and Huntington's patients, and child and adult head-injury patients. Assessments also included testing for norming and development of new neuropsychological instruments (WAIS-R-NI, California Card Sorting Task) and neuropsychological testing for a community catchments study. Responsibilities included data collection, data management, budget administration, subject recruitment, overseeing administration of grant submissions, and training research assistants.

1989-1990 Neuropsychological Technician
UCSD Stroke Center
Supervisor: John F. Rothrock, M.D.

Involved in long term neuropsychological testing of stroke patients at their initial hospitalization and six-month post recovery. Involved in clinical drug trials for an anticoagulant. Responsibilities included testing, scoring, and data management.

1982-1984 Undergraduate Research Assistant, Department of Psychology
University of California, Santa Barbara
Advisor: Daphne Bugentahl, Ph.D.

Involved in a research study investigating family systems interaction in child abuse settings. Responsibilities included interviewing family members, rating facial expressions in family dyads, and rating interactions in between caregivers and children.

Supervised Clinical Experience

1998-1999 UCSD Child and Adolescent Psychiatry Inpatient Hospital
Clinical and Neuropsychological Practica
Supervisor: Sandra Brown, Ph.D.

Training in the assessment and treatment of children and adolescents in an inpatient psychiatric hospital setting. Responsibilities include both neuropsychological and psychological evaluations, case conceptualization, report writing and feedback to staff, patients and their families. Additional responsibilities include co-leading child and adolescent group therapy sessions. Didactics included in-depth training in family systems therapy, play therapy and individual adolescent therapy, weekly seminars

regarding relevant issues to children in a psychiatric setting, weekly seminars on the neuropsychological and psychological assessment of children and monthly journal club meeting on child neuropsychology.

1997-1998 UCSD Outpatient Psychiatry Clinic
Neuropsychology Praticum
Supervisor: Robert K. Heaton, Ph.D. ABPP

Intensive training in the interpretation and communication of results of neuropsychological evaluations based on an expanded Halstead-Reitan battery. Written reports and case presentations involved an extensive review of each patient's medical, social, education, and psychiatric history. Patients included adults who suffered from head injuries, strokes, and a variety of other neurological and psychiatric disorders.

1997-1998 Sharp Memorial Rehabilitation Hospital
Clinical and Neuropsychological Practica
Supervisors: Barbara Schrock, Ph.D., ABPP
Nancy Markel, Ph.D.
Marc Norman, Ph.D.

Training in the assessment, and treatment of inpatients and outpatients with neurological insults such as stroke, traumatic brain injury, and spinal-cord injury in a 30-bed adult inpatient rehabilitation hospital. Responsibilities included case conceptualization, administering neuropsychological screening batteries and psychological tests, presenting patients' neurobehavioral assessments at weekly multidisciplinary rounds, writing progress notes and assessment reports, co-leading group therapy sessions, family intervention, patient feedback, and attending case conferences, didactic seminars, and weekly supervision meetings.

1995-1996 Neuropsychology Service, VA Medical Center, La Jolla
Supervisors: Dean C. Delis, Ph.D., ABPP
Terry Jernigan, Ph.D.
Greg Brown, Ph.D.

Conducted comprehensive neuropsychological assessments using a flexible battery, process approach. Assessments included review of the records, clinical interviews, written reports, patient feedback, case and neuropsychology presentations. Patients were inpatient and outpatient young and elderly adults with a variety of neurological and psychiatric disorders.

1994-1995 San Diego State University Psychology Clinic
Supervisor: Brenda Johnson, Ph.D.

Conducted diagnostic interviews, administered psychological tests, developed intervention plans, and provided cognitive therapy for individuals at an outpatient

psychology clinic. Received formal supervision in cognitive-behavioral therapy as well as progressive relaxation, social skills, and assertiveness training, and interpretation of mood and personality assessment measures.

Summer 1994 Neuropsychology Service, VA Medical Center, San Diego, CA
Supervisors: Dean C. Delis, Ph.D.
Terry Jernigan, Ph.D.
Jane Paulson, Ph.D.
Training in the flexible battery, process approach. Attended internship training, didactics, and seminars.

Teaching Experience

Spring 1999 Instructor
Department of Psychology, San Diego State University
Psychology, Cognitive Psychology
Duties included: Full responsibility for course instructions, including text selection, lecture preparation and presentation , test construction, office-hour consultation for students, and grade assignments.

Publications

Huckans M., Pavawalla S., Demadura T., Kolessar M., Seelye, A., Roost, N., Twamley, E., Storzbach D. (2010). A pilot study examining effects of group-based Cognitive Strategy Training treatment on self-reported cognitive problems, psychiatric symptoms, functioning, and compensatory strategy use in OIF/OEF combat veterans with persistent mild cognitive disorder and history of traumatic brain injury. *The Journal of Rehabilitation Research and Development*. *47*(1):43-60.

Watnick S, Wang PL, Demadura T, Ganzini L. (2005). Validation of 2 depression screening tools in dialysis patients. *American Journal of Kidney Disease*, *46*(5), 919-24.

Demadura T, Delis DC, Jacobson M, Salmon D. (2001). Do subgroups of patients with Alzheimer's disease exhibit asymmetric deficits on memory tests? *Journal of Clinical and Experimental Neuropsychology*, *23*(2), 164-71.

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Roman, M.J., Delis, D.C., Filoteo, J.V., Demadura, T.L., Paulsen, J., Swerdlow, N., Swenson, D.S., Butters, N., & Shults, C. (1998) Is there a “Subcortical” Profile of

Attentional Dysfunction?: A comparison of patients with Huntington's and Parkinson's Diseases on a global-local focused attention task. *Journal of Clinical and Experimental Neuropsychology, 20*(6), 873-84.

Roman, M.J., Delis, D.C., Willerman, L., Magulac, M., Demadura, T.L., de la Pena, J.L., Loftis, C., Walsh, J., & Kracun, M. (1998). Impact of pediatric traumatic brain injury on components of verbal memory. *Journal of Clinical and Experimental Neuropsychology, 20*(1), 1-14.

Filoteo, J.V., Delis, D.C., Salmon, D.P., Demadura, T.L., Roman, M.J., Shults, C.W. (1997). An examination of the nature of attentional deficits in patients with Parkinson's disease: Evidence from a spatial orienting task. *International Journal of Neuropsychological Society, 3*(4), 337-347.

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Massman, P.J., Delis, D.C., Filoteo, J.V., Butters, N., Salmon, D.P., & Demadura, T.L. (1993). Mechanism of spatial impairment in Alzheimer's disease subgroups: Differential breakdown of attention to global-local stimuli. *Neuropsychology, 7*, 172-181.

Filoteo, J.V., Delis, D.C., Massman, P.J., Demadura, T.L., Butters, N., Salmon, D.P. (1992). Directed and divided attention in Alzheimer's disease: Impairment in shifting attention to global and local stimuli. *Journal of Clinical and Experimental Neuropsychology, 14*(6), 871-883.

Delis, D.C., Massman, P.J., Butters, N., Salmon, D.P., Shear, P.K., Demadura, T., & Filoteo, J.V. (1992). Spatial Cognition in Alzheimer's Disease: Subtypes of Global-Local Stimuli. *Journal of Clinical and Experimental Neuropsychology, 14*(4), 463-477.

Presentations:

2010

Tun, SM, Demadura, T, McCall, K & Storzbach, D. (2009). Interim findings on diagnosis of PTSD predicting subjective cognitive complaints, and not objective cognitive performance in blast-exposed Operation Enduring Freedom/Operation Irqai

Freedom (OEF/OIF) veterans. Poster session to be presented at the annual meeting of the International Neuropsychological Society. February 2009, Acapulco, Mexico.

2009
Huckans, M., Pavawalla, S., Demadura, T., Kolessar, M., Seelye, A., Roost, N., Tun, S., McCall, K., Twamley, E. & Storzbach, D. (2009). A pilot study examining the effect of a group-based cognitive strategy training intervention on self-reported psychiatric symptoms, functioning, and compensatory strategy utilization in OIF combat veterans with mild traumatic brain injury. Poster session presented at the annual meeting of the American Academy of Clinical Neuropsychology, San Diego, CA.

Demadura, T, McCall, K, Tun, SM, Johnson, A & Storzbach, D. (2009). Effects of Blast Exposure on Cognitive, Psychiatric, and Adaptive Functioning Poster session presented at the annual meeting of the American Academy of Clinical Neuropsychology, San Diego, CA.

Tun, SM, Demadura, T, McCall, K and Storzbach, D. (2009). Interim findings on diagnosis of PTSD predicting subjective cognitive complaints, and not objective cognitive performance in blast-exposed Operation Enduring Freedom/Operation Iraqi Freedom (OEF/OIF) veterans. Poster session presented at the annual meeting of the International Neuropsychological Society February 2009, Atlanta, Georgia.

1999
Jacobson, M., Delis, D.C., Demadura, T.L., Norman, M., Strause, T., Salmon, D.P., & Bondi, M.Set-switching deficits in ApoE-e4 Adults on the California Stroop Test. Presented at the 27th annual meeting of the International Neuropsychological Society, Boston, Massachusetts

1998
Demadura, T.L., Delis, D.C., Jacobson, M., Loftis, C., Stricher, J. & Salmon, D.P. (1998) Differential Deficits in Conceptual Shifting in Patients with Alzheimer's and Parkinson's Disease. Poster presented at the 26th annual meeting of the International Neuropsychological Society, Honolulu, Hawaii

Jacobson, M., Delis, D.C., Demadura, T.L., Loftis, C., Stricher, J., Salmon, D.P., Galasko, D., & Bondi, M.W. (1998) Asymmetric Cognitive Profiles in the Preclinical Phase of Alzheimer's Disease. Presented at the 26th annual meeting of the International Neuropsychological Society, Honolulu, Hawaii

Roman, M., Magulac, M., Demadura, T.L., Loftis, C., Gladsjo, J.A., & Delis, D.C. (1998) Acute Psychiatric Sequelae of Pediatric Traumatic Brain Injury. Poster presented at the 26th annual meeting of the International Neuropsychological Society, Honolulu, Hawaii

Jacobson, M., Kane, M., Delis, D.C., Loftis, C., & Demadura, T., Stricher, J., Salmon, D.P., Galasko. (1998) Neuropsychological Deficits in Late-Onset Metachromatic Leukodystrophy. Poster presented at the 26th annual meeting of the International Neuropsychological Society, Honolulu, Hawaii

1997

Roman, M., Delis, D., Demadura, T., Loftis, C., & Taylor, R. (1997) An examination of Executive Functioning after Pediatric Traumatic Brain Injury Using the CCT. Poster presented at the 25th annual meeting of the International Neuropsychological Society, Orlando, Florida

1996

Demadura, T.L., Roman, M.J., Delis, D.C., Squib, S., & Salmon, D.P. (1996). Performance of Subtypes of Alzheimer's Disease Patients on Traditional Verbal and Visual Memory Tasks. Presented at the 24th annual meeting of the International Neuropsychological Society, Chicago, Illinois

1995

Roman, M.J., Delis, D.C., Filoteo, J.V., Demadura, T.L., Paulsen, J.P., Swenson, M, & Swerdlow, N. (1994) Performance in Patients with Huntington's Disease on a Global-Local Directed Attention Task. Presented at the 23rd annual meeting of the International Neuropsychological Society, Seattle, Washington

Filoteo, J.V., Delis, D.C., Roman, M.J., Butters, N., Salmon, D.P., Demadura, T.L., Paulsen, J.P., Swenson, M, (1994). Mechanisms of visual-perceptual deficits in patients with Huntington's disease or Alzheimer's disease. Presented at the 23rd annual meeting of the International Neuropsychological Society, Seattle, Washington.

1993

Filoteo, J.V., Delis,D.C., Maddox, W.T., Demadura, T.L., Butters, N., Salmon, D, & Shults, C. (1993) Perceptual Processing in Parkinson's Disease. Presented at the 22nd annual meeting of the International Neuropsychological Society, San Antonio, Texas.

Abstract of the Dissertation

Qualitative Memory Changes in Alzheimer's Disease

by

Theresa Demadura

Doctor of Philosophy in Clinical Psychology

University of California, San Diego, 2014
San Diego State University, 2014

Professor Dean C. Delis, Chair

Alzheimer's Disease (AD) is a devastating disorder that affects thousands of elderly adults each year. Impairments in memory are among the earliest and most profound symptoms of this disorder. At the time of diagnosis, most AD patients have already advanced into moderate to severe levels of memory impairment. In addition, the nature of the memory profile after conversion to AD has been studied extensively and has been well characterized as reflecting an encoding/storage impairment that affects both recall and recognition measures. However, what is not well known is the nature of the memory profile in individuals who are in a preclinical stage of AD (preAD). Do preAD individuals also display an encoding/storage memory profile, albeit to a mild degree? Or do they first pass through a stage of exhibiting a retrieval memory profile (similar to patients with subcortical disorders) before developing their hallmark encoding/storage profile? This knowledge is important for both improving early diagnosis of this disorder and for not misdiagnosing these individuals as having a primarily subcortical process prior to their conversion to AD. To address this

question, the present study examined qualitative elements of episodic memory in three subject groups: (1) patients with AD; (2) former normal control subjects who converted to preAD and then were given AD diagnoses and were tested during their preAD stage; and (3) normal controls (NC) who did not display evidence of cognitive decline over time. The current research design was employed in a sample of 100 individuals diagnosed with probable Alzheimer's disease (mean age = 73.60; mean education = 14.71), 19 preAD patients (mean age = 73.60; mean education = 15.00) and 50 demographically-matched healthy older adults (mean age = 73.38; mean education = 15.16). The groups were not significantly different on age (p = .98), education (p = .34) or gender (χ^2 (2) = 2.16; p = .34). Episodic memory changes were studied using qualitative variables from the California Verbal Learning Test (CVLT) in the three subject groups over three serial assessments. The first CVLT administered at the ADRC was used as the subject's baseline test. The CVLT variables examined included Total Immediate Recall (TotImm), Long Delay Free Recall (LDFR), Delayed Retention Rate (RetRate), serial position effects, proactive interference, semantic clustering, intrusion errors, and Recognition Discriminability (RecogDis). Both a simple ANOVA at Time 1 and a repeated measures mixed model ANOVA were employed, with group as the between subject factor and time as the within subject factor. At Time 1, as expected, the AD group was significantly impaired relative to the NC group on the TotImm (p < .0005, d = 2.57), LDFR (p < .0005, d = 2.94, RetRate (p < .0005, d = 2.20), Total Intrusions (p < .0005, d = .96), and RecogDis (p < .0005, d = 2.85) measures. Importantly, on all five measures, the PreAD group performed significantly worse than the NC Group, TotImm (p < .0005, d = 1.56),

LDFR ($p < .0005$, $d = 1.57$), RetRate ($p < .0005$, $d = 1.20$), Total Intrusions ($p < .0005$, $d = .87$) and RecogDis ($p < .0005$, $d = 1.37$) and significantly better than the AD group on the TotImm ($p < .0005$, $d = 1.06$), LDFR ($p < .0005$, $d = 1.08$), RetRate ($p = .001$, $d = .90$), and RecogDis ($p < .0005$, $d = 1.17$) measures. The one exception was that the PreAD group did not differ significantly from the AD group ($p = .45$ $d = .42$) in Total Intrusions; however, a small to medium effect size in the same direction suggests that the small preAD group size and associated limited power played a role in this analysis. In the repeated measures ANOVA, there were no significant interactions of time by group for any of the CVLT qualitative variables. There were significant main effects of time for both recency ($p = .005$, *partial* $\eta^2 = .05$) and RecogDis ($p = .009$, *partial* $\eta^2 = .03$). As expected, the AD group was impaired on all qualitative variables as compared to the NC group ($p < .0005$) while the preAD group was impaired on proactive interference ($p < .0005$), semantic clustering ($p < .0005$) and RecogDis ($p < .0005$) compared to the NC group over time. Taken together, the findings from the study suggest that PreAD individuals do not first pass through a retrieval memory profile before converting to AD, but rather they generally display the classic encoding/storage profile, albeit to a mild degree, early in the disease course.

I Introduction

Alzheimer's Disease (AD) is a devastating disorder that affects thousands of elderly adults each year. Impairments in memory are the most profound and deleterious symptoms of this disorder followed by impairments in visuospatial functioning, executive skills, attention, and language. There is considerable evidence that episodic memory is impaired early on in Alzheimer's Disease (Bondi et al., 1994; Fuld et al., 1990; Albert et al., 2001). In fact, by the time of diagnosis, most AD patients are well into the moderate to severe stages of memory impairment. Although episodic recall has been well examined, little work has been done to examine how impairments in component functions of verbal learning in AD are affected over time.

The present study proposes to examine qualitative elements of episodic memory in three groups of people: (1) normal controls (2) AD patients who are pre-symptomatic (preAD) at the time of testing and (3) patients with AD.

BACKGROUND

Alzheimer's Disease

Pathology

Alzheimer's Disease is a degenerative neurologic disease that is characterized by neuronal atrophy, synapse loss, and abnormal accumulation of neuritic plaques and neurofibrillary tangles within widespread regions of the cortex (Terry et al, 1999). The global neuroanatomical changes observed in Alzheimer's Disease result in a progressive dementing condition for most patients. Episodic memory impairments

appear relatively early on in the disease process (Martin, 1986). Later, other cognitive deficits in AD occur, including deficits in language and semantic knowledge (i.e., aphasia), abstract reasoning and other executive functions, attention, and constructional and visuospatial abilities (Adams, 1997; Moss and Albert, 1988).

The cognitive and behavioral changes seen in AD are associated with specific neurologic changes. Initially, the hippocampus and entorhinal cortices are typically affected, followed by association cortices as the disease progresses (Fox et al., 1996, Hyman et al., 1984). Degeneration of the neocortex and hippocampus, leading to deeper and wider sulci in the temporal and parietal lobes, has been documented on autopsy in AD patients (Serrano-Pozo, 2011). Neuropathological findings include a widespread loss of nerve cells mostly involving the cerebral cortex, perivascular amyloidosis, neuritic plaques, neurofibrillary tangles, and granuolovascular degeneration of neurons especially in the pyramidal cells of the hippocampus (Adams et al, 1997, Glenner, 1980, Corsellis, 1984).

Neurochemical changes have also been found in brain tissue from AD patients. Biopsies reveal lower levels of acetlycholine (Francis, 1999), which is considered to be secondary to a significant decrease in cholinergic neurons in the nucleus basalis of Meynert in the basal forebrain (Whitehouse et al., 1981). Degeneration of cholinergic neurons in the medial septum, which projects to the hippocampus, has also been found (Nakano and Hirano, 1984). It is believed that specific loss of neurons containing choline acetyl-transference (ChAT) (Wolozin & Davies, 1987) contributes to the

lowered acetylcholine levels in the brain because of decreased availability of that precursor enzyme. Neurons from the monoaminergic, noradrenergic, GABAnergic, and serotonergic systems are also depleted. In addition, glutamate and neuropeptides such as substance P, somatostatin, and cholecystokinin have been found to be reduced in both cortical and subcortical areas (Sasaki et al., 1986).

Longitudinal Cognitive Changes in AD

Patients with AD experience a wide variety of cognitive impairments. The Diagnostic and Statistical Manual of Mental Disorders (5th ed.; DSM-5; American Psychiatric Association, 2013) diagnosis requires that patients with AD meet criteria for major neurocognitive disorder, have an insidious onset and gradual progression of impairment in one or more cognitive domain. Patients must show clear evidence of decline in memory and learning and at least in one other cognitive domain (based on detail history or serial neuropsychological testing). Steady progressive, gradual decline in cognition, without extended plateaus should be demonstrated. There should be no evidence of mixed etiology (i.e. absence of other neurodegenerative or cerebrovascular disease or other neurological, mental or systemic disease likely contributing to cognitive decline). A defining characteristic in the updated DSM-5 diagnostic criteria for AD is the progressive nature of the disease process. An understanding of the progression of AD is vital to studies of the relationship between clinicopathological changes and therapeutic interventions.

Past longitudinal studies of AD have attempted to define stages of the disease

process, predict rates of decline, and describe patterns of cognitive deficits. Longitudinal cognitive studies of AD have typically relied on retrospective analyses of neuropsychological databases of elderly subjects who were followed for several years. Methodological differences across studies, including size and composition of the study population, degree of patient attrition, heterogeneity of baseline scores, length of follow-up and differing cognitive instruments, have produced varied results. In preparation for this study, studies that have investigated stages and patterns of cognitive decline in AD will be reviewed.

Stages of Alzheimer's Disease

From the time of diagnosis, on average, the AD process continues for 10 or more years until death; however, there is substantial variability around this average (Heyman A, Peterson B, Fillenbaum G, Pieper C, 1996). This variability in estimates may have occurred in part because longitudinal studies of AD patients (a) rarely follow patients for more than two to three years; (b) experience significant patient attrition; and (c) are limited by problems in using the same neuropsychological tests to measure cognitive abilities over the span of the disorder. Moreover, the insidious onset of AD has made it difficult to measure rates of decline because the onset of the disease can only be estimated.

Within this time frame, researchers have conceptualized cognitive deficits in AD as occurring in different severity stages, usually mild, moderate, and severe. For example, Lezak, Howieson, & Loring (2004) have described a sequence of cognitive

deficits that commonly occur during the course of the disease process.

Table 1. Stages of Alzheimer's Disease from Lezak et al., 2004

Early	Patients exhibit problems in memory (delayed recall of verbal and visual information), complex mental tracking (e.g., trail making test), confrontation naming and verbal fluency. Also symbol substitution and construction tests
Moderate	Cognitive deficits become more broad and severe. Aphasia and apraxia become more prominent along with various agnosias. Dysfluency, paraphasias, bizarre word combinations, and intrusions are common mid-stage speech defects.
Severe:	Patient becomes nonfluent, repetitive and largely non-communicative. Auditory comprehension is limited often accompanied by different forms of mutism.

Stages of AD often have been defined using global cognitive tasks that tap into multiple cognitive domains, such as the Mini Mental Status Examination (MMSE) (Folstein et al., 1975) and the Dementia Rating Scale (DRS) (Mattis, 1988). These tasks are frequently used to classify AD patients into different severity groups; however, cutoff scores for severity levels vary across studies. Most longitudinal neuropsychological studies of AD have investigated patients in the mild to moderate stages, because, at severe levels of AD, floor effects are common across multiple neuropsychological tests (Nyenhuis & Garron, 1997; Peavy et al., 1996; Morris, 1997). Recently, researchers have focused on Mild Cognitive Impairment (MCI), which is often the pre-clinical phase of AD. MCI has sometimes been conceptualized as the stage which refers to the span of time between the earliest detection of deficits and until a patient meets criteria for a clinical diagnosis of AD.

Pre-clinical Phase of Alzheimer' Disease

As potential therapeutic interventions become more likely, it has become

increasingly important to develop methods that reliably identify patients who may be in an early pre-clinical stage of AD. Several studies have retrospectively examined neuropsychological data of AD patients obtained many years prior to their diagnosis (Masur et al., 1994; Jacobs et al., 1995; Fox et al., 1998). Many of these studies have found that those patients who are in the preclinical phase of AD showed deficits in episodic memory while other cognitive abilities tend to remain relatively stable.

Deficits in episodic memory can appear from 6 to 8 years before the diagnosis of AD (Jost & Grossberg, 1995; Bäckman et al., 2001). Although most studies are retrospective, a few prospective studies have been published, for instance, a study by Chen et al. (2001) prospectively investigated changes in cognitive performance of patients during the preclinical phase of AD. Of the limited number of studies that have examined patients in the preclinical phase of AD, most have been able to look at only these patients just before diagnosis. Chen and colleagues were able to follow patients over multiple time points before diagnosis. The results of their study indicated that patients in the preclinical phase of AD experienced accelerated declines in both episodic memory and in executive functions from 1.5 to 3.5 years before diagnosis.

Patterns of Cognitive Deficits in AD

Multiple studies have examined patterns of cognitive decline associated with AD over time. Most have found that AD patients tend to show initial impairments in memory. As pathology spreads from medial temporal lobe to other cortical areas, multiple cognitive skills are affected. In a longitudinal study of 12 subjects with AD,

Perry and Hodges (2000) found that impairments in attention and semantic memory developed after episodic memory deficits and before impairments in visuospatial function and auditory verbal short-term memory. Other studies have indicated that executive functions are affected early in AD, followed by deficits in visuospatial skills, attention and short-term memory span. (Perry & Hodges, 1999; Bäckman et al., 2005; Storandt et al., 2006; Twamley et al., 2006) These patterns of cognitive changes are consistent with the spreading of the neuropathological process in AD.

Changes in executive skills are thought to be related primarily to neocortical degeneration of the frontal lobes (Morris, 1996). Deficits in semantic memory for concepts, the meaning of words, and factual knowledge have been linked to neuropathological changes in infolateral temporal neocortex. Semantic memory is thought to deteriorate at a slower rate than episodic memory. It is believed that those neuroanatomical areas such as the infolateral temporal neocortex that support semantic memory are affected later in the disease process. Attention is considered one of the last cognitive abilities to decline in AD. Impaired attentional abilities in AD are thought to be associated with deterioration in primarily subcortical-frontal systems.

Declarative Memory in AD

Disorders of memory are an early and prominent cognitive deficit associated with AD. (Butters et al., 1987; Petersen et al., 1994; Welsh et al., 1991; Fox et al., 1998) Patients with AD exhibit severe decrements in their ability to learn and retain new information (anterograde memory). In addition, they often are impaired in their

recall of “over-learned” past information (retrograde memory).

Research has demonstrated that memory is not a unitary construct (Cohen & Squire, 1980; Tulving, Schacter, & Stark, 1982; Shimamura & Squire, 1987). Memory often is conceptualized as having multiple subsystems. These subsystems are thought to differ from one another in “their rules of operation, in the types of information they process, and in their neuroanatomical substrates.” (Salmon, 2000). Although these memory systems are considered independent, they also are interactive. A common distinction between memory subsystems is that between the declarative (explicit) and nondeclarative (implicit or procedural) forms of memory. Declarative memory refers to those memories that can be communicated (or declared) such as facts and past events. In contrast, non-declarative or implicit memory refers to recall of information that is considered unconscious. Although one cannot recall specific information they were exposed to previously, the unconscious knowledge serves to improve performance on related tasks (called procedural events). Declarative memory can be furthered divided into episodic and semantic memory. Episodic memory pertains to recall of contextually based information, which relies on temporal and/or spatially referenced information. In contrast, semantic memory refers to our general fund of knowledge that does not depend on contextual cues for its retrieval. Because episodic memory is characterized by the ability to consciously recall past events or to actively recall something to mind (Squire, 1987), it is often tested in a recall and/or recognition memory paradigm.

The most common presenting complaint of people with AD is increasing forgetfulness and memory loss. Several studies have indicated that memory impairment occurs very early in the disease process. By the time a diagnosis of AD has been made, most patients are experiencing moderate to severe impairments in recall abilities (Reid et al., 1996; Locascio et al, 1995). Deficits in episodic memory have been attributed to damage in hippocampal and related structures such as the dentate gyrus, subicular complex, entorhinal cortex, and the diencephalic regions (Zola-Morgan & Squire, 1993). Both CT and MRI imaging studies have identified medial temporal atrophy in early AD (Burton et al., 2009; Jobst et al., 1994; Deweer et al., 1995; Fox, et al., 1996). However, learning and memory are also found to be dependent on the integrity of other supporting neuroanatomical structures. Positron emission tomography (PET) has shown that right frontal region, anterior cingulate, parietal lobes, cerebellum, bilateral medial temporal lobes, and prefrontal regions (including orbitofrontal cortex) are activated during encoding and retrieval of verbal information (Nyberg, McIntosh, Houle, Nilsson & Tulving, 1996). Thus, episodic memory is a multi-faceted cognitive ability and subsequent global cognitive impairments seen in the moderate stages of AD affect the depth of the memory impairments in AD.

Executive Functions in AD

Many “higher order” cognitive abilities fall under the rubric of executive functions. Most studies of executive skills in AD have assessed cognitive flexibility (e.g. set shifting such as Halstead–Reitan Trail Making Test - Form B; Reitan, 1958;

The Stroop Neuropsychological Screening Test; Trennery et al, 1989, abstract reasoning (e.g. Similarities subtest from the Wechsler Adult Intelligence Scale (WAIS);Wechsler, 1955), and planning and organizing (e.g., Tower of London; Shallice, 1982). In a study investigating early detection of AD, Larumbe (1997) examined 14 normal controls, 12 patients with possible dementia, and 24 AD patients. The results indicated that delayed recall and executive function measures best predicted AD. Studies that have examined the rate of decline in cognitive abilities have demonstrated that those abilities that showed the greatest deterioration over time in AD were affected early in the course of the disease (Chen et al., 2000, 2001). Chen and colleagues (2000) found that executive functions and memory were deficient early in the disease process and discriminated between those individuals who eventually converted to AD and those who remained undemented. Perry & Hodges (1999) found that after initial deficits in memory, tasks of divided attention and selective attention were found to be "particularly vulnerable" in early AD.

It has been shown that memory abilities are sometimes dependent on intact executive functions. For example, while item memory is dependent primarily on the medial temporal lobe system, source memory (memory for context) has been found to rely primarily on frontally-based systems (Janowsky, Shimamura, & Squire, 1989; Spencer & Raz, 1995). In addition, elderly normal controls have been found to show disproportionate difficulty with source memory compared to item memory. This may be due in part to age-related memory decline associated with frontal-lobe dysfunction. Studies on working memory have also implicated temporal and frontal-lobe systems

for successful execution of this ability (Goldman-Rakic, 1992; Moscovitch, 1994).

Impairments in executive functions affect one's ability to hold information in conscious memory while performing other cognitive operations. Learning strategies are thought to be executive abilities that contribute to better memory performance. A number of imaging studies have indicated that the prefrontal cortex is associated with organizational strategies that support and enhance episodic memory (Blumenfeld & Ranganath, 2006; Demb et al, 1995; Fletcher et al., 1998a,1998b; Buckner et al., 1999; Savage et al., 2001). Executive functions, such as reorganization of items in working memory (Fletcher et al., 1998a) and semantic processing (Demb et al, 1995), have been investigated. Reorganization of items in working memory is described as semantic clustering on such tasks as the California Verbal Learning Test (CVLT) (Delis et al., 1983, 1987). Semantic clustering is an encoding strategy that facilitates recall of semantically related words. This type of learning strategy requires an individual to regroup a list of words into semantic categories while attempting to encode the words into memory. In a functional imaging study that used a semantic organization task that was modeled closely on the CVLT, Savage and colleagues found that activations of the prefrontal cortex in normal controls corresponded to levels of semantic clustering (Savage et al, 2001).

Semantic Memory in AD

Semantic memory represents learned knowledge and language (Tulving, 1987). Confrontation naming, verbal fluency, and semantic priming are classified as

semantic memory tasks that are often deficient in AD (Hodges et al., 1991, Bowles et al., 1987; Butters et al., 1987; Monsch et al., 1992; Salmon et al., 1988). AD patients with compromised semantic memory tend to communicate in a vague, "empty" manner, and circumlocutions and paraphasias are common. Cognitive models of the structure and organization of semantic memory suggests that information is organized as a complex network of concepts. Those concepts that have many attributes in common are strongly associated in the semantic network. Strongly associated concepts are grouped into conceptual categories. It is thought that these conceptual categories become progressively compromised in AD by the loss of specific information for concepts, which results in the breakdown of the "organization and structure" of the semantic network (Au et al., 2003; Butters et al., 1990; Grober et al., 1985; Martin, 1987; Smith et al., 1989). In a study by Chan et al. (1997), the integrity of an AD patient's cognitive map, which was thought to represent the semantic network, was negatively correlated with the Dementia Rating Scale (DRS). In other words, as the disease progresses, AD patients were less likely to use abstract conceptual categories and relied on more concrete conceptualization such as physical characteristics (e.g., size) rather than more abstract categorization (e.g., domestic vs. wild) to cluster types of animals. A series of studies by Chan and colleagues have shown that the semantic network involving "animals" is abnormal in mildly impaired AD patients, with the structure of this network appearing "chaotic" (Chan, et al., 1993a, 1993b, 1995, 2001).

Longitudinal studies of semantic memory in AD have illustrated progressive

compromise of the semantic networks over time (Salmon et al., 1999; Perry & Hodges, 2000). In a study by Salmon et al. (1999), the integrity of the semantic network was examined by comparing AD patients on letter and category fluency. Category fluency is thought to be primarily semantically driven, whereas letter fluency is facilitated by primarily phonemic-based information. In addition to exhibiting advancing deterioration across both fluency tasks, the AD patients showed relatively worse category fluency than letter fluency compared to controls over time. Furthermore, these researchers found that AD patient's performance on semantic fluency declined over time at a faster rate than their performance on phonemic fluency. A qualitative analysis revealed that items recalled on an initial test were highly unlikely to be recalled a year later, whereas normal controls were more consistent across test periods in their responses. The authors interpreted this as an indication of the "gradual deterioration of the organization and content of semantic memory "as the disease progressed. Perry & Hodges (2000) found that semantic memory deficits occurred after deficits in episodic memory but before impairments in attention.

Attention in AD

AD patients have been found to be impaired in many aspects of attention. Impairments have been documented in length of attention span (Morris & Baddeley; 1988), divided attention and cognitive shifting (Parasuraman & Haxby; 1993), and reaction-time choices (Nestor et al., 1991). Sustained attention has been found to be a relative strength until the later stages of the disease (Fuld, 1978; Schachter, Kaszniak,

& Kihlstrom, 1989; Reid et al., 1996; Linn et al., 1995). In contrast, divided and shifting of attention have been found to be affected early in the disease (Perry, Watson, & Hodges, 2000). In a large epidemiological study of 1,000 non-demented elderly who were followed for 13 years, Linn and colleagues found that in those patients who went on to develop AD, semantic recall as measured by the WMS Logical Memory subtest preceded deficits in attention as measure by the WAIS Digit Span subtest. Studies that have employed more complex measures of attention (divided attention and shifting of attention) have found impairments early in the disorder (Parasuraman & Haxby; 1993). These more complex tasks are thought to rely more on "executive abilities" then sustained attention tasks.

These deficits may be related in part to deterioration in the frontal cortex, involvement of the basal forebrain nuclei, and the "laminae of neocortical association areas that participate in cortico-cortico connections" (Braak & Braak, 1996, De Lacoste & White, 1993).

Complex relationship between episodic memory and other cognitive abilities

Although it is well established that learning and memory are affected early in Alzheimer's Disease, the eventual outcome of the disorder is global cognitive impairments. Verbal learning and memory is a higher-order cognitive ability that is dependent on other cognitive abilities such as attention, language, and executive functions. Therefore, it would be expected that the longitudinal deficits seen in episodic memory are not just related to neuroanatomical abnormalities in the medial

temporal lobes. This conceptualization predicts that as the disease progresses, those cognitive abilities that are affected later on in the disease process will contribute to the profound memory deficits seen in the later stages of AD. However, most studies of verbal learning and recall tend to use instruments that quantify only total correct scores (e.g., total recall over trial, amount recalled after a delay) and not other qualitative features of learning and memory. Hence, a qualitative examination of AD patient's verbal recall may produce a better understanding of the relationship between learning and memory and other cognitive systems.

Quantitative and Qualitative Memory Changes in AD as assessed by the CVLT

The California Verbal Learning Test (CVLT) is a standardized neuropsychological test that measures immediate and delayed recall and recognition for auditorially-presented verbal material. Patients are asked to learn and recall a list of 16 words (List A) administered over five trials. List A is comprised of four words from each of four semantic categories (Fruit, Tools, Clothing, and Spices & Herbs). A distractor list of 16 words (List B) is then presented for one trial, immediately followed by free and semantically-cued recall of List A. Following a 20-minute delay period during which non-verbal testing occurs, free recall and semantically-cued recall of List A is evaluated. A yes/no recognition memory test concludes the administration of the CVLT. The CVLT yields both quantitative learning and memory scores (e.g., learning across Trials 1-5, Short Delayed Recall, and Long Delayed Recall) and a number of qualitative "process scores," including measures of intrusions, perseverations, serial-position effects, recall consistency, and the ability to use

organizational strategies such as semantic versus serial clustering.

Compared to amnesic patients, AD patients have been found to have similar memory profiles, with comparable levels of learning, recall, semantic clustering, primacy-recency effects, recall consistency, intrusion and perseveration rates, vulnerability to interference, and recognition discriminability (Delis et al., 1991). The CVLT performance of the AD patients is exemplified by impairments in learning, delayed recall, rapid forgetting, recognition memory, ineffective use of semantic clustering, elevated recency effects, and sharp increases in intrusion and false positive errors (Delis et al., 1991; Greenaway et al., 2006; Lacritz et al., 2001 & Fox et al., 1998).

Deficits on the CVLT also have been found in normal elderly controls that were at risk for AD (Bondi et al, 1995). In an attempt to elucidate early cognitive impairments in patients at high risk for AD, Bondi and colleagues compared the performance of nondemented older adults with and without the epsilon 4 allele of the apolipoprotein E (APOE-epsilon 4). Although both groups were comparable across demographic and mental status variables, they differed significantly on nine CVLT variables. These variables included List A Trial 5, Short Delay Free Recall, Long Delay Free Recall, Long Delay Cued Recall, Percent of Long Delay Savings, Semantic Clustering, Percent Recency Recall, Learning Slope, and Cued Recall Intrusions. Although the mean scores of the APOE- ε4 patients fell within the

average range for their normative age group, the nature of their mild deficits paralleled the pattern of performance found in patients with early stage AD. APOE-ε4 patients showed flatter learning curve, recalled fewer items on delayed recall, and tended to use less effective organizational learning strategy (Bondi et al, 1995.

Several studies have documented episodic deficits in AD using the CVLT (Delis et al., 1987, 1991; Massman et al., 1993, Ober et al., 1985; Libon et al., 1998; Fox et al., 1998; Kohler et al., 1999; Bayley et al., 2000; Lange, 2002). In general, during the learning phase, AD patients tend to exhibit flat learning curves, impaired primacy recall, and intrusion errors (Delis et al., 1991; Massman et al., 1993; Fox et al., 1998; Kramer et al, 1998). After a short delay, AD patients at moderate to severe stages, show a profound amnesia that is not facilitated by category cues or a recognition format (Delis et al, 1991; Massman et al., 1993). A few studies have looked at verbal memory among Alzheimer patients at different stages of the disease process using the CVLT but few have examined verbal learning and recall longitudinally (Fox et al., 1998; Bayley et al, 2000; Mickes et al., 2007; Albert; 2001; Lekeu et al., 2010). Some studies have also investigated more qualitative or "process" CVLT variables (e.g., serial position effects and intrusions in AD patients) (Bayley et al., 2000; Greenway et al., 2006). For example, Bailey and colleagues examined serial position effects in AD patients who were mildly and very mildly demented. Greenway et al, 2006 examined multiple CVLT indices to characterize the pattern of verbal memory dysfunction in MCI, AD and Normal aging (AG) subjects. In addition

to looking at traditional measures of the CVLT (Total recall form trials 1-5, short delay recall and long delay recall), the authors analyzed qualitative errors including total intrusion errors and percent intrusions. Results from discriminant function analyses indicated that the more traditional measure of delayed recall and total learning were better able to distinguish the groups. However, the manner in which these variables are affected over time has not been well illustrated.

The current study examines quantitative and qualitative of episodic verbal memory in AD. Initial baseline analyses will assess the patient's performance on traditional quantitative measures of recall including total immediate recall (TotImm), long delay free recall (LDF) and a measure of recall savings, delayed retention rate (RetRate) as well as qualitative variables at subject's first CVLT test administration. It is hypothesized that the AD subjects will be the most impaired on traditional episodic measures of verbal list learning and the preAD patients will exhibit a similar but 'milder' profile and that both groups will be impaired in comparison to the NC group.

The CVLT offers a rich assortment of qualitative variables to assess longitudinal changes in Alzheimer's disease. The variables of interest in this study include serial position effects, proactive interference, organizational strategies, intrusion errors, and recognition discriminability.

Serial Position Effects

On list-learning tests, each item occurs in a particular position on the list. Performance on list-learning tasks can be examined as a function of where the recalled item was originally found on the list. The general label given to differences in memory performance as a function of position on the list is the serial position effect. Serial position effects for normal controls indicate that recall is best for items at the beginning and end of the list (respectively, primacy and recency effects; (Murdock, 1962, 1983). Several studies have documented diminished primacy effects and or exaggerated recency effects in asymptomatic middle aged children of patient with AD, patients with mild cognitive impairment, and patients diagnosed with mild AD; (La Rue et al., 2008; Howieson et al. 2010, Bayley et al., 2000). For example, in a study by Bayley and colleagues (2000), serial position effects were studied on a small cohort of AD patients. They found that mildly demented AD patients exhibited a reduction in the primacy effect (first 2 words on the list) but not the recency effect (last two words on the list). Alzheimer's patients tend to show an elevated recency effect, indicating that their ability to encode information is impaired and their recall may simply reflect their relatively better attentional skills. These results suggest that it may be fruitful to investigate serial position effects longitudinally. It is hypothesized that Control Subjects will exhibit normal primacy and recency effects and these effects will remain relatively stable over time. It is hypothesized that preAD patients will initially exhibit a mild decline in primacy recall and normal or mildly elevated recency recall. AD patients will exhibit moderate declines in primacy recall and moderately elevated recency recall.

Proactive Interference

On a verbal learning task, proactive interference (PI) occurs when previously learned material interferes with the acquisition of new material. On the CVLT, PI is best illustrated when information learned from List A interferes with the recall of List B. A PI effect occurs if recall of List B is significantly lower than recall of Trial 1 on List A. If proactive interference is prominent, intrusions of List A words on the List B Recall Trial may also occur (Lezak, 1995; Libon et al., 2011). PI effects tend to vary as a function of the severity of the memory disorder (Kopelman, MD, 1991; Helkala, 1989; Woodward & Bjork, 1999). According to Rouleau (2001), "the PI effect is dependent on the level of learning; the more material that was learned previously, the more difficult the learning of new material will be, especially if the new and old material is alike." Consistent with these findings, it is predicted that as the disease progresses, AD patients will exhibit a significant decrease in the PI effect. In addition, as AD patient's ability to retain information decreases (Total Recall for Trials 1-5 on the CVLT), their level of PI will decrease over time as well. It is also hypothesized that patients who are pre-symptomatic will exhibit a mild decrease in PI effect relative to control subjects, and these findings should become more prominent over time. Control Subjects will exhibit the largest PI effect, which will change little over time.

Semantic Clustering

The CVLT was designed to analyze types of recall strategies when encoding verbal information. Two types of learning strategies are examined. One of the strategies is called serial clustering. This strategy reflects the extent to which a subject

attempts to recall the list in the same order as it was presented. Semantic clustering, on the other hand, reflects an individual's ability to reorganize the target words into categorical groups. On the CVLT, semantic clustering reflects the extent to which a patient is able to use the different semantic categories (fruit, tools, clothes, and spices) represented in the list to enhance recall. Semantic clustering in AD is affected early in the disease process (Delis et al., 1991; Bondi et al., 1995). While elderly normal controls have been found to use semantic clustering strategies on the CVLT, APOE-epsilon 4 subjects (who went on to develop AD) have been found to use a less effective organizational strategy (serial clustering) when learning verbal list information, even though overall mean recall scores on the CVLT were within normative limits for their age group (Bondi et al., 1995). AD patients considered to be in the mild stages of AD have been found to rely primarily on a serial clustering strategy (Delis et al., 1992). Wegesin et al (2000) found that decline in semantic clustering is more closely related to changes in semantic knowledge rather than a processing limitation in working memory. For the current study, it is hypothesized that as AD progresses, levels of semantic clustering will decline. Pre-symptomatic AD patients will exhibit mild declines in semantic clustering and normal correlations between semantic clustering. Control Subjects will exhibit stable levels of semantic clustering.

Intrusions

Intrusion errors are words recalled that are not found on the original list. Intrusion errors occur early in AD (Loewenstein, Wilkie, Eisdorfer, Guterman,

Berkowitz, & Duara, 1989; Loewenstein, D'Elia, Guterman et al., 1991; Fuld, Katzman, Davies, & Terry, 1982; Kramer, Delis, Blusewicz, et al., 1988; Kamer, Levin et al., 1989; Reed et al., 1988; Greenway et al., 2006). As the disease progresses, intrusion errors tend to proliferate (Fuld, Katzman et al., 1982). In a longitudinal study, intrusion errors were found to increase as a function of severity (Fox et al., 1998). In studies of AD patients classified as mildly to moderately demented, intrusions errors made up 47% (Delis et al., 1991) and 71% (Kramer et al., 1988) of subject's responses.

In early studies of Alzheimer's disease, intrusion errors were examined for their sensitivity in differentiating AD from normal controls and patients with other neurological and psychiatric disorders. Fuld (1983) found that intrusions differentiated AD from other dementing processes (Fuld et al., 1983; Fuld, Katzman, et al., 1982), while Gordon et al., (1984) and Loewenstein et al., (1989) found that the presence of intrusion errors did not distinguish AD from other neurological groups. Other authors found that the frequency of intrusions did not distinguish AD from normal controls (Ober, Koss, Friedland, & Delis, 1985). However, when intrusions occur on recall measures (Immediate vs. Delayed Recall Trials) and subtypes of intrusion errors have been found to be more sensitive in distinguishing AD from normal controls and other neurological disorders (Loewenstein et al, 1989, 1991; Rouleau et al, 2001). Examining intrusion errors qualitatively was also helpful in characterizing clinical groups in a study of patients in the pre-clinical stages of AD. Specifically, mild elevations of intrusions on the Cued-Recall Trials of the CVLT were found to

distinguish pre-clinical AD patients from normal controls (Bondi et al., 1995, 1999).

There are many types of intrusions errors described in the literature (Loewenstein et al., 1989; Fuld et al., 1982; Shindler, Caplan, & Hier, 1984)). Loewenstein and his colleagues (1989, 1991) identified five kinds of intrusions that are listed in Table 2.

Table 2. Classification of Intrusion Errors from Loewenstein et al., 1989

Intrusion Errors	Description
Test Intrusions	Intrusions that originate from distractor tasks
Shift Intrusions	Intrusions that reflect difficulties shifting from a previous task.
Conceptual Intrusions	Intrusion responses that are conceptually similar to previous task items.
Confabulatory Intrusions	Intrusion errors that consist of a single word and that arise from a combination of two target items.
Unrelated Intrusions	Intrusion errors that do not relate in any way to the target items presented.

In the 1989 study, intrusion types were examined in an attempt to differentiate AD patients from other neurological patients known to make intrusions errors (vascular dementia). The authors found that unrelated errors (later renamed in subsequent studies as semantic errors) were more frequent in AD and reliably distinguished mildly impaired AD patients from other neurological groups. Specifically, using a selective reminding paradigm, which required subjects to alternate between free-recall and distractor trials, mildly impaired AD patients were more likely to make unrelated intrusion errors ("those responses unrelated to either the to-be-remembered targets or distractor items.") than patients with vascular dementia, even though the both groups had equivalent scores on the MMSE.

Using the Rey Auditory Verbal Learning Test (RAVLT), Rouleau, Imbault, Laframboise, & Bédard (2001) examined intrusion errors in patient with AD, Parkinson's Disease (PD), and dementia with prominent frontal lobe symptoms (FD) patients. A qualitative analysis of the type of intrusions made is illustrated in Table 2.

Table 3. Classification of Intrusion Errors from Rouleau et al., 2001

Intrusion Error	Description
Same Category	Intrusion semantically related to a word on the list to be remembered (functional or categorical)
Phonemic	Intrusion with acoustic similarity *to* a word on the list.
Unrelated	Intrusion without any obvious categorical, functional, or acoustic relationship with the words on the list.
Free Associations	Production of a series of intrusions often related to each other but without any obvious relationship with the words on the list.
Prior List Intrusions	1. Words from List A reported while recalling List B and 2. Words from List B reported while recalling List A

Results indicated that unrelated intrusion errors best differentiated the groups, with PD patients having far fewer unrelated intrusion errors than both AD and FD patients. Unrelated intrusion errors were "seen as reflecting a deficit in the self-regulatory mechanism, that is, an inability to inhibit relevant information during recall" (pg. no. 248)

The authors of the CVLT-II (Delis, Kramer, Kaplan & Ober, 2000), the revised version of the CVLT, have proposed a number of different ways to examine intrusion errors qualitatively. One distinction is made between category and non-category intrusions. Category intrusions are those intrusion errors that belong to one of the six

categories on List A or List B (i.e., fruit, spices & herbs, tools, clothing, desserts, or furniture from the original CVLT) but are not one of the target words. Two subtypes of category intrusions include synonym and subordinate Intrusions. A synonym intrusion occurs when an examinee recalls a synonym of a target word instead of the actual target word (e.g. pants for slacks). A subordinate intrusion error occurs when an examinee reports a specific subtype of a target word (e.g., red grapes for grapes). A non-category intrusion is a non-target word that does not belong to any of the categories to which the subject has been exposed to at the time the intrusion was reported. For example, a non-category intrusion does not belong to one of the six categories on List A or List B once the List B Trial has been administered.

Table 4. Classification of Intrusion Errors on the CVLT-II

Type of Intrusion Error	Description
Categorical Intrusions:	Intrusion errors that belong to one of the six categories on List A or List B from the original CVLT, includes fruit, spices and herbs, tools, clothing, desserts, or furniture.
Non-Categorical Intrusions	A non-target word that does not belong to any of the categories to which the subject has been exposed to at the time the intrusions was reported.
Across List Intrusions	A List-A word is reported on a List-B Trial. Or a List-B word is reported on a List A Delayed Recall Trials.
Synonym Intrusion	A synonym of a target word is recalled (pants for slacks).
Subordinate Intrusion	A subtype of a target word is recalled (red grapes for grapes).

In the current study, it is hypothesized that AD patients will make significantly more intrusion errors in general, than the other two groups. In addition, it is expected

that AD patients will make a large number of intrusion responses and the percentage of intrusion responses will increase as the disease progresses. PreAD patients may likely evidence elevated intrusion errors on cued recall trials when compared to normal controls.

In the current study, qualitative analysis of intrusion errors also will be examined longitudinally. Unlike the findings from the Rouleau et al. study (2001), it is expected that AD patients will make a larger number of category intrusions, as the CVLT words are derived from semantic categories. In this study, intrusion errors that belong to one of four of semantic categories on the CVLT will be considered categorical Intrusions. Of particular interest is how intrusion errors change over time for AD patients.

It is believed that intrusion errors in AD may be best studied within the context of the breakdown of the semantic network. With a relatively intact semantic network, intrusion errors will be expected to be exemplars from the categories used. For example, the word “apple” may be expected as a category Intrusion from the semantic category, “fruit.” (It should be noted that the four most prototypical exemplars of each category on the CVLT were excluded from the target lists (Delis et al., 1987)). It is hypothesized that Control Subjects will exhibit normal levels of intrusion errors and primarily category intrusions. PreAD patients will exhibit mildly elevated levels of intrusion errors and primarily category intrusion errors. It is hypothesized that as AD progresses, levels of intrusion errors will increase and there will be a higher

percentage of noncategory intrusion errors.

Recognition Discriminability

The CVLT also provided measures of recognition memory. The recognition items consist of the 16 target words, 16 phonemically similar distractor words, 8 semantically related words, 8 unrelated items, and 8 items from the distractor List "B". Research has shown that AD patients are impaired on recognition discriminability on the CVLT and the CVLT-II (Delis et al, 1991; Troster et al., 1993; Baldo et al., 2002; Fine et al., 2008). Much of this research has been aimed at differentiating profiles of memory disorders between patient groups that exhibit cortical (AD patients) or subcortical profiles (Huntington's and Parkinson's disease patients). Finding from these studies tend to support the idea that AD patients impairment on yes/no recognition verbal memory tasks is related to mesial-temporal pathology whereas Huntington's and Parkinson's Disease patients who tend to show disproportion advantage on the same tasks have relative sparing of subcortical structures (Braak & Braak, 1991). What has not been studied is how recognition discriminability changes over time. It is hypothesized that has Control subjects will evidence normal recognition discriminability scores. It is also hypothesized that preAD will exhibit mildly elevated recognition discriminability scores while AD patient will exhibit moderately elevated recognition discriminability scores. As AD progresses the level of recognition discriminability will increase for both preAD and AD patients.

Research has shown that in moderate stages of the disease process, a large proportion of AD patient's responses on the recognition task are false alarms (Deweer

et al., 1993). Of interest are the number of false positive errors AD patients make. It is hypothesized that Control Subjects will make normal levels of false positives. It is also hypothesized that PreAD patients will exhibit mildly elevated levels of false positives. As AD progress, levels of false positives will increase for AD patients.

The purpose of the present study is to characterize episodic memory in preclinical AD patients and AD patients relative to normal controls. An initial analysis of the patient groups at their first assessment will be conducted and this analysis will followed by a second analysis with special emphasis on qualitative measures from the CVLT, over 3 serial assessments. Please see Table 5 for a summary of hypotheses.

Table 5. Summary of Hypotheses:

Initial Assessment:	
H1	It is hypothesized that the AD subjects will be the most impaired on traditional measures of verbal list learning and the preAD patients will exhibit a similar but 'milder' profile and that both groups will be impaired in comparison to the NC group.
Over Serial Assessments**:**	
H2a	Control Subjects will exhibit normal primacy effects and these effects will remain relatively stable over time, while pre-clinical AD patients will initially exhibit a mild decline in primacy recall. AD patients will exhibit moderate declines in primacy recall.
H2b	Control Subjects will exhibit normal recency effects and these effects will remain relatively stable over time. PreAD patients will initially exhibit a normal or mildly elevated increase in recency recall. AD patients will initially exhibit moderately elevated percent recency recall and this will increase slightly over time.
H3	Over time AD patients will exhibit a significant decrease in the PI effect. Pre-symptomatic AD will exhibit a mild decrease in PI effect relative to control subjects, and these findings should become more prominent over time. Control Subjects will exhibit the largest PI effect, which will change little over time.
H4	AD patient's levels of semantic clustering will decline over time. PreAD patients will exhibit mild declines in semantic clustering over time. Control Subjects will exhibit normal levels of semantic clustering.
H5a	It is hypothesized that Control Subjects will exhibit normal levels of intrusion errors and PreAD will exhibit mildly elevated levels of intrusion errors, while AD patient's intrusion errors will be the most elevated.
H5b	Overtime AD and preAD patient's rate of intrusion errors will increase over time.
H5c	Both AD and preAD patients will primarily make category intrusions and over time their percentage of category intrusions will decrease while their noncategory intrusion levels will increase
H6a	Recognition Discriminability scores will be more impaired for AD and preAD subjects over time while Control Subjects Recognition Discriminability scores will remain stable over time.

II Methods

Subjects

A total of 144 individuals with archival data at the Alzheimer's Disease Research Center (ADRC) at the University of California, San Diego were included in this study; 102 AD patients, 20 PreAD patients, and 25 normal controls. All AD, PreAD, and NC were participants in an ongoing longitudinally study at the University of California, San Diego (UCSD) Alzheimer's Disease Research Center (ADRS) though which they received annual, physical, neurological, and neuropsychological evaluations. On the basis of these evaluations and a number of laboratory tests used to rule out other causes of dementia (e.g., hypothyroidism, vitamin, B12 deficiency, electrolyte imbalance). All AD patients received a diagnosis of Probable or Possible AD by two senior staff neurologists according to the criteria developed by the work group of the National Institute of Neurological and Communicative Disorders and Stroke (NINCDS) and the Alzheimer's Disease and Related Disorders Association (ADRDA; McKhann et al., 1984). All subjects in the study were screened for a history of head injury, alcoholism, or serious psychiatric difficulties. To reduce the possibility of including multi-infarct dementias, patients with a score of 5 or greater on the Hachinski scale (Hachinski et al., 1975) were excluded from the AD group. Only those AD patients who had a MMSE score ranging from 18 or greater at the time of their first evaluation were included in the longitudinal analysis. The pre-symptomatic AD patients were Alzheimer's Disease patients, who initially entered the study at the ADRC as normal controls. Upon their first evaluation, all preAD patients were judged

to be cognitively normal by two senior staff neurologists based on medical, neurological, and neuropsychological evaluations. Diagnosing neurologists were not privy to specific neuropsychological tests scores but were given summary results of the cognitive assessments. At the time the first CVLT protocol was used, the DRS total scores for the pre-symptomatic patients were in the normal range for their age groups. The preAD patient's received a diagnosis of either Normal Control or At risk for AD at the first evaluation. The time from the administration of the first CVLT until the preAD group were given a diagnosis of Probable AD ranged was 1 to 7 years with an average of 3.5 years to a diagnosis of Probable Alzheimer's disease.

The AD and preAD patients were matched for age and education to 50 normal controls who remained cognitively healthy for the duration of their participating in the ADRC study. The exclusion criteria for the NC group also included a history of severe head injury alcoholism, or serious psychiatric disturbance.

Demographics

Demographic data for 102 AD patients (38 men and 62 women), 19 pre-symptomatic AD patients (7 men and 12 women, and 50 normal controls (25 men and 25 women) were examined for this study. The mean age, education, DRS, MMSE, and gender distribution for each group at the time of the first evaluation are shown in Table 6. Using an alpha level of .05, One-way analyses of variance (ANOVA) showed no difference in age, $F(2, 141) = .03$, $p = .97$, years of education, $F(2, 141) = .33$, $p = .72$ among the three groups. There was, however, an overall significant effect

of group for both the MMSE and DRS (both *p* values < .005) among the three groups. Post-hoc pairwise comparisons with Tukey's test showed that at expected, the AD and the preAD groups scored lower than the NC group and the AD group scored lower than the preAD group on the MMSE. On the DRS the AD group scored lower than the NC group and the pre AD group but the preAD group did not score statically significantly lower than the NC group ($p = .17$).

Table 6. Demographic Characteristics of Subject Groups

Groups			
	AD	preAD	NC
	N = 100 M (SD)	N = 19 M (SD)	N = 50 M (SD)
Demographics			
Age	73.60 (7.42)	73.60 (7.43)	73.38 (6.24)
Education	14.71 (3.16)	15.00 (3.16)	15.16 (3.09)
Gender (male/female)	38/62	7/12	25/25
MMSE	24.95 (2.47)	24.97 (.77)	27.74 (1.94)
DRS	122.16 (8.82)	135.89 (5.92)	139.43 (2.86)

Note . AD = Alzheimer's Disease, preAD = presymptomatic Alzheimer's Disease, NC = Normal Control, MMSE = Mini Mental Status Exam, DRS = Dementia Rating Scale

Procedure

Test Stimuli

At the ADRC, AD subjects are administered several neuropsychological tests as a part of the annual battery administered at the ADRC. The MMSE is a brief 30-point standardized cognitive screening instrument used to screen for cognitive impairment. It is also used to estimate the severity of cognitive impairment and to document the course of cognitive changes over time. The MMSE was administered according to the procedures of Folstein et al. (1975). The DRS is a screening

instrument designed to measure cognitive changes that often accompany dementias, such as the dementia associated with Alzheimer's Disease. The DRS includes five subscales that assess abilities commonly affected by dementia: Attention, Initiation, and Perseveration, Construction, Conceptualization, and Memory. The DRS was administered according to the procedures of Mattis (1976). Both the DRS and the MMSE were used to establish the level of cognitive impairment among the groups at the time of their first CVLT administration. The test to be analyzed in detail will be the California Verbal Learning Test (CVLT). The CVLT (Delis et al, 1987), a test of verbal memory, consists of the oral presentation of a "shopping list" of sixteen words (List A) for five Immediate Recall Trials. The list consists of four items from each of four categories. Following the five learning Trials, a second interference list (List B) is presented for one trial. Free- and Category-Cued Recall Trials of List A are then administered (the Short-Delay Trial). After a twenty-minute interval in which nonverbal testing occurs, the Long Delay Free Recall, Cued Recall, and Recognition of List A are again assessed.

The CVLT, MMSE, and the DRS were administered to all AD patients, preAD patients and NC participants as part of a larger battery of neuropsychological tests. The tests were administered on the same day within the same test session. All the patients were administered the CVLT, MMSE, and DRS at each consecutive annual evaluation. The participants were individually tested by trained psychometrists in a quiet, well-lit room.

Below are the variables selected for analysis to address study hypotheses.

Table 7. Description of the CVLT Variables Analyzed

Variables	Description
Total Immediate Recall	Total correct words recalled Trials 1-5
Long Delay Free Recall	Total number of correct words recalled on Long-Delay Free Recall, List A
Delayed Retention Rate	Total number of correct words recalled on Long Delay Free Recall (LDF) divided by the total number of correct words recalled on Trial 5 (T5), List A times 100. [(LDF/T5) x 100].
Semantic Clustering Ratio	Ratio of List A words from the same category recalled together over chance expected semantic clustering given number of words and categories recalled.
Percent Primacy Recall	Percentage of total words recalled on Trials 1-5 that are from the primacy region of List A (first four words).
Percent Recency Recall	Percentage of total words recalled on Trials 1-5 that are from the recency portion of the list (last four words).
Proactive Interference	Difference of total words recalled on List B subtracted from total words recall on Trial 1, List A.
Total Intrusions	Total intrusions errors made on all free recall and cued trials.
Category Intrusions	Total category errors made on all free recall and cued trials. A category is an intrusion that is a semantic member of a category on the target list (e.g. a subject says "hammer" on a List A Trials).
NonCategory Intrusions	Total noncategory intrusion errors made on all free recall and cued trials. A noncategory intrusions is an intrusion that is semantically unrelated to the categories on the list (e.g., a subject says "beach").
Synonym/Subordinate	Total synonym/subordinate intrusion errors made on all free recall and cued trials. A synonym intrusion errors is a synonym of a target word (e.g. says "pants" for slacks). A subordinate is similar to a synonym intrusion but it reflects a specific example of a target word (e.g., "red grape" for "grape.")
Across List Intrusions	List A word is used on a List B Trial, or a List B word is reported on a List A Delayed Recall Trials.
Recog Discrim	Signal detection measure of the ability to discriminate hits (signal) from false positives (noise) on a yes/no recognition test.
Recog Discrim False Pos	Number of distractor items identified as List A items on the recognition test

Statistical Analyses

To begin with, a series of one-way ANOVAs were performed to examine group differences on all baseline CVLT measures. Additionally, a 3 (groups) x 3 (time points) mixed model design was used to examine change in performance within and between groups. Follow-up analysis, including post-hoc comparisons were

performed as needed. To correct for multiple comparisons, the *p* value required for statistical significance will be lowered to .01 rather than the standard .05 value. While it is recognized that this may not entirely protect against Type I error, a more stringent criteria would increase Type II error due to a small sample size.

III Results

List Learning Recall at time of first CVLT administration:

The variables Total Immediate Recall (TotImm), Long Delay Free Recall (LDFR), Delayed Retention Rate (RetRate), serial position effects, proactive interference, semantic clustering, intrusion errors and Recognition Discriminability (RecogDis) were used as the dependent variables in the simple one-way ANOVAs.

Baseline Characteristics (Refer to Table 8 for mean values)

Total Immediate Recall

The assumption of homogeneity was violated for all variables, as assessed by Levene's Test of Homogeneity of Variance (*p* ranges = .0005 - .042). The groups were statistically significantly different on TotImm Welch's $F(2,46.02) = 101.24$, $p < .0005$. The AD group obtained an average of 23.38 $\pm$ (8.90), the preAD group an average of 33.21 $\pm$ (9.70) and the normal control group an average 49.76 $\pm$ (11.48). Games-Howell post-hoc analysis revealed that the AD group's TotImm was statistically significantly lower than the NC group (-26.38, 95% CI (-30.80 to -21.96), $p < .0005$) and the PreAD group (-9.83, 95% CI (-15.82 to -3.84), $p < .0005$) and that the PreAD group's TotImm was statistically significantly lower than the NC group (-16.55, 95% CI (-23.27 to -9.83), $p < .0005$).

Long Delay Free Recall

The groups were statistically significantly different on Long Delay Free Recall Welch's $F(2,42.50) = 129.40$, $p < .0005$. The AD group obtained an average of 1.49 $\pm$ (2.46), the preAD group an average of 4.84 $\pm$ (3.61) and the normal control group an average 10.46 $\pm$ (3.54). Games-Howell post-hoc analysis revealed that the AD group's long delay free recall scores were statistically significantly lower than the NC group (-8.97, 95% CI (-10.30 to -7.64), p <.0005) and the PreAD group (-3.35, 95% CI (-5.53 to -1.18), p <.0005) and that the PreAD group's Long Delay Free Recall was statistically significantly lower than the NC group (-5.62, 95% CI (-7.99 to -3.24), p <.0005).

Delayed Retention Rate

The groups were statistically significantly different on the delayed retention rate Welch's $F(2,48.13) = 67.54$, $p < .0005$. The AD group obtained an average of 23.67.33 $\pm$ (34.38), the preAD group an average of 53.30 $\pm$ (31.65) and the normal control group an average 84.36 $\pm$ (18.52). Games-Howell post-hoc analysis revealed that the AD group's delayed retention rate was statistically significantly lower than the NC group (-60.69, 99% CI (-73.61 to -47.77), p <.0005) and the PreAD group -29.63, 95% CI (-55.24 to -4.03), $p = .003$) and that the PreAD group's delayed retention rate was statistically significantly lower than the NC group 31.06, 99% CI(6.11 to 56.00), $p = .001$).

Serial Position Effects, Primacy

The groups were statistically significantly different on primacy, Welch's $F(2,47.51) = 16.09$, $p < .0005$. The AD group obtained an average of .21 $\pm$ (.30), the preAD group an average of .33 $\pm$ (.10) and the normal control group an average .30 $\pm$ (.05). Games-Howell post-hoc analysis revealed that the AD group's primacy scores were statistically significantly lower than the NC group (-.08, 95% CI (-12.30 to -.05), p <.0005) and the PreAd group (-.12, 95% CI (-.19 to - .06), p <.0005) and that the preAD group's primacy score was not statistically significantly different than the NC group (.04, 95% CI (-.02 to .10), $p = .28$).

Serial Position Effects, Recency

The groups were statistically significantly different on recency, Welch's $F(2,46.43) = 49.09$, $p < .0005$. The AD group obtained an average of .49 $\pm$ (.19), the preAD group an average of .33 $\pm$ (.12) and the NC group an average .28 $\pm$ (.06). Games-Howell post-hoc analysis revealed that the AD group's recency scores were statistically significantly higher than the NC group (.21, 95% CI (.16 to.25), p <.0005) and the PreAd group (.16, 95% CI (.07 to .24), p <.0005) and that the PreAD group's recency score was not statistically significantly higher than the NC group (.05, 95% CI (-.02 to .12), $p = .23$).

Proactive Interference

The groups were statistically significantly different on proactive Interference, Welch's $F(2,44.95) = 39.71$, $p < .0005$. The AD group obtained an average of 2.06 $\pm$ (1.99), the preAD group an average of 3.68 $\pm$ (2.29) and the normal control group an

average of .5.75 ± (2.53). Games-Howell post-hoc analysis revealed that the AD group's proactive interference scores were statistically significantly lower than the NC group (-3.69, 95% CI (-4.68 to. -2.70), p <.0005) but not the PreAD group (-1.62, 95% CI (-3.03 to -.22), p =.02) and that the PreAD group's proactive interference score was statistically significantly lower than the NC group (-2.07, 95% CI (-3.63 to -.50), p = .007).

Semantic Clustering

The groups were statistically significantly different on semantic clustering, Welch's $F(2,42.17) = 38.02$, $p < .0005$. The AD group obtained an average of 1.07 ± (.60), the preAD group an average of 1.40 ± (.94) and the normal control group an average of 2.31 ± (.91). Games-Howell post-hoc analysis revealed that the AD group's semantic clustering scores were statistically significantly lower than the NC group (-1.25, 95% CI (-1.59 to. -.91), p <.0005) but not the PreAD group (-.33, 95% CI (-.90 to .23), p =.32) and that the PreAD group's semantic clustering score was statistically significantly lower than the NC group (-.92, 95% CI (-1.53 to -.30), p = .003).

Total Intrusion Errors

The groups were statistically significantly different on total intrusion errors, Welch's $F(2,45.62) = 24.62$, $p < .0005$. The AD group obtained an average of 20.10 ± (21.44), the preAD group an average of 12.05 ± (10.27) and the normal control group an average of 5.25 ± 4.08). Games-Howell post-hoc analysis revealed that the

AD group's total intrusion errors were statistically significantly higher than the NC group (14.85, 95% CI (9.55 to. 20.14), p <.0005) but not the PreAD group (8.05, 95% CI (.36 to 15.73), p =.04) and that the PreAD group's total intrusion errors was not statistically significantly higher than the NC group (6.80, 95% CI .66 to 12.95), p = .03).

Recognition Discriminability

The groups were statistically significantly different on RecogDis, Welch's $F(2,47.16) = 14.16$, $p < .0005$. The AD group obtained an average of .67 $\pm$ (.12), the preAD group an average of .81 $\pm$ (.12) and the normal control group an average of .94 $\pm$ .06). Games-Howell post-hoc analysis revealed that the AD group's recognition discriminability was statistically significantly lower than the NC group (-.27, 95% CI (-.31 to -.24), p <.0005) and the PreAD group (-.14, 95% CI (-.21to -.08), p =.0005) and that the PreAD group's semantic clustering score was statistically significantly lower than the NC group (-.13, 95% CI (-.20 to -.06), $p < .0005$).

Table 8. Table of Means
One-Way ANOVA at first CVLT Administration

Recall Indices	AD M (SD), n	preAD M (SD), n	NC M (SD), n	OneWay ANOVA F value ($\eta^{2)}$	AD vs. NC *p*, *d*	preAD vs. NC *p*, *d*	AD vs. preAD *p*, *d*
Total Immediate Recall (Trials 1-5)	23.38 (8.90), 100	33.21 (9.70), 19	49.76 (11.48), 50	101.24*** (.59)	.0005, 2.57	.0005, 1.56	.0005, 1.06
Long Delay Free Recall	1.49 (2.46), 100	4.84 (3.61), 19	10.46 (3.54), 50	129.40*** (.65)	.0005, 2.94	.0005, 1.57	.0005, 1.08
Delayed Retention Rate (LDF/Trial 5)	76.33 (34.38), 97	46.70 (31.65), 19	15.64 (18.52), 50	67.54*** (.45)	.0005, 2.20	.001, 1.20	.003, 90
SPE: Primacy	.21 (.30), 98	.33 (.10), 19	.30 (.05), 50	16.09 *** (.14)	.0005, .42	.0005, .38	.28, .54
SPE: Recency	.49 (.19), 98	.33 (.12), 19	.28 (.06), 50	49.09 *** (.28)	.0005, 1.49	.23, .53	.0005, -1.01
Proactive Interference (A-B)	2.06 (1.99), 100	3.68 (2.29), 19	5.75 (2.53), 48	39.71*** (.36)	.0005, 1.62	.007, .86	.02, .76
Semantic Clustering	1.07 (.60), 93	1.40 (.94), 19	2.31 (.91), 50	38.02*** (.36)	.0005, 1.61	.03, .98	.32, .42
Total Intrusions	20.10 (21.44), 100	12.05 (10.27), 19	5.25 (4.18), 50	24.62*** (.13)	.0005, .96	.03, .87	.04, .48
Recognition Discriminability	.67 (.12), 98	.81 (.12), 19	.94 (.06), 50	14.16*** (.56)	.0005, 2.85	.0005, 1.37	.0005, 1.17

Welch's F used for Oneway ANOVA
Games-Howell statistics were used for pairwise comparisons
*** $P < .0005$

Repeated Measures Effects (Means and standard deviations are presented in Table 9)

The mixed ANOVA for the effect of time on the *serial position effect of primacy* revealed that the data were not normally distributed by examination of the Shapiro-Wilk test for the patient groups on years two and three. Both the AD and preAD group's data were positively skewed. The assumption of homogeneity of covariance, as assessed by Box's test of equality of covariance matrices was violated (p=.0005). Mauchly's test of sphericity indicated that the assumption of sphericty was not violated χ^2 (2) = 4.63, p = .10.

The time by group interaction effect was nonsignificant. $F(4,296) = 0.26$, p = .90, η^2 =.003. The main effect of time did not show statistically significant differences in primacy across three consecutive years of CVLT test administration $F(2,296)$ = 2.07, p = .13, partial η^2 =.01. The between subjects effect of group, however, showed that there was a statistically significant difference in primacy scores between patient groups $F(2,148) = 15.98$, $p < .0005$, partial $\eta^2 = .18$, with the AD group obtaining an average of .29 (SE = .01), the preAD group an average of .31 (SE = .02) and the normal control group .28 (SE = .04).

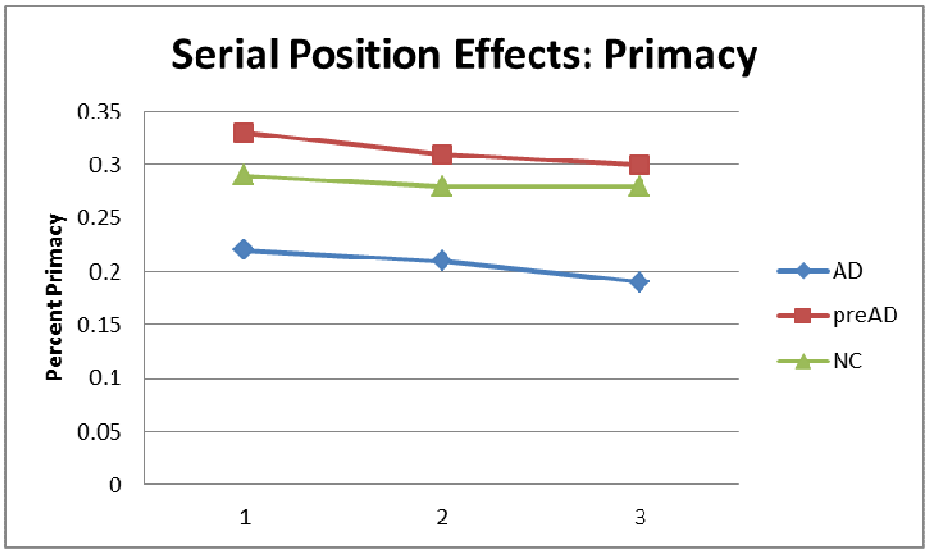

Figure 1: Mean primacy effects over time

For the mixed ANOVA using *serial position effect of recency* as the dependent measure, the data were normally distributed as assessed by the use of the Shapiro-Wilk test for the patient groups on across all years with the exception of year 2 for the normal controls. The assumption of homogeneity of covariance, as assessed by Box's test of equality of covariance matrices was violated (p=.0005). Mauchly's test of sphericity indicated that the assumption of sphericty was not violated χ^2 (2) = .14, p = .93.

The time by group interaction effect was not statistically significant. $F(4,288) = 1.95$, $p = .10$, $\eta^2 = .03$. The main effect of time showed a statistically significant difference in *recency effects* across the three test administrations $F(2,288) = 8.03$, $p = .0005$, partial $\eta^2 = .05$. The main effect of group indicated significant differences in recency scores between patient groups $F(2.144) = 44.19$, $p < .0005$, $\eta^2 = .38$ With the AD group obtaining an average of .52 (SE = .02), the preAD group an average of .36

(SE = .05), and the NC group .30 (SE = .02). Given the overall main effects of time, individual repeated measures were performed for each group. The results revealed that the AD group performed worse in year 3 relative to years 1 and 2, the difference between year's 2 and 3 approached significance (p = .03) , but no differences were found between years 1 and 2, F(2,172) = 9.57, p = .0005, partial η^2 =.10. Post hoc analysis indicated that there was an in increase in the *recency effect* from year 1 (M = .48, SD = .18) to year 3 (M = .57, SD = .20), a statistically significant mean increase of .09, .99% CI [.03, .15], p < .0005. Similar but non-significant result were found between years 2 (M = .52, SD = .21) and 3 (p = .03). The preAD group had a similar pattern to the AD group, in that their performance was worse in year 3 relative to years 1 and 2, but these findings were not statistically significant, F(2,32) = 3.77, p = .03, partial η^2 =.19.

The between subjects effect of group, however, showed that there was a statistically significant difference in *recency effect* scores between patient groups F(2,144) = 44.19, p < .0005, partial $\eta^{2=}$.38, with the AD group obtaining an average of .52 (SE = .01), the preAD group an average of .36 (SE = .03) and the normal control group .30 (SE = .02).

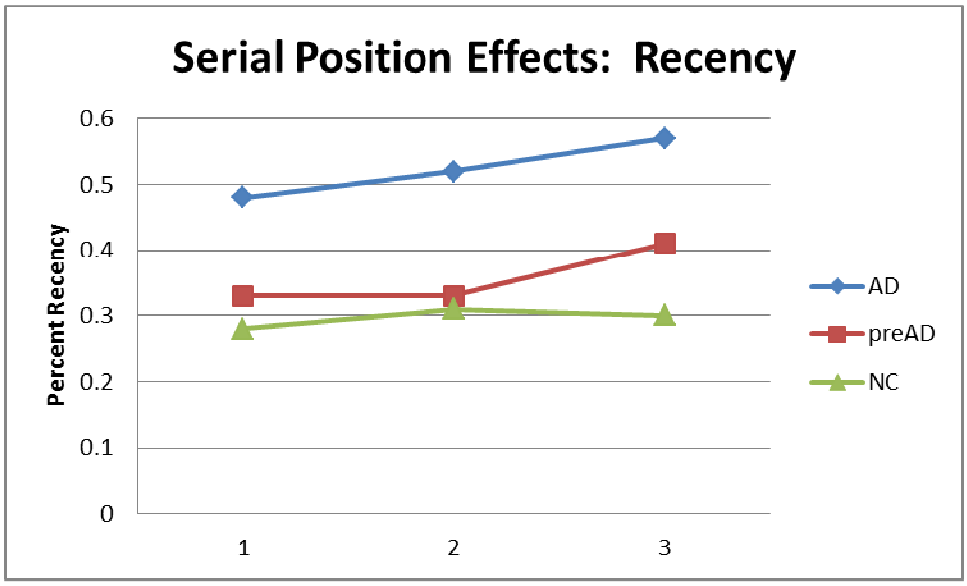

Figure 2: Mean recency effects over time

The mixed model ANOVA using *proactive interference* difference scores were normally distributed for each group, as assessed by examination of boxplots and the Shapiro-Wilk test (p>.05, respective). The assumption of homogeneity of covariance, as assessed by Box's test of equality of covariance matrices was not violated (p=.24). Mauchly's test of sphericity indicated that the assumption of sphericity had not been violated χ^2 (2) = 2.98, p = .22. Time by group interaction effects were not statistically significant, F(4,306) = .44, p = .78, partial η^2 = .01. The main effect of time did not show a statistically significant difference in proactive interference across three consecutive years of CVLT test administration F(2,306) = .36, p = .70, partial η^2 =.002. The between-subjects analysis indicated significant differences between the three groups in terms of proactive interference, F(2,153) = 68.74, p = .0005, partial η^2

= .05, with the AD group obtaining an average of 2.07 (SE = .17), the PreAD group an average of 3.67 (SE = .40), and the NC group 5.54 (SE =.24).

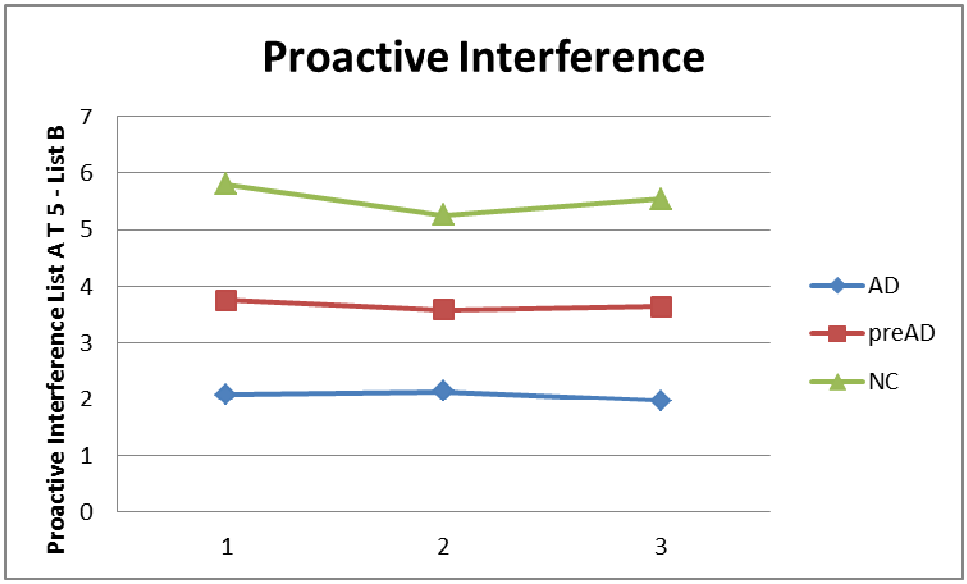

Figure 3: Mean proactive interference over time

A mixed ANOVA of *semantic clustering* revealed that the data were normally distributed for both the normal control and preAD groups as assessed by Shapiro-Wilk test; however, the data for the AD group were positively skewed for years 2 and 3. The assumption of homogeneity of covariance, as assessed by Box's test of equality of covariance matrices was not violated (p=.002). Mauchly's test of sphericity indicated that the assumption of sphericty was not violated χ^2 (2) = .45, p = .80. The time by group interaction effect was not statistically significant $F(4,256) = .89$, p = .47, η^2 =.01. The main effect of time was also not significant $F(2,256) = 1.11$, p = .33, partial η^2 =.01. The between-subjects analysis showed significant differences between the

three group in terms of semantic clustering, $F(2,128) = 62.19$, $p = .0005$, $\eta^2 = .49$ with the AD group obtaining an average of 1.63 (SE = .08), the pre AD and average of 1.65 (SE = .08) and the normal controls an average of 1.52, (SE = .08).

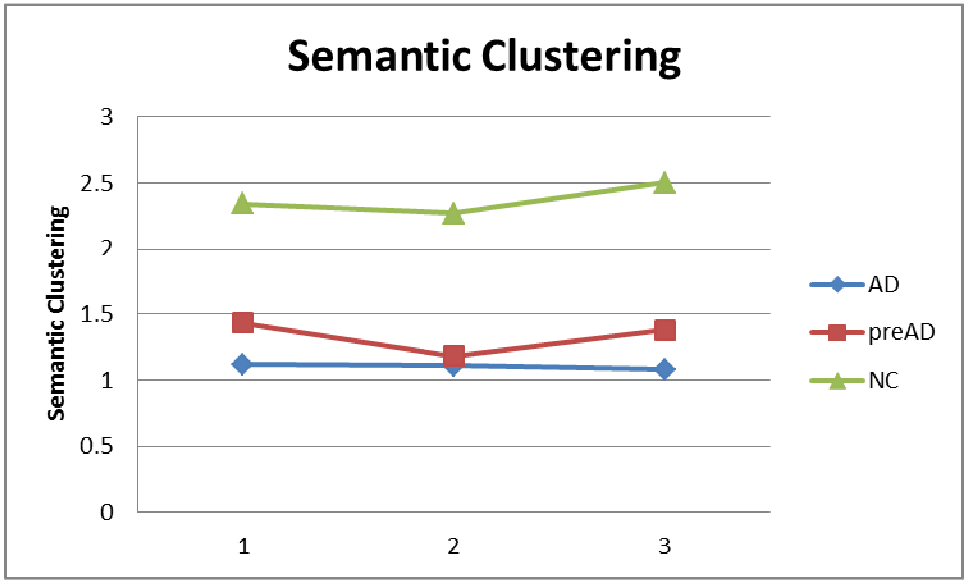

Figure 4: Mean semantic clustering over time

A 3 x 3 mixed ANOVA was conducted in order to determine the effect of time on *total intrusion errors* across all learning and recall trials. The data was not normally distributed for the AD group as examined by Shapiro-Wilk test. The PreAD's data was normally distributed for all years, while the normal controls data was normally distributed for years 1 but not years 2 or 3. The assumption of homogeneity of covariance, as assessed by Box's test of equality of covariance matrices was violated (p=.0005). Mauchly's test of sphericity indicated that the assumption of sphericty was not violated χ^2 (2) = 5.40, $p = .07$. Time by group

interaction effects were not statistically significant $F(4,298) = .45$, $p = .77$, partial $\eta^2 = .01$. The main effect of time did not show a statistically significant difference in *total intrusion errors* across the three different test points $F(2,298) = 1.07$, $p = .34$, partial $\eta^2 = .01$. The between-subjects analysis was significant for *total intrusion errors* $F(2,149) = 17.66$, $p = .0005$, partial $\eta^2 = .19$, with the Alzheimer's disease patients obtaining an average of 21.05, (SE = 1.55), the Normal controls an average of 5.31, (SE = 2.16) and the preAD group an average of, M= 13.43, (SE = 3.56).

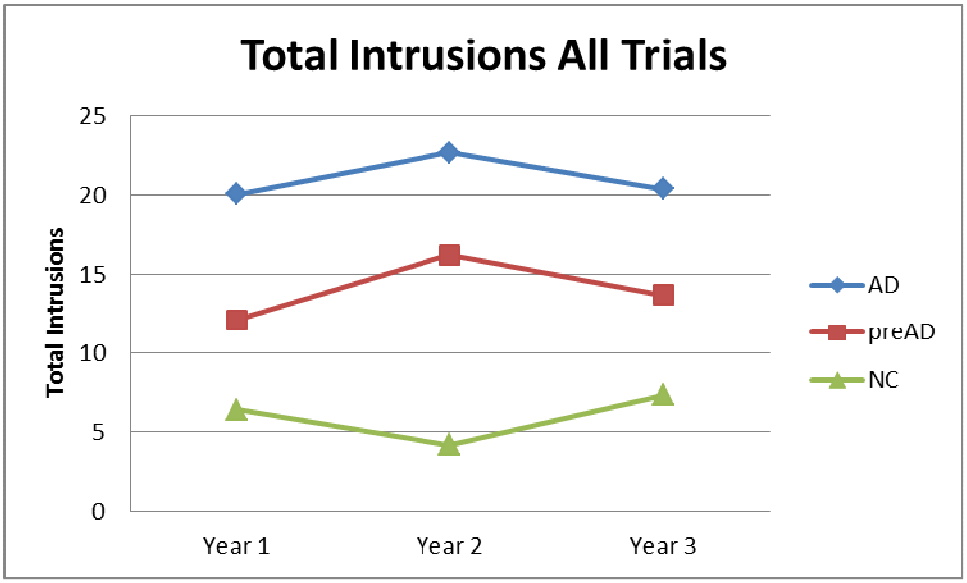

Figure 5: Mean total intrusions all trial over time

A 3 x 3 mixed ANOVA was conducted in order to determine the effect of time on *total percent category intrusion errors* across all trials. The data was not normally distributed for all the groups as examined by Shapiro-Wilk test. The assumption of homogeneity of covariance, as assessed by Box's test of equality of covariance matrices was violated (p=.0005). Mauchly's test of sphericity indicated that the

assumption of sphericty was not violated χ^2 (2) = 1.58, *p* = .45. Time by group interaction effects were not statistically significant *F*(4,260) = .40, *p* = .81, partial η^2 =.01. The main effect of time did not show a statistically significant difference in *total percent category intrusion errors* across the three different test points *F*(2,260) = 1.31, *p* = .27, partial η^2 =.01. The between-subjects analysis was not significant for *total percent category intrusion errors F*(2,130) = 3.51, *p* =.03, partial η^2 = .05 with the AD group obtaining an average of .57 (SE = .02), the preAD group an average of .48 (SE = .04), and the NC group an average of .49 (SE = .03).

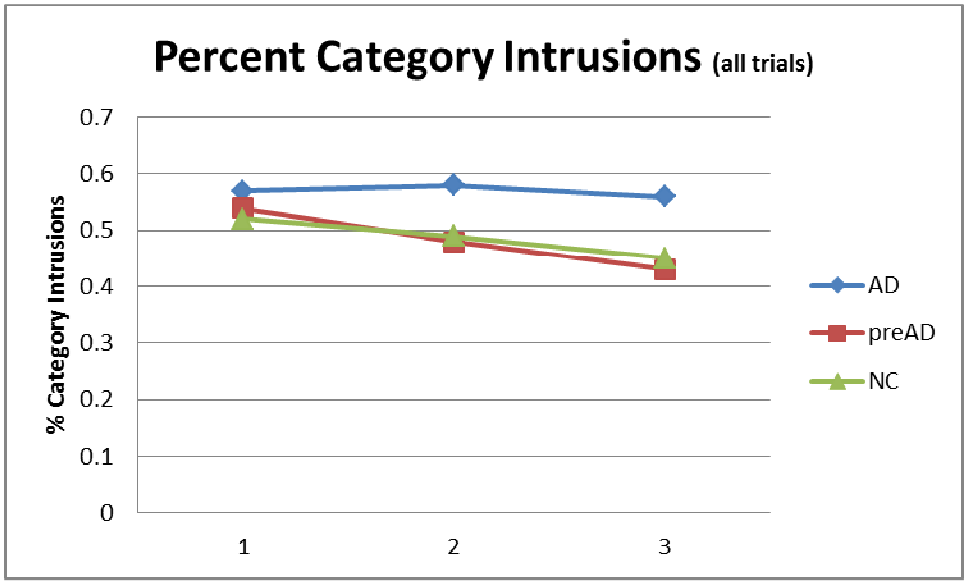

Figure 6: Mean percent category intrusions over time

Total percent noncategory intrusion errors were studied with a 3 x 3 mixed ANOVA to assess the effect of time on the percentage of noncategory intrusion errors

made on the CVLT. The assumption of homogeneity of covariance, as assessed by Box's test of equality of covariance matrices was not violated (p=.02). Mauchly's test of sphericity indicated that the assumption of sphericty was violated χ^2 (2) = 18.65, p = .005. The time by group interaction effects were not statistically significant, Greenhouse-Geisser $F(3.52, 227) = 2.37$, $p = .06$, $\eta^2 = .03$. There was no main effect of *percent noncategory intrusion errors* over time Greenhouse-Geisser $F(1.76,227) = .88$, $p = .41$, partial $\eta^2 = .01$ The between-subjects analysis indicated a statistically significant difference in *percent noncategory intrusion errors* between the subject groups $F(2,129) = 9.66$, $p = .0005$, partial $\eta^2 = .13$, with the AD group obtaining an average of .16(SE = .01), the preAD group an average of .13 (SE = .03), and the NC group and average of .06 (SE = .02).

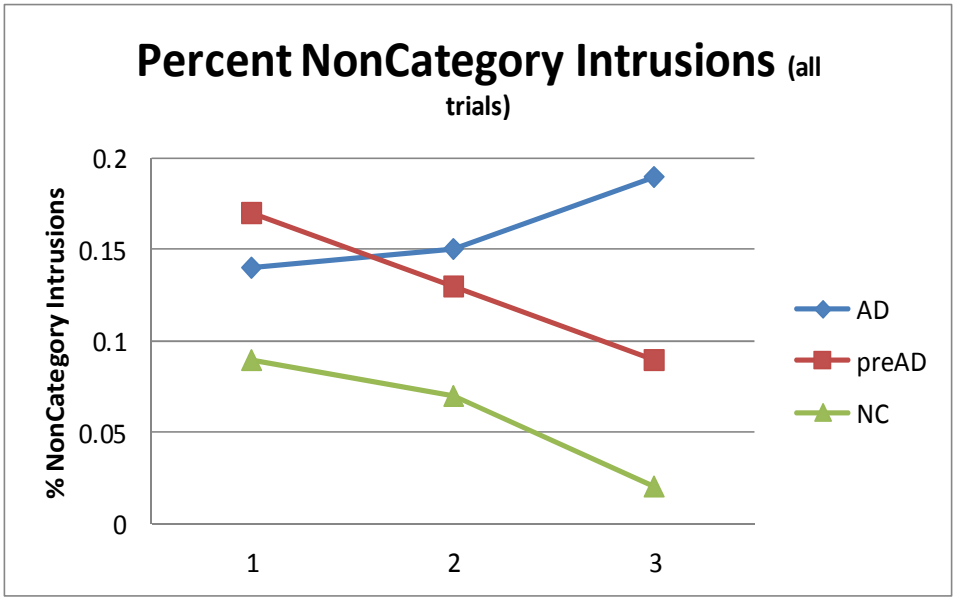

Figure 7: Mean percent category intrusions over time

A 3 x 3 mixed ANOVA was conducted in order to determine the effect of time on *recognition discriminability*. The data was normally distributed for both the AD and the preAD groups as examined by Shapiro-Wilk test; however, the data for the normal control group was not. The assumption of homogeneity of covariance, as assessed by Box's test of equality of covariance matrices was violated ($p < .0005$). Mauchly's test of sphericity indicated that the assumption of sphericty was not violated χ^2 (2) = .36, p = .83. Time by group interaction effects were not statistically significant $F(4,304)$ = 1.65, p = .16, partial η^2 =.02. There was, however, a significant main effect of time for recognition discriminability across the three different test points $F(2,304)$ = 4.78, p = .009, partial η^2 =.03. Given the overall main effects of time, individual repeated measures were performed for each group. The results revealed that the AD group performed worse in year 3 relative to years 1 and 2, but no differences were found between years 1 and 2, F(2,178) = 8.09, p < .00 5, η^2= .08. Post Hoc tests revealed that there was a decrease in recognition discriminability between year 1 (M = .67, SD = .12) to year 3 (M = .63, SD = .12), a statistically significant mean decrease of .04, 99% CI [.001, .077], p = .007. A similar pattern was found between year 2 (M = .68, SD = .12) to year 3, a statistically significant mean decrease of .05, 99% CI [.009, .085], p = .001. The repeated measures analysis for the preAD group revealed an identical pattern to the AD group, in that their performance was worse in year 3 relative to years 1 and 2, and no differences were found between years 1 and 2 but these differences were not statistically significant, F(2,32) = 1.16, p = .32, η^2= .07. The between-subjects analysis showed significant difference in recognition discriminability raw scores between the groups $F(2,128)$ = 81.11, p < .0005, partial η^2 = .56 with the AD

group obtaining an average of .16 (SE = .01), the preAD group an average of .13, (SE = .03) and the NC group and average of .06 (SE = .02).

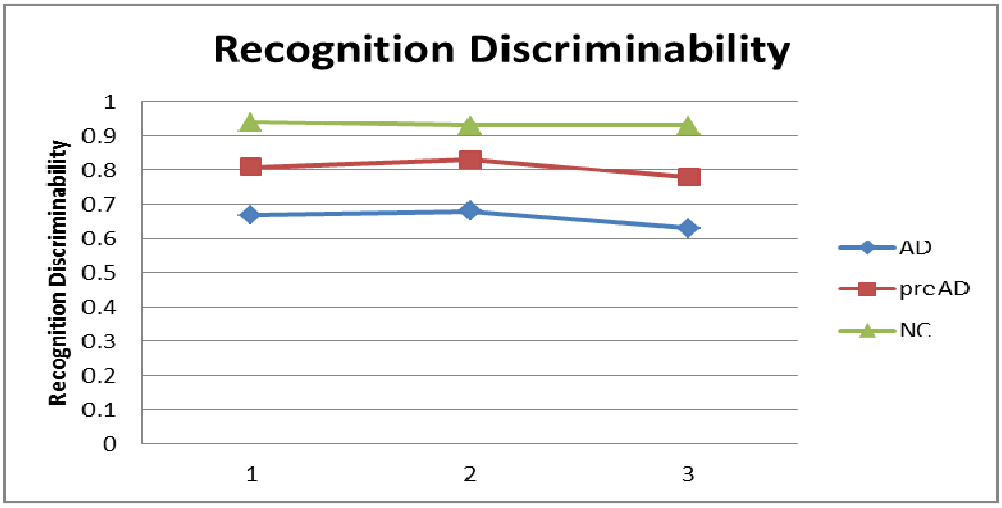

Figure 8: Means for recognition discriminability over time

Table 9. Table of Means for Mixed Model Analyses

Qualitative Variables			
	Time 1 M(SD), n	Time 2 M(SD), n	Time 3 M(SD), n
Serial Position Effects, Primacy			
AD	.22 (.14), 87	.21 (.15), 87	.19 (.14), 87
preAD	.33 (.10), 17	.31 (.13), 17	.30 (.13), 17
Normal Controls	.29 (.05), 47	.28 (.05), 47	.28 (.07), 47
Serial Position effects, Recency			
AD	.48 (.18), 87	.52 (.21), 87	.57 (.20), 87
preAD	.33 (.13), 17	.33 (.14), 17	.41 (.16), 17
Normal Controls	.28 (.05), 43	.31 (.07), 43	.30 (.07), 43
Proactive Interference (a-b)			
AD	2.09 (2.06), 93	2.15 (2.08), 93	1.98 (1.92), 93
preAD	3.76 (2.41), 17	3.59 (2.72), 17	3.65 (2.62), 17
Normal Controls	5.80 (2.55), 46	5.26 (2.35), 46	5.54 (2.70), 46
Semantic Clustering			
AD	1.12 (.58), 71	1.11 (.75), 71	1.08 (.73), 71
preAD	1.43 (.94), 17	1.18 (.74), 17	1.38 (.83), 17
Normal Controls	2.34 (.92), 43	2.27 (.96), 43	2.50 (.84), 43
Total Intrusions (All Trials)			
AD	20.07 (22.13), 89	22.70 (22.85), 89	20.38 (18.74), 89
preAD	12.12 (10.98), 16	16.25 (15.06), 16	13.69 (8.87), 16
Normal Controls	6.41 (3.83), 22	4.18 (4.24), 22	7.36 (6.47), 22
Percent Category Intrusions (All Trials)			
AD	.57 (.23), 86	.58 (.23), 86	.56 (.25), 86
preAD	.54 (.29), 15	.48(.28), 15	.43 (.34), 15
Normal Controls	.52 (.33), 32	.49 (.39), 32	.45 (.33), 32
Percent NonCategory Intrusions (All Trials)			
AD	.14 (.18), 86	.15 (.15), 86	.19 (.17), 86
preAD	.17 (.17), 15	.13 (.14), 15	.09 (.16), 15
Normal Controls	.09 (.22), 31	.07 (.14), 31	.03 (.09), 31
Recognition Discriminability			
AD	.67 (.13), 90	.68 (.12), 90	.63 (.12), 90
preAD	.81 (.12), 17	.83 (.11), 17	.78 (.14), 17
Normal Controls	.94 (.06), 48	.93 (.07), 48	.93 (.06), 48

IV Discussion

It has been well documented that an episodic memory deficit is the hallmark symptom in AD. The nature of the AD memory profile after conversion to AD has been studied extensively and has been characterized as reflecting an encoding/storage impairment that affects both recall and recognition measures. It is also well established that patients in the early to mid-stages of subcortical dementias often present with deficits in recall that are mediated by impairments in 'access to recall' or what is also called 'deficits in retrieval.' For example, on verbal list learning tasks Parkinson's disease patients and Huntington's disease patients have normal range recognition but impaired recall scores. What is not well known is the nature of the memory profile in individuals who are in a preclinical stage of AD. Do preAD individuals also display an encoding/storage memory profile, albeit to a mild degree? Or do they first pass through a stage of exhibiting a retrieval memory profile (similar to patients with subcortical disorders) before developing their hallmark encoding/storage profile? The primary aim of the current study was to investigate features of episodic verbal memory in those identified as preclinical Alzheimer's disease patients, Alzheimer's patients and normal controls.

Comparisons between the three groups at baseline supported Hypothesis One that the preAD group would perform significantly worse than the NC groups and significantly better than the AD group on traditional quantitative measures of episodic

memory. Although the AD group was significantly impaired relative to controls on all nine CVLT variables analyzed, the preAD group was only impaired relative to controls on seven of the nine CVLT variables examined (Total Immediate Recall, Long Delay Free Recall, Delayed Retention Rate, Proactive Interference, Semantic Clustering, Intrusion Errors and Recognition Discriminability). Table 7 displays a list of the group means for the initial one-way ANOVA analysis. In addition, the preAD group was impaired relative to the AD group on all qualitative measures with the exception of proactive interference, semantic clustering and total intrusions.

The results from the current study are consistent with previous research in episodic memory in patients with Alzheimer's disease patients. For instance, Delis et al., (1991; 2000) reported that severe impairments in learning, delayed recall savings scores, and a propensity to commit a high rate of intrusion errors characterized recall performance in patients with mild to moderate AD. The results of this study also supports previous research that AD patients display poor recognition discriminability and an inability to benefit from recognition testing. (Greenaway et al., 2006; Delis et al., 1991; Davis, 2002)

The current findings echo previous investigations of patients thought to be in the preclinical or prodromal stage of Alzheimer's disease who were impaired on immediate recall, delayed recall, and rapid forgetting on episodic recall tasks (Bondi et al., 1994; Mickes et al., 2007; Libon et al., 2011; Lange et al., 2002; Genon et al., 2012; Rabin et al., 2011; Chen et al., 2001; Greenaway, 2006; Smith, 1998). For

example, Bondi et al. (1994) found that normal control subjects with a positive family history of dementia compared to subjects with a negative family history were impaired on free recall. Only a few studies have examined verbal memory profiles using qualitative CVLT variables in patients diagnosed with MCI or the prodromal phase of AD (Greenaway; 2006; Libon et al., 2011; Bäckman et al, 2001). These studies have indicated that preAD and MCI patients are impaired on many qualitative features of the CVLT including serial position effects, recognition discriminability, and intrusion errors. Current results indicate that the preAD patients were impaired relative to NC's on quantitative and qualitative variables on the CVLT including immediate free recall, long delay free recall, delayed retention rate, proactive interference, semantic clustering and recognition discriminability.

Overall, the baseline analysis supporting Hypothesis One demonstrated that PreAD individuals do not first pass through a retrieval memory profile before converting to AD, but rather they generally display the classic encoding/storage profile, albeit to a milder degree, early in the disease course. The support for this assertion is best evidenced by the results obtained by the traditional quantitative CVLT measures (TotImm), LDFR, RetRat) and qualitative variables (RecogDis, Total Intrusions) between the groups at baseline. However, it should be noted that the initial baseline results did not replicate previous research findings on serial position effects where AD patients and some preclinical AD groups showed reduced primacy and increase recency effects.

It was hypothesized that those qualitative features of the CVLT indices;

primacy and recency effects, proactive interference, semantic clustering, intrusion errors, and recognition discriminability (hypotheses two through six) that characterize impairments in encoding and consolidation in AD would also be present in the preAD patients and they would decline over a three year period in a similar fashion as the AD group when compared to the normal control group. In general, findings from the longitudinal investigation did not meet the significant criterion ($p < .01$); however, there was a main effect of time for two qualitative variables, serial position recency effects and recognition discriminability. Examining the effect of time revealed that the AD group's recency effect scores increased statistically significantly over time. The preAD group recency effects scores also worsened overtime; however, the change in recency scores between times 1, 2 and 3 only approached significance ($p = .03$). As expected the normal control group's recency effect scores remained stable over time. These findings support previous research that recency effects are present in both AD and preAD groups. Longitudinal findings from the current study also indicated that the AD group's recognition discriminability scores diminished significantly over time. The preAD group showed a similar pattern but the decline of their score over time only approached significance ($p = .06$) while normal controls recognition discriminability remained stable. The longitudinal findings indicate that the AD and to some extent the preAD groups increased their reliance on recency strategy over the course of disease progression. Both groups also displayed a similar inability to benefit from recognition cues over time, while normal controls continued to benefit as would be expected. The finding from the longitudinal evaluation provide further support that at preAD stages individuals show an encoding/storage deficit as opposed to a

primary retrieval deficit.

The hypotheses (H2,3,4,5) for the longitudinal study regarding patterns of impairments of many of the qualitative variables including primacy effects, semantic clustering, proactive interference and intrusion errors were not supported in the current study. The absence of findings for the repeated measure effect of time could be related to the preAd group's small sample size and associated lack of power. It also quite possible that the AD group, who were performing close to" floor levels," influenced the study's inability to discriminate clinically significant change over time.

Although the longitudinal evaluation of qualitative variables did not find many distinctive patterns of change for the different groups, the findings *across tests* for all qualitative CVLT variables with the exception of percent Category Intrusions were remarkably consistent between the groups when compared to baseline findings but indicated additionally significant results. Hence, in addition to the longitudinal differences seen within the groups on Total Intrusions and Recognition Discriminability at baseline, significant differences between the groups *across* the three serial assessments were found on serial position effects for both primacy and recency (in the expected direction), proactive interference, semantic clustering, total intrusions and non-category intrusions.

Overall, the results demonstrated that PreAD individuals do not first pass through a retrieval memory profile before converting to AD, but rather they generally display the classic encoding/storage profile, albeit to a milder degree, early in the disease course. This conclusion was confirmed by examining baseline comparisons between groups on quantitative and qualitative variables of the CVLT.

Limitations

There are a number of limitations to the current study. These findings are most appropriately generalizable to outpatient neurological settings where patients self-refer as volunteers possibly due to concerns regarding memory or cognitive impairments but may not be generalizable to other settings. A limitation of the current study also includes the relatively small sample sizes for the normal control and preclinical groups. The smaller comparison groups coupled with a lack of homogeneity of variance for many of the analyses likely did not provide enough power to detect subtle changes over time in this cohort. Consequently, the negative findings with regard to the longitudinal data must be considered tentative until they can be replicated with a larger cohort of preclinical and clinical AD patients. The present sample of patients was primarily Caucasian and well educated, with 15 years of education in each group, and this limits the generalizability of our results to the general population.

The preclinical patient's included in this study all went on to earn a diagnosis of probable Alzheimer's disease, the duration of the disease process prior to their inclusion into the study ranged from one to six years and on average the preAD's baseline assessment occurred just 1.35 year before obtaining a non-normal diagnosis. As a result the findings from this study may better characterize AD patients just prior to diagnosis and not in a milder prodromal phase of AD when critical pharmacological treatments may be more helpful.

Future Directions

This study highlights the classic features of episodic memory impairment in AD and preAD patients. The differences seen between AD, PreAD, and NC's on many of the qualitative variables of the CVLT help to demonstrate that the pattern of impairments are a stable representation of decline at various stages of the disease process and may possibly help to identify those individuals at greater risk for developing Alzheimer's disease so that earlier interventions can be initiated. This study yields an important contribution to the study of AD patient in the preclinical phase of AD. It describes information about an area of research that remains unclear: the nature of the encoding patterns seen in the period preceding dementia in Alzheimer's disease.

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