A COMPARISON OF THE FRONTAL VARIANT OF ALZHEIMER'S DISEASE WITH TYPICAL ALZHEIMER'S DISEASE AND FRONTOTEMPORAL DEMENTIA

APPROVED BY SUPERVISORY COMMITTEE

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by

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ABSTRACT

A frontal variant of Alzheimer's Disease (FvAD) has been described in the literature in which prominent frontal lobe dysfunction accompanies typical temporal and parietal lobe dysfunction in the early stages of the illness. However, no study has investigated how executive deficits and neuropsychiatric symptoms of the FvAD subgroup differ from those

seen in frontotemporal dementias. The current proposal describes a study designed to examine neuropsychological and behavioral functioning in groups of AD, FvAD and FTD patients. It is predicted that the FvAD group will have an older age of onset and a lower ratio of males to females than the FTD group, and will perform similar to the AD group on measures of memory, language and visuospatial abilities. The FvAD group is also expected to perform similar to the FTD group on measures of executive functioning and exhibit a greater degree of behavioral symptoms than the AD group. Implications of possible outcomes of the study are then discussed.

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LIST OF ABREVIATIONS

AD	Alzheimer's disease
ADC	Clinic for Alzheimer's and Related Diseases (Alzheimer's Disease Center)
BEHAVE-AD	Behavioral Pathology in Alzheimer's Disease Rating Scale
BNT	Boston Naming Test
CDR	Clinical Dementia Rating Scale
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
FTD	Frontotemporal dementia
FvAD	Frontal variant of Alzheimer's disease
MMSE	Mini-Mental State Examination
MRI	Magnetic resonance imaging
NINCDS-ADRDA	National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association
NFT	Neurofibrillary tangles
NPI	Neuropsychiatric Inventory
PET	Positron emission tomography
SPECT	Single photon emission computerized tomography
WAIS-R	Weschler Adult Intelligence Scale-Revised
WCST	Wisconsin Card Sorting Test
WMS-R	Weschler Memory Scale-Revised

CHAPTER ONE
Introduction

The prevalence of dementing illnesses is significantly increasing as advances in medicine and improvements in nutrition have contributed to a high proportion of elderly in the population. As a result, these illnesses are receiving increased attention from researchers and practitioners. The most common cause of dementia in the elderly is Alzheimer's disease (AD), which involves deterioration of cognitive functioning with prominent impairment in memory as well as declines in other cognitive areas such as executive function and language and visuospatial abilities. The current criteria for the pathologic diagnosis of AD require the presence of both amyloid plaques and neurofibrillary tangles (NFT) in excess of the amount found in age-matched healthy controls (The National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1998; Gauthier, 1999).

Frontotemporal Dementia (FTD) is another common cause of dementia and is characterized by changes in personality as well as cognition. Symptoms of personality and behavior changes include inappropriate conduct, inertia and apathy, loss of insight, disinhibition, and perseverative behavior. These changes are often accompanied, or soon followed, by cognitive deficits in executive functions (i.e., judgment and planning), attention, language and memory processes. Visuospatial skills are typically preserved and memory impairment is less prominent in the early stages. Histopathological abnormalities for FTD include nerve cell loss, spongiform change and astrocytic gliosis (McKhann et al., 2001).

Although AD and FTD have distinct features that differentiate them, clinical differentiation is sometimes difficult due to similar symptoms exhibited in both groups of

patients (Varma et al., 1999). Furthermore, certain individuals with AD present with prominent, early executive dysfunction and have been identified as having a frontal variant of AD (Johnson, Head, Kim, Starr and Cotman, 1999; Back-Madruga et al., 2002; FvAD). These individuals demonstrate symptoms indicative of temporal and parietal lobe impairment in addition to prominent frontal lobe dysfunction, including poor judgment and impulsive behavior.

Researchers are now recognizing that AD is a heterogeneous disorder (Foster et al., 1983; Mayeux, Stern, and Spanton, 1985; Martin et al., 1986; Hof, Bouras, Constantinidis, and Morrison, 1989; Piccini et al., 1998), and have identified subgroups on the basis of discrepancies in cognitive profiles. Specifically, analyses of neurocognitive data provide evidence that subgroups of patients with AD exist who have significantly more verbal or visuospatial deficits relative to other cognitive difficulties (Foster et al., 1983; Martin et al., 1986; Becker at al., 1988; Piccini et al., 1998). These differences in verbal and visuospatial abilities have been found to be independent of dementia severity, as similar subgroups have been found to exist at all stages of dementia (Piccini et al., 1998). Literature examining a frontal variant of AD is sparse and has mainly focused on validating the existence of this subtype. As of yet, there is no research examining how individuals belonging to this subgroup differ in performance on neuropsychological testing from those with typical AD and FTD.

If differences in cognitive profiles among patients with AD represent subtypes, these subgroups may respond differently to treatment and may differ in disease progression. Therefore, treatment and research designs examining these subgroups may need to be

developed. Yet before this can occur, differences in overall cognitive abilities and neuropsychiatric symptoms between FvAD, AD and FTD need to be further investigated.

The current study proposes to examine the demographic variables, neuropsychological results and severity of behavioral symptoms of individuals considered to have FvAD, AD, and FTD. This study was undertaken in an effort to identify clinical characteristics of the frontal variant of AD (FvAD) in order to better distinguish it from classical AD and FTD.

CHAPTER TWO
Review of the Literature

Alzheimer's Disease

The aging of the population is one of the most profound changes affecting contemporary society. The proportion of older people in the population has grown dramatically, and with it, the number of age-related illnesses, such as Alzheimer's disease (AD). AD is a progressive neurodegenerative disorder that results in cognitive decline, behavioral symptoms, and impairment in overall functioning. Approximately 4.5 million Americans have AD, 50% of whom are aged 85 years and above, and it is estimated that by 2050, 11.3 to 16 million Americans will have the disease (About Alzheimer's, 2003). As this population grows, so does the need for treatment from health professionals.

AD usually occurs in late life with an onset most often after age 65 (Gauthier, 1999). The average age of onset has been found to be 73.5 years (Levy, Miller, Cummings, Fairbanks, & Craig, 1996) and women are reported to have higher rates of the disease than men (Gao, Hendrie, Hall, and Hui, 1998). Clinical criteria for the diagnosis of AD include insidious onset, progressive impairment of memory, deficits in two or more areas of cognition (e.g., language, praxis, attention, abstraction, and judgment), altered patterns of behavior, and impaired activities of daily living (McKhann et al., 1984). The temporal and parietal lobes are the brain regions most affected by the disease, with distinct abnormalities in these areas often evident during life on single-photon emission computerized tomography (SPECT; Neary et al., 1987; Duara et al., 1991) and at postmortem examination (Gauthier, 1999).

Memory impairment is usually the most prominent early symptom, along with word finding difficulties and visuospatial problems. As the disease progresses, there is a decrease in both verbal and visual memory. Executive aspects of cognition, such as planning and judgment, are also affected early in the disease and become more impaired in the later stages. Also evident is withdrawal from social situations, a worsening of language skills, problems with abstraction and sometimes psychosis. This cognitive decline eventually leads to a loss of functional independence, resulting in the inability to manage finances and perform household chores. During the later stages of the disease, slower motor function and behavioral problems, such as wandering or agitation, may occur. Eventually, patients may become incontinent, and lack comprehensible speech (Gauthier, 1999).

Although AD can be diagnosed clinically with nearly 90% confidence during life (Morris, McKeel, Fulling, Torack, & Berg, 1988), a diagnosis of definite AD requires histopathological confirmation based on abundant amyloid plaques and neurofibrillary tangles (NFT) in the neocortex (Khachaturian, 1985). Amyloid plaques are thought to result from an excess of beta amyloid protein within the brain. This protein self-aggregates to form the plaques of AD in the interstitial portion of the neocortex. Tangles are intraneuronal inclusions comprised of hyperphosphorylated tau protein. They are not, however, specific to AD and are found in other neurodegenerative disorders (e.g., progressive supranuclear palsy and corticobasal degeneration). The cognitive impairment in AD is probably related to decreased synapses and neuronal loss (The National Institute on Aging and Reagan Institute Working Group on Diagnostic Criteria for the Neuropathological Assessment of Alzheimer's Disease, 1998; Gauthier, 1999).

Executive Dysfunction in AD

Memory deficits are generally considered the distinguishing hallmark of early AD, but there is no consensus regarding the sequence of cognitive deficits that follow this impairment during the progression of the disease (Lafleche & Albert, 1995). Recent studies suggest that deficits in executive function may also occur early in the course of AD. Executive functioning refers to the capacity to plan and carry out complex behaviors and includes the ability to plan, organize, and sequence (Stuss & Benson, 1986).

In a longitudinal positron emission tomography (PET) study of eleven very mildly impaired AD patients, Grady et al. (1988) administered a battery of tests designed to measure executive function (i.e., Trail Making Part B, Porteus Maze test, Raven Progressive Matrices, and Stroop Interference test). Tests of memory, language and visuospatial function were also administered. At initial evaluation, four of the eleven patients exhibited impairments in both memory and executive function early in the course of the disease, whereas in the other seven patients, normal executive function was observed when a memory deficit was clearly evident. Longitudinal analysis revealed that a total of seven patients developed deficits in executive function prior to the onset of language and visuospatial deficits. For this subgroup of patients, significant frontal in addition to temporal abnormalities were evident on PET scans. These were followed by the development of persistent parietal abnormalities consistent with impairment in language and visuoconstruction. These results suggest that there is a selective loss of cognitive function for some patients in the early stages of AD, beginning with memory impairment, followed by deficits in executive function and then by deficits in language and visuoconstruction.

Other studies have also shown executive dysfunction in patients with early AD, supporting possible involvement of the frontal lobe in the early stages of the disease (Binetti et al., 1996). Twenty-five patients diagnosed with AD, identified as having mild or questionable dementia based on the Clinical Dementia Rating Scale (CDR = 1 or .5; Berg, 1988), and twenty-five normal elderly subjects were administered a group of tests assessing executive function, memory, language and visuospatial abilities. Executive function was evaluated with the Wisconsin Card Sorting Test (WCST), PFL verbal fluency test, Stroop test, and the release from proactive interference test. Executive dysfunction was defined as performance one standard deviation below the mean for controls on at least two of the four measures. Using this definition, seven AD patients were considered to show executive dysfunction (AD+) and 18 were not (AD-). Binetti et al. then examined these two AD subgroups for differences in demographic features and other cognitive functions. Statistical analysis revealed no significant differences between the subgroups in age, education or duration of illness. Comparisons of neuropsychological profiles also revealed no significant cognitive differences between the AD+ and AD- groups. These findings suggest that executive dysfunction, as defined in this study, is not always related to severity or duration of illness nor associated with a different pattern of impairment in other cognitive domains, thus indicating it may be an additional feature of early AD.

In a similar study, Swanberg, Tractenberg, Mohs, Thal and Cummings (2004) evaluated the performance of 137 AD subjects with mild to moderate dementia and 64 normal control subjects on two tests of executive functioning (letter cancellation and maze completion), a test of overall cognitive status (Mini Mental State Exam; MMSE; Folstein,

Folstein, & McHugh, 1975), and two tests of functional impairment (CDR and Alzheimer's Disease Cooperative Study Activities of Daily Living Inventory). Executive dysfunction (EDF) was deemed to be present in AD subjects if scores were more than 1.5 standard deviations below the mean obtained by the normal controls. Based on letter cancellation scores, 6% of normal controls and 64% of AD patients were classified as having EDF. Based on maze completion times, 2% of normal controls and 58% of AD patients were classified as having EDF. In addition, AD patients identified as having EDF had more severe dementia (based on CDR), lower MMSE scores, and poorer activities of daily living scores than AD patients without EDF. These results support the presence of executive dysfunction as a feature of AD that may be associated with a worse overall cognitive and functional status. However, this study did not specifically look at executive function in the early versus moderate stage of disease to compare prevalence of executive deficits by disease severity.

Many other studies support the existence of frontal lobe dysfunction in mild AD (Pillon, Dubois, Lhermitte, & Agid, 1986; Bhutani, Montaldi, Brooks, & McCulloch, 1992; Lafleche & Albert, 1995; Collette, Van der Linden, & Salmon, 1999; Sgaramella et al., 2001), yet its presence appears to be variable. However, when executive impairment is evident in the early stage of AD, it is less prominent than the memory disorder and tends to become more pronounced as the disease progresses (Duke & Kaszniak, 2000).

Behavioral Features of AD

In addition to declines in memory, language, visuospatial ability, abstraction and language skills, individuals with AD may exhibit behavioral disturbances as the disease

progresses. A variety of behaviors have been found to be associated with dementing illnesses, yet there are certain behavioral symptoms that are more common of AD.

Mendez, Perryman, Miller, and Cummings (1998) assessed behavioral symptoms in 29 AD patients as reported by caregivers on the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). The most common behavioral disturbance reported was activity disturbance (i.e., wandering), followed by aggressiveness (i.e., verbal outbursts, physical threats and/or violence, agitation), diurnal rhythm disturbances, affective disturbance (i.e., tearfulness, depressed mood and anxiety), and delusions.

In another study assessing characteristics of behavioral disturbances in subjects with AD, apathy was found to be the most common abnormality recorded by caregivers on the Neuropsychiatric Inventory (NPI; Cummings, 1997). Agitation was the second most common disturbance, followed by anxiety, irritability, dysphoria and aberrant motor behavior, disinhibition, delusions, hallucinations, and euphoria. Five of these abnormalities were found to increase with dementia severity: agitation, dysphoria, anxiety, apathy, and aberrant motor behavior, suggesting behavioral disturbances in AD worsen as the disease progresses.

Heterogeneity of AD

Although a common pattern of cognitive decline tends to be characteristic of AD, the disease can be heterogeneous in its presentation and course. Most researchers acknowledge that heterogeneity exists in the presentation of AD; however, many assert that differences observed in cognitive, emotional or functional profiles of AD patients are directly related to progression of the disease, therefore proposing that AD follows a stage model of decline

(Ritchie & Touchon, 1992). This theory assumes a homogeneous pattern of global decline, with stages differentiated by symptom severity, and rejects the notion of effects of individual differences in premorbid functioning. Thus, differences between individuals at time of testing are viewed as a direct consequence of differences in disease duration. For example, Constantinidis (1978) outlined four stages of deterioration characterized by progressive and simultaneous worsening of aphasic, apraxic, and agnostic symptomatology. Memory impairment, a universal feature of AD, is not included as a differentiating characteristic. Other models propose stages based primarily on deterioration of memory (Reisberg, Ferris, & Crook, 1982), in addition to orientation and social skills (Hughs, Berg, Danziger, Coben, & Martin ,1982).

Although evidence exists that individuals with AD exhibit similarities in their overall presentation of functioning, research demonstrates that the clinical course of the disease is heterogeneous. For example, Mayeux, Stern, and Spanton (1985) examined motor functioning in AD by reviewing records of 121 patients with AD and found that the presence of extrapyramidal signs and myoclonus indicated differing courses of illness. They found that the extrapyramidal group tended to be more severely impaired on brief cognitive testing and was more likely to show signs of psychosis, while the myoclonus group was characterized by an earlier age of onset and more rapid intellectual deterioration. These results must be interpreted with caution, however, due to the lack of pathological confirmation of AD in these patients.

Analysis of patterns of performance across neuropsychological measures has also been used to identify subgroups of AD patients. Becker et al. (1988) identified two distinct

subgroups of AD patients with focal deficits based on neuropsychological patterns at testing. Those who exhibited predominant impairment on verbal tests were classified into a verbal subgroup and those who exhibited predominant impairment on visuospatial tasks were classified into a visual subgroup. Piccini et al. (1998) also identified verbal and visual subgroups on neuropsychological testing and further established the consistency of these different cognitive profiles throughout all stages of the disease process. In addition, focal cognitive deficits in AD have been shown to correspond with lesions in specific cortical regions as identified on positron emission tomography (PET) (Foster et al., 1983). Patients with disproportionate deficits in language function had markedly reduced glucose metabolism in the left frontal, temporal and parietal regions. In contrast, patients with disproportionate constructional dyspraxia were observed to have reduced metabolism in the right temporal and parietal lobes.

In another study supporting the existence of cognitive heterogeneity, Martin et al. (1986) also identified subgroups of AD patients based on performance on tests of visuoconstructional abilities and semantic memory. Forty-two patients who met NINCDS-ADRDA criteria for AD and 21 normal controls were administered the Mattis Dementia Rating Scale (MDRS), WAIS, and Weschler Memory Scale, Form 1 (WMS). Posthoc comparisons revealed a group of patients who exhibited mild, moderate and severe global impairment without any discrepancy between verbal and visual-perceptual skills, a visual-perceptually but not verbally impaired group, and a verbally but not visual-perceptually impaired group. No differences were found between the visual-perceptually impaired and verbally impaired groups with regard to age at onset or duration of symptoms, suggesting

that the distinct groupings were separate from overall cognitive impairment. Martin et al. then examined differences in glucose metabolism among the three subgroups and controls using PET imaging. All AD patients exhibited a significant overall reduction of metabolic rate in comparison to normal controls [$F(1,24)=35.8$; $p<.001$]. Specifically, each subgroup with differing severity levels of global impairment showed significantly lower metabolic rates in the temporal and parietal regions relative to the frontal lobes ($p<.001$). In contrast, the visual-perceptually impaired and verbally impaired subgroups demonstrated patterns of glucose utilization consistent with their cognitive profiles. Specifically, the verbally impaired group showed lower metabolic rates in the left temporal region ($p<.001$) than the visual-perceptually impaired group, and the visual-perceptually impaired group showed greater reduction of glucose utilization in the right temporal and parietal regions ($p<.001$) than the verbally impaired group. These results further support the existence of distinct patient subgroups characterized by specific cognitive profiles with corresponding patterns of cerebral hypometabolism.

In another study, Hof, Bouras, Constantinidis, and Morrison (1989) reported evidence of a visuospatial variant of AD associated with increased NFTs in the inferioparietal and occipitoparietal regions of the brain, suggesting that subtypes of AD exist with differential distribution of pathology and corresponding symptomatology. The degree of NFT pathology in AD has also been associated with severity of dementia (Arriagada, Growdon, Hedley-Whyte, & Hyman, 1992; Gomez-Isla et al., 1996; Bobinski et al., 1997), which suggests that localized regions of increased NFT load may be associated with pronounced deficits in corresponding cognitive domains.

Evidence for a Frontal Variant of AD

Individuals with AD who present with a typical neuropsychological profile (i.e., deficits in memory, language, abstraction, and visual construction) yet exhibit pronounced executive dysfunction have been identified as having a frontal variant of AD (FvAD). This subgroup has been distinguished by disproportionately severe impairments on tests of frontal lobe functioning early in the course of the disease (Johnson, Head, Kim, Starr & Cotman, 1999). Individuals in this subgroup have also been found to demonstrate specific pathological features at autopsy.

Johnson, Head, Kim, Starr and Cotman (1999) reviewed 63 pathologically confirmed AD cases and found that 19 (30%) had a greater degree of NFT pathology in the frontal than entorhinal cortex. Based on this finding, the pathological and neuropsychological profiles of a subset of patients were examined. Neuropsychological testing included the Trail Making Test Part A, FAS verbal fluency, Word List Task, 30-item Boston Naming Test, animal fluency, Wechsler Adult Intelligence Scale-Revised (WAIS-R) Vocabulary and Block Design subtests, and the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Constructional Praxis. From the 63 AD patients, 16 were selected who had complete clinical assessments during the mild stage of dementia (MMSE $\geq$ 18). Review of neuropsychological profiles revealed a subset of 3 patients with disproportionately severe impairments on 2 tests of executive function (i.e., Trail Making Test A and FAS fluency) considered to be a frontal AD group. This subgroup was then compared to a second group of 3 patients with "typical" AD who were matched for MMSE score, educational level, and extent of NFT pathology in the entorhinal cortex. When compared to the typical AD group,

scores for the Trail Making Test Part A ($p = .002$) and FAS word fluency ($p = .02$) were significantly worse in the frontal AD group. A significant group difference was also found on the WAIS-R Block Design ($p = .01$), however, no significant group differences were found on any other tests. Neuropathological analysis of both groups revealed that the frontal AD group had a significantly higher NFT load ($p<.001$) in the frontal cortex than the typical AD patients, despite similar entorhinal NFT loads. In addition, there were no significant group differences in the degree of NFT pathology in the parietal or temporal regions. These results suggest that although patients in the early stages of AD often exhibit impairments in executive functioning, there is evidence for a frontal variant subgroup that presents with greater impairment in this domain with an otherwise typical AD profile. Furthermore, this frontal impairment was associated with a high degree of frontal tangle pathology at autopsy, suggesting the possible existence of a frontal variant of AD that has both distinctive clinical and pathological features. These results should be interpreted cautiously, however, as a very small sample size was used for these analyses.

Back-Madruga et al. (2002) examined functional disability, neuropsychiatric symptoms and caregiver burden in mild AD subjects (MMSE ≥ 20) with significant executive dysfunction to AD subjects with less executive deficits. Twenty subjects who met NINCDS-ADRDA criteria for AD and criteria for an executive variant of AD (EAD) were selected to be studied. Subjects were classified as EAD if they demonstrated impairment (scores falling at least 1.5 standard deviations below normative age and/or educational means) on at least three out of four executive functional measures (Trail Making Test Part B, FAS fluency, Stroop Test Part C, and WAIS-R Similarities). The EAD subjects were

matched to ten typical AD subjects with similar MMSE scores, age, education, and gender, and who did not exhibit executive impairment as defined above. Subjects were administered a comprehensive neuropsychological battery consisting of the WAIS-R, Stroop Test, Trail Making Test Part B, Boston Naming Test (BNT), Rey-Osterrieth Complex Figure, Logical Memory and Visual Reproduction subtests of the Weschler Memory Scale-Revised (WMS-R), and FAS. Neuropsychiatric features were assessed using the NPI. Impairment in activities of daily living was assessed using the Instrumental Activities of Daily Living (IADL) and caregiver burden was measured using the Domain of Caregiver Appraisal (DCA). Statistical analysis revealed no significant group differences in duration of illness or age of onset. Comparisons of the two groups on executive tests revealed significant group differences for three out of four executive measures (Trails B, [$t(13)=-2.42$, $p=.03$]; FAS [$t(18)=2.39$, $p=.03$]; and Stroop C, [$t(17)=-2.09$, $p=.05$]) with the EAD group performing more poorly. The groups, however, did not significantly differ on any of the other cognitive tests. Statistical analysis of the NPI revealed that the EAD group was associated with a greater frequency and severity of symptoms than found in typical AD. Analysis also indicated a significant group difference for agitation, with the EAD group scoring higher on this subscale. Trends were observed for greater disinhibition and eating abnormalities in the EAD group. Significant group differences were also found for the IADL and DCA, with more functional disability and caregiver burden documented in the EAD group. This study is one of the few examining the cognitive and behavioral profile of this subgroup as compared to those of typical AD. Although the results support the possible existence of a frontal variant of AD, the study lacks neuroimaging and pathological confirmation of this subgroup. In

addition, there is much circularity in that the measures used to classify EAD were used for analysis, therefore potentially contributing to significant group differences. Further research needs to be conducted to identify distinct features of FvAD as compared to AD as well as FTD for the purposes of accurate differential diagnosis.

Frontotemporal Dementia

Frontotemporal dementia (FTD) is a type of dementia that involves primary degeneration in the frontal and anterior temporal regions of the brain. The clinical profile of FTD may appear similar to that of AD due to overlap of symptomatology, and misdiagnosis often occurs (Litvan et al., 1997; Varma et al., 1999; Rosen et al., 2002). However, FTD has many distinct cognitive and behavioral features.

In 1994, the Lund and Manchester Groups (Brun et al.) established clinical diagnostic criteria for FTD, which were revised in 1998 (Neary et al.) and again in 2001 (McKhann et al.). The characteristic features include a profound alteration in personality and social conduct marked by disinhibition, emotional blunting, mental rigidity, and a decline in personal hygiene. Behavioral disturbances, such as disinhibition of impulses, inappropriate jocularity, and overeating, are also present early in the course of the disease and may become stereotyped or perseverative.

Unlike the onset of AD, individuals with FTD begin to exhibit symptoms earlier in life, between the ages of 35 and 75 years (McKhann et al., 2001). The mean age of onset has been found to be 65 years (Levy, Miller, Cummings, Fairbanks, & Craig, 1996) with the disease affecting more men than women (Ratnavalli, Brayne, Dawson, & Hodges, 2002). Problems in cognition typically begin with deficits in executive functions, including

difficulty with abstraction, cognitive flexibility, and mental set-shifting. Progressive language dysfunction can also occur with a stereotypy of speech, echolalia, perseveration, or a reduction in speech that may eventually lead to mutism. Visuospatial skills are typically preserved during the mild and moderate stages. Memory impairment is less prominent in the early stages of the illness than in AD, although memory problems tend to be present and worsen as the disease progresses. Furthermore, FTD may also be associated with symptoms indicative of motor neuron disease, including weakness and muscle wasting. Symptoms of parkinsonism, such as rigidity, may also be observed (McKhann et al., 2001).

Brain pathology in FTD is characterized by significant atrophy of the frontal and anterior temporal regions with relative sparing of the post-central areas (McKhann et al., 2001). Neuroimaging, such as SPECT, can reflect this selective degeneration and provide helpful information for differential diagnosis (Neary, Snowden, Northern, & Goulding, 1988; Miller et al., 1991; Mendez, Selwood, Mastri, & Frey, 1993; Neary et al., 1998). Histopathological abnormalities in FTD are highly variable, but include nerve cell loss and spongiform change in addition to astrocytic gliosis in the outer cortical layers (Brun et al., 1994).

Executive Dysfunction in FTD

The most common neuropsychological feature of FTD is impairment within the domain of executive functioning. Areas of attention, abstraction, planning and problem solving begin to deteriorate early in the disease process and tend to be more impaired than memory and constructional skills on neuropsychological testing. The following studies

provide evidence that patients with FTD demonstrate marked executive dysfunction in addition to memory impairment on neuropsychological testing.

Walker, Meares, Sachdev, and Brodaty (2005) examined neuropsychological test data on 11 patients who met Lund and Manchester criteria for FTD and 29 patients who met NINCDS-ADRDA criteria for AD in the mild stages of dementia (CDR ≤ 1). Twenty-seven healthy controls were also included in the analyses. Neuropsychological tests demonstrated sensitivity to subtle cognitive deficits in early-stage dementia were selected and included Mental Control and Digit Span subtest from the Weschler Memory Scale-Revised (WMS-R), Arithmetic subtest of Weschler Adult Intelligence Scale (WAIS-R), Digit Symbol subtest from the WAIS-R, Trail Making Test Part A, Logical Memory I and II subtests from the WMS-R, Visual Reproduction I and II subtests from the WMS-R, Rey Auditory Verbal Learning Test (RAVLT), Complex Figure Test, Controlled Oral Word Association Test, animal words, Similarities subtest from the WAIS-R, categories Wisconsin Card Sorting Test 2 (WCST), and Block Design from the WAIS-R. Raw test scores were converted to age-corrected scaled scores using appropriate normative data to control for age. Comparisons of the FTD and control groups showed that the FTD group performed more poorly on attention, psychomotor speed, memory acquisition, memory recall and executive function. In comparing the dementia groups, two significant differences were found. The FTD group performed more poorly than the AD group on measures of executive function but better on memory recall. The power of the neuropsychological indices to predict group membership was then calculated using a multinomial logistic regression model. Likelihood ratio tests were significant for memory recall ($p<.001$) and executive function ($p<.05$), with no other

indices reaching significance. The classification model correctly predicted group membership in 90% of the total sample, but only 64% of the FTD group. In contrast, 93% (27/29) of the AD group and 96% (26/27) of the control group were correctly classified. Although FTD was classified at a lower rate according to this model, the findings support a distinctive profile of cognitive functioning, with marked executive impairment and more preserved memory in mild FTD relative to that of mild AD.

Perry and Hodges (2000) administered four tests of attention and executive dysfunction (Map Search and Elevator Counting with Distraction subtests of the Test of Everyday Attention (TEA), Stroop Test, WCST, and Della Sala dual task) as part of a larger battery of tests to 10 FTD patients, 10 AD patients and 10 normal controls. The FTD subjects performed worse than normal controls ($p<.0001$) and AD patients ($p<.05$) on three out of the four tests (TEA Map Search, WCST, and TEA Eleveator Counting with Distraction). Post hoc analyses also revealed that AD patients were impaired on the executive measures relative to controls ($p<.01$).

Pachana, Boone, Miller, Cummings, & Berman (1996) examined the performance of 15 FTD patients, 16 AD patients and 16 elderly normal controls on neuropsychological assessment. Tests administered included WAIS-R Digit Span, Rey-Osterrieth Complex Figure, Rey Auditory Verbal Learning Test, WHO-UCLA Auditory Verbal Learning Test, Logical Memory subtest from the WMS-R, BNT, FAS verbal fluency, and Stroop Test. AD and FTD patients performed similarly across measures, with the only difference found on delayed recall from the Rey-Osterrieth Complex Figure, with FTD patients scoring significantly better than AD patients. Although there were no other significant findings, the

two patient groups did exhibit different patterns of performance on executive and nonverbal memory tasks. Specifically, AD patients performed worse on nonverbal memory relative to executive functioning, whereas FTD patients demonstrated an opposite pattern. Both AD and FTD patients showed impairment in executive skills, although FTD patients performed disproportionately more poorly on executive tests.

Miller et al. (1991) examined the neuropsychological characteristics of a group of 6 FTD patients and 6 age- and education-matched normal elderly subjects. Patients were administered a neuropsychological battery of tests, including the WAIS-R to assess IQ, WMS Logical Memory and Visual Reproduction, Rey-Osterrieth Complex Figure, constructional praxis, and BNT. Measures of various frontal lobe skills included the WCST, Stroop Test, Auditory Consonant Trigrams, WAIS-R Digit Span, and FAS verbal fluency. Statistical analysis found overall IQ to be significantly lower in the FTD group. T-tests comparing performances on executive measures revealed significant group differences with the FTD patients performing more poorly than normal controls on FAS, WCST perseverative responses, WCST categories, and Digit Span. There were no significant differences between the FTD and control groups, however, on any other cognitive measures. Although this study examined only a small sample, the findings support the notion that the cognitive profile of FTD is dominated by impairment in executive functioning.

Behavioral Features in FTD

Early personality and behavioral changes are common in many individuals with FTD. Hence, assessment of behavioral disturbances provides a means of further characterizing the disease to aid in management, treatment and differential diagnosis.

Levy, Miller, Cummings, Fairbanks and Craig (1996) examined the behavioral profile of 17 FTD patients and 30 AD patients with the Neuropsychiatric Inventory (NPI) and found the most common behavioral feature of FTD patients to be apathy, followed by aberrant motor behavior, disinhibition, agitation, anxiety, irritability, depression, euphoria and delusions. No FTD patients were found to have hallucinations. When compared to the AD profiles, patients with FTD had significantly more disinhibition, euphoria, apathy and aberrant motor behavior. Disinhibited behavior was defined as acting impulsively or making socially inappropriate remarks. Euphoria was identified as elevated mood or inappropriate jocularity and aberrant motor behavior was characterized as pacing, moving furniture, unpacking closets and rummaging through drawers.

In a similar study, Mendez, Perryman, Miller, & Cummings (1998) examined the behavioral profile of 29 AD patients and 29 FTD patients with the Behavioral Pathology in Alzheimer's Disease Rating Scale (BEHAVE-AD). The FTD group was found to score significantly worse on global scores than the AD group, with significantly higher frequencies of verbal outbursts (e.g., inappropriate personal comments) and inappropriate activity (e.g., disinhibited acts or immodest behavior). No other significant differences were found; however, the FTD group exhibited more activity disturbance and aggressiveness, and the AD group exhibited more affective disturbance and anxieties and phobias. Discriminant analysis indicated that the three subscales measuring affective disturbance, aggressiveness, and anxieties and phobias most accurately discriminated FTD patients from those with AD. The FTD patients were found to score higher on aggressiveness and lower on affective

disturbances and anxieties and phobias than those with AD. These three subscales accurately classified 82.8% of FTD patients and 55.2% of AD patients to the correct diagnostic group.

Kertesz, Nadkarni, Davidson, & Thomas (2000) assessed behavioral changes in 38 AD patients, 26 frontal lobe dementia (FLD; also referred to as FTD) patients, 11 patients diagnosed with Primary Progressive Aphasia (PPA), 16 patients with Vascular dementia (VaD), and16 patients with depressive disorder (DD) using the Frontal Behavioral Inventory (FBI). Post hoc tests showed that the FLD group scored significantly higher on total scores than all other groups ($p<.05$). The VaD group was also shown to have significantly higher total scores than the AD, PPA, and DD groups ($p<.05$); however, the AD, PPA, and DD groups did not significantly differ. Comparisons between individual items revealed that the FLD group rated significantly higher than the AD, PPA and DD groups on perseveration, indifference, inattention, inappropriateness, loss of insight, apathy, aspontaneity, inflexibility, disorganization, impulsivity, personal neglect and poor judgment. Discriminant analysis indicated that indifference (41%), alien hand (25%), inappropriateness (18%), perseveration (7%) and impulsivity (7%) were responsible for the overall separation between the FLD group and the non-FLD groups. Inflexibility (38%) was found to account specifically for the FLD versus AD comparison. Results of the discriminant analysis between the FLD and non-FLD groups showed that 5/82 (6.1%) non-FLD patients were classified falsely as FLD and 3/26 (11.5%) FLD patients were classified as non-FLD, indicating a diagnostic specificity of 89.5% and sensitivity of 93.9% for FLD using the FBI. Results also indicated that AD patients were correctly classified 100% of the time versus FLD patients.

Mendez, Selwood, Mastri and Frey (1993) conducted a retrospective analysis of behavioral profiles of 21 patients with pathologically confirmed Pick's disease (a specific form of FTD) and 42 pathologically confirmed AD patients in order to identify any differentiating features. Review of medical records for both groups revealed more frequent behavioral problems in the Pick group compared with the AD group. Specifically, the Pick sample was more likely to demonstrate roaming (e.g., walking or driving to search and examine a new area), disinhibition (e.g., wandering unclothed in front of others, sexually explicit comments, and inappropriate jokes), and hyperorality (e.g., eating or drinking of inedible objects such as plants, lotion and soap, stuffing the mouth with food or non-food items without swallowing, and eating food more than in the past). This review of clinical features suggests that the behavioral disturbances of FTD are distinct from and more frequent than those of AD, with disinhibition often one of the earliest and most distinguishing features of FTD (Miller et al., 1991). Furthermore, behavioral symptoms typically occur early in the course of FTD in contrast to AD where problematic behavioral features are more common as the disease progresses.

Differential Diagnosis

Accurate diagnosis of AD and FTD is important, as these groups may respond differently to treatment and management of cognitive and behavioral symptoms. Differential diagnosis would appear to be easy, as AD and FTD have distinct clinical features and symptoms that differentiate them (Neary, Snowden, Northen, & Goulding, 1988; Miller et al., 1991; Mendez, Selwood, Mastri, & Frey, 1993; Levy, Miller, Cummings, Fairbanks, & Craig, 1996; Perry & Hodges, 2000). FTD is characterized by profound alteration in

personality and social conduct, in addition to cognitive impairment primarily in frontal lobe executive functions. In contrast, AD is characterized by prominent impairment in memory, visuospatial functions, and language within the context of well-preserved social skills. However, despite distinct differences in neuropsychological and behavioral profiles, there is evidence that clinical differentiation remains poor.

In a study evaluating the use of the NINCDS-ADRDA criteria in the differentiation of AD and FTD, Varma et al. (1999) examined case records of 30 pathologically confirmed AD patients and 26 pathologically confirmed FTD patients who had undergone neuropsychological evaluation. Each case was retrospectively assessed to determine if the NINCDS-ADRDA criteria successfully identified those patients with AD and excluded those with FTD. Twenty-nine of the 30 AD patients met NINCDS-ADRDA criteria for probable AD, indicating high sensitivity (.93), while 21 of 26 FTD patients also met NINCDS-ADRDA criteria for probable AD, indicating low specificity (.23). These findings indicate that standard diagnostic criteria for AD do not adequately discriminate AD from FTD. As reported in this study, the poor discriminating power of the criteria is most likely due to the broad definitions of impairments necessary for a diagnosis of AD. For example, the criterion for memory impairment does not distinguish between the encoding deficits inherent in AD and the defective organizational strategies used during learning in FTD, both of which can lead to impairment on memory testing but for different reasons (Glosser, Gallo, Clark, & Grossman, 2002). In addition, the criteria do not differentiate which symptoms develop first or are more prominent in the disease process. The lack of clearly defined criteria can

therefore lead to misdiagnoses and support a need for more careful assessment of cognitive impairments for accurate differential diagnosis of FTD from AD.

Since patients classified as FvAD exhibit many clinical features observed in both AD and FTD, accurate diagnosis for this group is even more complicated. Specifically, the proposed study will focus on how typical AD patients, FvAD patients and FTD patients differ across demographic variables, neuropsychological results, and behavioral symptoms. For the purposes of this study, FvAD is defined as prominent, early executive involvement and behavioral changes in an otherwise typical AD presentation.

Further examining differences in behavior and executive functioning in FvAD may aid in identifying tools for differential diagnosis of AD and FTD, which are necessary due to the reliance on clinical criteria for diagnosis. It is important to identify patients with FvAD in order to address potential management and treatment issues, especially since frontal lobe impairment is often associated with specific behavioral disturbances that can require specialized patient management (Norton, Malloy, & Salloway, 2001; Boyle et al., 2003). Therefore, a clearer understanding of how cognitive and behavioral functioning is affected within this subgroup will offer important clinical information to aid researchers and practitioners in providing the best care to these individuals.

CHAPTER THREE
Hypotheses

Overall Goal: To compare the demographic, cognitive and behavioral features of individuals diagnosed with FvAD to those diagnosed with prototypical AD and FTD.

Specific Aim One: To identify differences in demographic variables among subjects diagnosed with AD, FvAD, and FTD.

Hypothesis 1: The FvAD group will have a significantly older age at onset than the FTD group but will be similar to the AD group.

Hypothesis 2: The ratio of males to females will be lower in the FvAD and AD groups than the FTD group.

Specific Aim Two: To examine differences in neuropsychological functioning among the AD, FvAD and FTD groups.

Hypothesis 3: The AD and FvAD groups will have greater memory deficits than the FTD group.

Hypothesis 4: The AD and FvAD groups will perform similarly on measures of language and visuospatial abilities but worse than the FTD group.

Hypothesis 5: The FTD and FvAD groups will perform similarly on measures of executive functioning (i.e., WCST, FAS, TMT) but worse than the AD group.

Specific Aim Three: To determine differences in the severity and frequency of behavioral symptoms among AD, FvAD, and FTD groups.

Hypothesis 6: The FTD and FvAD groups will exhibit a greater degree of behavioral symptoms on the NPI than the AD group.

CHAPTER FOUR
Method

Participants

Patients will be chosen from those evaluated at the Clinic for Alzheimer's and Related Diseases (ADC) and diagnosed via clinical group consensus, consisting of neurologists, psychiatrists and neuropsychologists. All patients received a comprehensive assessment including medical history, neuropsychiatric examination, magnetic resonance imaging (MRI) (and sometimes single photon emission computed tomography; SPECT), and neuropsychological testing. The current study will include 30 patients diagnosed with probable AD according to NINCDS-ADRDA criteria, 30 patients diagnosed with frontal variant Alzheimer's disease (FvAD) according to clinical consensus criteria, and 30 patients diagnosed with the behavioral presentation of frontotemporal dementia according to consensus criteria (Neary et al., 1998). A diagnosis of FvAD requires that subjects meet criteria for probable AD with additional symptoms such as executive dysfunction, apathy or disinhibition that suggest early, prominent frontal lobe dysfunction. Neary FTD criteria include an insidious onset of character change and decline in social interpersonal conduct with preservation of perception, spatial skills, praxis, and memory. Behavior may be stereotyped or perseverative. Other core diagnostic features are impairment in regulation of personal conduct, emotional blunting and loss of insight. In order to evaluate patients in the mild stages of dementia, an MMSE score of 20 or higher will be required for study entry.

Inclusion Criteria

Subjects from each group will be selected for the current study according to the following inclusion criteria:

1. A diagnosis of probable AD, FvAD, or FTD.
2. Completion of a comprehensive neuropsychological evaluation including the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery, Trail Making Test Parts A and B, FAS verbal fluency, Wisconsin Card Sorting Test (WCST), Boston Naming Test (BNT), and Clinical Dementia Rating (CDR).
3. A caregiver able to complete the CDR and Neuropsychiatric Inventory (NPI) with a trained study coordinator.
4. An age of 45 years or older.
5. An MMSE score of 20 or greater.
6. English as their first language.

Measures

Information about psychological and daily functioning will be taken from information obtained during initial evaluation at the ADC. This data is gathered from a pre-visit telephone interview with a caregiver or family member regarding the patient's past and current daily functioning (Dementia/Clinical History), and by interview and examination of subjects, as well as an interview of informants by a psychiatrist or neurologist. The initial dementia/clinical history is obtained at the ADC by trained personnel and consists of 52 items, including questions regarding memory problems, onset of symptoms, personality

changes, behavioral changes, depression, drug use and numerous questions regarding physical health. For the purpose of this research project, only the question related to age of onset of symptoms from this form will be used.

Neuropsychological Battery

Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay & Curtiss, 1993). The WCST is a measure of abstract reasoning and problem solving. In this test, four stimulus cards are placed in front of the subject, the first with a red triangle, the second with two green stars, the third with three yellow crosses, and the fourth with four blue circles. The subject is then presented with two identical decks of 64 cards, with designs similar to those on the stimulus cards, and is instructed to match each of the cards to one of the four stimulus cards. Each card varies in shape (triangles, circles, stars, and crosses), number of figures on the card (one to four), and color (red, blue, green and yellow). The cards can be matched in one of three ways: color, form, or number. Subjects must match the cards to each of the specific sorting principles (i.e., color, form, and number) for a series of ten consecutive trials, but he or she is not told how to match the cards or in what order. The subject is told each time whether the match is correct or incorrect, but no other help is given. The test is completed when the subject successfully completes each category twice in the designated order. The test can be discontinued after the first deck of 64 cards if the subject has not completed a single set. Performance is based on number of categories completed, the number of errors made, and the number of perseverations made. For this study, the normative data provided by Heaton, Grant and Matthews (1991) will be used. Inter-rater reliability has been reported at r = .93 for perseverative responses (Axelrod, Goldman, &

Woodard, 1992; as cited in Heaton, Chelune, Talley, Kay & Curtiss, 1993). In terms of construct validity, Paolo, Troster, Axelrod, and Koller (1995; as cited in Spreen & Strauss, 1998) factor analyzed the performance of a sample of healthy elderly on the WCST and found that the number of perseverations and categories completed loaded highly on an overall conceptualization and problem-solving factor.

Trail Making Test, Parts A and B (Reitan, 1992). The Trail Making Test is a measure of visual scanning and sequencing. It is commonly used as a screening measure for neurocognitive impairment. In Part A, the subject is asked to draw lines as fast as he or she can to connect consecutively encircled numbers from 1 to 25 that are randomly arranged on a page. This task requires attention as well as visual scanning and motor speed. In Part B, the subject is asked to draw lines as fast as he or she can to connect 25 encircled numbers and letters randomly arranged on a page. The subject must alternate between a circled number and a circled letter (e.g. 1-A, 2-B, etc.) for numbers 1 through 13 and letters A through L. Part B differs from Part A in that it also assesses cognitive flexibility, an integral part of executive functioning. A subject's performance is based on completion time. For this study, the normative data provided by Heaton, Grant and Matthews (1991) will be used. Good one year test-retest correlations for Parts A and B among normal elderly subjects has been reported ($r = .64$ for Part A and $r = .72$ for Part B; Snow et al., 1988; as cited in Spreen & Strauss, 1998). Tests of construct validity have demonstrated the Trail Making Test to be a highly sensitive measure of brain damage, with Part A being differentially effective from Part B in measuring attention, and Part B being a more effective measure of executive functioning (Spreen & Strauss, 1998).

FAS (Spreen & Strauss, 1998). FAS, a test of verbal fluency, measures a subject's ability to produce individual words under restricted search conditions. In this test, the subject is required to name as many words as he or she can in one minute beginning with a specified letter of the alphabet. The subject may not use proper names of people or places, numbers, or the same words with different endings such as 'eat' and 'eating'. This task is performed a total of three times, once for the letters F, A, and S. The subject's score is calculated by summing the number of words produced for each letter and noting the number of perseverations and losses of set. Perseverations are repetitions of the same word and losses of set are productions of words that are not in keeping with the category nor begin with the specified letter (e.g., the word 'phenomenon' for words that begin with the letter 'F'). One-year retest reliability among normal older adults has been reported as r = .70 (r=.70 for F, r=.60 for A, and r=.71 for S.; Snow, Tierney, Zorzitto, Fisher & Reid, 1988; as cited in Spreen & Strauss, 1998). Tests of construct validity in adult populations have found that this test loads mainly on a verbal knowledge factor. It has also been reported to have high sensitivity to frontal lobe damage regardless of side of laterality (Bruyer & Tuyumbu, 1980; as cited in Spreen & Strauss, 1998). PET scan studies show that word fluency activates bilateral temporal and frontal lobes (Parks et al., 1988; as cited in Spreen & Strauss, 1998).

Boston Naming Test (BNT;Kaplan, Goodglass, & Weintraub, 1993). The BNT is a measure of confrontation naming ability. In this test, the subject is presented with 60 black and white drawings one at a time, ranging from simple, high-frequency words (e.g., tree) to words of increasing complexity (e.g., abacus), and is required to name each object pictured.

Adult subjects begin with item 30 and are given credit for all preceding items if they name the first eight items presented correctly. However if any of the eight items are failed, the subject must proceed backward from item 29 until a total of eight consecutive preceding items are passed. Once this is complete, the subject resumes naming objects in a forward direction until all remaining items are passed or until the subject makes six consecutive errors in which case the test is discontinued. If an item is not correctly named within 20 seconds, and it is unclear if the subject comprehends what the drawing represents, the examiner provides the subject with a semantic cue (e.g., "something to eat" for mushroom). Another 20 seconds is provided for the subject's response. If he or she does not provide the correct response after semantic cuing, a phonemic cue and additional 20 seconds are given for responding (e.g., "starts with the sound 'ca'" for cactus). A semantic cue is not given if the subject clearly demonstrates that he or she understands what the drawing is meant to represent. Instead, the examiner proceeds directly to the phonemic cue. A total of 60 points is possible, one point for each spontaneous, correct response and for each correct response following semantic cuing. Age-, gender-, and education-corrected scores for the BNT will be obtained from the Heaton, Grant and Matthews (1991) normative sample. Split-half correlations among AD patients has been reported at r = .97 (Huff, Collins, Corkin, & Rosen, 1986; cited in Spreen & Strauss, 1998). Williams, Mack and Henderson (1989) reported that the 60-item BNT is a sensitive measure for detecting differences in naming ability among AD patients and healthy, elderly controls.

Consortium to Establish a Registry for Alzheimer's Disease (CERAD Constructional Praxis (Adapted from Rosen, Mohs, & Davis, 1984). The Constructional Praxis task is a

measure of visuoconstructional ability. The subject is presented with four simple geometric figures of increasing complexity (a circle, a diamond, intersecting rectangles and a cube), each on separate pieces of paper, and asked to copy the figures on the same page. Scoring criteria are provided in the training manual for CERAD administration. A maximum score is 11 points. One-month test retest correlations of r=.54 in an elderly control sample and r=.78 in a mild AD sample were reported by Morris et al. (1989). Constructional Praxis has been noted to improve discrimination between mild and moderate AD when used in conjunction with Word List Recall (Welsh, Butters, Hughes, Mohs, & Heyman, 1992).

CERAD Word List Learning (Adapted from Atkinson & Shiffrin, 1971). The CERAD Word List Memory task is a list-learning test. Subjects are told they will be presented with ten printed words, each on a separate card, and are then instructed to read each word out loud as they will be asked to recall as many words as possible once finished. The words are presented at the rate of 1 every 2 seconds and 90 seconds are allowed for spontaneous recall. Words given that are not on the list are recorded as intrusion errors. On each of 2 subsequent trials, the ten words are presented in a new random order and the subject again attempts to recall as many as possible. The maximum number of correct responses is 30 for the 3 trials. Morris et al. (1989) reported one month test retest correlations of r=.62 in an elderly control sample and r=.68 in a mild AD sample.

CERAD Word List Recall (Adapted from Atkinson & Shiffron, 1971). Word List Recall is a measure of delayed verbal recall. The CERAD Constructional Praxis is used as a distracter task between Word List Learning and Recall. Subjects are asked to recall as many of the words as they can from the Word List Learning trials. One point is awarded for each

word correctly recalled, and intrusion errors are noted. One month test retest correlations of *r*=.64 in an elderly control sample and *r*=.60 in a mild AD sample were reported by Morris et al. (1989). Delayed recall has been proven useful in discriminating between patients with very mild AD and normal elderly control subjects (Welsh, Butters, Hughes, Mohs, & Heyman, 1991).

Clinical Dementia Rating Scale (CDR ;Berg, 1988; Morris, 1993). The CDR is a rating of the functional severity of dementia, which is determined by assessment of the domains of memory, orientation, judgment and problem solving, community affairs, home and hobbies, and personal care. Using a semi-structured interview of both the subject and an informed collateral source, the clinician rates the degree of impairment in each of the six domains along a five-point rating scale in which impairment is rated as none = 0, questionable =.5, mild = 1, moderate = 2, and severe = 3. A global CDR score can be tabulated by adding the scores in each of the six domains for a maximum of 18 points (sum of boxes score), or the scores can be transformed using an algorithm (Morris, 1993), resulting in an overall impairment index ranging from 0 to 3. Excellent inter-rater reliability of clinicians trained on the CDR is reported (*r* = .91) for the overall impairment index and sum of boxes scores (Burke et al., 1988). The CDR has been validated neuropathologically. In samples selected to be free of other potentially dementing illnesses, a global CDR score of .5 or greater is associated with a histological diagnosis of AD while a CDR of zero is associated with few or no AD lesions (Berg, McKeel, Miller, Baty, & Morris, 1993). The CDR has also been found to be predictive of time of death in a sample of AD subjects (i.e., higher CDR

score is associated with shorter life expectancy) and to be significantly negatively correlated to the MMSE (Fillenbaum, Peterson & Morris, 1996).

Neuropsychiatric Inventory (NPI; Cummings, 1997). The NPI is a measure of neuropsychiatric symptoms in dementia patients. Scoring is based on a structured interview with a caregiver who is familiar with the subject. The NPI measures twelve neuropsychiatric domains: delusions, hallucinations, agitation, dysphoria, anxiety, apathy, irritability, euphoria, disinhibition, aberrant motor behavior, nighttime behavior disturbances, and appetite abnormalities. A screening question is first asked for each domain, followed by more detailed questions if the response to the screening question indicates the presence of abnormalities within that neuropsychiatric domain. Caregivers are asked to rate both the frequency and severity of symptoms in addition to the amount of caregiver distress associated with them. Scores for each individual neuropsychiatric domain are calculated by multiplying frequency and severity. The total NPI score is the sum of the individual item scores. Concurrent validity has been supported by moderate to good correlations with the BEHAVE-AD total score (r= .66), and inter-rater reliability was found to vary from 93.6% to 100% for different behaviors (Cummings et al., 1994). In other studies, the NPI has been shown to distinguish FTD from other dementias, including AD (Levy, Miller, Cummings, Fairbanks, & Craig, 1996), and to be sensitive to treatment effects in these populations (Cummings, 1997).

Mini Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975). The MMSE is a widely used screening measure for cognitive impairment. This test consists of 30 items and usually takes 5 to 10 minutes to administer. Test questions assess various domains

of cognition such as orientation to time and place, attention/concentration, immediate and delayed verbal recall, naming ability, ability to follow simple commands, and constructional skills. The test score is determined by totaling the number of correct responses. Good inter-rater reliability ($r > .65$) and two month test-retest reliability ($r > .80$) have been reported (Folstein, Folstein, & McHugh, 1975). Salmon, Thal, Butters & Heindel (1990) found that in patients with AD, scores drop over time, with an average annual drop of three points. Most studies report the MMSE to be a sensitive indicator of moderate to severe dementia; however it is less accurate when used to detect mild levels of cognitive impairment (Spreen & Strauss, 1998).

Procedures

All patients were evaluated at the ADC. Neuropsychological tests were administered by trained technicians using standardized procedures, but the order of presentation may vary to meet the needs of each subject. Trained study coordinators interviewed caregivers on the same day as testing in order to complete the CDR and NPI. All subjects or their legal representatives gave clinical consent prior to evaluation. After all data is collected, patient names will be removed from the database to ensure confidentiality.

CHAPTER FIVE
Data Analysis

Demographic Variables

To identify differences in demographic variables among subjects in the AD, FvAD, and FTD groups, five demographic variables (age, age at onset, education level, gender and race) will be compared across groups. Differences in age, age of onset and education will be investigated using one-way analyses of variance (ANOVA). Differences in gender and race will be examined using chi-square tests of independence. For all variables, Tukey Honest Significant Difference (HSD) post hoc tests will be used to assess any significant findings on one-way ANOVA's, and 2 X 2 chi square contingency tables will be used to investigate significant findings from chi-square tests of independence.

Neuropsychological Variables

To examine differences in neuropsychological functioning among the AD, FvAD and FTD groups, performance on neuropsychological variables will be compared across groups using a series of ANOVA's. Between group differences will also be assessed using a one-way analysis of covariance (ANCOVA) with the covariates being global CDR score, education, and age. HSD post hoc tests will then be used to assess any significant findings.

Behavioral Features

To identify differences in the frequency and severity of behavioral features exhibited among the AD, FvAD and FTD groups, mean total NPI scores will be compared across groups using a one-way ANOVA. Between group differences will also be assessed using a one-way ANCOVA with the covariates being global CDR score and age. HSD post hoc tests will be used to assess any significant findings. In order to identify differences in individual

behavioral features among the groups, mean individual subscale scores will be compared across groups using a Multivariate Analysis of Variance (MANOVA). Follow-up ANOVA's and HSD post hoc tests will then be used to assess any significant findings.

CHAPTER SIX
Implications

Analysis of Hypotheses

The first aim of this study is to identify differences in demographic variables among subjects diagnosed with AD, FvAD, and FTD. Specifically, hypothesis one predicts that the FvAD group will have a significantly older age at onset than the FTD group, but will be similar to the AD group. If analyses indicate that the AD has a later age of onset than the FTD group, this finding would be consistent with the results of other studies comparing these two groups (Gao, Hendrie, Hall, & Hui, 1998; Levy, Miller, Cummings, Fairbanks, & Craig, 1996; Pachana, Boone, Miller, Cummings, & Berman, 1996; Gauthier, 1999). If the FvAD group is also found to have a similar age of onset to the AD group but higher than the FTD group, it would suggest that these patients are more likely to be suffering from AD and that prominent frontal lobe dysfunction in early AD may indeed be a subtype of the disorder. However, if this hypothesis were not supported, then it might suggest that the FvAD group is a subgroup of AD patients with an earlier age of onset. This finding would then better characterize this subgroup for both research and clinical practice. Another possibility would be that some of these individuals are exhibiting symptoms of FTD rather than those of AD. In this case, autopsies would be needed for pathological confirmation.

Hypothesis two postulates that the FvAD group will have a similar ratio of males to females as the AD group, but one lower than the FTD group. If the ratio were found to be higher in FTD than AD, then this would support gender differences found in other studies (Gao, Hendrie, Hall, & Hui, 1998; Gauthier, 1999; Ratnavalli, Brayne, Dawson, & Hodges, 2002). If the FvAD group were found to have a lower ratio of men to women than the FTD

group (i.e., as in typical AD), then this finding would suggest that the gender composition of those with FvAD is similar to that of typical AD.

The second aim of this study is to examine differences in neuropsychological functioning among the AD, FvAD and FTD groups. Hypotheses three and four predict that the FvAD and AD groups will perform similarly on measures of memory, language and visuospatial abilities, but worse than the FTD group. Hypothesis five predicts that the FvAD group will perform similar to the FTD group on measures of executive functioning, but worse than the AD group. Such results would suggest that executive involvement in the FvAD group is the primary distinguishing neuropsychological feature from an otherwise typical AD cognitive profile. These results would also be consistent with the findings of other studies examining a frontal variant of AD (Back-Madruga et al., 2002; Johnson, Head, Kim, Starr, & Cotman, 1999), further supporting the existence of this subgroup. However if hypotheses three and four are not supported, then a question could be raised as to whether the FvAD patients do indeed have AD, or instead suffer from FTD given their significant executive dysfunction. If only hypotheses three and four could be supported while hypothesis five is not, the neuropsychological profiles of the FvAD group would look similar to typical AD overall, suggesting AD as the underlying disorder. Overall, a careful analysis of cognitive profiles across the groups would be needed to identify similarities and differences between the FvAD group and the AD and FTD groups to better understand the cognitive presentation of this proposed subgroup. Another possibility is that differences in the FvAD group may be evidenced more in behavioral symptoms than executive dysfunction.

In this case, both areas of functioning would need to be evaluated for accurate diagnosis of FvAD.

The third aim of this study is to determine differences in the severity and frequency of behavioral symptoms among the AD, FvAD and FTD groups. Hypothesis six proposes that the FTD and FvAD groups will exhibit a greater degree of behavioral symptoms on the NPI than the AD group. These results would support the findings of Back-Madruga et al. (2002) who found a greater frequency and severity of neuropsychiatric symptoms assessed by the NPI in a frontal AD subgroup than found in a typical AD group. Mendez, Selwood, Mastir, and Frey (1993) also found that patients with FTD demonstrate a greater frequency of behavioral problems than those with AD. If this hypothesis was supported, the findings would then imply that significant behavioral changes are early features of a frontal variant of AD. Specifically, the FvAD group is predicted to exhibit more apathy, aberrant motor behavior, and disinhibition, which have been found to be the most common behavioral disturbances in FTD patients using the NPI (Levy, Miller, Cummings, Fairbanks, & Craig, 1996). However, if this hypothesis is not supported, then the FvAD group may not be distinguishable from typical AD or FTD by a higher severity and frequency of behavioral changes, as measured by the NPI. In this case, some FvAD patients may show more executive dysfunction than behavioral symptoms and others may exhibit more behavioral symptoms than executive dysfunction. Therefore, clinicians would need to be aware of individual differences in the presentation of FvAD and behavioral changes early in the course of FvAD might require specific treatments and interventions in order to manage them effectively.

Limitations to the Current Study

One limitation to this study is that no specific clinical criteria were used to classify patients with a frontal variant of AD. Diagnosis was based on clinical group consensus requiring that patients meet NINCDS-ADRDA criteria for probable AD with additional symptoms that suggest prominent frontal lobe dysfunction. Although criteria used for the diagnosis of AD are standardized, the criteria for determining prominent frontal lobe dysfunction are not. Individuals with FvAD can be diagnosed based on a variety of symptoms that indicate frontal lobe dysfunction, leading to heterogeneity within this subtype. For example, some patients classified in this subgroup may exhibit apathy rather than disinhibition. Although the established criteria for AD are highly accurate (Morris, McKeel, Fulling, Torack, & Berg, 1988), better defined criteria for frontal lobe involvement may provide a method for better identifying this subtype that is worth recognizing in future research and clinical practice.

Another drawback is the circularity that is inherent to the study design. Some of the measures used to diagnose AD, FvAD and FTD (i.e., NPI and WCST) are included in the analyses, which could contribute to significant group differences. Another limitation is that the results can only be generalized to AD patients in the mild range of dementia severity. Furthermore, this study lacks pathological confirmation to provide support for the existence of AD and FTD in these patients, or for a frontal variant of AD subgroup with early onset executive dysfunction.

Future Research and Study

In order to gain a better understanding of the frontal variant of AD, criteria for identifying this subtype must first be established. Previous research has classified this subgroup based on neuropsychological patterns in the early stages of the disease (i.e., disproportionate impairment on executive measures in addition to memory deficits; Back-Madruga et al., 2002; Johnson, Head, Kim, Starr, & Cotman, 1999); however, the definition of executive impairment varies across studies. This lack of consensus criteria allows for debate among clinicians over whether the prominent executive impairment in patients is related to a subtype, oddities on the early stages of dementia, or individual variability. Until this debate is settled, subsets of patients with AD who have significant differences in their patterns of cognitive functioning may be classified as "atypical" rather than recognized as falling within a subtype of AD. In addition, patients with AD who have early, prominent executive impairment have been reported to exhibit more behavioral symptoms than those with typical AD (Back-Madruga et al., 2002); however, no study has examined how the behavioral changes in this subgroup differ from those evidenced in patients with FTD.

Once criteria for a frontal variant of AD become more clearly defined, longitudinal studies with neuroimagaing and pathological confirmation could then be conducted to determine the frequency and stability of this subtype throughout the progression of the disease. Such studies could also determine if these patients respond differently to available treatments as well as behavioral interventions. If conventional methods of treatment and intervention are not effective within this subgroup, different compensatory strategies could then be explored to fit the needs of these individuals more effectively.

The current study is an initial attempt to examine the neuropsychological results and severity of behavioral symptoms in a subset of AD patients with and without early, prominent executive dysfunction and behavioral changes, and those diagnosed with FTD. This study differs from others examining the frontal variant of AD in that the diagnosis for this subgroup requires the presence of behavioral changes in addition to early, prominent executive dysfunction. This definition allows for a subset of individuals who demonstrate a broader range of frontal lobe dysfunction, which is what is proposed to primarily distinguish this subset of patients from those with typical AD. This study also minimizes circularity that is inherent to other study designs examining frontal variant AD (Back-Madruga et al., 2002; Johnson, Head, Kim, Starr, & Cotman, 1999). Although some of the measures used for analysis were also used for clinical diagnosis (i.e., NPI and WCST), other aspects of the patients case history was considered when classifying them as FvAD, such as results from a neuropsychiatric exam and neuroimaging. If the results of the current study reveal that all hypotheses are supported, then they will provide further evidence for the existence of frontal variant AD and a better characterized clinical profile for this subgroup that can aid in differential diagnosis. In this case, the results could also be used to establish standardized criteria for diagnosis of FvAD in future studies. For example, specific criteria could be derived from the results of the current study and applied to pathologically confirmed AD and FTD cases to determine if a frontal variant AD subgroup could be identified, and if so, the sensitivity and specificity of the criteria could also be assessed.

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