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EVIDENCE FOR HETEROGENEITY IN MILD COGNITIVE IMPAIRMENT (MCI): DIFFERENCES IN NEUROPSYCHOLOGICAL PROFILE AND ASSOCIATED WHITE MATTER LESION PATHOLOGY

By

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EVIDENCE FOR HETEROGENEITY IN MILD COGNITIVE IMPAIRMENT (MCI): DIFFERENCES IN NEUROPSYCHOLOGICAL PROFILE AND ASSOCIATED WHITE MATTER LESION PATHOLOGY

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Lisa M. Delano-Wood

Since Alzheimer's disease (AD) and vascular dementia (VaD) are associated with considerable morbidity and mortality and together comprise roughly 80% of all dementia cases worldwide (Morris, 1994; Small, Rabins, Barry, & Buckholtz, 1997), delineating and elucidating early, pre-clinical manifestations of these dementia syndromes is essential. Although no reliable treatments currently exist for dementia, it is important to identify and define early stages of the dementing process with the goal of more clearly understanding how and why dementia progresses; in addition, identifying early manifestations of dementia is important in terms of possibly staving off future cognitive decline with existing pharmacological treatment. Mild Cognitive Impairment (MCI), a reliable clinical entity that has received considerable attention since its inception in 1997, is thought to represent a vulnerable population lying between normal aging and dementia (Morris et al., 2001; Petersen et al., 2001). Indeed, understanding what constitutes MCI is imperative as several studies have indicated that individuals in this at-risk group are at dramatically increased risk for dementia and mortality (Palmer et al., 2003; Petersen et al., 1999).

This study examined whether distinct neuropsychological profiles could be delineated within an MCI population as well as to investigate the contribution of white matter lesions (WML) to associated cognitive impairment. A clinical sample of 70 older adults diagnosed with MCI (age range 55-88) was assessed using neuropsychological test

scores (CERAD battery, Trails A and B, and Stroop Color Word Test). Additionally, WML found on structural MRI was measured using a semi-automated volumetric approach (Pixel Thresholding) with T2-weighted FLAIR (fluid-attenuated inversion recovery) images. Using cluster and discriminant analyses, three distinct groups (Cortical, Subcortical, and Amnestic) were formed based on neuropsychological scores. Results showed that each group differed on white matter lesion load, with the Subcortical group demonstrating the highest level of WML pathology. Finally, using regression analyses, the effect of lesion type (deep white matter (DWML) versus periventricular (PVL)) on neuropsychological performance was investigated. Only DWML was associated with greater cognitive impairment, likely due to frontal-subcortical circuitry disruption. Taken together, findings suggest that distinct neuropsychological profiles exist within MCI and that these profiles differ according to levels of WML. Clinical, theoretical, and methodological implications of these results are discussed.

This dissertation is dedicated to my father who is and always has been the strongest influence in my life.

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CHAPTER 1
INTRODUCTION

Recent population statistics have demonstrated that the "graying of America" is imminent. Indeed, current population estimates have revealed that over 51 million people in the United States (21% of the total population) are at least 55 years of age (U.S. Bureau of Census, 2000), a 10-fold increase over estimates in 1900. Furthermore, the "oldest old," or the 85 and older demographic, is expected to more than double from 4 million today to 8.5 million by 2030, making this age group the fastest growing segment of the population (Jeste, 1997).

It is striking that approximately 50% of those aged 80 and older demonstrate some kind of cognitive impairment or dementia (Hachinski, 1992). Indeed, older adults are at increasing risk for developing Alzheimer's disease (AD) or vascular dementia (VaD), two highly prevalent diseases that together comprise roughly 80% of all cases worldwide (Morris, 1994; Small, Rabins, Barry, & Buckholtz,, 1997). It has become glaringly apparent that increased research and resources need to be devoted to our older adult population if morbidity and mortality and the expense and suffering inherent to these dementias are to be appropriately controlled and attenuated.

Clearly, understanding and delineating the types and causes of dementia remain a significant priority for the medical, psychological, and neuropsychological fields. Before discussing white matter lesions and their potential role in neuropsychological impairment, a brief synopsis of Mild Cognitive Impairment (MCI)--a milder form of cognitive impairment which is thought to represent a pre-dementia state--will be provided. In addition, diagnostic criteria for AD and VaD will be discussed with the central aim of highlighting similarities and differences between the two dementia types;

this will provide the structure for the conceptual background of the present research, which aims to further elucidate the nature of white matter lesions and their significance with respect to neuropsychological functioning in MCI.

Mild Cognitive Impairment

Clinical and Diagnostic Definition

Mild Cognitive Impairment (MCI) is a condition representing an area between normal aging and dementia in which there are subtle, clinically manifest signs of cognitive impairment in the absence of overt deficits meeting criteria for dementia (Petersen, 1999, 2001). Research has shown that MCI represents an underlying disease process which can be differentiated from normal aging-related physiological changes and thus represents a transitional area between normal aging and dementia (Ritchie & Touchon, 2000; Almkvist et al, 1998; Jacobs et al., 1995j; Morris et al., 2001; Petersen et al., 2001; Petersen et al., 1999).

Mild Cognitive Impairment is a medical diagnosis currently in its infancy, and thus diagnostic criteria are somewhat inconsistent and there is no current agreed upon consensus in the field on a single set of criteria (Morris et al., 2001; Petersen et al., 2001; 2003). Current criteria for MCI include the following: 1) memory complaints, preferably corroborated by an informant, 2) objective memory impairment for age, 3) largely preserved general cognition, 4) essentially normal activities of daily living, and 5) no dementia (Petersen, 1997; 2001; 2003). However, as will be discussed in further detail below, Petersen has recently expanded to include deficits in at least two neuropsychological domains, after controlling for age and educational achievement (Petersen et al., 2001, 2003). Despite the variability in criteria, recent studies have

validated MCI as a useful, separate entity that is qualitatively different from both normal aging and dementia (Petersen et al., 1999; 2004; Bennett, Wilson, & Schneider et al., 2002; Larrieu, Letenneur, & Orgogozo et al., 2002; Smith & Ivnik, 2003). In the absence of a reliable biological marker, individual performance on neuropsychological tests is currently the most reliable way of detecting early phases of dementia.

Possible Subtypes of MCI

As the concept of an intermediate state of cognitive impairment between normal aging and dementia has advanced, it has recently been suggested that several clinical subtypes of MCI may exist (Petersen, 2003). Since some patients present with mild cognitive impairment in a cognitive domain other than memory or within multiple domains, the idea that MCI may represent other etiologies aside from Alzheimer's disease has begun to receive considerable attention (Petersen 2001, Petersen 2003; Rockwood et al., 2003). To this end, the concept of MCI has recently been expanded to include at least three subtypes: 1) Amnestic MCI in which a person has impairment only in memory; 2) Multiple-Domain MCI in which a person may have mild impairments in several cognitive domains with or without a memory impairment; and 3) Single Non-Memory Domain MCI in which a person is impaired in a non-memory area such as executive function or language.

In addition to the clinical subtypes, Petersen et al. (2003) posits that there may be multiple etiologies or causes for each subtype. For example, he has argued that the Multiple-Domain type of MCI may either progress to AD or, alternatively, it may be a phenotype of early vascular dementia. While research investigating the Non-Amnestic types of MCI is virtually absent from the field at this time, most research has focused

almost exclusively on the Amnestic type which has been shown to overwhelmingly progress to AD (Bennett et al., 2002; Larrieu et al., 2002; Petersen et al., 1999).

Clinical Outcome of MCI

Unlike previous concepts, MCI is based on a pathological model of cognitive change (Ritchie & Touchon, 2000). Indeed, reviews of several studies have indicated that individuals with MCI are at risk of higher rates of death (Bennett et al., 2002; Palmer et al., 2003) and it has been shown that up to 25% of those with MCI develop dementia annually (Petersen et al., 1999; Palmer et al., 2003). The most common converting type of dementia appears to be Alzheimer's disease with an annual converting rate that is ten times higher than in normal aging (Petersen et al, 2001).

Several studies have been conducted in recent years in a variety of research settings to measure outcome in subjects with MCI (Bozoki, Giordani, & Heidebrink et al., 2001; Rasquin, Lodder and Visser et al., 2005; Fiducia & DeFilippis, 2004). For example, a group of 220 older adults with a mean age of 79 were followed at the Mayo Alzheimer's Disease Research Center/Alzheimer's Disease Patient Registry for 3-6 years post diagnosis of MCI (Petersen et al., 1999). It has been shown that subjects in this study have progressed to dementia at a rate of approximately 12% per year (Petersen et al., 2001), indicating that roughly 80% of the individuals in this study will have converted to dementia within 6 years. Moreover, in the first population-based study of Amnestic and Multiple-Domain MCI (Cardiovascular Health Study), results indicated that the overall prevalence for the Amnestic subtype of MCI was 6% and Multiple-Domain MCI represented 16% (Lopez, Jagust, & Dekosky, 2003). These statistics highlight a greater need to better understand and characterize Multiple-Domain MCI

given its high prevalence; additionally, they underscore the high risk nature of this group as a whole.

In general, individuals with MCI function well in their activities of daily living and differentiation of any mild functional difficulty is often challenging. Thus, early symptoms of dementia are commonly overlooked because they are relatively mild, do not call for immediate medical attention, and are often dismissed as signs of old age (Hachinski, 1994; Bowler & Hachinski, 2003). Quite frequently, recognition of dementia comes too late when too much cerebral damage has occurred. At this point, cognitive decline progresses at an extremely rapid pace, the individual moves into severe stages of impairment, and any available treatment cannot be effective. Thus, early detection is critical for individuals afflicted with early dementia so that intervention can be beneficial. To this end, MCI research is currently focusing on recognition of the risk factors of disease progression for the purpose of identifying therapeutic interventions that may delay or possibly prevent the onset of dementia. One major goal in this field is to more clearly define MCI and to decipher whether the diagnosis primarily represents a risk factor for Alzheimer's disease specifically, or whether MCI is more accurately described as comprised of a heterogeneous group of individuals with different pathologies, neurological markers, and/or neuropsychological profiles (Looi & Sachdev, 2000a; Bowler, 2002; Rockwood, K., Davis, H., & MacKnight, C., et al., 2003). Before discussing research relevant to this question, a brief description of the two most prevalent types of dementia—Alzheimer's disease and vascular dementia—follows.

Distinguishing Alzheimer's Disease and Vascular Dementia

There is an increasing emphasis on the early diagnosis of dementia and, as preventive and early intervention strategies become better established, clinical differentiation between the two most common dementia types (Alzheimer's disease (AD) and vascular dementia (VaD)) will be essential. Indeed, AD and VaD differ in many respects and precision in diagnosis is thus very important (Chui & Gonthier, 1999; Rockwood et al., 2003). Specifically, research has demonstrated that the rate of progression and prognosis differ for the two disorders (Chui & Gonthier, 1999) and differential diagnosis has implications for effective long-term management and resources. While the etiology and risk factors are not completely understood in AD, risk factors for VaD such as hypertension and stroke are better established and are more likely to be modifiable. Indeed, it has been speculated by many that VaD may be more amenable than other dementia types such as AD to early intervention (Looi & Sachdev, 2000a; Bowler, 2002; Rockwood et al., 2003).

All dementias are characterized by a progression of cognitive and functional capacity. Conventionally, AD and VaD can be distinguished by separate risk factors, clinical course, neuroimaging characteristics, and neurological markers (Roman, Tatemichi, Erkinjuntti, Cummings, et al, 2001; Roman, 2001). For example, AD has been described as having an insidious onset that is followed by slow, progressive cognitive deterioration. It tends to have no or very little obvious focal neurological symptoms and signs and its neuropathology is well characterized as primarily degenerative (Braak and Braak, 1991).

Conversely, VaD has been *traditionally* thought of as having an abrupt onset of dementia symptoms, followed by stepwise deterioration of cognitive performance reflecting neurological signs and symptoms consistent with focal brain lesions (Roman et al., 2001). Current DSM-IV criteria indicate that cognitive loss in combination with evidence of stroke warrants diagnosis of VaD. However, recent research has demonstrated that VaD appears to be more heterogeneous in origin, pathogenesis, and clinical course compared with AD (Rockwood et al., 1999; Loeb & Meyer, 1996; Erkinjuntti, 2000; and Hachinski, 1994). In fact, Meyer et al. (2002) argue that VaD can be separated into two groups, with one group having abrupt onset caused predominantly by multi-infarct, strategic-infarct, or intracranial hemorrhage (in line with the traditional view of VaD); the other form of VaD appears to have an insidious onset, caused predominantly by subcortical small-vessel disease. Indeed, recent research has demonstrated that subcortical small-vessel disease appears to be an important etiology for VaD (Erkinjuntti, Inzitari, & Pantoni et al., 2000; Chui, 2001), with prevalence rates ranging from 36% to 67% (Erkinjuntti, 1987; Cummings, 1994; Brun, 1994; Ross, Petrovitch, & White, et al., 1999).

Unlike typical multi-infarct dementia, particularly that caused by large cortical strokes, VaD caused by subcortical small-vessel disease has a relatively insidious onset which can mimic the clinical course of AD (Chui, 2001, Erkinjuntti et al., 2000; Roman, Tatemichi, & Erkinjuntti, et al., 1993). Slow progression of neuropsychological deficits is thought to arise due to gradually progressive microvascular changes in the brain. Specifically, it has been posited that hypertensive arteriolar lipohyalinosis involving small penetrating vessels (cerebral microangiopathy) is responsible for underlying

neuropathological changes that promote VaD (Erkinjuntti & Hachinski, 1993; Filey, Franklin, & Heaton, et al., 1989; Chui, 2001). It is thought that these neuropathological changes associated with vascular risk factors (i.e., hypertension, hyperlipidemia, and diabetes) are present a relatively long time before VaD becomes diagnosable and may cause cognitive impairment over time (Meyer et al., 2002; Bowler & Hachinski, 2003). The relationship between vascular risk factors and subsequent cognitive decline will be discussed in detail in the sections that follow.

Given that there are different subgroupings of VaD, it has been somewhat challenging to identify homogeneous populations to study in terms of neuropsychological performance. Most research to date has focused on multi-infarct dementia and, although there is some overlap between the major subgroups, efforts to distinguish them according to dementia onset have clinical merit. Early identification of insidious-onset VaD (subcortical VaD) introduces an opportunity for clinical interventions such as control of vascular risk factors that may minimize, arrest, or even reverse cognitive deterioration (Skoog, 1998; Bowler & Hachinski, 2003; & Li et al., 2002).

Neuroanatomical /Neuropsychological Differences in AD and VaD

The neuropathological basis and pattern of cognitive deficits differs considerably in Alzheimer's disease and vascular dementia. Specifically, early VaD appears to preferentially affect subcortical and frontal lobe functions (i.e. speed of processing and executive functioning), while early AD primarily involves the medial temporal lobes and, consequently, memory functions (Bowler, 2002). Indeed, memory disturbance is an early feature in AD, with problems in new learning (Lafosse et al., 1997), a faster rate of information decay (Carlesimo et al., 1995), and a reduced ability to benefit from cues to

facilitate retrieval (Del Re et al., 1994). However, there is greater heterogeneity in the various neocortical regions affected and, consequently, neuropsychological profiles may vary somewhat, particularly later in the disease process (Fisher, Rourke, & Bieliauskas, et al., 1997).

Memory is supported by multiple neural systems, with particular involvement of the medial temporal and diencephalic structures (Ungerleider, 1995; Curran and Schacter, 1996; Haxby, 1996). In AD, the neuropathological lesions impact directly and early on structures closely associated with memory such as the hippocampus (Squire and Shimamura, 1996). During progression of the dementia process, widespread pathology spreads across the medial temporal lobe (Garrard et al., 1997) which, in addition to memory, is largely responsible for language and semantic knowledge. In contrast, memory and language abilities may be relatively spared in subcortical VaD due to greater heterogeneity of neuropathology and the frequent sparing of medial temporal lobe structures.

VaD is thought to primarily affect subcortical and frontal lobe functions (Bowler, 2002; Rockwood et al., 2003) and patients with this dementia type have been described in the literature to exhibit early executive impairment, slowed psychomotor functioning, and frequent depressive features (Bartres-Faz, Clemente, & Junque, 2001; Kramer-Ginsberg et al., 1999; Libon et al., 2001; Naarding et al., 2003; & O'Sullivan et al., 2001). Frontal-subcortical circuits have been an area of recent research interest (Mega and Cummings, 1994; Bartrez-Faz et al., 2001; Libon et al., 2001; Bigler et al., 2003) and the circuits disrupted in VaD appear to include: the dorsolateral prefrontal neuronal circuit mediating executive functioning, orbit-frontal circuit mediating emotional lability, and the anterior

cingulate circuit responsible for motivation and initiation (Almkvist, 1994; Cummings, 1994). Moreover, correlated imaging studies lend support to the conceptualization of VaD as being characterized by a greater degree of frontal-subcortical dysfunction than in AD of comparable severity (Aharon-Peretz et al., 1988; Starkstein et al., 1996; Lafosse et al., 1997; Libon et al., 1997; Villardita, 1997).

Problems with the DSM-IV VaD Diagnosis

More recently, the traditional DSM-IV diagnosis of vascular dementia (VaD) has been challenged as problematic and the foundations for the diagnosis are under scrutiny (Hachinski, 1994; Rockwood, 1997; Rockwood, Parhad, & Hachinski et al., 1994; Bowler, Eliasziw, & Steenhuis et al., 1997; Verhey, Lodder, & Rozendaal et al., 1996; Nolan, Lino, Seligmann, & Blass, 1998; Rockwood, Wentzel, & Hachinski et al., 2000). Indeed, it has been noted that the diagnosis of VaD is clouded by many false perceptions; specifically, these assumptions are 1) that the course of VaD is chronic and progressive, 2) that a large stroke or many strokes must precede VaD; and 3) that vascular dementias are quite rare (Brust, 1988). Contrary to present day criteria, focal neurological signs, sudden onset, step-wise progression, and relationship to known stroke(s) are argued to be unnecessary (Erkinjuntti & Rockwood, 2001; Bowler & Hachinski, 2003; Rockwood et al., 2000; Sachdev & Looi, 2003).

The DSM-IV criteria for VaD have been criticized as "Alzheimerized" (Sachdev & Looi, 2003) and thus inappropriate since the criteria were based primarily on AD (McKhann et al., 1984; Hachinksi, 1990, 1994, 1999). First, there is a requirement of memory impairment which is restrictive when applied to VaD since recent research has shown that memory impairment may not be an early or most salient feature of this

dementia type (Cosentino et al., 2004; Garrett et al., 2004; Bowler & Hachinski, 2003). Second, while individuals with AD typically evidence significant deficits on language and semantic knowledge tasks, recent research has shown that those with VaD often demonstrate few if any such deficits (Rockwood et al., 2001; Garrett, 2004; Cosentino, 2004). Instead, some studies have shown that, in contrast to AD, VaD is often characterized by dramatic impairment on tests of executive functioning, or higher-order thinking, encompassing domains such as cognitive flexibility, planning, and inhibition (Cosentino et al., 2004; Garrett et al., 2004; Rockwood et al., 2001; Bowler & Hachinski, 2000). The application of the 'Alzheimerized' definition to VaD diagnosis may lead to VaD being diagnosed at a relatively advanced state, or not being diagnosed at all (Bowler & Hachinski, 2003; Rockwood et al., 2000; Erkinjuntti et al., 2000).

The diagnosis of VaD is also problematic because there is currently no agreed upon set of criteria (Chui et al., 2000; Gold, Bouras, & Canuto et al., 2002). Several diagnostic criteria are in widespread use, including the Hachinski Ischemic Score (HIS), Diagnostic and Statistical Manual of Mental Disorders (DSM-IIIR, DSM-IV), International Classification of Diseases (ICD-10), State of California Alzheimer's Disease Diagnostic and Treatment Centers (ADDTC), and the National Institute for Neurological Disorders and Stroke–Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN). Unfortunately, the criteria are not interchangeable and can lead to a five-fold difference in the frequency of classifying VaD (Verhey et al., 1996; Wetterling et al., 1996; Chui et al., 2000; Gold et al., 2002). A recent retrospective analysis using four classification systems for the clinical diagnosis of VaD indicated that classification varied widely as a function of criteria used such that

patients diagnosed with VaD using one set of criteria were not necessarily diagnosed with VaD using other criteria (Cosentino et al., 2004).

While criteria such as the ICD-10 allow for a differentiation of vascular dementia into subtypes (vascular dementia of acute onset, multi-infarct dementia, subcortical vascular dementia, and mixed or unspecified types), most do not allow for subtyping and require evidence of significant ischemic brain injury by structural neuroimaging (i.e., multiple infarcts). The limitation that strokes be clinically evident is highlighted by the fact that only 40% of patients with VaD have such focal signs (Bowler, 2002). It is thus argued that the problems inherent in the diagnosis of VaD may be associated with inadequate detection and diagnosis (Bowler & Hachinski, 2003). Indeed, the current criteria may fail to identify patients with significant cognitive loss caused by cerebrovascular disease and the emphasis on dementia may underestimate the burden of disease associated with early VaD. (Hachinski, 1992; 1994).

Failing to identify early VaD may distract from the focus on prevention which may have negative consequences with respect to treatment since, in contrast to AD, vascular risk factors are treatable and strokes can be preventable (Hachinski & Bowler, 2003; Erkinjuntti et al, 2000). Such patients will likely not have the opportunity for secondary preventive measures to delay or stop their progression to dementia (Hachinski, 1991, 1992, 1994; Bowler, 1993; Erkinjuntti & Hachinski, 1993; Hachinski & Bowler, 2003; Rockwood et al., 2004). Calling for an overhaul of current VaD criteria, Bowler (2002) fervently argued that VaD reflects an "outmoded concept" since it is based on criteria for Alzeimer's disease and urged for increased attention to be focused on subtler forms of vascular-related impairment.

A New Proposal: Vascular Cognitive Impairment (VCI)

Although vascular dementia (VaD) has been the subject of increased clinical research (Rockwood et al., 2004; Hachinski & Bowler, 2003), far less is known about the factors that contribute to the development of dementia among people with chronic cerebrovascular disease (CVD) compared to Alzheimer's disease (AD). Bowler and Hachinski (2002) report that the total burden of cognitive impairment of cerebrovascular origin may be very high. Specifically, 78% of elderly patients at autopsy have evidence of cerebrovascular disease as do over 80% of those who are demented (Bowler & Hachinski, 2002) and about 9 in 1000 people aged 85 years or over may develop VaD each year (Hachinski & Bowler, 2003). Just as subtle cognitive impairment may be present several years before the clinical diagnosis of AD (Meguro et al., 2001; Masur et al., 1994), such understated vascular-related cognitive deficits may be evident in early VaD. The crucial question is whether this common and important problem can be detected and halted before significant cognitive loss has occurred.

It has been argued that vascular-related cognitive impairment (VCI) be used to describe the early stage of VaD (Bowler, 2002; Hachinski, 1994; Erkinjuntti & Rockwood, 2001). However, currently, no universally accepted criteria have been formalized (mostly due to a relative lack of data with respect to early cognitive loss) and it has been suggested that, until formal criteria are proposed, criteria for VCI should be wide-ranging and broad (Bowler & Hachinski, 2003). Specifically, Bowler and Hachinski (2002; 2003) indicate that individuals should be considered for VCI when there is any evidence of cerebrovascular disease (with or without known risk factors or

neuroimaging findings) in the presence of associated cognitive impairment that does not reach the level of dementia (Bowler & Hachinski, 2003).

Using these broad criteria, preliminary data appear to support the validity of this concept of VCI (Ballard et al., 2003; Meyer et al., 2002; Wentzel et al., 2001). For example, Wentzel et al. (2001) recently reported that 50% of the subjects in their sample who met criteria for VCI developed dementia over five years. Additionally, Meyer et al. (2002) attempted to answer the question of whether an MCI stage precedes some cases of VaD by longitudinally following 291 volunteer subjects over one to seven years. Subjects were initially screened with the Mini-Mental Status Examination (MMSE) and tested annually with neuroimaging (MRI or CT). Follow-up of the 73 subjects who were diagnosed with MCI occurred every 3 to 6 months and results indicated that, of the 27 subjects who developed VaD within 7 years, roughly 56% had prodromal MCI. Similarly, Ballard et al. (2003) showed that approximately 9% of their MCI sample developed VaD over one year and almost half of the patients developed dementia over 5 years of follow-up. Taken together, these findings suggest that individuals with cognitive difficulties secondary to CVD are at increased risk for further cognitive decline and conversion to dementia. Indeed, it appears that MCI may represent a clinically heterogeneous group of individuals who are at elevated risk for dementia that is not solely restricted to AD and thus the concept of VCI appears to be a clinically useful and relevant.

Continuum of Impairment in Vascular Cognitive Impairment (VCI)

Hachinski & Bowler (2000) and others (Bowler, Steenhuis, & Hachinski, 1999; Devasenapathy & Hachinski, 2000; Bowler, 2000; Bowler, Steenhuis, & Hachinski,

1999; Garrett, Browndyke, & Whelihan et al., 2004) proposed that VCI exists on a continuum that is comprised of three primary stages (brain-at-risk (R-CVD; vascular cognitive impairment—no dementia (VaCIND); and vascular dementia (VaD)). The first stage--brain-at-risk (R-CVD)--is comprised of individuals with cardiovascular or other system disease processes who are at risk for developing cerebrovascular disease (with no clinically significant cognitive or functional impairments). VaCIND is the first hypothesized *clinical* stage preceding VaD (Hachinski, 1993) and is analogous to mild cognitive impairment (MCI) (Bowler & Hachinski, 2003). Like MCI, individuals with VaCIND do not have significant impairment in their ability to complete basic activities of daily living.

Chui, Mack, Varpetian, and Mungas (2003) have conceptualized VCI with finer degradations within the course of VaD. Their stages include:

1. brain at risk (presence of vascular risk factors)
2. early ischemic brain injury, but clinically asymptomatic
3. early symptomatic, but prior to diagnosis (cognitive decline by neuropsychological testing)
4. clinical diagnosis of VaCIND
5. clinical diagnosis of VaD
6. advanced dementia (severe VaD); and
7. death

According to Chui et al (2003) and others (Hachinski & Bowler, 2003; Rockwood et al., 2003; Skoog & Gustafson, 2003; Inzitari, Lamassa, & Pantoni, 2003), detection and attempts at intervention do not typically occur until individuals reach stage five or six

of Chui et al.'s (2003) VaD continuum, mostly due to the restrictive nature of the current diagnostic criteria for VaD, as discussed above. Unfortunately, adequate intervention at these stages is futile given that excessive cerebrovascular damage has typically occurred at these later stages. While research on vascular-related cognitive impairment (VCI) is in its infancy and only a few studies have been conducted to date, VaCIND is thought to be the best established concept for identifying at-risk patients with cerebrovascular disease (Stephens et al., 2004). Empirical support for the clinical concept has begun to develop--particularly in Asia and Europe--with a strong interest and emphasis on the early phases of the disease process.

Neuropsychological Impairment in VCI

A greater understanding of neuropsychological impairment evidenced during the early stages of VaD may have significant clinical implications since therapeutic interventions initiated early in the disease process may prevent progression to dementia (Bowler, 2000; Devasenapathy & Hachinski, 2000; Garret et al., 2004). However, to date, the neuropsychological profile of VaCIND has not received significant study. It has been shown that neurocognitive difficulties associated with cardiac disease and mild cerebrovascular disease include reduced information processing speed and reduced cognitive flexibility (Kilander et al., 1998; Rockwood, Dobbs, Rule, Howlett, & Back, 1992; Waldstein et al., 1996). Additionally, recent neuroimaging studies conclude that the magnitude of cognitive impairment among patients with mild cardiovascular disease is significantly associated with neuropathological changes secondary to vascular damage (Chui & Gonthier, 1999; Raz, Rodrigue, & Acker, 2003). As will be discussed in further detail, research has suggested that cardiac risk factors can be associated with cognitive

and neuropathological changes in the absence of frank stroke or dementia (Skoog, 1994; DeCarli et al., 2001; Swan et al., 1998).

The finding that cognitive functions mediated by frontostriatal circuits (i.e., executive functioning) are most disturbed during the late phases of VaD raises the possibility that mild changes in these cognitive functions may occur during the early stages of this dementia process. However, it remains unclear whether clinically meaningful changes are evident among patients in early stages of VaD. Furthermore, it is of clinical interest to determine if the difficulties on measures of frontal lobe functioning exist in the context of preserved function in other cognitive domains such as memory. As noted by Garrett et al. (2004), a pattern of strengths and weaknesses on cognitive measures may prove to be a critical determinant of diagnostic differentiation between the various stages of vascular-related cognitive impairment, as well as distinguishing vascular etiologies from other dementing conditions. Thus, the identification of a pattern of neuropsychological changes associated with the early stage of VaD (i.e., Va CIND) would greatly benefit diagnosis and facilitate intervention (Garrett et al., 2004).

Outcome of VCI

Vascular cognitive impairment (VCI) is associated with an increased risk for adverse outcomes. Rockwood et al. (2000) found that a failure to consider VCI underestimates the prevalence of impairment and the associated risk for adverse outcomes. Specifically, this study compared the rates of adverse outcomes for older patients with no cognitive impairment, VCI, and probable AD. After reassessment 5 years later, VCI was the most prevalent form of cognitive impairment among older adults

aged 65 to 84 years. Most strikingly, rates of institutionalization for those with VCI were similar to that of those with VaD, and the mortality rate for VCI patients was similar to that of patients with AD. Data such as these support the view that increased attention on subtle vascular-related cognitive impairment is important and clinically relevant. Moreover, criteria which require the diagnosis of dementia likely underestimate the prevalence and burden of vascular cognitive disease (Hachinski, 1994; Rockwood et al., 1994).

White Matter Lesion (WML) Pathology

In 1986, Hachinski coined the term "leukoaraiosis" to describe abnormal cerebral white matter changes as seen on CT scans (Hachinski, Potter, & Merskey, 1986; Hachiski, Potter, & Merskey, 1987). At about the same time, Awad, Spetzler, & Hodak et al. (1986) characterized these white matter changes as seen on MRI as "Incidental Subcortical Lesions." Initially termed "UBO's," or Unidentified Bright Objects, these changes have more recently been termed white matter lesions (WML) or hyperintensities. They are typically found in deep cerebral areas and as cappings on the lateral ventricles (Drayer, 1988) and are identified as signal hyperintensities on T2- and proton-density weighted magnetic resonance (MR) scans.

Potential Causes of WML

The precise etiology of WML is debated since numerous potential causes have been identified (Chui, 2001; Pantoni, Inzitari, & Wallin, 2000; Brown, 2000). For example, it is thought that WML can be caused by either arteriosclerosis causing direct occlusion of small arteries or by partial occlusion of small arteries in combination with cardiovascular failure (orthostatic hypotension, carotid sinus sensitivity, and congestive

heart failure) (Chui, 2001). In addition, WML appear to be attributed to other alterations in the brain, including increased fluid in the white matter, infarcts (stroke), and enlarged perivascular spaces (Munoz et al., 1993). Moreover, WML have been posited to be caused by subclinical ischemia secondary to cerebral hypoperfusion (Pantoni, Inzitari, & Wallin, 2000). Indeed, the cerebral white matter is the least irrigated compartment of the brain and thus it may be more vulnerable to the effects of ischemia and hypoperfusion (Brown, 2000; Pantoni & Garcia, 1997). Interestingly, the prefrontal brain regions appear to be most vulnerable given lower vasodilatory capacity versus white matter found in other brain regions (Brown, 2000).

Recent studies show that the most frequently observed pathological correlates of WML include gliosis (Fazekas, Schmidt, & Scheltens, 1998), myelin pallor (Fazekas et al., 1993, 1998; Takao et al., 1999), atrophy of the neuropil (Fazekas et al., 1998), breakdown of the ependymal ventricular lining (Scarpelli et al., 1994), and ischemia in the white matter (Chui et al., 2001). Considered to be rare before neuroimaging advanced to the MRI, WML pathology is now receiving considerable attention with respect to the understanding of cognitive, behavioral, and motor decline seen in dementia and, more recently, subtler neuropsychological impairment (Raz et al., 2003; Stephens et al., 2004; Garrett et al., 2004).

Major subtypes of WML

WML, which are best identified on T2-weighted, fluid-attenuated inversion recovery (FLAIR) and proton density magnetic resonance images, comprise both periventricular hyperintensities (PVL) and deep white matter hyperintensities (DWML). PVL are defined as signal abnormalities directly lining the ventricular lumen and involve

the white matter around the ventricles. This type of lesion is most frequently found adjacent to the frontal horns of the lateral ventricle, although these lesions can also be found laterally around the ventricle as well as around the posterior horns (Raz et al., 2003).

Although WML occur in different disorders and arise from a range of pathological processes (Everall et al, 1999), DWML appear to be vascular in origin, representing areas of ischemia as well as infarction (Awad et al, 1986; Fazekas et al, 1993; Thomas et al., 2002) and thus it has been argued that PVL and DWML may differ in their pathogenesis. DeCarli & Scheltens (2002) stress the need for these lesion types to be analyzed separately, a recommendation which was recently corroborated by a clinical study among patients with AD and dementia with Lewy Body (DLB) (Barber, Gholkar, & Scheltens, et al., 2000). Specifically, in this study, total brain, ventricular volumes, and white matter lesions were visually rated and quantified. PVL were found to independently correlate with advancing age and increasing ventricular size (suggesting atrophy) in all subjects. In contrast, DWML did not correlate with measures of brain atrophy or age, but were associated with a history of hypertension. These findings support the hypothesis that PVL and DWML are likely pathologically diverse. In particular, PVL appear to be linked to atrophic processes involving ventricular enlargement while DWML appear to be associated with cerebrovascular risk factors.

Relationship Between WML and Vascular Risk Factors

WML appear to be related to physical illnesses such as diabetes mellitus (Longstreth et al., 1996; Longstreth et al., 2000) and reach their highest prevalence in patients who have vascular dementia (Smith, Snowdon, Wang & Markesbery, 2000) and

depression (Kumar, Bilker, Jin, & Udupa, 2000). There is little controversy that WML increase with the aging process (Gunning-Dixon & Raz, 2000; Inzitari, 2000; Pantoni & Garcia, 1995; Schmidt, Fazekas, & Kapeller et al., 1999) and a threshold effect for cognitive decline has been hypothesized to be present (Munoz et al., 2003). However, the debate over identified WML centers on their clinical significance and it is still unclear whether they represent a pathognomonic sign for brain disease (Munoz et al., 2003; DeCarli & Scheltens, 2002; Inzitari, 2000).

While much attention has focused on the rising prevalence of AD (Marshall, Bradley, & Marshall et al., 1988; Jones, Lythgoe, & Horsfield et al., 1999), the impact of cerebrovascular risk factors on cognitive function is just being recognized (Markus, Lythgoe, & Ostegaard et al., 2000; Schmidt, Fazekas, & Kapeller et al., 1998). Studies have shown that advancing age and hypertension represent the two most significant risk factors for stroke as well as cardiovascular and peripheral vascular disease, suggesting that these disorders may share a common mechanism of vascular insult (Pantoni & Garcia, 1995; Wahlund, Barkhof, & Fazekas et al., 2001; Fazekas, Schmidt, & Alavi, 1998). Although less attention has been paid to the possible spectrum of brain injury resulting from other cerebrovascular disease risk factors, hypertension has been shown to be associated with increased WML volume (Chabriat, Pappata, & Poupon et al., 1999; Hanyu, Asano, & Sakurai et al., 1999). Moreover, the fact that WML significantly predict future stroke (Awad, Masaryk, & Magdinec et al., 1993) lends further support to the notion that WML are likely part of a spectrum of vascular-related brain injury (Roob, Lechner, & Schmidt et al., 2000).

In the Rotterdam Scan Study, a large population study in Europe, 27% of subjects between the ages of 65-84 years of age had evidence of WML on MRI which increased in prevalence significantly with age (Breteler, van Amerongen, & van Swieten, et al., 1994). Elevated blood pressure and cholesterol levels as well as hypertension were significantly associated with the presence and severity of WML. Also related to increased WML were history of stroke or myocardial infarction, and later studies showed an association with atrial fibrillation and carotid artery atherosclerosis (de Leeuw, de Groot, & Bots et al., 2000; de Leeuw, de Groot, & Oudkerk, et al., 2000). Taken together, these studies support previous observations that WML may represent a general measure of vascular disease (Manolio, Burke, & O'Leary, et al., 1996; O'Leary, Polak, & Kronmal, et al., 1996; O'Leary, Polak, & Kronmal, et al. 1999).

A recent longitudinal study of the National Heart and Lung and Blood Institute (NHLBI) found a relationship between cardiovascular risk factors (i.e., high blood pressure) occurring in middle age and the development of later-life brain insult (DeCarli, Miller, & Swan, et al, 1999). Specifically, there were strong correlations between mid-life systolic blood pressure (SBP) and later-life WML volume. Additionally, those with higher levels of WML volume at advanced ages had significantly higher rates of coronary artery disease compared to those with no WML. Results of this study suggested that WML may be the consequence of blood pressure changes beginning early (in middle age) and provides further evidence that WML appear to be associated with incident vascular disease. The authors of this study suggest that early and aggressive treatment of high blood pressure in middle age might significantly reduce vascular disease in later life (DeCarli et al., 1999).

VCI and White Matter Lesions

The contribution of WML to cognitive impairment is beginning to receive increased attention. Recent research has shown that 33% to 97% of cases of VaD evidence extensive WML (Wetterling, Kanitz, & Borgis, 1996; Pohjasvaara, Mantyla, Ylikoski, Kaste, & Erkinjuntti, 2000; Campbell & Coffey, 2001) and less extensive white matter lesions are thought to be evident in VCI (Erkinjuntti & Rockwood, 2001; Pohjasvaara et al., 2000). Bowler and Hachinski (2003) have reported that there is a need for research to focus on WML in terms of their association with subtle forms of cognitive impairment as well as how best to define the borders between normal aging, VCI, and VaD (Bowler & Hachinski, 2003).

The presence of vascular risk factors or cerebrovascular events in general may be sufficient to be diagnosed with VCI (Erkinjuntti & Rockwood, 2001). Although current criteria require evidence of stroke for a diagnosis of VaD, some studies are showing that silent infarcts and white matter lesions are relevant and may comprise early cases of VaD, or individuals with VCI (Erkinjuntti & Rockwood, 2001). Indeed, it has been shown that evidence of ischemic disease on neuroimaging (in the absence of stroke and atrophy) appear to be associated with cognitive impairment (Bowler, 2002). In fact, some researchers (Phillips & Mate-Kole, 1997; Emory, Gillie, & Ramdev, 1994) have argued that WML represent the beginning stage of a series of pathological processes which precede tissue infarction and suggest the term "pre-infarct state" to account for cognitive changes in patients who evidence WML, regardless of whether they evidence cerebral infarcts. Current research is beginning to focus on more subtle lesions and how they may be associated with neuropsychological impairment (Raz et al., 2003; Stephens

et al., 2004; Garrett et al., 2004). According to Sachdev & Looi (2003), more clearly defined differentiation of VaD from AD is likely to be greatly influenced by the extent of WML in the two groups.

In a longitudinal study of 27 individuals with MCI by Wolf et al. (2000), it was demonstrated that subjects who developed dementia after 2-3 years had more severe white matter lesions. In addition, there was an inverse relationship between WML and the degree of temporal lobe atrophy in those who progressed to dementia during the follow-up interval; thus, high WML severity was associated with lesser degree of temporal lobe atrophy and higher global cognitive performance, as measured by the SIDAM (Structured Interview for the Diagnosis of Dementia of Alzheimer Type). This illustrates how Subcortical (VCI) and Cortical seem to differ in their course and clinical picture. Specifically, it appears likely that those with greater levels of WML's and less medial temporal lobe atrophy may progress to VaD, whereas those with little to no WML and evidence of significant medial temporal lobe atrophy may be more likely progress to AD. Thus, WML appear to play a role in the dementia process and may accelerate decline in individuals with mild cognitive impairment.

Neuropsychological Deficits Associated with WML

Early research involving white matter lesions was quite mixed. While some studies pointed to a relationship between such lesions and neuropsychological functioning (Almkvist et al., 1992; Breteler et al., 1994a, 1994b), many found no relationship after controlling for age (Hunt et al., 1989; Tupler et al., 1992). It has been suggested that earlier research was hampered by many factors, including small sample sizes (Erkinjuntti et al., 1994; Mirsen et al., 1991), the use of inadequate and insensitive

tests that are rarely used with older populations (Mirsen et al., 1991; Hunte et al., 1998), differences in subject settings (Rao et al., 1989; Hershey et al., 1987), and the use of CT scans which are not very sensitive to WML (Diaz et al., 1991; Miyao et al., 1992; Skoog et al., 1993; Hershey et al., 1987).

Contrary to previous studies, more recent reports have demonstrated that WML appear to disrupt cognitive functioning and thus may have clinical significance (Amar et al., 1996; Breteler et al., 1994a, 1994b, Garrett et al., 2004; Rockwood et al., 2001). Indeed, although the effects are often subtle and mild, there has been a link between early VCI and white matter lesions and cognitive loss (Bowler, Hachinksi, Steenhuis, & Lee, 1998; Garrett et al., 2004; Rockwood et al., 2001). Consistent with deficits often evidenced in VaD, older individuals with numerous white matter lesions appear to perform worse on tests of speed and visuospatial function, even after controlling for age (Garrett et al., 2004; Cosentino et al., 2004). Additionally, while few studies have examined the distribution of WML and their effect on cognitive function, there is some evidence that the extent and pattern of WML is important in influencing cognitive performance (Raz et al., 2003). Specifically, associated deficits appear to be of a frontal-subcortical nature, affecting neuropsychological functions such as speed of processing and executive functioning; this relationship appears to be stronger with respect to deep white matter lesions (DWML) versus periventricular (PVL) WML (Garrett et al., 2004; Raz et al., 2003), although data is preliminary.

Recent studies have noted that the neuropsychological impairment sometimes seen in association with WML is similar to other types of subcortical dementing illnesses (Giovannetti-Carew, Lamar, Cloud, & Libon, 1997; Padovani et al., 1995; Libon et al.,

2001). Libon et al (1997) found a dissociation between tests of verbal declarative memory and executive systems functioning such that patients with vascular dementia obtained lower scores and made more perseverative errors on executive systems tests, but exhibited less forgetting, obtained higher tests scores on delayed free/cued recall and recognition test conditions, and made fewer intrusion errors than AD patients. This study also found that the pattern of neuropsychological impairment seen in dementia associated with subcortical WML was more similar to other subcortical dementing illnesses, such as Parkinson's disease (PD) and Huntington disease, than cortical dementing illnesses such as AD. Similar finding have been reported by Doody, Massman, Mawad, and Nance (1998).

In a more recent study by Libon and colleagues (2001) subjects were assessed with regards to WML quantity independent of clinical diagnosis. Individuals with a diagnosis of either vascular or Alzheimer's dementia were placed in groups representing either minimal-mild WML or significant WML. After being compared to patients with PD, it was found that neuropsychological testing failed to distinguish between those with PD and those with significant WML; additionally, those with significant WML demonstrated disproportionate impairment on tests of visuoconstruction and executive systems functioning, whereas patients with little WML showed greater impairment on tests of declarative memory and semantic knowledge. These findings point to a pattern of cognitive impairment associated with significant WML as distinctly different when compared to AD.

WML and Depression

Depression is a common psychological disorder in late life, with prevalence rates between 2% and 3% for major depression and 12% -- 15% for all depressive syndromes (Beekman et al, 1999). Recent growing evidence suggests that there may be a subtype of depression in later life—commonly termed "vascular depression"--that is characterized by a distinct clinical presentation and an association with cerebrovascular disease and thus the presence of white matter lesions (Alexopoulos et al, 1997; Krishnan, Hys, & Blazer, 1997; Krishnan, 2000). Similar to vascular dementia, it is thought that vascular disease somehow predisposes, precipitates, or worsens pre-existing depression. Indeed, depression is increased in dementia, with much higher rates in vascular dementia as opposed to Alzheimer's disease (Newman, 1999).

It is known that depression is highly prevalent in patients with diseases involving the cardiovascular system, such as hypertension, diabetes, coronary artery disease, and myocardial infarction (Carney et al, 1987; Rabkin et al, 1983). In addition, clinical studies have shown compelling links in both directions between some vascular disorders and depression. Indeed, depression is frequently elevated following a myocardial infarction and independently predicts an increase in mortality of about 350% during the next six months (Glassman & Shapiro, 1998). Conversely, longitudinal studies of initially healthy subjects have shown that depression itself can increase the risk of subsequent myocardial infarction or coronary artery disease by 300-400% (Glassman & Shapiro, 1998; Ford et al, 1998). Furthermore, hypertension is associated with a three-fold increase in major depression (Rabkin, Charles, & Kass, 1983) and depressive

symptoms appear to double the rates of subsequent hypertension (Jonas, Franks, & Ingram, 1997).

Other evidence that supports the vascular theory of late-life depression stems from research which has demonstrated that depression is a common occurrence in many patients in their first year post-stroke (House et al, 1991), with rates of depression reported ranging from 20-65% (Gordon & Hibbard, 1997; Pohjasvaara et al, 1998). In addition, the Alameda County Study recently demonstrated depressive symptoms to be an independent risk factor for subsequent fatal stroke, increasing fatal stroke by 50% over about 30 years (Everson et al, 1998). Finally, silent stroke has been associated with depression, even in the absence of a genetic predisposition or significant psychosocial events (Fujikawa et al, 1997).

In addition to the clinical work cited earlier, many MRI studies have consistently shown a relationship between WML and depression (Videbech, 1997; De Groot, 2000). WML associated with depression appear to be located predominantly in the deep white matter (Alexopoulos, Myers, & Yong, et al., 1997; Krishari, Hays, & Blazer et al., 1997; O'Brien et al, 1996). Interestingly, De Groot (2000) found that this relationship occurred independent of cognitive status, indicating that depressive symptoms may not be caused largely by a psychological reaction to declining cognitive function. In addition, the relationship between WML severity and depressive symptoms did not change when other possible confounders were controlled for such as presence of stroke and cortical atrophy.

As life expectancy continues to increase dramatically, the severity and incidence of neuropsychological impairment and dementia are expected to rise; the prevalence of vascular disease is estimated to increase as well. Thus, there is a significant need to

elucidate the relationship between alterations in cognitive state and white matter lesions. In addition, now that it is clear that Mild Cognitive Impairment represents a useful clinical entity, a focus must elucidate what constitutes MCI in an effort to identify those patients who may be helped by medical intervention before a full dementia syndrome is evidenced (i.e. those with cerebrovascular underpinnings).

CHAPTER 2
AIMS AND HYPOTHESIS

Primary Aims.

The primary aim of this study was to explore the relationship between white matter lesions (WMLs) and neuropsychological functioning in a sample of at-risk, pre-clinical, older adults who presented at the MSU Geriatric Neurology clinic and were diagnosed with Mild Cognitive Impairment (MCI) between the years 2000 and 2004. Structural MRI scans were analyzed for presence/absence of white matter lesions and volumetric analyses were used to assess the extent of pathology. In addition, neuropsychological test performance using the CERAD neuropsychological battery, Trails A and B, and the Stroop Color and Word Test were used to assess the relationship between WMLs and cognitive functioning in individuals with MCI.

Specific aims of the current study include the following:

I. Provide a detailed description of an MCI population in terms of neuropsychological performance. All cognitive data will be analyzed in order to evaluate whether MCI is indicative of a homogeneous group (i.e., evidencing a similar neurocognitive profile across neuropsychological domains) or, alternatively, if those with MCI represent a heterogeneous population with differing neuropsychological profiles.

II. Provided that reliable, distinct groups exist within the sample (based on neuropsychological performance), an analysis will be conducted to evaluate whether and how the groups differ with respect to total WML volume. Identifiable differences would provide evidence that MCI may arise through multiple etiologies rather than being exclusively attributed to Alzheimer's disease. While many different etiologies for MCI could be expected, major groups anticipated to emerge from the analyses (based on

current base rates for dementia) include a subpopulation demonstrating features of a cortical, degenerative etiology (i.e., pre-Alzheimer's dementia with corresponding neuropsychological deficits) as well as a subpopulation characterized by early vascular dementia (based on increased WMLs and their associated neuropsychological profile).

III. To date, research investigating neuropsychological deficits associated with WML types (periventricular and subcortical hyperintensities) has been largely contradictory and inconclusive. Therefore, the current study seeks to elucidate specific patterns of impairment associated with both lesion types by applying newer methodology (i.e., volumetric analyses of WML) and relating neuroimaging findings to neuropsychological performance.

Hypotheses.

Based on the theory that cognitive impairment associated with white matter lesions (WML) can be viewed within the context of a subcortical dementing syndrome (i.e., vascular dementia) the following hypotheses will be tested in this study:

1) Since it is thought that WMLs interrupt neural communication, it is expected that increased WML volumes will be associated with greater global cognitive impairment as evidenced by decreased performance on the MMSE.

2) It is expected that MCI does not represent a homogeneous population (i.e., solely Cortical) and will be better characterized as a heterogeneous group based on neuropsychological scores. Using cluster analysis, it is expected that the following two major groupings will emerge:

2a) One subpopulation is expected to evidence a neuropsychological profile consistent with early vascular dementia (Subcortical), with primary

deficits demonstrated on tasks of executive functioning, processing speed, and visuospatial/constructional abilities. This particular profile is expected given that vascular dementia arises from disruption of frontal-subcortical circuits, which are thought to be related to these specific aspects of neuropsychological performance.

2b) A second group with a profile similar to those with early Alzheimer's disease (Cortical) is hypothesized to exist within the sample. Based on numerous studies suggesting early degeneration of the medial temporal lobes in AD, specific impairments in memory and language (naming and fluency) are expected. Indeed, the medial temporal lobes are known to largely mediate memory and language functions.

3) If the expected groups are found within the sample (Subcortical and Cortical), the groups will be further assessed to determine whether they differ in terms of WML volumes. A functional dissociation of neuropsychological performance is expected with regards to levels and severity of WML as delineated below:

3a) Given that WML pathology has recently been shown to be associated with various vascular conditions such as hypertension and stroke, it is expected that the Subcortical group (based on neuropsychological profile) will evidence greater lesion load. This relationship is theorized to exist based on disruption of frontal-subcortical circuits within the brain secondary to WML pathology.

3b) Conversely, it is expected that subjects who appear more AD-like in terms of neuropsychological profile (greater deficits in language and

memory relative to executive functioning, speed of processing, and visuospatial skills), will evidence little or no WML pathology.

4) Although it is clear that two very distinct types of WML exist (deep white matter lesions (DWML) and periventricular white matter lesions (PVL)), specific associations with neuropsychological impairment are not well known. Therefore, both types of WML will be used to evaluate neuropsychological functioning in this sample as a whole and the following relationships are hypothesized to exist:

4a) DWML will be associated with greater overall neuropsychological impairment across cognitive domains versus PVL, irrespective of group membership. The relationship is posited to exist based on the theory that DWML may interrupt a larger number of critical neuropathways that are important for complex neuropsychological functioning.

4b) It is expected that DWMLs will more strongly predict executive impairments, slowed processing speed, and visuospatial/constructional difficulties, but will not be related to impairments on tests thought to be more sensitive to cortical or temporal lobe functions such as memory and language. Consistent with neuropsychological deficits evidenced in VaD, the relationship has been posited due to disruption between frontal-subcortical circuits associated with subcortical WML.

CHAPTER 3
METHOD

Sample

The sample for this study consisted of 70 community-dwelling older adults (aged 55 and older) who presented for cognitive complaints at the MSU Geriatric Neurology Clinic (an outpatient subspecialty of the MSU Neurology and Opthalmology Department). Subjects meeting criteria for MCI were included in this study after a careful health screening (described below). The participants consisted of 33 males (47%) and 37 females (53%), and ranged in age from 55 - 88, with a mean age of 75 (SD = 7.9). The mean years of education completed was 13.3 (range = 8 - 24, SD = 3.4). Finally, MMSE scores ranged from 24-30 (per outlined criteria for MCI described below), with a mean of 26.3 (SD = 1.6). All patients who underwent neuropsychological testing and neuroimaging (MRI) as part of their clinical care and data collected between February, 2000 and July, 2004 were included in this study. The average number of months between neuroimaging and neuropsychological assessment was 4 months (range 1 week to 13 months), with neuropsychological testing typically taking place before imaging was completed. The procedures in the present study were approved by the Michigan State University Committee on Research Involving Human Subjects (UCRIHS).

Medical history was obtained for the patients through clinic records and patients were carefully screened for and excluded from the study based on any current or past diagnoses of neurological or psychiatric disorder, stroke, thyroid disease, diabetes, known head injury, or any significant visual or auditory impairment which precluded them from participating in neuropsychological testing. Additionally, individuals not meeting neuropsychological criteria for MCI (i.e., demented or cognitively normal) were not

included in this study. Neuropsychological classification of MCI was conducted independently of the white matter lesion (WML) quantitative analyses. From the original sample of 99 patients who met criteria for MCI using Petersen's guidelines (Petersen, 1999, 2001; see below), 15 were excluded from the study due to severe health conditions such as multiple sclerosis or stroke, as well as psychiatric reasons (i.e., schizophrenia, severe depression). Seven subjects were excluded because only CT scans were available, making reliable identification of WMLs difficult. Three individuals identified as outliers were excluded based on extreme white matter pathology found on MRI indicative of white matter disease. Finally, 4 subjects were excluded based on poor scan quality due to movement-artifact or insufficient image sequences to perform all of the analyses required for this study.

Procedures

Diagnosis of Mild Cognitive Impairment (MCI)

A diagnosis of MCI was based on meeting all of the following criteria delineated by Petersen (2004): 1) subjective patient memory complaints; 2) normal activities of daily living; 3) absence of diagnosable dementia; 4) normal MMSE score as determined by a score of 24 or greater; and 5) mild quantifiable impairments of cognitive function; specifically, greater or equal to 1.2 standard deviations below the mean on any neuropsychological subtest.

To identify participants with MCI, all neuropsychological scores were standardized with a z-score transformation on the basis of the CERAD or other normative data of the neuropsychological tests (Welsh et al., 1994), following the guidelines for such calculations as outlined by Moser et al. (2000). Scores that reflected number of

errors or response times were multiplied by -1, so that negative z-scores consistently reflected poor performance. Impairment on a single test or subtest was operationally defined as a z-score of -1.2 or lower (after controlling for age, education, and gender using adjusted norms), indicating a level of performance worse than 88.5% of the population (mildly to moderately impaired range).

Neuropsychological Test Battery

Prior to testing, all participants were interviewed in order to obtain necessary demographic information. A neuropsychological test battery and a depression screen (Geriatric Depression Scale) were administered. All cognitive tasks were administered to each participant individually by a technician who was blind to the participant's medical status and MRI results. All tests were administered in standard paper/pencil format and the sequence of neuropsychological tests was the same for all subjects. The battery of tests administered was selected to assess a broad range of neuropsychological functions including attention, executive functioning, language abilities, memory, and visuospatial/construction. Specifically, the neuropsychological battery of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) neuropsychological battery (Welsh et al., 1994), Trails A and B, and Stroop Color Word Test were administered. General cognitive status was assessed with the Mini-Mental Status Examination (MMSE) (Folstein, Folstein, & McHugh, 1976).

The CERAD is a brief neuropsychological assessment battery which was developed for the diagnosis and staging of dementia (Morris et al., 1989). Altogether, it is a reliable, well-standardized, and normed battery which includes seven individual tests that tap several domains including executive functioning, memory (Word List Memory

Task; Welsh, Butters, et al., 1994), praxis/visuoconstruction, attention/orientation, and language functioning (naming, animal fluency).

Specific test components of the CERAD include: *Verbal fluency* (Isaacs & Akhtar, 1972) that requires naming as many animals as possible in 60 seconds; *Modified Boston Naming* (Kaplan, Goodglass, & Weintraub, 1983) that requires naming 15 drawings (of the original 60) ranging in frequency of occurrence in common usage; *Word List Learning* that requires immediate recall of words in 10-item list, presented in random order on three consecutive occasions; *Word List Recall* that requires free recall of words on 10-item list; *Word List Recognition* that requires identification of the original 10 words of Word List from a list of 20 words; *Mini-Mental State Examination (MMSE)* (Folstein, Folstein, & McHugh, 1975) that requires answering questions and/or performing activities related to several areas of cognitive functioning; *Constructional Praxis* (Rosen, Mohs, & Davis, 1984) that requires copying four basic geometric designs; and *Constructional Praxis Recall* that requires recall of the geometric designs drawn in the original condition;

In this study, the CERAD battery was supplemented by the inclusion of additional common neuropsychological tests to augment the assessment of processing speed and executive functioning (Trails A and B and Stroop Color Word Test). Trails A, a test of psychomotor speed, involves visual scanning and drawing lines between numbers from 1-20. Trails B, a measure of executive functioning, is a more complex version of Trails A which requires the subject to mentally alternate drawing lines between numbers and letters, in chronological and alphabetical sequence. To control for speed of processing, time to complete Trails A was subtracted from time to complete

Trails B. Finally, the Stroop Color and Word Test is a measure of cognitive flexibility and inhibition ability. This timed test measures the subject's ability to inhibit the tendency to read words and, instead, focus on the color of incongruent word/color pairs.

MRI Protocol

All MR imaging was performed on 1.5-T Signa scanners (General Electric, Milwaukee, WI). WML volumes were estimated from T2-weighted axial Fluid-attenuated inversion recovery (FLAIR) images with the following parameters: FOV = 20 x 20 cm; matrix = 256 x 256; flip angle = 90 degrees, TE=142 ms, TR=10000 ms, 5 mm slice thickness with no interslice gap. All MR scans were examined for space-occupying lesions, and all questionable cases (lesions or other neurological conditions such as white matter disease) were evaluated by a neuroradiologist (Mark Delano, MD).

Quantification of White Matter Lesions

WMLs have been shown to be better identified on MR versus CT scans (Kirshner et al., 1985; Paty et al., 1998); therefore, only MR scans were considered for evaluation. The current study employed a semi-automated volumetric approach (Pixel Thresholding) using T2-weighted FLAIR images, a methodology which was recently shown to be the most reliable approach for the analysis of WML when compared to other image types and traditional quantitative visual rating scales (Price, Schmalfuss, Sistrom, 2005). Training to reliably measure WML took place at Wayne State University, following the protocol established by Raz et al. (2001) and Gunning-Dixon and Raz (2000) who have published extensively on white matter pathology. Volumetric measures of WML were obtained based on 17-21 axial, T2-weighted FLAIR images per subject using GE's Advantage Workstation software (v. 4.2). This user-automated program is widely used to complete

volumetric analyses on MR images. Hyperintense regions, defined as circumscribed areas of increased signal intensity within the white matter, were identified and measured on axial slices of the T2-weighted FLAIR images beginning at the most inferior slice on which the inferior horn of the lateral ventricles could be seen. Hyperintensities were coded according to their presence, volume, and type (periventricular (PVL) and deep white matter (DWML). Briefly, WML were considered to be PVL if the largest diameter was abutted next to the ventricular lining; otherwise, they were considered to be subcortical. All questionable cases were resolved by consulting an experienced neuroradiologist and the correlative images in an MRI neuroanatomy atlas (Damasio, 1995; DeArmond, Fusco & Dewey, 1976; Montemurro & Bruni, 1988; Ono, Kubik, & Abernathy, 1990).

As described in detail by Raz, Rodrigue, and Acker (2003), the total volume of each region in cubic centimeters was calculated by multiplying the summed pixel cross-sectional area in square centimeters by slice thickness in centimeters. Intra-rater and inter-rater reliabilities for this method have been shown to be high (DeCarli et al., 1992b). Since two operators completed the WML measurements, inter-rater reliability coefficients were computed based on a random sample of 5 traced brains. The intraclass correlation formula for two random raters (ICC(2); Shrout & Fleiss, 1979) was used, and the resulting reliability estimates for all regions of interest and types of WML exceeded 0.80. Finally, relative head size was controlled for by taking into account gender in all WML analyses.

Statistical Analyses

A number of statistical procedures were used to address our hypotheses and a) evaluate the presence of distinct groups within the sample based on neuropsychological performance across domains, b) examine the role of white matter lesions on cognitive performance, and c) further characterize these groups based on neuropsychological profile and white matter pathology. Additionally, statistical analyses were conducted to investigate the role of deep white matter lesions (DWML) and periventricular white matter lesions (PVL) on cognitive performance. Cluster analysis using Ward's method, discriminant analysis, analysis of variance (ANOVA), and multiple regression were used for this study and all statistical analyses were performed using the Statistical Package for the Social Sciences for Windows (SPSS, 2004). Before beginning any statistical analyses, missing data were estimated based on the expected maximization algorithm using the computer software program Systat (Version 11). Approximately 5% of the data for two variables (Stroop and GDS) needed to be estimated (because these instruments were added to the clinic's neuropsychological battery a few months after data collection began).

Correlational analyses were conducted to determine whether total lesion load was associated with poorer performance on the MMSE, a global measure of cognition (Hypothesis 1). Cluster analysis was performed in order to assess for the presence of groups based on neuropsychological performance (Hypothesis 2). Specifically, Ward's minimum variance cluster analysis (Ward, 1963; Kaufman & Rousseau 1990) was used to identify patterns of impairment. This type of hierarchical agglomerative method takes into consideration all possible combinations of profiles, computes a distance measure

(squared Euclidean distance) between profiles, and combines the pair with the smallest sum of squared difference to the first cluster. Profiles are continued to be combined which minimizes the increase to the within-group sum of squared variance. Ward's technique parcels the total sum of squares into within-group and between-group variability, thus yielding a measure of the percentage of variability accounted for by the clustering solution.

Before beginning the cluster analysis, composite scores were computed for the various cognitive domains of interest. When performance in the various cognitive domains was assessed by more than two tests, the test scores were combined (their significant correlations supported this approach). Specifically, two composite scores were computed (one for executive functioning and one for memory). A composite score for executive functioning was computed due to the presence of a high correlation between total time to complete Trails B and the Stroop Color-Word Test Interference score ($r = .69$, $p < 0.001$). Additionally, a composite score for memory was computed by combining the CERAD word list delayed and recognition memory scores as well as the praxis (visual) memory score, all of which were moderately correlated (between .26 and .42; $p < .05$).

All neuropsychological scores were converted to z-scores before being entered as variables for the cluster analysis [(Memory composite (Mem), Executive Functioning composite (EF), Processing Speed (Speed), Visuospatial/Construction (VS), Confrontation Naming (Naming), and Verbal Fluency (Fluency)]. The number of clusters was set *a priori* to two to reflect the expected theoretical distinction between cortical dysfunction (Cortical) and subcortical impairment (Subcortical). However, given

that patients may exhibit cognitive profiles consistent with both types of pathology, an additional cluster analysis was performed with the number of clusters set to three (allowing for the possibility of a "mixed" profile to emerge). A comparison was made between all cluster structures to identify best data fit. In all cluster analyses, no constraints were imposed on the numbers of participants in each cluster or the profiles of neuropsychological performance across groups. Thus, the data were allowed to empirically define the subgroups to address the question of whether the cognitive profiles exhibited by patients with MCI segregate into theoretically meaningful subsets. Finally, to assess whether group differences based on cognitive performance were statistically meaningful, a 3 (group) X 6 (cognitive domain) MANOVA was conducted. Post hoc analyses were employed using Tukey's HSD to evaluate how each group differed with respect to neuropsychological functioning.

To determine whether neuropsychological scores (predictors) can be combined to predict group membership reliably and whether neuropsychological test scores accurately predicted the cluster groups (classification), discriminant analysis was performed. Discriminant analysis (DA) maximizes group differences by creating a weighted linear combination of the predictor variables (Kleinbaum et al., 1988), such that differences between groups are maximized using weights in the disciminant function. The Wilk's lambda coefficient was computed to test the significance of the discriminant function and the partial Wilk's lambda was used as a measure of the contribution of individual neuropsychological variables to the discriminant function (Norusis, 1988). The partial Wilk's lambda of a given variable ranges between 1 (when all group means are equal) and 0 (when between groups variability largely outweighs within groups variability).

To determine whether groups differed on white matter lesion load (Hypothesis 3), a univariate analysis of variance (ANOVA) was conducted. Group membership was entered as the independent variable and total lesion load was entered as the dependent variable, while controlling for age, education, gender, and depression. All group differences were evaluated in post hoc analyses using independent samples t-tests. All differences were considered statistically significant at $p < 0.05$.

To evaluate Hypothesis 4, a series of linear regression analyses was used to determine which lesion type (DWML or PVL) predicted poorer overall neuropsychological performance across cognitive domains. Lesion type was entered as the independent variable and overall neuropsychological functioning (NP) was entered as the dependent variable (computed as a composite variable from all neuropsychological tests), after controlling for age, education, gender, and depression in the first block. Additionally, a 3 (group) x 2 (lesion type) MANOVA was conducted to examine differences in the severity of WML (DWML and PVL) across group. Finally, several linear regression analyses were performed to determine the effect of DWML on each neuropsychological measure or domain.

CHAPTER 4
RESULTS

Table 1 provides descriptive statistics and intercorrelations for all variables of interest in this study. As can be seen in the table, there was a reasonable amount of variability in all of the measures with two exceptions. Variability was lacking for the MMSE (possibly related to its truncrated range (24-30) per MCI criteria, and some of the CERAD neuropsychological measures (i.e., low ranges for memory and naming). Ceiling effects can be expected given that the sample is comprised of individuals who, despite some mildly to moderately impaired scores, are relatively high functioning. As might be expected, higher age was associated with overall poorer neuropsychological functioning. In addition, higher levels of education and lower levels of depression appeared to be strongly associated with higher performance on overall neuropsychological functioning as well as lower volumes of white matter lesions (regardless of type). The results of more detailed analyses, which take into account specific neuropsychological variables and cluster groupings are found below.

Hypothesis 1

A Pearson's correlation coefficient was computed to test the hypothesis that WML would be associated with MMSE performance. Results indicated that total WML was not found to be significantly correlated with MMSE ($r = -.122$).

Hypothesis 2:

To determine whether distinct groups could be identified within the sample based on cognitive performance, a cluster analysis was performed. Initially, the number of clusters was set *a priori* to two, reflecting the theoretical distinction between cortical dysfunction (Cortical) and subcortical impairment (Subcortical).. Results indicated that

the 2-cluster solution produced widely unbalanced groups (group 1, n = 60; group 2, n = 10) and the resulting dendogram indicated that group 2 could be split into two distinct subgroups. Consequently, an additional cluster analysis was performed with the number of clusters set to three, allowing for expression of greater heterogeneity in the sample. The resulting solution produced three groups (n = 18, 18, and 34). The means and standard deviations for each of the three groups on the six cognitive variables are presented in Table 2.

The profiles of neuropsychological performance for the different clusters conformed to expectations concerning the existence of both cortical and subcortical groups. That is, based on group means, group 1 (labeled "Cortical"), demonstrated a neuropsychological profile consistent with a cortical process, performing significantly worse on tests of memory and language (fluency and confrontation naming). Conversely, group 2, labeled "Subcortical," demonstrated the opposite pattern of results, with poorer executive functioning (EF), visuoconstruction (VS), and processing speed (Speed). Both the Cortical and Subcortical groups exhibited impaired fluency, with the Cortical group performing more poorly. The third group exhibited only impaired memory and was labeled "Amnestic." Interestingly, the Amnestic group performed better than the other two groups in most domains (i.e., fluency, processing speed, and visuoconstruction). A graphical representation of the neuropsychological performance of each group can be found in Figure 1.

One-way ANOVA indicated that each cluster group differed with respect to overall neuropsychological functioning ($F_{(2, 67)} = 49.5$, $p < .001$). Results from a MANOVA with group as the independent variable showed that the groups differed

significantly on EF, VS, Speed, VS, Fluency, and Naming ($p < .001$). Additionally, group differences existed based on memory performance. However, memory performance was the weakest predictor ($F = 3.26$, $p < .05$) and post hoc analyses using Tukey's HSD demonstrated that the Cortical and Subcortical groups did not differ on this domain. Furthermore, the Amnestic group performed significantly better on fluency than both Cortical and Subcortical groups ($p < .001$). It is important to note that the Cortical group and the Subcortical group did not differ significantly on fluency performance. Finally, the Cortical group performed significantly worse on naming than the other 2 groups ($p < .001$); however, no significant differences were found between the Subcortical and Amnestic groups on this measure.

Demographically, the clusters differed significantly by age ($F_{(2, 67)} = 4.19$, $p < .02$), education ($F_{(2, 67)} = 8.21$, $p = .001$, and levels of depression ($F_{(2, 67)} = 9.24$, $p < .001$). However, no group differences were found based on MMSE scores or gender. Table 3 includes the demographic data for the 3 groups defined by the cluster analysis. Post Hoc tests using Tukey's HSD demonstrated that the Cortical group was significantly older than the Amnestic group ($p < .02$), but no difference in age was found between the Subcortical group and the Cortical group or the Amnestic group. The Amnestic group was significantly more educated than both the Cortical ($p = .001$) and Subcortical groups ($p < .020$), but there was no significant difference in education between the Cortical and Subcortical groups ($p > .05$). Finally, the Subcortical group was significantly more depressed than the Amnestic group ($p < .001$). There was also a trend toward significant difference based on depression between the Cortical and Amnestic groups on depression

($p = .075$). Overall, a linear relationship was found for depression according to each cluster group as illustrated in Figure 2.

To determine whether group membership could be predicted from the neuropsychological test scores as a whole, a direct discriminant function analysis was performed using the six cognitive variables as predictors of membership in the three cluster groups. Because the discriminant analysis was performed between three groups, two discriminant functions were generated and subject classification was based on a weighted combination of the scores along each function. The first discriminant function accounted for 81 % of the differences among the three groups ($F_{(2, 67)} = 144.4$; Wilk's lambda = 0.085, $p < .001$). Individual discriminant scores correlated significantly ($p < 0.001$) with executive functioning, processing speed, and visuospatial/construction as illustrated in the structure matrix (Table 4). The first discriminant function appears to be consistent with what would be expected in subcortical, or vascular dementia (i.e., primary deficits in executive functioning, processing speed, and visuoconstruction). ANOVA results showed a significant group effect of discriminant scores ($F_{(2, 67)} = 144$, $p<0.001$) and post hoc analysis revealed that each group differed significantly from each other. The group categorized as Subcortical had a significantly different pattern of neuropsychological results with generally poorer executive functioning, processing speed, and visuospatial/visuoconstructional skills than the other groups. The group discriminant score means (group centroids) for the discriminant function are presented in Table 5.

The second discriminant function explained the remaining variance (19%) and was significant ($F_{(2, 67)} = 44.7$; Wilk's lambda = .476, $p < 0.001$). Individual discriminant

scores correlated significantly ($p < 0.001$) with naming, fluency, and memory, neuropsychological domains which are largely implicated in a cortical dementia such as Alzheimer's disease. However, it is important to note that the absolute correlation for memory was only .17, indicating that this variable was not generally important in defining the discriminant function. The group discriminant score means are listed in Table 5. Post hoc analyses (Tukey's HSD) demonstrated that, while the second function discriminated between all other groups, it did not significantly discriminate between the Subcortical and Amnestic groups. Using the full predictive model, the six variables correctly classified 18 Cortical subjects (100%), 18 Subcortical subjects (100%), and 33 Amnestic subjects (97.1%). The overall rate of correct classification was 98.6% and all but one subject used to derive the discriminant function was correctly classified.

Examination of the biterritorial map of standard scores on the first and second discriminant functions (Figure 3) revealed three distinct clusters consistent with a unique neuropsychological pattern for each group. The Amnestic group clustered in the positive range of the first function (Subcortical), but near zero in the second function (Cortical). The Cortical group clustered around zero on the first function and in the negative range of the second function. Finally, the Subcortical group tended to cluster in the negative range of the first function and around zero of the second function. As shown in Figure 3, the first discriminant function maximally separated VaD from the other two groups, while the second discriminant function discriminated AD from the other two groups.

The stability of the classification procedure was checked by a cross-validation run using leave-one-out classification in SPSS. Classification for the originally derived cases was 98.6% and fell somewhat to 94.3% for the cross-validation cases. One Cortical

person was misclassified as Amnestic and 3 Amnestics were classified as Cortical. Overall, this pattern indicates a high degree of consistency in the classification scheme.

Although the Amnestic group was not initially hypothesized to exist in the sample, results provide support for Hypothesis 2 in terms of specific neuropsychological profiles found for the other two groups in the sample (Cortical and Subcortical). Specifically, the Cortical group demonstrated deficits primarily in language and verbal memory with relatively preserved executive functioning, processing speed, and visuoconstruction; conversely, the Subcortical group demonstrated the opposite pattern of results.

Hypothesis 3:

Given that distinct subgroups were identified within the MCI patient sample, all three groups were assessed in terms of total WML volume. A one-way ANOVA revealed that total WML volumes differed by group membership ($F_{(2, 67)} = 30.82, p < .001$). Planned comparisons revealed that the Subcortical group had significantly greater WML volume load than both the Cortical ($t_{(34)} = -4.82$, $p < .001$) and Amnestic groups ($t_{(50)} = -9.13$, $p < .001$). The Cortical and Amnestic groups did not differ significantly in terms of total lesion load; however, there was evidence of a trend ($t_{(50)} = 2.00$, $p = .051$). Although lesion volume between the Cortical and Amnestic groups did not significantly differ, the Cortical group demonstrated a slightly greater lesion load than the Amnestic group. Moreover, the Subcortical exhibited roughly twice as much WML as the Cortical group and almost three times the total WML volume of the Amnestic group as can be seen in Figure 4. Means and standard deviations, and specific contrasts between means that were significant can be seen in Table 6.

Hypothesis 4:

In order to assess whether DWML versus PVL is associated with greater neuropsychological impairment, the effect of lesion type on overall neuropsychological functioning (NP) was tested using correlation analyses and hierarchical multiple regression. First, to assess overall neuropsychological functioning (NP), a composite variable was created using all the means for the six neuropsychological variables. Correlations were calculated to assess relationships between lesion type and overall NP. Results demonstrated that PVL and DWML were highly correlated ($r = .76$, $p < .001$) and that overall neuropsychological functioning was negatively associated with both PVL ($r = -.47$, $p < .001$) and DWML ($r = -.54$, $p < .001$) as can be seen in Table 3. Although age was strongly related to overall NP ($r = -.41$, $p < .001$), no relationship was found for gender. Additionally, higher levels of education were associated with better overall NP ($r = .42$, $p < .001$). Interestingly, level of depression was more strongly associated with overall NP than age or education ($r = -.53$, $p < .001$).

Linear regression was performed in order to assess prediction of overall neuropsychological functioning from lesion types. Given the high correlations between the predictors (PVL and DWML), separate regressions were conducted on each lesion type. Age, education, gender, and depression were entered into the first block and lesion type was entered in block two (see Table 7). For the first regression with PVL as the predictor of interest, age, education, gender, and depression alone accounted for 45.9% of the variance in the model ($F_{(4, 69)} = 13.81$, $p < .001$). In block 2, PVL volume did not significantly add to the prediction of overall NP functioning ($\Delta R^2 = .09$, $p > .05$). For the second regression (see Table 8), with DWML as the main predictor of interest, the

prediction of NP functioning incremental to that of the predictors in Step 1 was significant ($\Delta R^2 = .034$, $p < .001$), although the main effect was not large. Interestingly, correlational analyses demonstrated that age appears to be positively associated with PVL ($r = .253$, $p < .05$), but not DWML. Moreover, education was associated with both PVL ($r = -.346$, $p < .01$) and DWML ($r = .284$, $p < .02$). Finally, level of depression was strongly correlated with both lesion types (PVL, $r = -.612$, $p < .001$; DWML, $r = -.631$, $p < .001$).

In order to assess the relationship between DWML and individual neuropsychological variables, correlations were first examined. As indicated by Table 3, DWML was correlated significantly with executive functioning, processing speed, and visuospatial/construction ($p < .001$). DWML was also negatively correlated with Fluency ($p < .05$). A series of standard multiple regressions were performed with DWML entered as the dependent variable and each of the neuropsychological variables as independent variables, after controlling for age, education, gender, and depression. As expected, DWML strongly predicted poorer Executive Functioning ($\beta = -.65$; $\Delta R^2 = .25$, $p < 0.001$), Processing Speed ($\beta = -.56$, $\Delta R^2 = .18$, $p < .001$), and Visuospatial/Construction ($\beta = -.53$, $\Delta R = .17$, $p < .001$) as can be found in Tables 9-11. In addition, DWML was not found to significantly predict Naming, Fluency, or Memory (see Tables 12-14 which summarize the results of each of these analyses). While the relationship was not significant, there was a trend for Fluency to be negatively associated with lesions in the deep white matter.

CHAPTER 5
DISCUSSION

The clinical concept of mild cognitive impairment (MCI) has recently been proposed to describe the transitional state between healthy aging and early dementia (Petersen et al., 1999; 2001; 2003) and, while research to date has demonstrated considerably high conversion rates to dementia (Petersen et al., 1999; Palmer et al., 2003), many researchers and clinicians have conceptualized MCI as representative of pre-clinical AD, with little attention paid to possible heterogeneity of this vulnerable, at-risk population. This study set out to examine whether heterogeneity exists in MCI in terms of neuropsychological performance. Additionally, the role of white matter lesions was investigated in order to better understand cerebrovascular contributions of pre-clinical cognitive decline within the sample. The current study investigated both neuropsychological and neurological correlates in a clinical sample of patients diagnosed with MCI in an effort to better characterize the population.

Relationship of White Matter Lesion Volume to Overall Cognitive Functioning

The first hypothesis set out to assess whether total WML volume in the brain is associated with global cognitive impairment as measured by the MMSE. However, contrary to expectations, the relationship was not significant. Given that the scores on the MMSE ranged from only 24 to 30 in keeping with MCI criteria, it is likely that ceiling effects occurred due to the truncated range of scores. Thus, identifying impairment in this relatively high functioning sample based solely on the MMSE was difficult given the narrow range of scores. Additionally, the MMSE is not sensitive to subtle neuropsychological impairment and the measure largely taps verbal and memory functions, cognitive domains which are known to be negatively impacted in early

manifestations of AD but not VaD. Indeed, the MMSE does not measure executive functioning or psychomotor speed and minimally measures visuospatial/constructional skills, major areas of neuropsychological functioning which are thought to be primarily impacted in VCI. Moreover, other recent studies have not found differences in AD and VaD patients regarding the total amount of WML and MMSE scores (Aharon-Peretz et al., 1998) and other measures of global cognition (Giubilei et al., 1997).

Neuropsychological Performance and MCI Group Membership

Results of the cluster analysis based on neuropsychological scores indicated that, at least for the present sample, MCI can be described as a heterogeneous population. Specific groups were found within the sample which generally conformed to expectations. Specifically, one group demonstrated deficits on tests of memory and language, with relatively intact executive functioning, processing speed, and visuospatial/construction, appearing consistent with what might be expected with a cortical etiology such as AD. A second group emerging from the analysis (labeled Subcortical), demonstrated the opposite pattern of results, with primary deficits revealed on tests of executive functioning, processing speed, and visuospatial/construction.

The initial clustering of two forced clusters produced widely unbalanced groups and suggested the inclusion of a third group. It was initially presumed that the third group would be indicative of subjects with a "mixed" pathology (i.e., subjects who present with deficits commensurate with the combination of early Alzheimer's disease and concomitant vascular pathology); however, results indicated otherwise. Specifically, evaluation of group means indicated that this group performed within normal limits on all

neuropsychological domains, with the exception of memory. Interestingly, this group, labeled "Amnestic," was the largest, with an *n* almost twice that of the other groups.

Given that a large percentage of individuals with MCI do not convert to dementia, it is reasonable to posit that the identified third group may itself be heterogeneous for a variety of reasons, representative of subjects who present with isolated memory impairment for numerous reasons. First, given that it is well documented that early AD is marked by memory impairment, this group may be comprised of individuals who are in very early stages of early AD. Indeed, this group evidenced the lowest volume of WML which might be expected with a degenerative dementia such as AD. Second, although subjects with severe depression were not included in the study, it is likely that individuals in this group may show isolated memory impairment secondary to psychiatric reasons such as mild to moderate depression or anxiety (the latter of which was not measured in this sample). Furthermore, individuals in this group may exhibit memory as a relative weakness in relation to other neuropsychological functions as a function of what might be expected in a normally distributed population (i.e., these individuals may fall on the low end of the normal curve on memory functions). Alternatively, it may be that this third group possesses more cognitive reserve given significantly higher levels of education compared to the other groups. Indeed, research has shown that higher levels of education may be a protective factor which may delay or prevent the development of progressive dementia (Bennett, Wilson, & Schneider et al., 2003; Cabeza, Anderson, & Locuntore, 2002; Mortimer, Snowdon, & Markesbery, 2003). Finally, the Amnestic group presented with significantly lower levels of depression which also may have served as a buffer against cognitive decline. Thus, the third group is perhaps most interesting as it is likely

composed of at-risk individuals for dementia as well as those who show subtle memory deficits secondary to normal aging or psychiatric reasons.

Discriminant analysis demonstrated that group membership could be predicted from neuropsychological performance and overall predictive classification was high. The first discriminant function, with significant correlations with executive functioning, speed, and visuospatial/construction, maximally separated the Subcortical group from the other groups, while the second discriminant function, with significant correlations with memory, naming, and fluency discriminated the Cortical group from the other groups. Thus, the first discriminant function is consistent with hypothesized deficits which would be expected in a population with subcortical or vascular etiology and the second discriminant function is in line with a cortical process such as Cortical. In terms of overall neuropsychological functioning based on severity of deficits, results indicated that, while the Amnestic group differed significantly from both the AD and Subcortical groups, there was no difference in severity between both the Cortical and Subcortical groups. Thus, while considerable differences existed between the types of deficits exhibited in these groups, overall severity did not differ.

The strongest predictor for the first disciminant function was executive functioning, with speed and visuospatial/construction contributing equally. Conversely, the strongest predictor for the second discriminant function was confrontation naming ability which is known to be impaired early in the process of early AD. While poorer memory correlated with this discriminant function, its overall contribution was rather minimal. This finding was somewhat unexpected given that memory has traditionally been thought to be one of the earliest indicators of early AD. Thus, this study highlights

the possibility that language (naming ability) and not memory may be more differentially affected early in the process of a dementing syndrome such as AD. Indeed, a recent study using fMRI demonstrated that, despite adequate memory, language appears to be affected early in normal aging (Wierenga, Perlstein, & Benjamin et al., 2005) and, possibly, early dementia. In the current sample, education predicted naming ability more strongly than any other neuropsychological variable and thus it is reasonable to assume that the Cortical group performed more poorly than the other groups on this task given their lower educational level. However, the Cortical group demonstrated significantly poorer naming ability than the other groups, even after controlling for education.

Direct comparisons between groups revealed that all groups differed significantly with respect to executive functioning, visuospatial/construction, and processing speed. However, it is interesting to note that, while naming ability discriminated between the two most impaired groups (Cortical and Subcortical), semantic fluency did not (they were equally impaired). Recent research has shown that fluency impairment tends to be equally impaired in both vascular dementia and Alzheimer's disease (Vuorinen, Laine, and Rinne, 2000) and, while no differences appear to exist between the dementia types with respect to semantic fluency, letter fluency appears to best discriminate between the groups, with the VaD group performing significantly worse (Canning, Leach, Stuss, Ngo, & Black, 2004). Unfortunately, a limitation of the current study is that only semantic fluency was measured in the sample.

Interestingly, although memory has received the most attention in terms of diagnoses of mild cognitive impairment and dementia of the Alzheimer's type, it only discriminated between the Subcortical and Amnestic groups and, overall, served as the

weakest predictor in our analyses. While there was a trend for memory to discriminate between the most impaired groups (Subcortical and Cortical) the relationship was not significant. This relationship may exist for a few reasons, namely that memory testing as part of this study was not extensive and ceiling effects may have occurred. Indeed, the range of scores on learning and recall tasks was narrow, ranging from 0 to 10, which may not have been large enough to detect subtle fluctuations in memory functioning in this generally high functioning sample. Additionally, only verbal memory (and not visual memory) was assessed which may have lead to limited findings.

Although age was strongly related to overall neuropsychological functioning, no relationship was found for gender. Additionally, education appeared to be a protective factor, with higher levels being associated with better overall neuropsychological performance. It is interesting to note that level of depression was more strongly associated with overall cognitive functioning than age or education. Overall, results indicated that the two most impaired groups (Cortical and Subcortical) were not significantly different in terms of age, education, or levels of depression; however, qualitatively, the Cortical group tended to be older, less educated, and less depressed. As stated earlier, the Amnestic group was younger than the other groups, with significantly higher levels of education. Moreover, the Amnestic group as a whole was significantly less depressed than the other groups.

Total White Matter Lesion Volume and MCI Group Membership

Each cluster group was evaluated in terms of total WML volume in order to determine whether group differences existed within the sample. As expected, the group with a neuropsychological profile consistent with what would be expected in vascular

dementia (Subcortical) evidenced significantly greater WML volume than the group whose neuropsychological profile appeared consistent with a cortical degenerative etiology (Cortical). The third group which was not initially hypothesized to exist within the sample demonstrated the least total WML pathology. Although the Cortical and Amnestic groups did not differ statistically in terms of lesion load, the Amnestic subgroup appeared to be the least impaired in terms of both neuropsychological profile as well as mean total WML pathology found on MRI.

Interestingly, all MCI subgroups evidenced some level of WML. Given the relationship of WML with age (Papademetriou, Narayan, & Rubins et al., 1998; Jorgensen, Nakayama, & Raaschou et al., 1994) and common vascular risk factors such as hypertension (Knopman et al., 2001) and atherosclerosis (Phillips & Mote-Kole, 1997), it is reasonable to assume that all groups as a whole would demonstrate WML on MRI. However, in terms of expression of significant neuropsychological impairment meeting criteria for MCI (and possibly later expression of dementia), a threshold may exist whereby clinically salient cognitive deficits may be driven by the preponderance of early WML pathology. Indeed, some studies have shown a threshold effect where extensive amounts of WML are necessary before cognitive impairments are seen (DeCarli, Murphy, & Trank et al., 1995; Schmidt, Fazekas, & Koch et al., 1995; Boone, Miller, & Lesser et al., 1992).

More recently, studies have shown WML in AD (Barber, Scheltens, & Gholkar et al., 1999; Fazekas, Kapeller, & Schmidt et al., 1996; Scheltens, Barkhof, & Leys et al., 1995); however, this relationship is not well understood. First, some researchers have begun to question the prevalence of "pure" dementia syndromes and it may be that many

patients evaluated in this study are representative of mixed pathologies not limited solely to vascular dementia or Alzheimer's disease. Second, heterogeneity may exist within AD. While research in this area is limited, a recent study (Leeuw, Barkhof, & Scheltens, 2004) argues for the identification of two syndromes within Alzheimer's disease, one of which evidences greater cerebrovascular disease and small vessel disease involvement. More research in this area is clearly needed as this, to date, appears to be the only study suggesting this relationship. Alternatively, WML in AD may be representative of a different process or pathology. For example, WML may exert its deleterious effects on the brain in a different manner (i.e., by primarily inducing neurodegeneration). Alternatively, WML may interact with AD to increase the prevalence of dementia in late life (Breteler, Bots, & Ott, 1998; DeCarli & Scheltens, 2003). Indeed, a recent study suggests that WML may increase the likelihood of conversion to AD (Wolf et al., 2000). Finally, there may be heterogeneity in terms of white matter changes such that other non-vascular etiologies of dementia may lead to WML. Specifically, WML in AD may be the consequence of amyloid deposition in cerebral vessels (Alonzo, Hyman, Rebeck, and Greenberg, 1998).

While a relationship was expected between WML and depression based on previous published studies, it was somewhat surprising that depression was the most significant correlate and predictor of WML in this study (over and above the effects of age and education). This association highlights the need for additional studies investigating the relationship between vascular risk factors and depression in the context of aging (i.e., vascular depression hypothesis). Additionally, while a recent study demonstrated that higher educational attainment appears to modulate the impact of WML on cognition (i.e.,

high level of education protects against the cognitive deterioration related to vascular insults of the brain) (Dufouil, Alperovitch, & Tzourio, 2003), the current study demonstrated that higher education may protect against the mere presence of WML seen on MRI. This relationship is difficult to explain, however higher education is likely associated with greater cognitive reserve as described above which may protect against neurological insult. Additionally, higher education may be linked to lower levels of cerebrovascular disease given environmental factors such as greater access to health care.

Periventricular and Deep White Matter Lesion Volumes and MCI Group Membership

Given that very few studies have analyzed white matter lesion types separately, this study set out to examine the contribution of both PVL and DWML on neuropsychological functioning in MCI. Results indicated that, while the Cortical and Subcortical groups differed considerably in terms of DWML (with the Subcortical group evidencing significantly greater volume as expected), the groups did not differ significantly in terms of PVL. Additionally, only DWML significantly predicted overall poorer neuropsychological functioning and this type of lesion significantly predicted performance on tests of executive functioning, speed of processing, and visuospatial/constructional skills but not tests of verbal memory or language.

Overall, all groups demonstrated similar levels of PVL and, in these analyses, this lesion type appeared to be less important in differentiating the groups. This relationship may be explained by a relative lack of range of PVL volume scores as compared to DWML volumes across groups. Additionally, it may that PVL is not representative of pathological change in the brain and, instead, represents normal changes with age. Indeed, some researchers have argued that WML located along the borders of the

ventricles reflect breakdown of the ependymal lining and are both more common and less reflective of pathology than DWML (Coffey, 2000; Van Petten et al., 2004). Indeed, PVL are commonly observed in non-demented, healthy elderly (Shinkawa, Ueda, & Kiyohara et al., 1995; Ott, Stolk, & van Harskamp et al., 1999). Finally, while DWML appears to be related to ischemia, examinations comparing imaging results with histopathological findings indicate that some PVL appear to be related to myelin pallor or rarefaction without other convincing evidence for ischemia (Hachinski, Potter, & Merskey et al., 1986; Hachinski, Potter, & Merskey, 1987; Yue, Arnold, Longstreth et al., 1997). Indeed, PVL tends to correlate more strongly than DWML with advanced age and atrophy than the Hachinski Index (Hachinski, Iliff, & Zilhka, 1975), a commonly employed measure of vascular burden. Morever, the Hachinski Index was recently found to be weakly related to PVL (Bigler et al., 2003).

Unlike PVL, there appears to be strong evidence that DWML is caused by ischemia (Hachinski, Potter, & Merskey et al., 1987;Steingart, Hachinski, & Lau et al., 1987) and correlative MRI-histopathological studies provide support for a relationship between DWML and microangiopathy. For example, extensive DWML are usually associated with arteriolar vessel-wall changes (Hachinski et al., 1987; Steingart et al., 1987) and the frequent observation of concomitant lesions such as lacunes is also in support of vascular mechanisms leading to WML. Further compelling evidence comes from the large number and extent of WML usually found in patients with known microangiopathy such as those suffering from intracerebral hemorrhage (DeCarli, Miller, & Swan et al., 1999).

Interestingly, a double dissociation was evidenced between type of WML and neuropsychological profile (group). Specifically, while the Cortical and Amnestic groups demonstrated similar WML profiles (slightly higher levels of PVL versus DWML), the Subcortical group exhibited the opposite lesion pattern (much higher level of DWML versus PVL). To date, this appears to be the only existing study which has demonstrated this pattern of relationship between neuropsychological profiles in MCI and their association with WML. Since PVL appears to be related to atrophy and age, it may be that this lesion type is associated with both aging and early AD, although additional research is needed in this area in order to elucidate this relationship.

Given the strong association in other studies between DWML and ischemia and other vascular risk factors (i.e., hypertension, atherosclerosis), combined with the neuropsychological pattern of results associated with DWML in the current study, it may be that early manifestations of vascular cognitive impairment associated with DWML lead to deficits in neuropsychological impairments dependent on the integrity of frontal-subcortical circuits (executive functioning, speed of processing, and visuospatial/constructional skills). Specifically, these neuropsychological deficits may be the result of small vessel disease disrupting frontal-subcortical pathways (Cohen et al., 2002; Burton et al., 2003; Vataja et al., 2003 Meyer et al., 2004). More substantial global cognitive impairment seen in later stages of dementia may be more multi-factorial and related to a combination of specific infarcts coupled with concurrent atrophy and more extensive small vessel disease. Recently, Stephens et al. (2004) showed that attentional and executive impairments occur early in the process of VaD, with memory and language

deficits more indicative of individuals who are more progressed in the process of dementia.

Limitations and Future Directions

To our knowledge, the results presented here represent one of the only studies to date employing cluster analysis to an MCI population and investigating the relationship of WML to associated neuropsychological impairment. However, it is important that the findings reported here be viewed within the context of several methodological limitations. Specifically, in an effort to increase sensitivity to subtle cognitive impairment, inclusion criteria may not have been appropriately strict and thus subjects aging normally may have been included (i.e., MCI was often conceptualized as impairment in only one neuropsychological domain). Additionally, the cross-sectional nature of this study makes it difficult to assess the accuracy of group membership as well as whether and how groups convert to dementia. Finally, it should also be noted that some of the neuropsychological measures used in this study (CERAD) were designed as screening instruments in the assessment of cognitive deficits of aging and disease (Welsh *et al., 1994*). As such, some of the tests used in this study represented abbreviated versions of the original, which likely restricted the range of neuropsychological performance. Indeed, using abbreviated tasks may result in less sensitivity in detecting brain-behavior relationships.

There are a few confounds in terms of the neuroimaging aspect of this that are worthy to note. For example, while this study attempted to assess heterogeneity in MCI, no specific measure of cerebral atrophy was employed. This is important given that atrophy is a common finding in AD. Additionally, MRI methods used in this study

cannot elucidate underlying cellular mechanisms of WML. As mentioned above, some studies have indicated that white matter abnormalities reflect a number of pathological processes and structural MRI prevents a reliable discrimination among such mechanisms. Furthermore and, perhaps most importantly, the current technology does not allow identification of specific affected white matter tracts. Better differentiation of white matter lesions as well as clarification of the underlying pathological causes of WML should be easier to attain with newer MRI approaches that are becoming more available (i.e., diffusion tensor imaging (DTI), magnetization transfer) (Kapeller, Ropele, & Fazekas, 2000). Specifically, DTI allows for the assessment of the directionality of white matter damage which should make clearer specific associations of individual tracts and bundles in the white matter (Peled, Gudbjartsson, & Westin et al., 1998).

Finally, the generalizability of the findings reported here is limited to those individuals who are typically highly educated, independent, and relatively free of age-associated cerebrovascular risk factors such as TIA or stroke. Therefore, this sample is likely neither typical nor representative of the general population of older adults. However, given that the selection criteria restricted the range of white matter abnormalities observed in this study, these results may represent a conservative estimate of the role of WML in MCI.

Conclusion

The concept of Mild Cognitive Impairment (MCI) has only recently been proposed to describe the transitional state between normal cognitive functioning and dementia. Given that there is currently no reliable treatment or intervention available for cognitive impairment that reaches the level of dementia, there has been a shift towards

better identification and understanding of pre-clinical manifestations of progressive cognitive impairment. Using the most reliable quantification approach (pixel-thresholding) and MRI sequences (FLAIR) available for measuring and identifying WML (Price et al., 2005), this study provided evidence for heterogeneity within MCI and related WML pathology to identified groups within the sample, demonstrating that groups differed with respect to total WML as well as overall lesion profile. Moreover, results of this study indicate that WML appears to be associated with specific neuropsychological deficits dependent upon frontal-subcortical circuitry, including executive functioning, processing speed, and visuospatial/construction.

Future directions should attempt to address the possibility of the co-mingling of vascular pathology, aging, and early AD pathology (Arvanitakis & Hachinski, 1999) as well as the use of newer techniques described above (i.e., diffusion tensor imaging). Given the growing prevalence of cognitive disorders in late life (associated with population increases of older adults) and advances in health care, longitudinal studies following older subjects (with and without vascular risk factors and associated WML) from very early stages of cognitive impairment will be important in order to further elucidate and understand early, preclinical manifestations of cognitive impairment which may progress to dementia.

Table 1: Descriptive statistics and intercorrelations among demographic, neuropsychological, and WML variables.

	M	SD	1.	2.	3.	4.	5.	6.	7.	8.	9.	10.	11.	12.	13.	14.
1. Age	75.5	7.5	1													
2. Educ	13.3	3.4	-.09	1												
3. MMSE	26.3	1.6	-.39*	.24*	1											
4. Speed	-59.4	24.8	-.24*	.24*	.23	1										
5. VS	9.6	1.4	-.17	.18	.13	.47*	1									
6. Naming	13.6	1.1	-.20	.28*	.08	.03	.02	1								
7. Fluency	15.0	3.8	-.22	.46*	.16	.37*	.33*	.22	1							
8. EF	0.0	.75	-.33*	.29*	.38*	.71*	.52*	.07	.29*	1						
9. Memory	0.0	.92	-.01	-.01	.28*	-.10	-.07	.19	-.00	-.04	1					
10. WML	12.0	8.1	.21	-.34*	-.09	-.58*	-.48*	-.04	-.25*	-.75*	.21	1				
11. PVL	5.8	3.4	.25*	-.35*	-.09	-.44*	-.29*	-.20	-.22	-.60*	.07	.21	1			
12. DWML	6.2	5.3	.15	-.28*	-.06	-.59*	-.54*	.05	-.25*	-.76*	.28*	.25*	.75*	1		
13. GDS	7.7	6.7	.13	-.34*	-.08	-.40*	-.34*	-.23	-.40*	-.56*	.08	.66*	.61*	.66*	1	
14. Tot NP	0.0	.58	-.41*	.42*	.36*	.71*	.66*	.44*	.64*	.74*	.28*	.13	-.49*	-.52*	-.53*	1

Notes: Edu = Education; VS = Visuospatial/Construction; EF = Executive Functioning; WML = white matter lesions; NP = Neuropsychological Functioning; PVL = Periventricular lesions; DWML = Deep white matter lesions; DEP = Depression; Tot NP = Total Neuropsychological Functioning; Means for EF, Memory, and Tot NP are 0 since these represent composite scores. N = 70. *p < .05.

Table 2: Group means and standard deviations on neuropsychological variables by group membership.

	Clusters		
Variable	**Subcortical**	**Cortical**	**Amnestic**
Executive Functioning (EF)	-1.27 (.45)	.06 (.80)	.64 (.60)
Memory (Mem)	.49[b] (.74)	-.27[b] (.79)	-.12[b] (1.14)
Visuospatial/Constructional (VS)	-1.04 (1.04)	-.25 (.72)	.68 (.40)
Processing Speed (Speed)	-1.13 (1.06)	.04 (.43)	.57 (.62)
Category Fluency (Fluency)	-.44[c] (.94)	-.72[c] (.68)	.61 (.79)
Confrontation Naming (Naming)	.41[d] (.65)	-1.04 (1.08)	.33[d] (.63)

Note. Within each row, means having the same letter in their superscripts are not significantly different from each other at the .05 level.

Table 3: Demographic data (means and standard deviations) by cluster groupings.

	Clusters		
Variable	Subcortical	Cortical	Amnestic
Age	76.3 (7.2)	79.2 (5.8)	73.2 (7.8)
Gender	6M, 12W	9M, 9W	18M, 16W
Education	12.2 (2.9)	11.5 (1.8)	14.9 (3.7)
MMSE	25.8 (1.7)	25.9 (1.2)	26.8 (1.7)
Depression (GDS)	12.2 (6.3)	8.7 (8.2)	4.8 (4.4)

Table 4: Structure of the discriminant functions

Variable	Structure Matrix	
	DF1	DF2
Executive Functioning (EF)	.59*	-.12
Visuospatial/Construction (VS)	.49*	.15
Processing Speed (Speed)	.46*	-.09
Confrontation Naming (Naming)	.00	.75*
Verbal Fluency (Fluency)	.27	.48*
Memory (Mem)	-.12	.17*

Table 5: Functions at Group Centroids (Means)

Groups	DF 1	DF 2
Cortical/Cortical	-.20	-1.74
Subcortical/Subcortical	-3.26	.70[a]
Amnestic	1.83	.55[a]

Note: Within each column, means having the same letter in their superscripts are not significantly different from each other at the .05 level. Unstandardized canonical discriminant functions were evaluated at group means.

Table 6: Means and standard deviations on WML Total Volume across clusters

Group	Mean	Standard Deviation
Cortical	11.4_a	7.9
Subcortical	$21.0_{a, b}$	3.2
Amnestic	7.5_b	5.8

Note: Means with same subscripts differ significantly from each other using the Tukey post-hoc test ($p < .001$).

Table 7. Hierarchical regressions for PVL as a predictor of overall neuropsychological functioning (NP).

Step and Predictors	Statistics for Step					Statistics for Predictors	
	R^2	df	ΔR^2	Δdf	ΔF	β	t
Step 1	.459	4	—	—	13.81**		
Age						-.34	-3.63**
Education						.24	2.49*
Gender						-.02	-.20
Depression						-.40	-4.01**
Step2	.468	5	.09	1	11.26**		
PVL						-.13	-1.02

Notes: * $p < .02$ and **$p < .001$. Dependent variable is Overall Neuropsychological Functioning. PVL = Periventricular lesions.

Table 8. Hierarchical regressions for DWML as a predictor of overall neuropsychological functioning (NP).

Step and Predictors	Statistics for Step					Statistics for Predictors	
	R^2	df	ΔR^2	Δdf	ΔF	β	T
Step 1	.459	4	—	—	13.81**		
Age						-.34	-3.64**
Education						.24	2.49*
Gender						-.02	-.20
Depression						-.40	-4.01**
Step2	.493	5	.034	1	12.47**		
DWML						-.24	-2.07*

Notes: *p < .05 and **p < .001. Dependent variable is Overall Neuropsychological Functioning. DWML = Deep white matter lesions.

Table 9. Hierarchical regressions for DWML as a predictor of executive functioning (EF).

Step and Predictors	Statistics for Step					Statistics for Predictors	
	R^2	df	ΔR^2	Δdf	ΔF	β	T
Step 1	.388	4	—	—	10.32**		
Age						-.25	-2.49*
Education						.11	1.01
Gender						.01	.13
Depression						-.50	-4.66**
Step2	.635	5	.247	1	22.23**		
DWML						-.65	-6.57**

Notes: * $p < .05$ and **$p < .001$. DWML = Deep White Matter Lesions.

Table 10. Hierarchical regressions for DWML as a predictor of Processing Speed (Speed).

Step and Predictors	Statistics for Step					Statistics for Predictors	
	R^2	Df	ΔR^2	Δdf	ΔF	β	T
Step 1	.202	4	—	—	4.122*		
Age						-.19	-1.63
Education						.10	.85
Gender						-.02	-.15
Depression						-.33	-2.75*
Step2	.379	5	.177	1	7.800**		
DWML						-.56	-4.26**

Notes: * p = .02 and **p < .001. DWML = Deep White Matter Lesions.

Table 11. Hierarchical regressions for DWML as a predictor of Visuospatial/Construction (VS).

Step and Predictors	Statistics for Step					Statistics for Predictors	
	R^2	Df	ΔR^2	Δdf	ΔF	β	T
Step 1	.136	4	—	—	2.55*		
Age						-.12	-1.02
Education						.07	.53
Gender						-.00	-.01
Depression						-.30	-2.40*
Step2	.303	5	.167	1	5.56**		
DWML						-.53	-3.92**

Notes: *p < .001; **p<.05. DWML = Deep white matter lesions.

Table 12. Hierarchical regressions for DWML as a predictor of Confrontation Naming (Naming).

Step and Predictors	Statistics for Step					Statistics for Predictors	
	R^2	Df	ΔR^2	Δdf	ΔF	β	T
Step 1	.126	4	—	—	2.35		
Age						-.16	-1.31
Education						..23	1.81
Gender						.02	.14
Depression						-.14	-1.08
Step2	.134	5	.008	1	1.43		
DWML						.10	1.12

Notes: DWML = Deep white matter lesions.

Table 13. Hierarchical regressions for DWML as a predictor of Verbal Fluency (Fluency).

Step and Predictors	Statistics for Step					Statistics for Predictors	
	R^2	Df	ΔR^2	Δdf	ΔF	β	T
Step 1	.320	4	—	—	7.66**		
Age						-.19	-1.78
Education						.34	3.10*
Gender						-.15	-1.41
Depression						-.22	-1.94
Step2	.324	5	.004	1	6.13**		
DWML						.08	.57

Notes: * $p < .02$ and **$p < .001$. DWML = Deep white matter lesions.

Table 14. Hierarchical regressions for DWML as a predictor of Memory (Mem).

Step and Predictors	Statistics for Step					Statistics for Predictors	
	R^2	Df	ΔR^2	Δdf	ΔF	β	T
Step 1	.102	4	—	—	1.85		
Age						-.29	-2.34*
Education						-.01	.08
Gender						.08	.60
Depression						.10	.77
Step2	.135	5	.033	1	1.54		
DWML						.15	.82

Notes: * $p < .05$. DWML = Deep white matter lesions.

Figure 1: Neuropsychological Profiles by Cluster Group

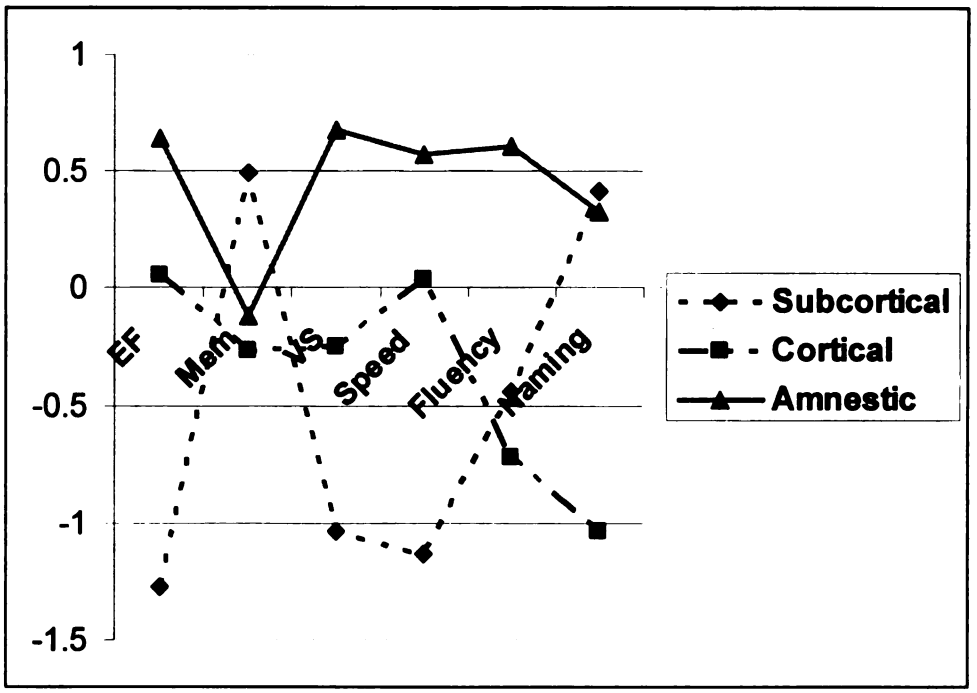


Figure 2: Depression Levels as a Function of Group

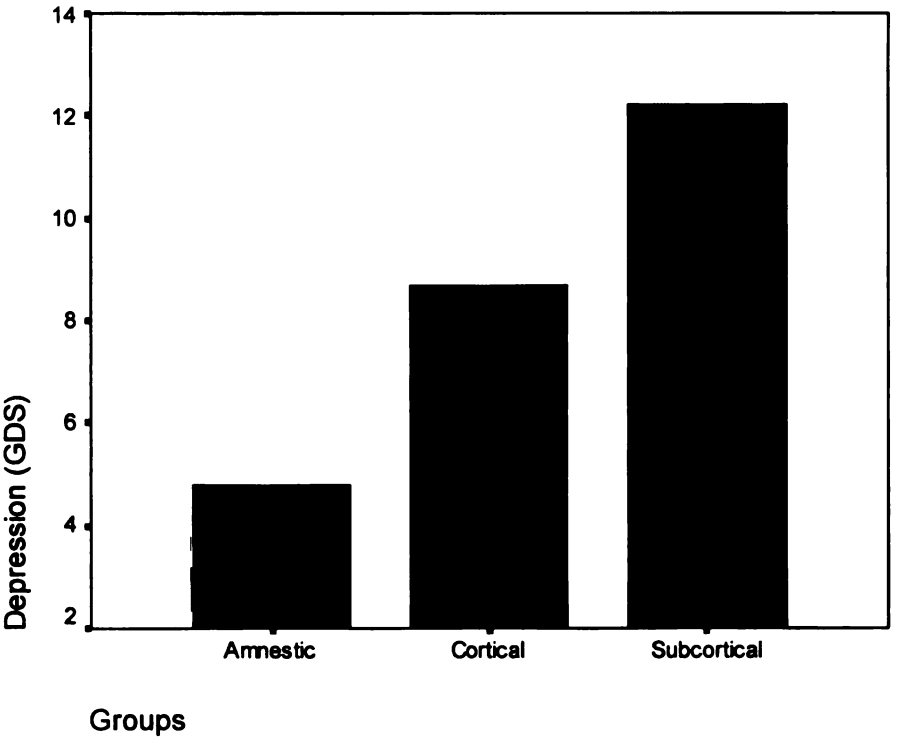


Figure 3: Biterritorial Map of Discriminant Functions

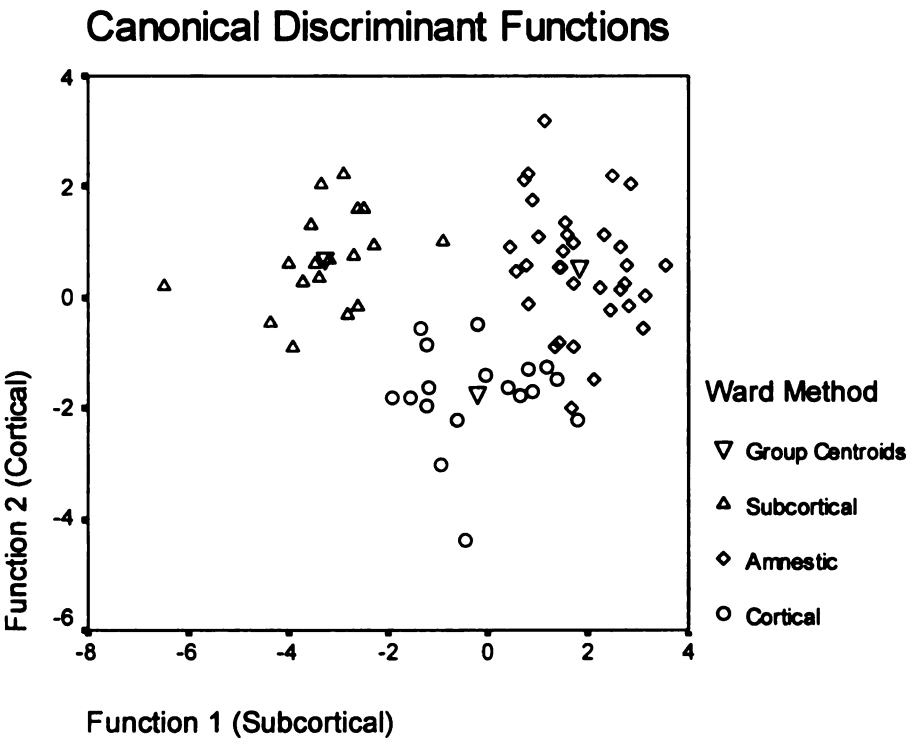
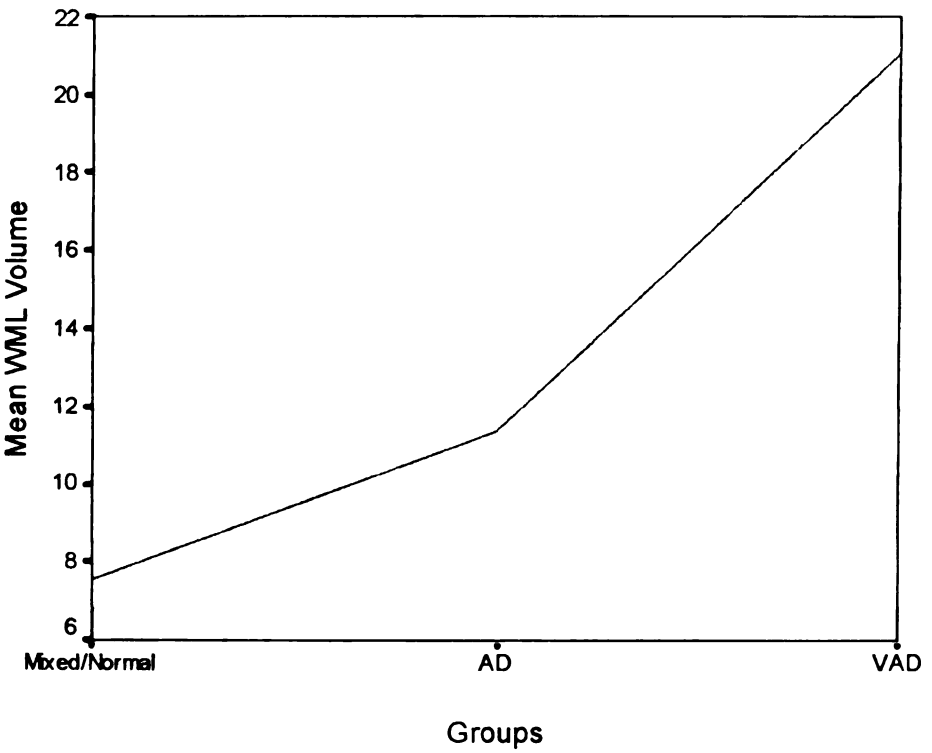


Figure 4: WML Volume as a Function of Group



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