NEUROPSYCHOLOGICAL CORRELATES OF LEUKOARAIOSIS IN ALZHEIMER'S DISEASE, MILD COGNITIVE IMPAIRMENT, AND NONDEMENTED ELDERLY

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Dedicated in loving memory to

Gilbert Carroll McDonald and Alma Jane Norris

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ABSTRACT

Leukoaraiosis (LA) refers to neurodegenerative white matter changes that are associated with age and appear as areas of hyperintensity on magnetic resonance imaging (Hachinski, Potter, and Merskey, 1987). Leukoaraiosis has been associated with cognitive impairment and

vascular risk factors in nondemented elderly (DeCarli et al., 1995; deGroot et al., 2000), while the relationship with demented elderly is unclear. The current study examined the severity of LA, the relationship between vascular risk factors and LA, and associations between neuropsychological functioning and LA across three groups with varied levels of cognitive functioning. Total LA was more severe among subjects with Alzheimer's Disease (AD, $n = 30$) than those with Mild Cognitive Impairment (MCI, $n = 30$) and nondemented elderly (NE, $n = 30$), but MCI did not have more severe LA than NE. Periventricular and subcortical LA were more severe in AD than MCI, but not NE. Age was a significant predictor of both periventricular and subcortical LA, but hypertension and homocysteine were not independently related to LA. Total LA was inversely associated with neuropsychological performance for all subjects, though correlations were low to moderate ($r = -.23$ to $r = -.36$), and were not significant after controlling for the effects of age and cerebral atrophy. Within the AD group, several significant positive correlations between LA and neuropsychological measures emerged, but were reduced when controlling for age, but not atrophy. Results for periventricular LA were similar to total LA findings, while subcortical LA had fewer correlations with neuropsychological measures. Neuropsychological measures of general cognitive functioning, verbal fluency, memory, and executive functioning were associated with increased total and periventricular LA, while measures assessing confrontation naming, visuoconstructional ability, and attention were less affected. Across all subjects, age and cerebral atrophy contributed to associations between neuropsychological performance and LA. Despite greater atrophy and LA in the AD group, neuropsychological functioning was not associated with increased LA within the AD group

in the current study. This suggests that relationships between LA and neuropsychological functioning may be identifiable in normal controls, but that disease characteristics play a larger role in cognition in dementia populations such as Alzheimer's disease.

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CHAPTER ONE: INTRODUCTION

Vascular dementia and Alzheimer's disease (AD) have been historically regarded as separate clinical entities. More recently, considerable evidence has emerged to demonstrate that vascular risk factors and cerebrovascular disease may increase the risk of both vascular dementia and AD. However, vascular risk factors and cerebrovascular disease can lead to various cognitive deficits that may or may not progress to dementia.

Leukoaraiosis (LA) is a term that refers to neurodegenerative white matter changes that are associated with increasing age and other risk factors, and are captured by neuroimaging techniques (Hachinski, Potter, & Merskey, 1987). Leukoaraiosis is prevalent in vascular dementia, AD, and in the nondemented elderly population. The causes, risk factors, and clinical significance of LA, especially regarding its impact on cognition, are largely unknown but are a current focus of research. The etiology of LA is not clearly understood, but appears to be multifactorial resulting from ischemic, genetic, and other physiological processes. Risk factors for LA include age, hypertension, plasma homocysteine levels, and other cerebrovascular risk factors (Hogervorst, Ribeiro, Molyneux, Budge, & Smith, 2002; Sawada et al., 2000). Risk factors for LA overlap with those found in vascular dementia and AD. The prevalence and severity of LA increase with age, and studies suggest that 30% to 80% of nondemented individuals over the age of 60 possess some degree of LA on neuroimaging (Coffey & Figiel, 1991). LA is more common in individuals with vascular dementia, followed by AD and then nondemented elderly (Leys et al., 1990).

Recent developments in neuroimaging technology have allowed for easier detection of these white matter changes and spurred research to better understand its contribution to various disease processes.

Recent clinical evidence supports LA as more than a secondary factor in a dementing process. Those with LA have a poorer prognosis in terms of increased rates of death, stroke, and myocardial infarction. It also appears that LA may be an independent risk factor for stroke (Inzitari, 2003). Psychiatric disorders such as depression have been associated with LA, and neurological concomitants exist, including disruption in gait, balance, grasp reflex, and incontinence (Merino & Hachinski, 2000).

Leukoaraiosis has been associated with decline in cognitive functioning in nondemented and demented elderly individuals in some studies, although findings are contradictory. Studies in normal aging have found associations between LA and impairment in basic attention, speed of information processing, and executive functioning (Boone et al., 1992; DeCarli et al., 1995). Few studies have explored neuropsychological correlates of LA in AD, and even fewer in mild cognitive impairment (MCI). As with normal elderly, studies in AD have reported that LA detrimentally affects attention and concentration, overall speed of cognitive processing, and executive functioning (Skoog, Berg, Johansson, Palmertz, & Andreasson, 1996; Tsisdaridze, Shakarishvili, Janelidze, Vashadze, & Chikhladze, 1998). Vascular risk factors have been associated with an increased risk of MCI. For

example, De Carli et al. (2001) found that hypertension and LA might increase the risk of MCI. The neuropsychological correlates of LA in MCI have not been examined. The literature suggests that LA is associated with neurological, cerebrovascular, and cognitive impairment. Although vascular risk factors are purported to contribute to LA, the relationship between those factors and LA remains unclear. Furthermore, the associations between LA and cognitive functioning are also unclear. The current study was designed to explore and clarify the risk factors that contribute to LA, and to further examine the relationship between LA and cognitive performance in individuals with AD, MCI, and normal elderly controls (NE). A review of relevant literature follows.

CHAPTER TWO: LEUKOARAIOSIS

The term "leukoaraiosis" (LA) was introduced by Hachinski (1987) to refer to neurodegenerative white matter changes associated with age. These changes can be detected on magnetic resonance (MR) images as areas of hyperintense signal, and on computed tomography (CT) images as areas of hypodensity, in regions of the cerebral white matter. The development, pathological substrate, risk factors, and clinical significance of LA remain largely unknown.

History and Terminology

In 1854 Maxime Durand-Fardel, known as the father of gerontology, first described white matter changes in post mortem cases, which he labeled "l'atrophie interstielle du cerveau" or "brain interstitial atrophy" (Coffey & Figiel, 1991). While Durand-Fardel was the first to describe the decrease in density, or rarefaction, of white matter from a macroscopic anatomical perspective, Otto Binswanger was the first to speculate about the possible association of clinical symptoms to these changes (Coffey & Figiel, 1991; Pantoni & Garcia, 1995). In 1894 Binswanger described the case of one patient in detail, and mentioned seven additional patients by footnote, that developed a form of dementia and pathologically demonstrated significant enlargement of the lateral ventricles, atrophy of cerebral white matter, ependymal thickenings, and minimal intracranial atherosclerosis. He did not include histological data, but proposed that the white matter rarefaction was the result of decreased

perfusion due to arteriosclerosis (Coffey & Figiel, 1991; Pantoni & Garcia, 1995). Those findings appear to describe the breadth of Binswanger's work with white matter atrophy.

In 1902 Alois Alzheimer added histological data from one additional case to support Binswanger's findings of white matter atrophy with intact cortical tissue. Alzheimer also suggested the white matter atrophy was related to arteriosclerosis and coined the term "Binswanger's disease" (Pantoni & Garcia, 1995). The early research of this suggested disease was limited to only a few cases, and in 1987, as cited in Pantoni and Garcia, a review by Babikian and Ropper indicated that the pathological diagnosis of this vague clinical category included less than 50 total cases. The advancement of neuroimaging techniques such as CT and MRI in recent decades has revealed that white matter changes occur in greater frequency than was ever predicted. Furthermore, these changes can occur with or without clinical symptoms. Historically, these changes were believed to represent the degenerative picture of Binswanger's disease, and currently the terms are often used interchangeably. Research indicates that it is incorrect to use both terms interchangeably to describe white matter changes, as the presence of these changes on MRI or CT may occur in people who do not have other clinical features of the disease. Some authors suggest Binswanger's disease refers to cases of white matter changes in the presence of concomitant clinical symptoms indicative of a multiinfarct dementia (Coffey & Figiel, 1991), while others assert that Binswanger's disease is a controversial diagnosis with

vague descriptors that ultimately lacks medical relevance (Pantoni & Garcia, 1995). Leukoaraiosis is widely regarded as a more appropriate term to describe the neuroimaging abnormalities in the subcortical and periventricular matter. These changes are now known to appear in individuals with AD, cerebrovascular disease, and psychiatric illness, as well as in the normal elderly and individuals with dementia of vascular origin (Coffey & Figiel, 1991).

Multiple terms have been suggested to account for the imaging changes with the intent to separate these findings from their prior association with the controversial diagnosis of Binswanger's disease. Examples of suggested terms include "white matter lucency," "incidental MRI lesions," "leukoencephalopathy," and "unidentified bright objects" (Coffey & Figiel, 1991). Hachinski (1987) proposed the term leukoaraiosis as a neutral term,

> …exact enough to define white-matter changes in the elderly or the demented, general enough that it serves as a description and a label, and demanding enough that it calls for a precise clinical and imaging description accompanied when possible by pathologic correlations. (p. 22)

Furthermore, he predicted that this neutral term would ultimately be replaced by subcategories and specific labels as this broad descriptive category became more clearly differentiated and understood. Coffey and Figiel (1991) suggest the term "subcortical encephalomalacia," coined by Awad, Johnson, Spetzler, and Hodak (1986), is the most appropriate term. They believe the other terms are limited by

referring only to changes in the subcortical white matter, since deep gray matter nuclei and the brain stem are also frequently involved. While recognizing that there is controversy in the nomenclature, the present study will focus specifically on white matter changes, referred to most frequently in the literature as leukoaraiosis, with the recognition that changes in the gray matter may contribute to the etiology and/or progression of such changes.

Imaging/Radiologic Appearance

Computed Tomography.

Leukoaraiosis appears as areas of bilateral patchy or diffuse hypodensity with poorly defined margins on computed tomography (CT) images and can be divided into two categories: periventricular LA and LA of the centrum semiovale (also referred to as "subcortical leukoaraiosis," or "deep white matter hyperintensities"). Periventricular LA appears as regions of hypodensity contiguous to the ventricles, and subcortical LA is distinguished by regions of hypodensity that reside within the centrum semiovale, apart from the ventricles (Inzitari, 2003; Oishi, Mochizuki, & Takasu, 1997). While CT scans clearly distinguish between brain tissue, cerebrospinal fluid (CSF), and bone, white matter is not clearly differentiated from gray matter on CT. CT is not sensitive to white matter pathology and it is possible for individuals with significant pathology to appear normal on CT (Filley, 2001).

Magnetic Resonance Imaging.

Magnetic resonance imaging (MRI) is superior to CT in depicting detailed images of the cerebral white matter (Kertesz et al., 1988; Filley, 2001). Leukoaraiosis appears as areas of hyperintense signal on MRI T2-weighted images in the periventricular regions and centrum semiovale. The periventricular changes are commonly represented by areas of hyperintensity referred to as rims: regions of thin hyperintense lesions along the lateral ventricles, and caps: rounded areas of increased signal around the poles of the frontal or occipital horns. Additionally, isolated punctuate or diffuse foci of hyperintensity are commonly detected in the centrum semiovale and are often called "unidentified bright objects" and "subcortical leukoaraiosis" in the literature (Coffey & Figiel, 1991; Kertesz et al., 1988; Takao et al., 1999). Although T2-weighted images are good at discriminating gray from white matter, the cerebrospinal fluid appears bright and can interfere with the ability to discriminate periventricular leukoaraiosis from the cerebrospinal fluid. Fluid attenuated inversion recovery (FLAIR) imaging is an alternative MRI approach which maintains the T2-weighting of the brain parenchyma and also suppresses the signal from the ventricular cerebrospinal fluid (Filley, 2001). FLAIR images give optimal discrimination for both periventricular and subcortical leukoaraiosis.

Frequency of LA

In Dementia.

The prevalence and severity of LA have been shown to increase with age, cerebrovascular risk factors, and some forms of dementia, although these relationships vary greatly and are not clearly understood (Kozachuk et al., 1990). Leukoaraiosis is frequently reported in imaging findings of patients with AD, vascular dementia, and cerebrovascular diseases. Among studies examining the prevalence of LA among AD patients, it is detected in 19% to 78% of patients in CT studies, and in 7.5% to 100% in MRI studies. Leukoaraiosis is more prevalent among patients with vascular dementia. A study by Almkvist, Wahlund, Andersson-Lundman, Basun, and Backman (1992) found evidence to highlight these differences in prevalence, as their results showed that volumes of LA were greater among AD patients than controls, and among demented patients, volumes of LA were greater in vascular dementia than in AD. In CT studies of vascular dementia, LA has been detected in 41% to 100% of cases, and by MRI in 64% to 100% of cases (Pantoni & Garcia, 1995). The discrepancies in the ranges are likely due in part to variance in the sample characteristics (e.g., range of age, number and types of cerebrovascular risk factors) and MRI parameters (e.g., field strength and pulse sequence variations). However, the higher prevalence of LA in vascular dementia, as compared to AD, is purported to be related to the increased presence of cerebrovascular risk factors that are associated with vascular dementia, which suggests an ischemic pathogenic process may underlie

LA (Erkinjutti et al., 1987; Kobari, Meyer, Ichijo, & Oravez, 1990; Pantoni & Garcia, 1995).

Several studies have shown the prevalence of LA among AD patients to be significantly greater than in control populations (Barber et al., 1999; Bowen, Barker, Loewenstein, Sheldon, & Duara, 1990; Diaz et al., 1991; Tsiskaridze, Shakarishvili, Janelidze, Vashadze, and Chikhladze, 1998). For example, Bowen et al. (1990) examined periventricular and subcortical LA separately on MRI and found that periventricular LA was present in nearly 100% of subjects with AD (n = 87) while subcortical LA was found in approximately 50% of subjects with AD. The presence of both subtypes of LA was significantly greater in AD than normal controls. Similarly, Barber et al. (1999) explored the prevalence of LA in dementia (AD, n = 28) and normal controls (n = 26) on MRI. They found that subjects with AD had significantly greater total prevalence of periventricular and subcortical LA than normal controls. The prevalence of total periventricular LA was 100% in AD versus 92% in controls, while the prevalence of total subcortical LA was 89% in AD versus 73% in controls. Other studies by Diaz et al., (1991) and Tsiskaridze et al., (1998) found higher prevalence rates of LA in AD populations than are commonly cited in the literature for control populations. However, neither of those studies included control populations for direct comparison.

Regarding frequency of LA in specific brain regions in AD patients and controls, Capizzano et al. (2004) found that the mean percent of total LA was divided

into the following areas: 70% of LA was located in the frontal lobes, 22% in the parietal lobes, 3.5% in the temporal lobes, and 1.0% in the occipital lobes. Barber et al. (1999) also found the highest prevalence of subcortical hyperintensities in the frontal and parietal lobes of AD patients and controls.

In Nondemented Elderly.

Leukoaraiosis also appears to be a common finding on CT and MRI among nondemented individuals over age 60. However, the prevalence of LA among the "normal" elderly remains unclear as studies have shown significant discrepancies due to the variance in operational definitions of "normal" across studies. Steingart et al. (1987) investigated a cohort of 105 "normal" elderly participants, (M = 71.2 years), with CT and neuropsychological testing, and found that 9 of the 105 (8.6%) had LA, which they asserted was particularly noteworthy given that the sample was selected to exclude history of dementia and cerebrovascular disease. Another study by Schmidt, Fazekas, Kapeller, Schmidt, and Hartung (1999) examined the rate and progression of LA on MRI during a 3-year follow-up period with 273 normal elderly participants (M = 60 years) from the Austrian Stroke Prevention Study. They found that 176 people (64.5%) had white matter hyperintensities at baseline. Of those, 49 (17.9%) demonstrated a progression of white matter hyperintensity severity during the 3-year period; progression was minor in 27 (9.9%) and marked in 22 (8.1%). Progression was defined as either minor or marked increase in the grade and number of white matter hyperintensities from baseline to follow-up, and was assessed by direct scan

comparisons. The findings further revealed that participants demonstrating progression in frequency and extent of LA were older, had higher diastolic blood pressure, higher fibrinogen (soluble plasma protein that contributes to blood coagulation) levels, and had higher severity and amount of LA at baseline.

Across studies of nondemented elderly, LA has been detected on 0% to 21% of brain CT scans, and in 0% to 100% of MRI studies (Coffey & Figiel, 1991; Ferro & Madureira, 2002; Pantoni & Garcia, 1995). Pantoni and Garcia indicate that the ranges are still too discrepant, due to the range in defining "normal" across studies, to determine the prevalence of LA in the normal population. However, they indicated that two population-based studies found the presence of LA on MRI in 27% and 38% of participants with mean age of 65 years.

Etiology of LA

Associations between LA and vascular risk factors such as hypertension are widely recognized, but the pathogenesis and etiology of LA are not yet fully understood. Histologically, the condition is represented by demyelination, loss of glial cells, and spongiosis (Amar, McGowan, Wilcock, Lewis, & Scott, 1998; Brown, Moody, Challa, Thore, & Anstrom, 2002; Brown, Moody, Thore, & Challa, 2000; Janota, Mirsen, Hachinski, Lee, & Merskey, 1989). Ischemic demyelination, small-vessel disease, and chronically reduced blood flow in the white matter are regarded as significant pathogenic factors in LA (Szolnoki, Somogyvari, Kondacs, Szabo, & Fodor, 2001; Szolnoki et al., 2004). Brown et al. (2000) described LA as a

multifactorial disease that has multiple pathogenic agents. They suggested that cerebrovascular pathology, ultimately resulting in white matter ischemia, underlies LA. Pathological contributers may include: "intimal hyperplasia and atherosclerosis; medial fibrinoid necrosis, hyaline degeneration, arteriosclerosis, lipohyalinosis, amyloidosis, and dissection; adventitial calcifications, siderosis, and Charcot-Bouchard microaneurysms" (Brown et al., 2000, p. 40). Additionally, some cases examined by Brown et al. (2000) with extensive confluent LA had significant collagenous thickening in the walls of periventricular veins. They suggested that as a result, venous narrowing or blockage could cause chronic edema in the white matter, which could potentially serve as a cause for LA.

Research has demonstrated that LA appears to be related to ischemia and that it is strongly correlated to increasing age and vascular risk factors (Amar et al., 1998; Pantoni & Garcia, 1995). Despite these associations, vascular risk factors only contribute a portion of the etiological variance, which indicates that other mechanisms, such as genetic factors, also play a role. Genetic factors such as the angiotensin-converting enzyme (ACE) gene and APOE4 allele have been associated with increased susceptibility to certain vascular problems such as ischemic damage (Amar et al., 1998; Szolnoki et al., 2004). Amar et al. (1998) found an association between LA and the ACE polymorphism but not with the APOE4 allele. Furthermore, they concluded that the ACE gene alteration, specifically a deleterious effect of the D allele (ACE D/D), represented a risk factor for LA, primarily when combined with the

presence of ischemic stroke. Alternatively, Szolnoki, Somogyvari, Kondacs, and Szabo (2001) found that the combined presence of the homozygous methylenetetrahydrofolate reductase (MTHFR) 677TT mutation and the ACE D/D genotype, both of which are associated with small-vessel disease, was a risk factor for LA. Furthermore, members of the same research team hypothesized that the presence of APOE4, in combination with one or both of those mutations would further increase the risk of LA. Results demonstrated that, as predicted, both the MTHFR 677TT mutation and ACE D/D genotype in combination with APOE4 or APOE2 contributed to the development of LA (Szolnoki et al., 2004).

Demographic and Vascular Risk Factors of LA

Age and Gender.

Of the risk factors associated with LA, age is widely cited as most universal risk factor (Merino & Hachinski, 2000). The original definition of LA by Hachinski (1987) incorporated aging as a factor associated with these white matter changes. Studies have found further evidence to confirm the association. A large population based study by Longstreth et al. (1996) examined the association of LA severity with potential vascular risk factors among 3301 elderly individuals in the Cardiovascular Health Study and found that the severity of LA increased with age. Similarly, Diaz et al. (1991) compared patients with AD that had LA on CT to those who did not, and found that those with LA were significantly older (*M* age 75 vs. 68 years, respectively). Other studies have also found an association between increased

prevalence and severity of LA and aging (deGroot et al., 2000; Schmidt et al., 1999; Steingart et al., 1987). There is also evidence to suggest that the severity of periventricular and subcortical LA both increase with age when analyzed separately (deGroot et al., 2000).

In addition to age, gender has also been associated with differences in frequency and severity of LA. deGroot et al. (2000) found that women had more LA than men, before and after controlling for age, in a large population based study. Other studies have confirmed this finding and have shown greater severity of LA in elderly women versus men (Diaz et al., 1991; Longstreth et al., 1996).

Hypertension.

Hypertension and history of stroke are also regarded as significant risk factors for LA in the literature (Kuo & Lipsitz, 2004). To study the relationship between LA and hypertension, Schmidt et al. (1991) examined a young group of 35 people with essential hypertension (*M* age = 38.7 years) who were otherwise asymptomatic, and 20 controls. Results demonstrated that LA was present in 38% (*n* = 12) of the hypertensive participants compared to 20% (*n* = 4) of controls, although age was also significantly higher among hypertensive participants with LA than those without. Other studies have found that in addition to age and gender, higher systolic blood pressure or diastolic blood pressure were significantly and independently associated with severity of LA (deLeeuw et al., 1999; Longstreth et al.,1996).

However, not all studies have found evidence to suggest a direct relationship between LA and hypertension. For example, Raiha, Tarvonen, Kurki, Rajala, and Sourander (1993) found that lower systolic blood pressure is a risk factor for LA in AD, and Hogervorst et al. (2002) found systolic blood pressure was not an independent risk factor for LA. Other research has shown that hypertension and history of stroke are related to LA through an interaction, rather than as separate risk factors. For example, Inzitari et al. (1987) found that history of stroke was the most significant predictor of LA on multiple regression analyses, while hypertension was only a significant predictor when combined with presence of stroke (on CT).

Homocysteine.

Homocysteine is a thiol-containing amino acid that results from demethylation of methionine and has an important role in metabolism (Sachdev, 2004). Normal serum levels of homocysteine range from 5 to 15 μmol/L (Reutens & Sachdev, 2002) with a normal reference range for women of <12 μmol/L and for men of <15 μmol/L. Hyperhomocysteinemia, or high serum level of homocysteine (HCY), can result from genetic or acquired factors (e.g., deficiencies of the cofactor folate, or vitamins B12 or B6, smoking, age, and renal failure; Reutens & Sachdev, 2002). Hyperhomocysteinemia has been well established as a risk factor for cerebrovascular disease, and some researchers have shown that it is also an independent risk factor for LA (Hogervorst et al., 2002; Sachdev et al., 2004). Others have found evidence to suggest high levels of HCY are a risk factor for brain atrophy, AD, and cognitive

decline (Reutens & Sachdev, 2002; Sachdev, Valenzuela, Wang, Looi, & Brodaty, 2002; Seshadri et al., 2002).

To study the relationship of HCY levels with LA, brain atrophy, and cognitive function, Sachdev et al. (2004) examined a sample of 385 healthy elderly, ranging in age from 60 to 64. Correlation analyses showed that total HCY levels were associated with volume of subcortical LA, although the correlation was low (r = .14), but not periventricular LA or measures of brain atrophy. Total HCY levels accounted for only 1.2% to 1.8% of the variance in LA, though the association was maintained in regression analyses. Regarding cognitive factors, total HCY was correlated with measures of verbal memory and fine motor speed, but the relationships were not significant after adjusting for covariates (e.g., levels of folate, vitamin B12, and creatinine).

Hogervorst et al. (2002) also found total HCY to be an independent risk factor for subcortical LA in AD patients (n = 137) and controls (n = 277). They found that with a 5-µmol/L increase in total HCY the risk for moderate to severe LA nearly doubled among controls, and tripled among subjects with AD. Overall, they found the risk for moderate to severe LA increased by 40% (for every 5-µmol/L increase) after adjusting for other cerebrovascular risk factors and diagnosis. Individuals with increased total HCY, particularly those with AD, showed increased severity of subcortical LA compared to periventricular LA.

Cerebral Atrophy

Cerebral atrophy occurs with normal aging and is more severe in AD, particularly in the frontal, temporal, and parietal cortices (Rosenzweig et al., 2002). Atrophy of the brain adversely impacts cognition. Atrophy has been associated with cognitive domains such as executive functioning, global cognitive functioning, verbal fluency, motor function, memory, and processing speed (Soderlund, Nyberg, & Nilsson, 2004; Swan et al., 2000). Soderlund et al. (2004) recognized the importance of examining cortical and subcortical atrophy separately, to determine the impact of each type of atrophy on cognitive functioning. They studied a sample of 129 nondemented individuals ranging from age 64-74 in Sweden and found that in men, cortical atrophy was associated with word fluency, processing speed, and motor speed, and in women, subcortical atrophy was associated with motor speed impairment. However, it was important to indicate that most of these associations were dependent upon age.

Given the strong relationship between atrophy, aging, and cognition, and the association between LA and aging, studies have begun examining the relationship between LA and atrophy. For example, in a study of AD and nondemented elderly, Capizzano et al. (2004) utilized a quantitative scoring method to measure volumes of gray matter, white matter, LA, and cerebrospinal fluid of each brain lobe, which were converted to percentages of total intracranial volume. LA was found to be the most significant predictor of cortical atrophy in the frontal, temporal, parietal, and occipital

lobes, and LA was inversely correlated with white matter volume in the frontal and parietal lobes (Capizzano et al., 2004). Additionally, the relationship between atrophy and LA was independent of other critical risk factors such as age, hypertension, and presence or absence of cognitive impairment. Periventricular and subcortical LA were not analyzed separately in the study, nor were cortical and subcortical atrophy compared. However, the results demonstrated that LA was associated with a quantitative measure of cortical atrophy.

Chapter Summary

Leukoaraiosis is a term for degenerative white matter changes in the brain that are associated with aging, and may or may not present with clinical concomitants. While LA can be viewed on CT or MRI, MRI FLAIR images are among the best techniques available for enhancing the appearance of LA. LA is common in nondemented individuals over the age of 60, with higher prevalence in AD and vascular dementia. Etiologically, LA appears to be related to ischemia as well as genetic factors. Vascular risk factors such as hypertension, history of stroke, and homocysteinemia may significantly impact the severity and progression of the condition. Furthermore, LA is more prevalent in women than men, and may also be impacted by other risk factors such as hyperlipidemia, diabetes, and smoking. Some studies have also found an association between LA and cerebral atrophy, which may interact or function independently to impact cognition. To further explore the

relationship between LA and cognitive functioning, studies with nondemented populations will be examined in the following section.

CHAPTER THREE: COGNITIVE FUNCTIONING AND LEUKOARAIOSIS IN NONDEMENTED ELDERLY

Studies investigating the potential impact of LA on the cognitive functioning of nondemented elderly individuals have produced conflicting results. Since 1986, many studies have suggested that LA appears to progress insidiously with age, in the presence of vascular risk factors, and may result in cognitive decline (Schmidt, Fazekas, Kapeller, Schmidt, & Hartung, 1999). However, studies are difficult to compare and differences in study populations, scanning methodologies, neuropsychological assessment measures, and categorization of extent and severity of lesions, have resulted in contradictory findings (Tupler, Coffey, Logue, Djang, & Fagan, 1992).

The cognitive deficits associated with LA appear to include frontal lobe and subcortical abilities. The deficits that are associated with LA appear more extensive than those that occur due to normal aging, and they may be attributable to the presumed ischemic pathogenesis of LA (Boone et al., 1992). Similar types of cognitive impairment have been documented in other populations with cerebral diseases of the white matter. For example, Baumhefner, Tourtellotte, and Syndulko (1990) examined patients with multiple sclerosis and found declines in frontal abilities such as information processing speed, abstract reasoning, and memory. Furthermore, studies by Kinkel, Jacobs, Polachini, Bates, and Heffner (1985) and Gupta et al. (1988), report findings of a "frontal system defect" in neurologic patients with

presence of LA manifested by cognitive slowing, decreased attention and concentration, blunting of affect, and depressed learning rate and recall. While some studies of nondemented, healthy individuals with LA have demonstrated cognitive correlates similar to those found in studies of populations with cerebral diseases of the white matter, other studies have not supported those findings. Although the topic remains controversial, a growing body of evidence supports the presence of cognitive correlates of LA in nondemented elderly individuals.

Findings from CT

Cranial tomography is not as sensitive as MRI in the detection of LA. However, early studies relied upon CT, and some found relationships between presence of LA and cognitive functioning in nondemented elderly populations. An early study by Steingart et al. (1987) was one of the first to find this association in a cohort of 105 healthy elderly volunteers (*M* age = 71.2 years). Furthermore, they demonstrated LA was more prevalent in the normal elderly population than was previously believed. Participants underwent CT scans and a neuropsychological evaluation that consisted of the Extended Scale for Dementia. The prevalence of LA in their sample was 8.6% (*n* = 9), which they believed was surprisingly high in a population that had no evidence of dementia or history of cerebrovascular disease. Their results showed that participants with LA demonstrated a significantly lower total score on the Extended Scale for Dementia, even when adjusting for age, education, sex, and presence of infarct on CT.

A more recent study by Skoog, Berg, Johansson, Palmertz, and Andreasson (1996) included a more extensive neuropsychological battery than that of Steingart et al. (1987), among nondemented (n = 134) 85-year-olds. They found that participants with LA had poorer performance on the Mini Mental State Examination (MMSE), and tests of verbal ability, spatial ability, perceptual speed, visual memory, and basic arithmetic compared to those with no detected presence of LA. The severity of LA had no impact on neuropsychological functioning. Skoog et al. (1996) concluded that healthy elderly participants with LA on CT have been shown to demonstrate significant impairment on visuospatial tasks and slowing of mental processes, indicative of subcortical dysfunction. The authors suggested that this impairment might have been reflective of a pathophysiological mechanism that disrupted fronto-subcortical connections.

The two aforementioned CT studies found evidence for an association between LA and cognitive decline in nondemented elderly, but further studies were needed to clarify the nature of the association between these factors. The following section will review the literature examining LA and cognition with MRI to expand on the sparse data provided by CT.

Findings from MRI

Magnetic resonance imaging is superior to CT in the detection of white matter hyperintensities and since its development, the body of literature examining LA and cognitive functioning has expanded. Several studies that examined LA and cognitive

functioning with MRI in nondemented elderly found evidence to suggest LA was associated with impairments in cognition, primarily general cognitive abilities and mental processing speed. For example, a study by Junque et al. (1990) examined a sample of 41 nondemented elderly (n = 41; M = 66 years) with vascular risk factors. They concluded that the total LA score on MRI correlated with performance on neuropsychological tasks measuring speed of complex information processing, as assessed by the Stroop Test. Similarly, Ylikoski et al. (1993) examined nondemented participants (n = 120; age = 55 to 85) from the Helsinki Aging Brain Study. Periventricular and subcortical LA were examined separately and graded for severity. Neuropsychological testing consisted of assessment of memory, constructional abilities, language, speed and attention, speed of mental processing, and simple psychomotor speed. After controlling for age, Trails A and Stroop Test performances were significantly correlated with total LA. Furthermore, they found that speed of mental processes, as assessed by the Stroop test, was significantly related to the presence of periventricular LA.

The findings of Ylikoski et al. (1993) were corroborated by Fukui, Sugita, Sato, Takeuchi, and Tsukagoshi (1994) in a group of 43 nondemented participants. Semiquantitative measures of subcortical and periventricular hyperintensities were compared to neuropsychological test performance on the Hasegawa Dementia Scale, (a screening test for dementia that is similar to the MMSE), and additional neuropsychological measures. Multivariate linear regression results indicated that

presence of periventricular LA was an independent factor associated with dysfunction in attention and speed of processing (as measured by the Stroop Test). No other significant associations were found between LA and cognitive functions.

Schmidt et al. (1993) also found that decreased performance on almost all neuropsychological tests was associated with presence of LA on MRI. Subjects were divided into two groups based on absence or presence of LA, and analysis of covariation (ANCOVA) tests were conducted to adjust for group differences in age and cerebral atrophy. Statistical significance was reached on tests assessing attention, processing speed, complex reaction time, and fine and gross motor dexterity, indicating LA was associated with poorer performance on those measures. Pearson correlations between neuropsychological functioning and total LA failed to result in significant associations, which may be partially explained by the small number of subjects in the severe group ($n = 6$; LA > 10 cm^2).

Although the aforementioned studies found evidence to suggest that the presence of LA was related to cognitive impairment, several studies have found evidence to the contrary. Hendrie, Farlow, Austrom, Edwards, and Williams (1989) examined the association between LA on MRI and cognitive function in a sample of 27 healthy elderly participants. Their neuropsychiatric battery included the DeMyer Standard Interview, Cambridge Mental Disorders of the Elderly Examination (CAMDEX), including the cognitive subscale of the CAMDEX, the CAMCOG, which includes items similar to the MMSE, and the Digit Symbol subtest from the

Wechsler Adult Intelligence Scale (WAIS). LA was detected on MRI among 59% (*n* = 16) of the sample, and while age was strongly associated with grade of LA, cognitive performance was not. O'Brien, Desmond, Ames, Schweitzer, and Tress (1997) also failed to find a relationship between LA and cognitive function. They used the CAMCOG, but quantified LA differently than Hendrie et al. (1989) by measuring periventricular and deep white matter hyperintensities separately, according to a commonly accepted four-point rating scale developed by Fazekas et al. (1987).

A more recent prospective study by Whitman, Tang, Lin, and Baloh (2001) also failed to find an association between LA on MRI and cognition, as assessed by the MMSE, although they found neurological correlates of LA. Results indicated that gait and balance disturbance were associated with increasing LA, particularly as age increased into the eighth and ninth decades.

It is possible that the studies by Hendrie et al. (1989), O'Brien et al. (1997), and Whitman et al. (2001) failed to find an association between LA and cognition due to limitations of their cognitive testing battery. All used primarily general measures of cognition, rather than specific neuropsychological tests designed to evaluate areas that were associated with LA in other studies, such as attention, processing speed, and executive functioning. Prospective studies by Wahlund, Almkvist, Basun, and Julin (1996) and Schmidt, Fazekas, Kapeller, Schmidt, and Hartung (1999) addressed this possible limitation in studies that examined the rate of progression and cognitive sequelae of LA. Wahlund et al. (1996) found progression of LA in the deep white

matter of a group of 24 nondemented elderly participants over a 5-year follow-up period, but despite the use of more extensive neuropsychological tests, they found no relationship between progression of LA and cognitive functioning. Their study included measures of general intelligence, memory, simple reaction time, and finger tapping. Similarly, Schmidt et al. (1999) followed 273 participants from the Austrian Stroke Prevention Study for a 3-year follow-up period. The test battery was comprehensive and assessed memory and learning abilities, conceptual reasoning, attention, and speed of processing. The results showed that LA was present in 65% (n = 176) at baseline, and progression occurred in 18% (n = 49). However, Schmidt et al. (1999), like Wahlund et al. (1996), found no relationship between progression of LA and cognitive functioning, even in individuals marked progression (8%, n = 22).

Hunt et al. (1989) and Rao et al. (1989) found results similar to Hendrie et al. (1989) when using extensive neuropsychological batteries. Both studies evaluated groups of healthy, nondemented elderly participants (n = 46; n = 54, respectively) with MRI and neuropsychological test batteries that examined verbal ability, spatial ability, memory, attention and concentration, and executive functions. Hunt et al. (1989) found that severity and prevalence of LA increased with age while cognitive performance declined with age; however, they found no evidence of an association between LA and cognitive performance. In Rao et al. (1989), LA was rated for presence but not severity, and 20% (n = 10) of participants demonstrated LA on MRI. They found no significant differences between subjects with and without LA on

neuropsychological testing, although they included an extensive array of measures. They did find significant group differences on a Consonant Trigrams measure, the Benton Facial Recognition Test, and the President's Test, but concluded that the relationships could be attributed to chance due to the large number of group comparisons. Furthermore, they suggested that the degree of LA may have been too mild to be associated with cognitive impairment, as severity was not assessed in the study. The authors suggested that a "threshold" of severity might be necessary before neuropsychological functioning is impacted.

Similarly, a study by Tupler, Coffey, Logue, Djang, and Fagan (1992) found that LA was present in 72.7% (n = 48) of nondemented elderly participants and was associated with increasing age and higher prevalence of vascular risk factors, but not neuropsychological performance. The presence of LA was classified as mild in 66.7% (n = 32) of participants and severe in 8.3% (n = 4). The authors noted that the majority of participants demonstrated a mild degree of white matter changes and they suggested a higher level of severity might be necessary to reach a threshold which would detrimentally impact cognition. The following section reviews studies that found evidence for a "threshold effect."

Evidence for Threshold Effect of LA on Cognition

Several studies argued that a "threshold" of LA must be present in order to cause neuropsychological deficits. A study by Boone et al. (1992) highlighted this point, as they found significant neuropsychological impairments were associated with

LA on MRI in participants with "large" white matter lesion areas compared to those with no, minimal, or moderate total lesion areas. They divided a group of healthy elderly participants (n = 100) into groups based on total extent of area of LA. More than half of the participants had LA, and among them, 11% (n = 6) had severe LA (>10 cm^2). The neuropsychological test battery was extensive and included standardized measures of executive function, intellectual function, memory, attention and information processing speed, language, and visuospatial skills. They found that severe LA was associated with impairment in basic attention and frontal lobe functions, demonstrated by significantly poorer performance on forward digit span and a divided attention task, and more perseverative responses and fewer categories on the WCST, respectively. The results suggested that white matter lesions were associated with frontal and/or subcortical impairment, as defined by the decline in attention, categorization, and increase in perseverative behavior, particularly when LA was extensive, although the sample size was small in the severe group (n = 6). This study was the first MRI study to demonstrate an association between LA and cognitive decline. At the time of publication, only three other studies demonstrated this relationship and all utilized CT.

DeCarli et al. (1995) further supported findings of Boone et al. (1992) regarding the presence of a "threshold" effect and concluded that severe LA was associated with decreased frontal lobe cognitive abilities in addition to decreased frontal metabolism, as measured by 18-fluoro-2-deoxy-D-glucose Positron Emission

Tomography. They quantified the severity of LA with volumes obtained through MRI segmentation and compared those with comprehensive neuropsychological test performance in 51 healthy elderly participants. They defined large LA volumes as greater than 0.5% of intracranial volume. Large volumes were found in approximately 10% of participants, all of who were over age 50, and the mean volume for participants in the large volume group was 0.8% (M = 0.19% in age-matched controls). Results demonstrated that those with large LA volumes had significantly lower scores on immediate and delayed visual memory, FAS, and Trails B time.

Impact of Periventricular versus Subcortical LA on Cognition

Studies have begun to explore whether periventricular and subcortical LA affect cognition in distinct ways. deGroot et al. (2000) indicated that the anatomical differences of these separate regions likely entail different mechanisms in cognition. The subcortical region is described to have "a high density of short looped U-fibers, which connect adjacent cortical areas" while periventricular areas have "many long association fibers that connect the cortex with subcortical nuclei such as the striatum and more distant cortical areas" (p. 145). While some studies have failed to demonstrate significant relationships between regions of LA and cognitive function (O'Brien et al., 2003; Wahlund et al., 1996), others have found evidence to support it.

Overall, studies examining periventricular and subcortical LA separately have found periventricular LA to be more significantly related to cognitive impairment. For example, Fukui et al. (1994) and Ylikoski et al. (1993) found that dysfunction in

attention and speed of processing was associated with periventricular hyperintensities but not subcortical hyperintensities. Matsubayashi, Shimada, Kawamoto, and Ozawa (1992) also found that severity of periventricular hyperintensities was associated with decreased performance on the MMSE, Hawegawa Dementia Scale, visuospatial cognitive performance test (VCP), and a test of manual dexterity, although they did not study subcortical hyperintensities in their study. Furthermore, deGroot et al. (2000) examined 1,077 nondemented elderly (age range 60 to 90 years) and found that severity of periventricular and subcortical white matter hyperintensities correlated with worse performance across the neuropsychological battery with tests that assessed speed of cognitive processes, memory, and global cognitive function. However, when periventricular and subcortical LA were analyzed conditionally upon the presence of the other, the relationship between subcortical LA and cognitive function dissolved, while the association between periventricular LA and cognitive functioning remained significant. Among neuropsychological measures, decreased performance in processing speed was most strongly correlated with the presence of periventricular LA, corroborating the earlier findings of Fukui et al. (1994) and Ylikoski et al. (1993).

While the association between periventricular LA and cognition has been documented in several studies, subcortical LA has not been as consistently associated with impairment in cognition. Researchers have postulated that a certain "threshold" of subcortical LA may be required before these associations are revealed (Rao et al., 1989; Schmidt et al., 1999; Tupler et al., 1992). Additionally, it is possible that the

neuropsychological tests selected in many studies were more sensitive to periventricular damage. Tasks designed to tap adjacent cortical areas may be more sensitive to associations with subcortical LA.

Chapter Summary

In conclusion, several studies found associations between LA and a variety of variables including neurological factors (e.g., gait and balance), age, and vascular factors, but failed to find a relationship between LA and cognitive function among nondemented elderly samples. Differences in imaging techniques may contribute to the lack of association in some studies. In addition, neuropsychological tests such as the CAMCOG and the MMSE, may lack sensitivity in detecting mild LA (Bonnano et al., 1999; Hendrie et al., 1989; Malloy et al., 1997). Other studies using more comprehensive neuropsychological batteries have demonstrated a relationship between LA and cognition (Steingart et al., 1987; Skoog et al., 1996). However, several studies that utilized more extensive neuropsychological batteries did not find a relationship (Hunt et al., 1989; Rao et al., 1989; Wahlund et al., 1996). Another possible explanation for the lack of association in these studies was that the level of severity of LA failed to reach a certain threshold level necessary to detect an impact on cognitive changes. (Boone et al., 1992; DeCarli et al., 1995). The presence, extent, and severity of LA in some studies of healthy elderly may not have been substantial enough to affect cognitive decline.

Among studies that have documented a relationship between LA and cognition among nondemented elderly, LA was prevalent and associated with frontal lobe dysfunction, particularly cognitive tasks that require speed. Periventricular LA appeared to be more strongly associated with cognitive dysfunction than subcortical LA, although further studies are needed examine and clarify these findings. In addition, some of these studies did give evidence to suggest that a threshold of LA was necessary to detect a relationship with cognitive functions, and that severe LA correlated with declines in abilities associated with the frontal lobe such as attention, processing speed, and executive functioning (Boone et al., 1992; DeCarli et al., 1995). The following section will examine studies that have focused on the nature of the relationship between LA and cognition in AD.

CHAPTER FOUR: COGNITIVE FUNCTIONING AND LEUKOARAIOSIS IN ALZHEIMER'S DISEASE

The literature on the relationship between LA and cognitive function among patients with AD is limited and yields conflicting findings. Fewer studies to date have examined the potential cognitive correlates of LA in AD than in normal elderly controls. The effect of white matter changes on cognition is difficult to elucidate in the presence of an advanced dementing process (Hachinski, Potter, & Mersky, 1987). Furthermore, as in studies of normal elderly, inconsistencies in methodologies, imaging technologies, and classifications of LA make comparisons across studies challenging. Despite a number of negative findings, overall the literature suggests that AD patients with LA perform worse on neuropsychological testing than those without, thereby supporting a relationship with cognitive performance (Brown et al., 2000). A comprehensive review of studies that examine the relationship between LA and cognitive function in AD follows.

Findings from CT

Steingart et al. (1987) conducted one of the earliest studies examining LA (on CT) and cognitive functioning among demented patients. They included 113 participants from an AD cohort study in the University of Western Ontario, London Dementia Study. Of the 113 participants, 80.5% (n = 91) were clinically diagnosed with AD, and others had mixed presentations (vascular dementia and AD, depressive pseudodementias, Parkinson's disease, etc). All subjects underwent CT scan and

cognitive testing with the Extended Scale for Dementia (ESD). After controlling for age, subjects with LA were compared to those without LA, and cognitive scores were not significantly related to the presence of LA. However, when AD cases were clustered according to presumed stage of disease progression, based on ESD scores, those with LA were found to be in the moderately severe range, while few early or late cases with LA were found. This suggested that LA was associated with dementia in AD, and that the association was most evident before the dementing process became considerably advanced. Furthermore, those with AD who scored 70 or above on the ESD (maximum score = 250, with lower scores indicating greater impairment) were compared for the presence or absence of LA, and a significant trend emerged that indicated LA was associated with greater impairment. Thus, the authors concluded that LA was associated with cognitive impairment among individuals with AD.

Similarly, Diaz et al. (1991) examined the relationship between LA (on CT) and cognition (with the Extended Scale for Dementia) in a group of 85 individuals with AD. Their sample was derived from the same population as Steingart et al. (1987). Cognitive impairment was correlated with presence of LA. Those with LA produced a mean score difference of 56-points lower (*M* ESD score = 98.6) than those without LA (*M* ESD score = 154.4). While it was determined that 12% (*n* = 10) of patients had diffuse and 28% (*n* = 24) had focal LA, those differences did not result in a significant association with cognitive functions. Further analyses demonstrated that LA contributed 11.6% of the variation in ESD scores.

While Steingart et al. (1987) and Diaz et al. (1991) examined cognition in AD with a measure of overall functioning, Gupta et al. (1988) used more extensive neuropsychological tests to explore LA (on CT) and cognition in AD. Twenty-seven subjects with AD (*M* age = 62.5, range 50 to 71 years) and 17 age-matched controls underwent neuropsychological testing which included measures of temporal orientation, learning and memory, attention and concentration, visuospatial skills, verbal fluency, and a test of general knowledge. Patients with LA performed significantly worse than controls on all tests except temporal orientation and the general knowledge test (WAIS-R Information). Mental concentration and divided attention were found to be impaired almost universally among the LA group. Overall, the group with LA was found to possess slowness of thought and motor processes, decreased attention and concentration, reduced rate of learning and spontaneous recall in comparison with the non-LA group. Further findings included affective blunting, reduced spontaneity, and impaired problem solving capacities in the LA group. The authors posited that the findings were suggestive of frontal lobe dysfunction, as seen in subcortical dementia, similar to what has been noted by Almkvist et al. (1992) and in many studies examining LA in normal elderly populations.

Summary

Computerized tomography scan studies found that LA was significantly associated with cognitive functioning in AD. Despite differences in study methodologies, it appears that LA was associated with general cognitive functioning

(Diaz et al., 1991; Steingart et al., 1987) in addition to motor impairment, decreased attention and concentration, and decreased rate of learning and spontaneous recall (Gupta et al., 1988). Several additional studies have used MRI to examine these relationships, and those findings will be reviewed in the following section.

Findings from MRI

Several MRI studies have found associations between LA and specific domains of neuropsychological functioning that are similar to the findings of CT studies. The cognitive domains that are primarily affected by LA across studies include cognitive processing speed (Almkvist et al.,1992), attention and concentration, memory, and executive functioning (Tsiskaridze, Shakarishuili, Janelidze, Vashadze, & Chikhladze, 1998). Almkvist et al. (1992) included 50 AD patients and 23 healthy controls. All participants underwent MRI and cognitive testing with the MMSE and a battery of more sensitive neuropsychological tests. Extent of LA was not associated with global cognitive performance among AD patients or controls. However, the presence of LA in specific regions among demented patients detrimentally influenced performance on neuropsychological tests including Finger-tapping, Tactile Identification of Objects, Simple Reaction Time, Block Design, and Object Assembly. When analyzed separately, the AD group with LA performed worse on Tactile Identification of Objects than those who had AD without presence of LA. The findings demonstrated that tests which were impaired all had a time component, which

provided further evidence that LA may slow cognitive processes in both dementia and elderly controls.

Additional evidence was found by Tsiskaridze, Shakarishuili, Janelidze, Vashadze, and Chikhladze (1998), who attempted to avoid the confounds that aging, brain atrophy, and the dementing illness itself can cause by examining an age, education, brain atrophy, and dementia-degree matched pure group of AD, with and without LA. The sample included 37 probable AD patients that underwent MRI, the MMSE, Washington University Clinical Dementia Rating, and a neuropsychological battery which assessed memory, language, attention and concentration, visuospatial functions, verbal intelligence, and executive functioning. They discovered that the presence of LA was associated with impairment in verbal memory, attention and concentration, and executive functions.

These findings differ from an earlier study by Kertesz, Polk, and Carr (1990) which demonstrated that patients with dementia and LA had significantly poorer performance on tests of attention and language, while those with dementia and no LA performed worse on tasks of conceptualization and memory. However, Kertesz et al. combined vascular and AD patients into one group for their analyses, which may explain the differences in results when comparing them to the more homogeneous, pure AD group of Tsiskaridze et al. (1998). The results demonstrated by Tsiskaridze et al. (1998) further supported findings of Almkvist et al. (1992) which suggested that frontal lobe dysfunction was related to LA in AD. Tsiskaridze et al. (1998) asserted

that this dysfunction was a syndrome caused by "fronto-subcortical dorsolateral disconnection" (p. 21), and that the additive effects of LA to AD could only be clearly detected in the initial states of the dementing process. They believed that as AD progressed to more advanced stages, the effects of LA on frontal dysfunction were overshadowed by global cognitive impairment associated with dementia.

Several studies failed to find a relationship between LA (on MRI) and cognitive functioning in individuals with AD. Smith, Snowdon, Wang, and Markesbery (2000) measured periventricular LA and cerebral white matter volume on the postmortem MRI scans of 52 women from the Nun Study cohort. The Nun Study was a longitudinal, population-based study of AD comprised of members of the School Sisters of Notre Dame congregation. Smith et al. (2000) hypothesized that the extent and severity of periventricular LA would be associated with cerebral white matter volume, the presence of dementia, and cognitive performance on test scores obtained prior to death. Neuropsychological assessment was derived from the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) battery. A significant relationship between periventricular LA and age was found, but not with white matter volume, total parenchymal volume, brain weight, cerebral atrophy, or dementia. Periventricular LA was not associated with cognitive performance on any measures. However, all of the cognitive scores (MMSE, delayed word recall, naming, verbal fluency, and instrumental daily activity performance) were significantly associated with white matter volume, total parenchymal volume, and brain weight.

Therefore, decreased white matter volume, as measured on MRI, was associated with dementia and decreased cognitive performance, while periventricular LA was not.

Other studies that relied on broad measures of cognitive functioning also failed to find an association between LA and cognition in AD. For example, Kozachuk et al. (1990) examined the prevalence of LA on MRI and its association with dementia severity among a group of patients with AD (n = 22), age-matched elderly healthy controls (n = 20), and younger healthy controls (n = 10), all of whom had no major cerebrovascular risk factors. Results showed that among the AD group, prevalence and severity of LA were not associated with cognitive decline as assessed by the MMSE. Mirsen et al. (1991) examined LA on MRI and cognition with the Extended Scale for Dementia in AD patients (n = 30) and a group of controls (n = 50). Although they found a higher prevalence of periventricular LA in AD compared to controls, they did not find correlations between the mean ESD scores and the presence of periventricular LA, or total LA, within the AD and control groups. However, they did find a trend for decreased ESD scores among those with periventricular LA, when AD and control participants were analyzed together.

Chapter Summary

Contradictory results have emerged in the literature regarding LA and its potential impact on cognitive functioning in AD. It is difficult to compare most studies given the variability in methodologies (e.g., imaging techniques and parameters, quantification of LA, and neuropsychological measures). CT studies

found an association between LA and general cognitive functioning as well as abilities associated primarily with the frontal lobe (Diaz et al., 1991; Gupta et al., 1988; Steingart et al., 1987). Several MRI studies found no significant relationship between presence of LA and cognitive performance among cohorts of AD patients (Kozachuk et al., 1990; Leys et al., 1990; Mirsen et al., 1991), while other studies have reported significant associations. A major difference between studies that found an association and those that did not appeared to be differences in the neuropsychological measures. Most studies that failed to find a relationship used limited neuropsychological screens such as the MMSE, and had small sample sizes. The studies that found an association between LA and cognitive functioning in AD used comprehensive neuropsychological batteries. The most common associations found across studies suggested LA was related to impairments in overall cognitive slowing (Alkvist et al., 1992; Skoog et al., 1996; Tsiskaridze et al., 1998). Additional relationships were also found among LA and visuospatial tasks (Skoog et al., 1996); as well as verbal memory, attention and concentration, and executive functioning (Tsiskaridze et al., 1998) among individuals with AD.

CHAPTER FIVE: LEUKOARAIOSIS AND MILD COGNITIVE IMPAIRMENT

The term 'Mild Cognitive Impairment' (MCI) was introduced to capture individuals with subtle deficits in cognitive functioning, most commonly memory, in the presence of normal general cognitive functioning, intact activities of daily living, and absence of dementia (Petersen, 2003). Individuals within the nondemented elderly population appear to meet these criteria with an incidence rate of 9.9/1,000 (Larrieu et al., 2002). MCI is often considered on a continuum between cognitive changes seen in normal aging and those associated with diagnosable forms of dementia. The risk of developing AD and other forms of dementia is higher among those who meet criteria for MCI. Early detection of MCI allows for intervention with therapeutic techniques with the intent of delaying the progression to dementia. The etiology and pathology of MCI are still largely unknown, and the clinical presentation is heterogeneous (Petersen, 2003). To this end, studies are attempting to further clarify the etiolology and clinical presentation of MCI to further improve diagnostic and treatment strategies.

Defining and Classifying MCI

Memory impairment is the primary feature associated with the most common type of MCI, amnestic MCI, although MCI appears to be heterogeneous in clinical presentation and etiology. Petersen (2003) described three theoretical types of MCI: amnestic, multiple domain, and single non-memory domain. Amnestic MCI is represented by significant memory impairment that is approximately 1.5 standard

deviations below the normal population. More subtle cognitive impairments in other cognitive domains may also be present, but do not extend beyond 0.5 to 1.0 standard deviations below the normal population. Etiologically, amnestic MCI appears to be more commonly associated with a degenerative process than other subtypes, and individuals with amnestic MCI are at an increased risk of progressing to AD. While the literature cites a fairly broad range of conversion from MCI to AD (1% to 25% per year), a study by Petersen et al. (1999) found the conversion rate in a group of amnestic MCI individuals to range between 10% to12% per year, compared to 1% to 2% in normal controls. Multiple-domain MCI is represented by the presence of multiple areas of mild cognitive impairment (from 0.5 to 1.0 standard deviations below average). This subtype may progress to AD or vascular dementia in some individuals, which suggests heterogeneity within the etiology. The third classification, single non-memory domain MCI, is used to capture individuals with impairment in a single non-memory cognitive domain. Depending on the cognitive domain impaired, the person may progress from MCI to a variety of forms of dementia, which again is indicative of multiple etiologic factors. Petersen (2003) emphasizes that each subtype is subject to multiple etiological processes, including normal aging.

Vascular risk factors have been associated with the development of both vascular dementia as well as AD, and these risk factors, particularly elevated baseline blood pressure and cholesterol, have also been associated with milder forms of cognitive impairment (Tervo et al., 2004). Limited research exists that has examined

the relationship between vascular risk factors and MCI, defined according to Petersen's criteria. The study by Tervo et al. (2004) examined the relationships among vascular risk factors and MCI (defined by Petersen's criteria) and found that age, presence of ApoE4 allele, and hypertension were significant independent risk factors for conversion from normal elderly to MCI over a 3-year follow-up period. The study did not include imaging measures of LA, and few studies exist that examine the relationship between LA and MCI (DeCarli et al., 2001; DeCarli et al., 2004). Vascular risk factors have been associated with higher prevalence and severity of LA, and given that the literature suggests LA is associated with cognitive decline in normal elderly and in those with AD, it is suspected that LA may also impact MCI (DeCarli et al., 2001). A review of studies examining the relationship between vascular risk factors, including LA, and the development of MCI follows.

Influence of Risk Factors

The extent to which vascular risk factors and LA may impact the development and course of MCI is largely unknown, although DeCarli et al. (2001) studied the relationship between vascular risk factors, LA volume, and MCI in a group of 369 nondemented men from the National Heart, Lung, and Blood Institute (NHLBI) twin study. The study examined cardiovascular disease and risk factors longitudinally in a cohort of male twins with follow-up at 10, 16, and 25 years. MCI was defined as 1.4 standard deviations or more below the group mean on the California Verbal Learning Test (CVLT) delayed free recall measure. They found that individuals with MCI were

significantly older, had significantly lower average alcohol intake, and had significantly greater LA volumes than those without MCI. Their results also indicated that age, LA volume, elevated diastolic blood pressure, and the ApoE4 genotype were associated with increased risk of MCI, even exclusively among the group of participants with no history of symptomatic cerebrovascular disease. These results suggested that elevated blood pressure and LA volume might increase the risk of MCI in patients with no history of symptomatic cerebrovascular disease. Furthermore, DeCarli et al. (2001) found that ApoE4 genotype status and LA volumes were independently associated with increased risk of MCI. This evidence suggested that MCI could be a pathologically heterogeneous condition.

More recently, DeCarli et al. (2004) examined the impact of cerebrovascular disease on progression of MCI to AD ($n = 52$). A number of individuals had significant cerebrovascular disease and multiple vascular risk factors. However, results failed to demonstrate a relationship between cerebrovascular disease depicted by vascular risk factors, stroke, or extensive LA, and progression from MCI to AD. They found that baseline performance on neuropsychological measures of executive functioning and memory best predicted conversion. Possible explanation regarding lack of findings with cerebrovascular disease and LA could be lack of severity of each factor. It is possible that a certain threshold level of severity of risk factors and/or LA is necessary to detect a relationship with progression. Other studies that focused on the relationship between LA and cognition in nondemented and AD subjects also

found evidence for a threshold effect (Boone et al., 1992; DeCarli et al., 1995). Only 4 of 16 individuals who were categorized as having "large" LA volumes progressed within the 3 year timeframe of the study, limiting the ability to detect an effect.

A recent study by Maruyama et al. (2004) attempted to further clarify why some patients with MCI progress to AD while others appear to remain cognitively stable over time. Their study supported the findings of DeCarli et al. (2001), who suggested MCI might be a pathologically heterogeneous condition, as Maruyama et al. found evidence suggesting that two pathological processes may influence progression from MCI to dementia. They examined 57 amnestic MCI patients and prospectively followed them for 2 years. They evaluated LA on MRI, vascular risk factors such as hypertension, hypercholesterolemia, and diabetes, APOE, and cerebrospinal fluid (CSF). They found that 41 of 57 patients (72%) with or without conversion to AD showed progression of cognitive decline during the study, and the other 16 (30%) remained cognitively stable using the MMSE. They found an annual conversion rate to AD of 16.5%. The CSF-tau levels were significantly higher in the group that showed progression of cognitive decline than in those who remained cognitively stable, while no significant difference was found in the levels of the progressive MCI group (subjects who had cognitive decline but did not convert to dementia) and those who converted to AD. Periventricular LA was more prevalent in those who remained stable cognitively than in those who showed progression of cognitive decline or conversion to dementia. Thus, evidence from Maruyama et al. (2004) suggested that

there might be two etiologic pathways for the development of MCI: a CSF-tau related pathology that appears linked to AD progression, and an ischemic pathology in the form of greater severity of LA that may represent a risk for vascular dementia. Although no association was found between LA and vascular risk factors, the small sample size (n = 12) and lack of quantitative measures of LA may have interfered with the findings. Further studies are needed to examine the potential link between stable MCI and LA to determine if conversion to vascular dementia occurs with time.

Chapter Summary

Individuals with MCI are at an increased risk of progressing to AD and other forms of dementia. The etiological and pathological processes of MCI appear heterogeneous. Risk factors associated with increased incidence of MCI include age, vascular risk factors, and genetic factors. The impact of vascular risk factors on MCI has become the focus of recent studies, with some evidence to suggest that LA and hypertension may increase the risk of MCI (DeCarli, 2001).

Recent studies have suggested that two independent pathways may lead to the development of MCI. One consists of an ischemic process and is associated with the presence and possibly the severity of LA (DeCarli et al., 2001; Maruyama et al., 2004), while the other pathway appears more closely aligned with the degenerative process resulting in AD and involves the impact of ApoE 4 (DeCarli, 2001) and CSF-tau levels (Maruyama et al., 2004). It is evident that further studies are needed to further elucidate these relationships, as it is not yet clear whether they do comprise

independent paths. There is support in the literature for an association between LA and cognitive decline in normal, nondemented elderly individuals and in AD. However, it can be difficult to clearly delineate the relationship between white matter changes and cognitive functioning in AD, particularly in advanced stages of the disease. Thus, examination of relationships in MCI may help to clarify the impact of LA on cognition.

CHAPTER SIX: PURPOSE OF STUDY AND HYPOTHESES

Purpose of Study

The current study was designed to examine the relationship between LA and cognitive performance in mild AD, MCI, and normal elderly controls (NE). Subjects underwent cranial MRI and a battery of neuropsychological measures. MRI scans were assessed by a semi-quantitative method to obtain values for the severity of LA. Three main sets of analyses were performed. First, the severity of LA (total, periventricular, and subcortical) was analyzed across the three groups (AD, MCI, and NE). Second, the relationship among vascular risk factors and both subtypes of LA (periventricular and subcortical) were explored within the group as a whole, to determine which risk factors most strongly predicted severity of LA. Third, the relationship between neuropsychological functioning and LA was examined within the entire sample, to determine which neuropsychological functions were most strongly associated with LA. Neuropsychological functions that were examined included global cognitive functioning, attention and concentration, memory, language, executive functioning, and visuoconstructional ability.

The major purpose of this study was to examine the contribution of LA to the neuropsychological impairment found in AD and MCI. An additional goal was to clarify the vascular risk factors associated with periventricular and subcortical LA in these samples. By examining relevant predictive risk factors, this study sought to provide information that could ultimately assist health providers make better-informed

decisions regarding prevention and patient intervention. To elaborate, by further clarifying which vascular risk factors, if any, were predictive of LA, healthcare providers could educate patients to make critical lifestyle changes and/or medication changes to reduce those factors.

Aims and Hypotheses

Specific Aim I: To examine the severity of leukoaraiosis (LA) in Alzheimer's disease (AD), Mild Cognitive Impairment (MCI), and normal elderly controls (NE).

Hypothesis 1: There will be significant differences in the severity of total LA, periventricular LA, and subcortical LA among the three populations. The AD group will show the greatest severity, followed by MCI, and then NE: AD > MCI > NE.

Specific Aim II: To examine the risk factors associated with leukoaraiosis.

Hypothesis 2A: Severity of periventricular LA will be most strongly predicted by age followed by hypertension. Older age and hypertension will be better predictors of severity than homocysteine level, gender, or a combined sum of additional vascular risk factors including: smoking, hyperlipidemia, diabetes, and cardiovascular disease.

Hypothesis 2B: Severity of subcortical LA will be most strongly predicted by age, followed by hypertension, and total homocysteine level. Older age, hypertension, and higher total homocysteine level will be better predictors of severity than gender or a combined sum of additional vascular risk factors including: smoking, hyperlipidemia, diabetes, and cardiovascular disease.

Specific Aim III: To examine the relationships between LA and measures of neuropsychological functioning across the three populations (AD, MCI, and NE).

Hypothesis 3A: Severity of LA (total, periventricular, and subcortical) will have significant inverse correlations with performances on neuropsychological measures (CERAD Total Score, MMSE, Verbal Fluency (animals), modified Boston Naming Test, Word List Learning, Recall, and Recognition, Constructional Praxis and Recall, Digit Span Backwards, and Trail Making Test Part A and B), with strongest inverse correlations for CERAD Total Score, MMSE, Verbal Fluency, Digit Span backwards, and Trail Making Test Part A and B.

Hypothesis 3B: Periventricular LA will correlate more strongly with measures of general cognitive functioning, attention, and speed of processing [CERAD Total Score, MMSE, Digit Span Backwards, Trail Making Test Part A and B, Verbal Fluency (animals)] than severity of subcortical LA.

CHAPTER SEVEN: METHOD

Subjects

AD sample.

The current study included 30 individuals diagnosed with probable AD as defined by NINCDS-ADRDA criteria (Table 1; McKhann et al., 1984). AD subjects were drawn from a pool of 71 seen at the Clinic for Alzheimer's and Related Diseases (ADC) at the University of Texas Southwestern Medical Center at Dallas, as part of a larger medical and neuropsychological study examining vitamin therapy for hyperhomocysteinemia in AD. Subjects were selected according to the following inclusion criteria.

Inclusion Criteria for AD:

1. Age 60-100
2. Early stage AD based on MMSE score between 19 and 28.
3. Medically stable with a stable medication regimen for ≥ 2 months prior to the study.
4. Significant focal lesions excluded by neuroimaging since onset of memory impairment.
5. Completed a neuropsychological evaluation, including the CERAD neuropsychological battery, MMSE, Digit Span Backwards, and Trail Making Test.

6. Completed a medical evaluation and MRI (FLAIR images) within one year of neuropsychological testing.
7. English was their primary language.
8. Subject or legally authorized representative must have provided written Informed Consent.

Normal elderly sample.

A sample of 30 cognitively intact elderly subjects were selected from a larger pool of individuals that were seen at the Clinic for Alzheimer's and Related Diseases (ADC) at the University of Texas Southwestern Medical Center at Dallas. The individuals were evaluated as part of a larger medical and neuropsychological study examining vitamin therapy for hyperhomocysteinemia in AD. Normal elderly subjects were primarily recruited from family and friends of AD patients and were selected according to the following inclusion criteria.

Inclusion for Normal Elderly:

1. Age 60-100
2. No cognitive complaints
3. MMSE score ≥ 28
4. Medically stable with a stable medication regimen for ≥ 2 months prior to study.

5. Completed a neuropsychological evaluation, including the CERAD neuropsychological battery, MMSE, Digit Span Backwards, and Trail Making Test.
6. Completed medical evaluation and MRI (FLAIR images) within one year of neuropsychological testing.
7. English was their primary language.
8. Subject must have provided written Informed Consent.

Exclusion Criteria for AD and Normal Elderly Subjects:

1. Enrollment in any other investigational drug study within 2 months.
2. Current evidence or history in the past 2 years of epilepsy, focal brain lesion, major cortical infarction, head injury with loss of consciousness/amnesia for > 30 minutes, or met DSM-IV criteria for Axis I disorder.
3. Blindness, deafness, language difficulty, or any other significant disability that prevented participation in the protocol.

MCI Sample.

A sample of 30 individuals diagnosed with MCI were selected. Subjects were diagnosed with MCI according to criteria listed in Table 2. Subjects were evaluated at the ADC or the Neuropsychology Service at UT Southwestern Medical Center at Dallas as part of a longitudinal study of MCI. The following inclusion criteria were used in the selection of participants.

Inclusion Criteria:

1. Age 45 years or older.
2. Clinical Dementia Rating (CDR) = 0.5.
3. Completed a neuropsychological evaluation, including the CERAD neuropsychological battery, MMSE, Digit Span Backwards, and Trail Making Test.
4. Completed medical evaluation and MRI (FLAIR images).
5. English was their primary language.
6. Subject or legally authorized representative must have provided written Informed Consent.

All subjects included were selected according to the inclusion and exclusion criteria listed above. From the original pool of 71 AD subjects, those who did not have MRI Flair images available from the Rodgers Imaging Center at U.T. Southwestern were eliminated (n = 35). AD subjects who had more than one year between time of MRI (n = 6) and time of neuropsychological testing were also eliminated. Exactly 30 subjects were found who met these criteria within the MCI group. The ranges and frequency distributions of age and education level were matched as closely as possible between the MCI and AD groups and the NE group to control for variation in these factors. No significant differences were found in age or education across the groups.

Materials

All subjects were administered the CERAD neuropsychological assessment battery (Morris et al., 1989). The CERAD neuropsychological battery includes the Mini-Mental State Examination (MMSE; Folstein, Folstein, & McHugh, 1975) in addition to seven measures including: 1) modified 15-item Boston Naming Test, 2) Animal Verbal Fluency, 3) Constructional Praxis Design copy, 4) Constructional Praxis Recall, 5) Word List Learning immediate recall, 6) Word List Recall delayed, and 7) Word List Recognition. A CERAD Total Score was calculated by summing all subtests, except for Constructional Praxis Recall, according to the method detailed by Chandler et al. (2005). All subjects were administered additional tests to supplement the CERAD battery including the Trail Making Test (Parts A and B; TMTA, TMTB) (Reitan & Wolfson, 1993), and Digit Span Backwards (adapted from Wechsler Adult Intelligence Scale-Third Edition, Digit Span subtest; WAIS-III; Wechsler, 1997)

MCI subjects were administered additional tests as part of a larger neuropsychological study including: the 60-item Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983), California Verbal Learning Test (CVLT; Delis, Kramer, Kaplan, & Ober, 1987), Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtiss, 1993), FAS and Category Fluency Tests (Spreen & Strauss, 1998), and Rey-Osterrieth Complex Figure (Rey-O; Corwin & Bylsma, 1993). A complete description of each test can be found in Appendix A.

Procedure

Approval for this study was obtained from the Institutional Review Board of the University of Texas Southwestern Medical Center at Dallas. All subjects (or their legal guardian) gave clinical consent prior to neuropsychological testing and MRI. Subjects were administered the neuropsychological test battery by thoroughly trained technicians who had no prior knowledge of the purpose of the current study. All efforts were made to elicit the best possible performance by each subject on testing. Subjects were given breaks as needed in compliance with testing standards.

In addition to neuropsychological testing, blood samples were obtained for biochemical analysis, and fasting plasma total homocysteine (tHCY) levels were obtained. Information regarding history of other relevant vascular risk factors was collected through medical chart review including: hypertension, smoking, hyperlipidemia, diabetes, and cardiovascular disease. History of hypertension was operationally defined as one of the following at time of testing: received treatment for hypertension, used antihypertensive agents, or seated systolic/diastolic blood pressure higher than 150/90 mm Hg. Significant smoking history was defined as > 1 cigarette per day for at least 1 year. History of hyperlipidemia was documented if the subject had a history of treatment, or if their serum cholesterol at evaluation showed a total cholesterol level > 220 mg/Dl. Diabetes mellitus was considered present if the subject reported a history of treatment for the disease. Finally, cardiovascular disease was considered present if patients had a known history or clinical demonstration of

myocardial infarction, coronary revascularization procedure, congestive heart failure, peripheral arterial disease, deep venous thrombosis, or any other indication of heart disease.

All subjects underwent MRI with a Philips Intera 1.5 Tesla scanner (Philips Medical Systems North America, Cleveland, OH). The system had PowerTrak gradients to allow for echo-planar imaging. The protocol included FLAIR acquisition to identify leukoaraiosis and edema. FLAIR is a heavily T2 weighted inversion-recovery technique that nulls fluid such that white matter lesions can be recognized (Hirono et al., 2000). The FLAIR images were acquired in the axial plane with a slice thickness of 5.0 mm, and an interslice gap of 0.5 mm. MRI images were transferred to Osiris (Windows version 4.19), which is a downloadable viewer for Papyrus and DICOM that was developed at the Service for Medical Computing of the Radiology department of the University Hospitals of Geneva.

Severity of leukoaraiosis was assessed with a modified semi-quantitative scale similar to the one developed by investigators from the Rotterdam Scan Study (deGroot et al., 2000). The scale used in the Rotterdam Study was developed and validated with T2 images in a population of 1,077 nondemented elderly. The use of FLAIR images in the current study was the most significant deviation from the original scale, in addition to the application of the scale to AD and MCI samples. The scale can be found in Appendix B, and the scoring manual is included as Appendix C. Periventricular and subcortical LA were rated separately. The number and size of

subcortical white matter lesions were rated according to their largest diameter in categories of small (< 3 mm), medium (3-10 mm), or large (> 10 mm) lesions. Lesions were assumed to be spherical in shape with a fixed diameter per size category, and the total volume of subcortical leukoaraiosis was estimated. Periventricular white matter lesions were rated in three regions: adjacent to the frontal horns, adjacent to the lateral ventricles, and adjacent to the occipital horns. Periventricular ratings ranged from 0 to 3: 0 (no lesions), 1 (pencil-thin line), 2 (smooth halo), and 3 (large confluent lesions). Overall periventricular severity was calculated by adding the three subscores (range 0-9). The total LA score was calculated by recoding the subcortical and periventricular scores to an equivalent scale and summing the results for each subject. The method used to calculate total LA is based on the data found in the current study and will be more thoroughly explained below in Chapter Eight. Subcortical atrophy was assessed with three ventricle to brain ratios. The ratios were calculated by taking the biventricular width at the level of the frontal horns, caudate nucleus, and occipital horns and dividing each width by the corresponding brain width at each of those levels. The total subcortical atrophy score is the mean of the three ventricle to brain ratios for each subject. Total cortical atrophy was assessed by rating the extent of atrophy in the areas of the Temporal Horns, Perisylvian Cistern, and Convexity Sulci (0-3), and then summing the total of all three areas.

The primary investigator of the current study rated all scans. Preliminary interrater reliability was established with an experienced neurologist who was blind to

the subjects' groups. The interrater intraclass correlation (ICC) coefficients were as follows: periventricular LA, ICC = .77; subcortical LA, ICC = .88; cortical atrophy, ICC = .83; and subcortical atrophy, ICC = .98, which indicated good to excellent agreement. The good to excellent range of the ICC gives evidence of the reliability of the scale. The ICC values were similar to the reliability data obtained by deGroot et al. (2000) who found weighted kappa values for periventricular data between $k = .79$ to .90, and ICCs for subcortical volumes between ICC = .88 to .95. Evidence for the validity of the scale was also found in the current study. Age was noted to be the most significant factor associated with LA in the literature, and all measures of LA were significantly correlated with age in the current study (total LA, $r = .44$, $p < .001$; periventricular LA, $r = .40$, $p < .001$; subcortical LA, $r_s = .42$, $p < .001$). In addition, each of the three measures of LA were correlated with each other, providing further evidence of validity of the scale, (total LA and periventricular LA, $r = .86$, $p < .001$; total LA and subcortical LA, $r = .67$, $p < .001$; periventricular LA and subcortical LA, $r = .52$, $p < .001$).

Statistical Analyses

Data were analyzed with the Statistical Package for the Social Sciences for Windows, version 12.0 (SPSS, 2003). Additional analyses were conducted with G POWER, a power analysis program (Faul & Erdfelder, 1992). A variety of statistical analyses were conducted to explore the proposed aims and hypotheses. The probability for significance was set at $p < .05$.

Hypothesis 1: There would be significant differences in the severity of LA among the three populations. Individuals with AD would have the greatest severity of all LA (total, periventricular, and subcortical), followed by MCI, and then NE.

Hypothesis 1 was evaluated using one way analysis of variance (ANOVA) to compare the severity of each type of LA across the three groups. The Bonferroni post-hoc test was used to control for Type I error across the pairwise comparisons. The probability for significance was set at $p < .05$. In addition, a post hoc power analysis was conducted to determine the effect size for the ANOVA comparing total LA across the three groups. Testing at $\alpha = .05$, the calculated effect size of the study was $d = .46$ which supports a sample size of 90 and power of 95%.

Hypothesis 2A and 2B: Among risk factors for leukoaraiosis, age and hypertension will most strongly predict severity of periventricular leukoaraiosis, and age, hypertension, and homocysteine level will most strongly predict severity of subcortical leukoaraiosis.

Hypotheses 2A and 2B were examined by multiple regression analyses to determine how well the risk factors predicted severity of periventricular and subcortical leukoaraiosis. The predictors were age, hypertension, homocysteine level, gender, group, duration of disease, and the combined sum of additional cerebrovascular risk factors. The criterion was severity of periventricular leukoaraiosis for 2A, and subcortical LA for 2B. For hypothesis 2A, it was expected that age and hypertension would be better predictors of severity of periventricular

leukoaraiosis than other predictors. Those variables were entered, in that order, followed by the remaining predictors. The first multiple regression model was followed by an additional exploratory stepwise regression model in which all of the predictors were entered simultaneously. For hypothesis 2B, it was expected that age, hypertension, and homocysteine would predict of severity of subcortical leukoaraiosis better than other predictors. Those variables were entered in that order, followed by the remaining predictors, in the first multiple regression model. An exploratory stepwise regression model was also conducted in the same manner as Hypothesis 2A.

Hypothesis 3A: Severity of leukoaraiosis (total, periventricular, and subcortical) would be inversely correlated with performance on neuropsychological measures with strongest inverse correlations on the CERAD Total Score, MMSE, Verbal Fluency, Digit Span Backwards, and Trail Making Test, A and B.

To explore these hypotheses, Pearson Product-Moment correlations were computed between the LA score and all neuropsychological measures. Scatterplots and data were analyzed for all correlations to ensure assumptions of Pearson correlations were not violated. Spearman correlation coefficients were performed as an alternative, if assumptions necessary for Pearson were violated. Correlations were also conducted, following the aforementioned format, within each of the three groups. Partial correlations were performed as necessary to control for age. Additionally, the entire sample was divided into high and low severity of total LA, and independent-

samples *t*-tests were performed to compare performance on each of the neuropsychological measures.

Hypothesis 3B: Periventricular LA would correlate more strongly with performance on neuropsychological measures of general cognitive functioning, attention, and speed of processing than subcortical LA, as measured by the following tests: the CERAD Total Score, MMSE, Verbal Fluency (animals), Digit Span Backwards, and Trail Making Test, A and B.

For hypothesis 3B, a test of correlations for dependent samples was used according to the formula in Cohen and Cohen (1975, p. 53), to determine whether periventricular LA correlated more strongly than subcortical LA with the predicted neuropsychological measures. Tests were performed for pairs of significant correlations. Spearman correlations were substituted for Pearson correlations for this analysis due to nonlinear distributions.

Exploratory Analyses, MCI: For the MCI group, additional neuropsychological measures were completed as part of a larger study. Leukoaraiosis and Performance on additional neuropsychological measures, including the WCST, BNT, FAS, CVLT, and Rey-O, were analyzed to determine if associations existed that were not clear based on the briefer battery used for the study. To explore these relationships, Pearson Product-Moment correlations were computed. In addition, the sample was divided into high and low severity of LA and independent-samples *t*-tests were conducted to compare performance on each of the neuropsychological measures.

Exploratory Analyses, Cerebral Atrophy: Additional analyses were performed to explore the relationships between measures of subcortical and cortical atrophy, LA, and neuropsychological functioning. First, subcortical and cortical atrophy (total scores and individual regions comprising each type of atrophy) were analyzed by one way ANOVAS across the three groups. Post hoc comparisons were made with the Bonferroni method to control for Type I error, $p < .05$. Pearson correlations were also computed to compare the overall subcortical and cortical atrophy scores to LA (total, periventricular, and subcortical), across and within the groups. Additional Pearson correlations were computed to compare the overall subcortical and cortical atrophy scores to all neuropsychological measures, across and within the groups. As was done in Hypothesis 3B, a test of correlations for dependent samples was used to determine whether subcortical atrophy correlated more strongly than cortical atrophy with the neuropsychological measures, for pairs of significant correlations only.

CHAPTER EIGHT: RESULTS

Demographic Characteristics

A total of 90 participants who met inclusion criteria and had cranial MRI scans with axial FLAIR images and neuropsychological testing were included in the study. There were 30 participants in each of the three groups: AD, MCI, and NE.

Demographic information for the total group of 90 participants is provided in Table 3. The sample as a whole had a mean age at assessment of 71 years (*SD* = 7.3), and was nearly equally composed of men and women (% male = 56.7). The average years of education across the entire group was 14.8 (*SD* = 2.9). Ninety-two percent of the sample was Caucasian, 6% Hispanic, and 2% African American.

Insert Table 3 here

Demographic information for the AD, MCI, and NE groups is presented in Table 4. There were no significant differences between the groups for age (F (2, 87) = 0.47, p = .63) or education (F (2, 87) = 0.03, p = .97). The AD group was predominantly male (M/F = 20/10), but there was no significant gender difference between the groups (X^2 (2, N = 90) = 1.90, p = .39). The racial compositions of the groups were similar, as the samples were primarily Caucasian (AD = 87%, MCI = 97%, NE = 93%). The duration of illness was significantly longer for the AD group

(M = 5.1 years) than the MCI group (M = 3.8 years), t (58) = -2.15, p = .04, and a moderate effect size was observed ($|d|$ = .55).

Insert Table 4 here

Research Hypotheses

Study Aim One

The first study aim was to examine the severity of LA across the groups. To address this aim, a total semiquantitative LA score was derived from the periventricular and subcortical scores and compared across the groups. The total LA score was calculated by examining the frequency distributions of the results for the periventricular LA scores and the subcortical LA scores. The distributions were evenly divided into thirds and recoded 1, 2, and 3 according to low, medium, and high severity of LA, based entirely on the data for the current study. For periventricular LA, the low group included scores 2-4 (n = 32), medium group included scores 5-6 (n = 32), and the high group ranged from 7-9 (n = 26). The subcortical LA was divided with 30 subjects in each of the three groups with low ranging from 0 - .255 cm^3, medium from .256 to 1.37 cm^3, and high from 1.38 to 11.13 cm^3. To calculate the total LA score, the newly coded periventricular (range = 1-3) and subcortical (range = 1-3) scores for each subject were summed (total range = 2-6). The total LA measure was significantly correlated with periventricular LA (r = .86, p < .001) and subcortical

LA ($r = .67$, $p < .001$). Periventricular LA and subcortical LA were also correlated ($r = .52$, $p < .001$). The means, standard deviations, and results as they pertain to Hypothesis 1 can be found in Table 5.

Insert Table 5 here

Hypothesis 1 stated that there would be significant differences across the groups in severity of total LA, periventricular LA, and subcortical LA. It was predicted that the AD group would have the greatest severity on all three LA scores, followed by the MCI group and then NE. This hypothesis was partially supported. Analysis of variance demonstrated that there were significant differences in total LA between the groups. Post hoc analyses of all pairwise combinations were conducted with the Bonferroni test ($p < .05$). Results indicated that the AD group had significantly greater severity of total LA than the MCI and NE groups. It was predicted that the MCI group would have a higher mean score than the NE group, but this was not supported, as there was no significant difference between the MCI ($M = 3.2$, $SD = 1.3$) and NE ($M = 3.8$, $SD = 1.2$) groups for total LA ($p = .22$); in fact, the NE group actually had slightly higher values.

Significant group differences were also found with periventricular LA. As predicted, post hoc analysis with the Bonferroni test demonstrated significantly greater severity of periventricular LA in the AD versus the MCI group. Although the AD

group demonstrated a higher mean severity score than the NE group, this difference was not statistically significant. The prediction that the MCI group would demonstrate greater severity of periventricular LA than the NE group was not supported. In fact, the opposite was found, as the NE mean periventricular LA (M = 5.4, SD = 1.5) was significantly greater than the MCI group mean (M = 4.3, SD = 1.8).

Significant group differences in total subcortical LA volume (cm^3) were also found, with greater volumes in the AD versus the MCI group, which partially supported the hypothesis. However, no significant differences were found between the volumes of the AD and NE groups or the NE and MCI groups. As with the total LA and periventricular LA findings, the NE group subcortical LA volume was greater than in the MCI group, although the difference was not significant.

Study Aim Two

The purpose of the second study aim was to explore the risk factors associated with LA in order to determine the factors that best predict severity of periventricular and subcortical LA. The descriptive data of the risk factors can be found in Table 6.

Insert Table 6 here

Hypothesis 2A stated that severity of periventricular LA would be predicted most strongly by risk factors of age followed by hypertension. To test this hypothesis, a multiple regression analysis was first conducted by entering the variables in the order of prediction in three models. Results for these models (Model 1-3) can be found in Table 7.

Insert Table 7 here

The results indicated that age accounted for a significant amount of the variability in severity of periventricular LA, R^2 (change) = .125, F (1, 71) = 10.16, p = .002, which supported the hypothesis and indicated that older individuals had greater severity of periventricular LA. However, hypertension did not contribute significantly to periventricular LA, as predicted, after controlling for the effects of age, R^2 (change) = 0, F (1, 70) = .037, p = .85. Homocysteine level, gender, and the combined sum of cerebrovascular risk factors (smoking, hyperlipidemia, diabetes, and cardiovascular disease) were added to the regression model, along with group membership (AD, MCI, or NE) and duration of disease. The linear combination of all of the additional predictors was significantly related to severity of periventricular LA, after controlling for the effects of age, hypertension, and homocysteine, R^2 (change) = .211, F (6, 64) = 3.39, p = .006.

For exploratory purposes, a stepwise regression was used to examine the order in which the predictor variables would structurally enter the model. The MCI group variable emerged as the most significant outcome predictor, $R^2 = .181$, F (1, 71) = 15.66, $p < .001$, with age also accounting for a significant amount of variability in severity of periventricular LA, R^2 (change) = .114, F (1, 70) = 11.29, $p = .001$. Homocysteine data was not available for 14 subjects in the MCI group, which lowered the overall number of subjects that were included in the regression analyses. To determine whether this had an impact on the regression models, homocysteine was removed and the models were reexamined without it. No changes were found in any of the models by excluding homocysteine.

Hypothesis 2B stated that age, hypertension, and total homocysteine level, in that order, would most strongly predict severity of subcortical LA. The hypothesis was tested with a multiple regression analysis by entering the variables in the order of prediction in three models. The results of these models (Models 1-3) can be found in Table 8.

Insert Table 8 here

Age accounted for a significant amount of the subcortical LA variability, $R^2 = .09$, F (1, 71) = 6.80, $p = .01$, demonstrating that older individuals tended to have higher

volumes of subcortical LA. However, none of the other risk factors (gender, group, duration of disease, and sum of additional vascular risk factors) accounted for significant variability in severity of subcortical LA.

As in Hypothesis 2A, a stepwise regression was conducted for exploratory purposes, and age was the only significant outcome predictor variable, $R^2 = .09$, F (1, 71) = 6.80, $p = .01$. This partially supported the hypothesis as older individuals had greater severity of subcortical LA. However, hypertension, homocysteine, and the other vascular risk factors were not found to be significant predictor variables, which did not support the hypothesis. As in hypothesis 2A, homocysteine was removed and the models were re-examined without it. No changes were found in any of the models by excluding homocysteine.

Study Aim Three

The third study aim was to explore the relationships between LA and neuropsychological performance. The neuropsychological measures examined in the primary hypotheses and additional exploratory analyses are presented in Table 9. The means and standard deviations of the neuropsychological measures, across all subjects and within the AD, MCI, and NE groups, are presented in Table 10.

Insert Tables 9 and 10 here

As can be seen in Table 10, significant differences were found between the groups for all neuropsychological measures, with AD demonstrating significantly poorer performance than MCI and NE. Both the AD and MCI groups performed significantly worse on Verbal Fluency than the NE group. While the AD group demonstrated the greatest impairment across all measures, the MCI group means fell between the AD and NE group means for most measures, as expected.

Hypothesis 3A stated that severity of LA (total, periventricular, and subcortical) would be inversely correlated (greater severity of LA correlated with poorer performance on neuropsychological tests) with performance on neuropsychological measures assessing general cognitive functioning, speed of mental processing, attention, language, memory, visuoconstructional ability, and executive functioning. It was also predicted that the correlations for general cognitive functioning, processing speed, attention, and executive functioning would demonstrate stronger inverse correlation coefficients than other neuropsychological measures.

Total LA Results.

Pearson correlation coefficients for total LA and neuropsychological test performances across and within the three groups are presented in Table 11. Spearman rank order correlation coefficients (Spearman *rho*) were conducted if assumptions necessary for Pearson correlations were violated, such as nonlinearity. Table 12

displays the Pearson partial correlations for total LA and neuropsychological performance controlling for the effect of age.

Insert Tables 11 and 12 here

The results partially supported the hypothesis. When all subjects were combined, most measures showed significant inverse correlations with total LA, although the strength of the correlations ranged from low to moderate, r = -.23 to r = -.36. It should be noted that multiple correlations were conducted, which may limit the meaningfulness of the correlations that were significant. The highest correlations were for measures of general cognitive functioning (CERAD total score, r = -.31; MMSE, r = -.36), verbal fluency (CERAD animal fluency, r = -.34), and verbal learning and memory (CERAD word list learning and recall, r = -.32, and -.32). Also significant were measures of executive functioning (Trails B, r = -.29), visuospatial memory (Constructional Praxis Recall, r = -.27), and verbal recognition memory (CERAD Word List Recognition, r = -.23).

Additional exploratory analyses were conducted to examine the relationship between total LA and neuropsychological functioning within the AD, MCI, and NE groups (see Table 11). Total LA was only significantly correlated in the inverse direction with one of the measures of neuropsychological functioning across the three groups. The significant correlation was in the NE group for Digit Span longest digits

backwards (r = -.41, p < .05). However, a few correlations occurred in the opposite direction from what was expected. Within the AD group, total LA was positively correlated with CERAD Word List Recall (r = .51), Constructional Praxis Recall (r = .43), and the modified total Digit Span and Longest Digit Span Backwards measures (r = .52 and r = .59, respectively).

Age was significantly correlated with total LA, periventricular LA, and subcortical LA (r = .44, p < .001; r = .40, p < .001; and r_s = .42, p < .01, respectively). Additional Pearson correlations were conducted to examine the association between age and neuropsychological functioning across all subjects and within the AD, MCI, and NE groups. Age was not significantly correlated with neuropsychological functioning on any of the 13 measures when all subjects were combined, or for the MCI or NE groups. However, age was associated with 11 of the 13 neuropsychological measures when the AD group was analyzed separately. The strength of the correlations ranged from moderate to large, r = .39 to r = .60, with largest correlations for the Digit Span longest digits backward test, r = .60, total digits backward, r = .57, and MMSE, r = .55. The positive direction of the correlations in the AD group indicated that neuropsychological performance was less impaired for older subjects, which was opposite from the expected direction. Based on these associations between age and neuropsychological functioning in the AD group, Pearson partial correlations were conducted to examine the association between the variables while controlling for the effect of age (see Table 12). Results demonstrated

that the strength of the positive correlations decreased across all neuropsychological measures in the AD group, though the majority of the correlations (11 of 13) remained in the positive direction, contrary to what was expected. Only two were statistically significant after controlling for age (Word List Recall, $r = .38$; Longest Digits Backward, $r = .37$). In addition to age, cerebral atrophy was also associated with LA, particularly for all subjects and the AD group, and neuropsychological functioning. Therefore, Pearson correlations partialling out the effects of age and cerebral atrophy were also performed. For all subjects, there were no significant correlations between total LA and any measures of neuropsychological functioning after controlling for the effects of age and atrophy. However, among those with AD, five significant correlations were found: Word List Memory, $r = .40$, $p = .047$; Word List Recall, $r = .55$, $p < .01$; Constructional Praxis Recall, $r = .44$, $p = .03$; Digit Span longest digits backward, $r = .55$, $p < .01$; and Digit Span total digits backward, $r = .54$, $p < .01$.

In addition to within-group correlations, independent-samples *t*-tests were performed with all subjects and within the AD, MCI, and NE groups to examine differences in neuropsychological functioning for individuals with high versus low total LA scores. Individuals were divided into two categories (high, low) based on two separate methods. In Method 1, the group was divided roughly in half, with the intent of having approximately equal group sizes, based on the frequency distribution of total LA across all subjects, and within each of the three groups (AD, MCI, and NE). In Method 2, the frequency distribution of total LA was used to divide the

groups into thirds, and the highest and lowest thirds were compared. Frequency distributions were used to ensure adequate and relatively equal samples for comparisons, as there was variability across groups regarding the range of LA scores. Specific ranges and sample sizes for high and low *t*-test comparisons can be found in Table 13 and significant t-test results are shown in Table 14.

Insert Tables 13 and 14 here

When all subjects were included in the *t*-test comparisons by Method 1, significant mean differences resulted for the CERAD total score, Verbal Fluency, Word List Learning, Word List Recall, and Trails B. The low total LA group had higher means on neuropsychological measures than the high total LA group, which indicated better neuropsychological performance occurred in the group that had less total LA, as expected. When the whole sample was divided by Method 2, mean differences were found on the CERAD BNT and Word List Recognition, again with higher means in the low total LA group. In the AD group, *t*-tests (Method 1) revealed significant mean differences for Constructional Praxis, Word List Recall, total Digit Span backwards, and longest Digit Span backwards. Additional group differences were found by Method 2 for CERAD total, MMSE, Word List Learning, and Trails A, though it should be noted that there was a small $n = 6$ in one of the groups. For each of the comparisons (Methods 1 and 2), the results were opposite from the predicted

direction as higher mean performances on the cognitive measures were also found in the group with higher severity of total LA. There were four significant *t*-tests within the NE group, observed for CERAD total score, Verbal Fluency, Word List Learning, and longest Digit Span Backwards sequence in the high versus low LA group. As predicted, for each of the measures in the NE group, higher means were found in the low total LA group.

Periventricular LA Results.

The correlation coefficients for periventricular LA and neuropsychological measures can be found in Table 15. Partial correlation coefficients can be found for the same factors, controlling for the effect of age, in Table 16.

Insert Tables 15 and 16 here

Statistically significant inverse correlations were found for the majority of neuropsychological measures, although the coefficients fell in the low to moderate range (r = -.26 to r = -.32). Inverse correlations were found between severity of periventricular LA and measures of general cognitive functioning (MMSE, r = -.32; CERAD total score, r = -.29), language (CERAD animal category, r = -.28), memory (CERAD Word List Learning, r = -.29; Recall, r = -.28; Recognition, r = -.26; Constructional Praxis Recall, r = -.28), and executive functioning (Trails B, r = -.29). Therefore, Hypothesis 3A for periventricular LA was partially supported. However,

contrary to what was predicted, there were no significant correlations with a test of visuoconstructional ability or measures of attention.

Further exploratory correlations were computed to examine the relationship between periventricular LA and neuropsychological functioning within each of the three groups (see Table 15). The only significant inverse correlations found were in the NE group in the area of memory (CERAD Word List Learning, r = -.45; and CERAD Word List Recall, r = -.38). The majority of the correlations between periventricular LA and neuropsychological functioning were in the expected direction for the MCI and NE groups, although none reached statistical significance. There were two positive correlations in the AD group for measures of memory and attention (CERAD Word List Recall, r = .42; and Total Digit Span Backwards, r = .50), which once again were opposite from the expected direction.

Periventricular LA and age were significantly correlated (r = .40, p < .001) for all subjects, and the majority of neuropsychological measures correlated significantly with age in the AD group. Therefore, Pearson partial correlations were computed to control for the effects of age (see Table 16). Not surprisingly, the correlations did not change substantially for all subjects, or for the MCI or NE groups. However, the correlations for neuropsychological functioning and periventricular LA in the AD group decreased as a result of partialling out the effect of age. Additional Pearson correlations were computed, partialling out the effects of age and cerebral atrophy. Results were similar to those found for total LA, as no significant correlations

remained for all subjects after controlling for the effects of age and atrophy. Within the AD group, the magnitude of the correlations remained similar to the findings when partialling out the effect of age. Two significant correlations were found with the Digit Span backwards variables in AD (longest digits, $r = .54$, $p < .01$; and total digits, $r = .46$, $p = .02$). Partialling out the effects of both age and atrophy did not significantly change findings within the NE and MCI groups.

As with total LA, independent-samples *t*-tests were performed with all subjects, and within the AD, MCI, and NE groups, to examine differences in neuropsychological functioning for individuals with high versus low periventricular LA scores. Specific ranges and sample sizes for high and low *t*-test comparisons can be found in Table 17. Statistically significant results can be found in Table 18.

Insert Tables 17 and 18 here

First, comparisons were made by dividing all subjects according to Method 1. Mean differences were found for the majority of measures including the CERAD total score, MMSE, Verbal Fluency, CERAD BNT, Word List Learning, Recall, and Recognition, Constructional Praxis Recall, and Trails A and B. Similar to previous findings, the low periventricular LA group resulted in better mean neuropsychological performance than the high LA group. The use of Method 2 with all subjects did not result in any

additional significant mean differences. Comparisons in the AD group, resulted in significant differences in Word List Learning, Word List Recall, Digit Span total digits backwards, and Digit Span longest backwards between high and low LA groups. The group means were in the opposite direction from what was predicted by the hypothesis as subjects in the high periventricular LA group performed better than those in the low periventricular LA group. Only the *t*-tests for the CERAD Total and Verbal Fluency were significant for the MCI group, with better performance in the low versus high periventricular LA group. In the NE group, only CERAD total score was significant, with lower scores in the high versus low periventricular LA group.

Subcortical LA Results.

Table 19 depicts the correlation coefficients for subcortical LA and neuropsychological measures, and Table 20 portrays partial correlation coefficients for those factors, controlling for the effect of age.

Insert Tables 19 and 20 here

Examining the relationships between subcortical LA volume and neuropsychological functioning across the groups resulted in four significant inverse correlations, which provided partial support for the hypothesis. The correlations were significant on both measures of general cognitive functioning (CERAD total, r = -.24;

and MMSE, r = -.24) and measures of memory (CERAD Word List Learning, r = -.29; CERAD Word List Recall, r = - .24). No other significant correlations were found. No correlations remained significant after controlling for the effect of age, and almost all were reduced below r = -.10.

Additional exploratory analyses were performed within each of the three groups to examine relationships between subcortical LA volume and neuropsychological functioning. A significant correlation was found in the NE group for CERAD Word List Recall, r = -.36, before age corrections, and for the Trails A T Score, r = .50, after age corrections. Although few correlations were found in the expected inverse direction within the groups, the AD group had many significant positive correlations. Increase in volume of subcortical LA in the AD group was associated with better performance on neuropsychological measures in domains of general cognitive functioning, memory (verbal and nonverbal), visuoconstructional ability, and attention and processing speed. The strongest correlation was found with a memory measure (CERAD Word List Recall, r = .57) while other correlations were moderate, and ranged from r = .38 to r = .48. However, once the effects of age were controlled for, only two correlations remained significant (Word List Recall, r = .51, and Trails A, r = .47) in the AD group. Age and atrophy corrections were similar to age corrections for all subjects, with the exception that a significant correlation was found for Trails A (r = .24, p = .04) in the opposite direction from what was expected. Controlling for age and atrophy resulted in three significant correlations within the AD

group (CERAD total score, $r = .47$, $p = .02$; Word List Recall, $r = .59$, $p < .01$; Trails A, $r = .52$, $p < .01$), all of which were opposite from the predictions. No significant correlations were found in the MCI group, and Trails A remained significant in NE ($r = .50$, $p < .01$).

Exploratory independent-samples *t*-tests were also performed to examine mean differences on neuropsychological functioning for individuals categorized into high versus low subcortical LA scores across and within in each of the three groups (AD, MCI, and NE). Comparisons were made for all neuropsychological measures, and The specific ranges of subcortical volumes and sample sizes for high and low *t*-test comparisons can be found in Table 21. Table 22 depicts only the *t*-test results for comparisons that were statistically significant.

Insert Tables 21 and 22 here

The entire sample was divided into high and low subcortical LA groups according to Methods 1 and 2. For Method 1, Word List Learning and Recall were significantly different, with lower scores in the high versus low subcortical LA group, as expected. The trend was in the same direction (lower cognitive scores in high LA group) for the other variables, but did not reach statistical significance. Comparisons by Method 2 for all subjects did not result in additional mean differences. Differences were found

in the AD group in Word List Recall, Constructional Praxis, Praxis Recall, and Trails A using Method 1, and in the CERAD total score by Method 2. Again, contrary to the prediction, higher scores were found in the high versus low subcortical LA group for all comparisons. The *t*-tests for the MMSE and CERAD BNT were significant for the MCI group, with better performance in the low versus high subcortical LA group, as expected. In the NE group (Method 1), CERAD Total, Word List Learning, and Word List Recall measures were significant, also with better performance in the low versus high subcortical LA group.

Hypothesis 3B stated that periventricular LA would demonstrate stronger inverse correlations with neuropsychological functioning than subcortical LA on measures of general cognitive functioning (CERAD Total score and MMSE), attention and speed of processing (Trail Making Test, Part A and B), and Verbal Fluency. To test this hypothesis, a test of correlations for dependent samples was conducted only on pairs of significant correlations, according to the formula found in Cohen and Cohen (1975, p. 53). The results of these comparisons can be found in Table 23.

Insert Table 23 here

The neuropsychological measures that correlated significantly with both subtypes of LA were the CERAD Total score, MMSE, Word List Learning, and Word List Recall.

The test of correlations for dependent samples demonstrated that while correlations were slightly higher for periventricular LA, they did not significantly differ from those with subcortical LA, and thus, the hypothesis was not supported. However, there were four additional neuropsychological measures that correlated significantly with periventricular LA, but not subcortical LA across all subjects. These measures were Verbal Fluency (r = -.28), Word List Recognition (r = -.26), Constructional Praxis Recall (r = -.28), and Trails B (r = -.29). The fact that Verbal Fluency and Trails B correlated with periventricular LA and not subcortical LA provided partial support for this hypothesis.

Exploratory Analyses

Neuropsychological Functioning and LA in MCI

In addition to the primary hypotheses, exploratory analyses were performed to examine the MCI cohort more extensively. These analyses explored relationships between LA and neuropsychological functioning, within the MCI group, with a more extensive neuropsychological battery that was not available for the AD and NE groups.

Within the MCI group, severity of total, periventricular, and subcortical LA (all analyzed independently) and neuropsychological performance were examined on the Wisconsin Card Sorting Test (WCST), Boston Naming Test (BNT), Phonemic Fluency (FAS), California Verbal Learning Test (CVLT), and Rey-Osterrieth

Complex Figure (Copy and Delayed Recall) to further determine whether a relationship existed between LA and cognitive functioning.

The Wisconsin Card Sorting Test variables that were analyzed included total perseverative responses (T-score), and number of categories completed. Pearson correlations were performed between those variables and the measures of LA across the MCI group and one significant correlation emerged ($n = 28$) for the total perseverative responses T-score and total LA ($r = .55$, $p < .01$). This correlation indicates that as severity of total LA increases, performance on the WCST improves, which is counter to what would be expected. However, it is possible that the correlation is limited by restriction of range due to a small sample size (n= 28), and thus low power, in the MCI group. The correlations were followed by a series of independent samples *t*-tests in which the MCI group was divided into a high and low category based on severity of total LA, and the means of the WCST variables were compared between the two groups. The mean difference between the high ($M = 53.4$, $SD = 9.1$) and low ($M = 44.0$, $SD = 8.1$) total LA groups on the total perseverative responses *T*-score was significantly different, $t\ (27) = -3.85$, $p < .01$. This result did not support the hypothesis as the high total LA group had significantly better performance than the lower total LA group. Similar findings were found when comparing the mean high versus low subcortical LA groups. Again, the high ($M = 59.3$) subcortical LA group had significantly better performance on the WCST than the low ($M = 44.9$) subcortical LA group.

BNT total raw scores and T-scores (n = 29), FAS total raw scores (n = 30), and Rey-Osterrieth total copy, immediate and delayed recall scores (n = 30) of the MCI group were also compared with each measure of LA with Pearson correlations. In addition, the CVLT Trial 1-5 total raw score (n = 30), T-score (n = 29), Short Delay free recall total (n = 29), Long Delay free recall total (n = 29), and Recognition Discriminability (n = 29) were examined in the same manner as above. No significant correlations or *t*-test mean differences emerged, and it is possible that limited power interfered with the ability to detect results in the analyses.

Cortical and Subcortical Atrophy

Additional exploratory analyses were conducted to examine the relationships between measures of brain atrophy, LA, and neuropsychological functioning across and within the three groups. These analyses were purely exploratory and no specific hypotheses about the outcomes were postulated a priori.

In the first analysis, measures of subcortical and cortical atrophy were compared across the groups using one way analysis of variance. Means, standard deviations, and results of group mean comparisons are listed in Table 24.

Insert Table 24 here

Post hoc analyses demonstrated that the overall measure of subcortical atrophy and each of the three regions that comprise it (e.g., frontal horns, occipital horns, and body of caudate) were significantly different. Cortical atrophy results followed the same pattern. The AD group demonstrated greater subcortical and cortical atrophy than the MCI and NE groups. The only significant difference in atrophy between the MCI and NE groups was the convexity sulci measure of cortical atrophy (NE > MCI, $p = .045$).

The second exploratory analysis examined the relationship between subcortical atrophy, cortical atrophy and LA, across and within the three groups of the study (AD, MCI, and NE).

Insert Table 25 here

As can be seen in Table 25, the overall subcortical and cortical atrophy scores correlated significantly with all three measures of LA (total, periventricular, and subcortical) when examining all subjects together. Correlations were positive, suggesting increased severity of LA was associated with increased atrophy, and fell in the low to moderate range for both subcortical atrophy, $r = .30$ to $r = .39$, and cortical atrophy, $r = .20$ to $r = .43$. Within the AD group, the correlation between total LA and subcortical atrophy was moderate, $r = .38$. Additional correlations between total and periventricular LA and cortical atrophy were significant in the MCI group, $r = .40$ and $r = .51$, respectively. Correlations partialling for the effect of age were examined

since age correlated significantly with subcortical ($r = .27$, $p < .05$) and cortical atrophy ($r = .34$, $p < .01$), and with LA when all subjects were combined. Controlling for age reduced the magnitude of the correlations between LA and atrophy among the MCI group, but did not result in other significant changes.

Additional analyses were conducted to further explore the associations between LA and atrophy by examining the subcortical and cortical regions separately.

Insert Table 26 here

As depicted in Table 26, correlations and partial correlations controlling for the effect of age were calculated for LA and subcortical atrophy. The effect of age was partialled out due to significant correlations between age and LA, as well as between age and the Frontal Horn and Caudate regions when all subjects were analyzed together ($r = .32$, $r = .37$, respectively, $p < .01$). In addition, age was significantly correlated with the Frontal Horn region in the NE group ($r = .54$, $p < .01$), and the Caudate region with the MCI group ($r = .52$, $p < .01$) and NE group ($r = .58$, $p < .01$). Results showed that when all subjects were analyzed together, total LA and periventricular LA were significantly associated with the Caudate region and the Occipital Horn region, although correlations were low to moderate. In addition, subcortical LA was associated with all three regions, and total LA was also significantly associated with the Frontal Horn region. Within-group comparisons

revealed significant correlations between the Caudate and Occipital Horn regions and total LA among the AD group, before and after controlling for age. Lastly, the NE group was significantly correlated with the Frontal Horn region, but only after the influence of age was partialled out.

When the cortical atrophy regions were analyzed separately, age was significantly correlated with all regions (see Table 27).

Insert Table 27 here

There were age correlations with the Temporal Horn and Convexity Sulci regions when all subjects were analyzed together ($r = .27$, $p < .05$; $r = .37$, $p < .01$, respectively). The MCI group had the highest age correlations with the regions, ranging form $r = .48$ for the Temporal Horn, to $r = .78$ for the Convexity Sulci region. The AD group had no association between cortical atrophy and age, and the NE group was only associated at the Convexity Sulci region ($r = .44$, $p < .05$). Regarding LA and cortical atrophy correlations when all subjects were analyzed together, total LA and periventricular LA were significantly associated with all three regions of cortical atrophy, with strongest associations with the Convexity Sulci, before age was controlled. Subcortical LA was significantly associated with the Temporal Horn and Convexity Sulci regions, but not the Perisylvian Cistern. Within the MCI group, all measures of LA correlated significantly with the Convexity Sulci region, with

moderate correlations before controlling for age. These correlations were no longer significant after age was partialled out however. There were a few additional within group significant correlations, but none were significant after controlling for the effect of age (see Table 27).

The third group of exploratory analyses was an examination of the relationships between brain atrophy and neuropsychological performance across and within the three groups. The correlations between subcortical atrophy and neuropsychological performance can be found in Table 28.

Insert Table 28 here

All neuropsychological measures correlated significantly with the overall measure of subcortical atrophy across the combined groups. Correlations were inverse and of moderate size, ranging from r = -.36 to r = -.60. The highest inverse correlations were found with the CERAD Word List Recognition (r = -.60), CERAD total score (r = -.57), and CERAD Boston Naming Test (r = -.55). Few significant correlations resulted when examining the AD, MCI, and NE groups separately. Only the AD group demonstrated significant correlations between neuropsychological measures and subcortical atrophy. The significant correlations for the AD group were all inverse indicating that increased subcortical atrophy was related to lower performance on certain neuropsychological tests including: CERAD BNT (r = -.51), Word List

Recognition (r = -.48), CERAD Total (r = -.47), Verbal Fluency (r = -.46), and Word List Learning (r = -.44).

Correlations between cortical atrophy and neuropsychological performance across and within the groups can be found in Table 29.

Insert Table 29 here

All neuropsychological measures correlated significantly with the overall measure of cortical atrophy when examining the combined groups. The correlations were inverse and moderate, ranging from r = -.37 to r = -.60. The highest inverse correlations were found for the CERAD total score (r = -.60), MMSE (r = -.57) and Cerad Verbal Fluency (r = -.56). Four significant inverse correlations were found when analyzing the AD, MCI, and NE groups separately. All four were within the AD group and included: CERAD BNT (r = -.36), Word List Learning (r = -.41), CERAD Total (r = -.48), and Verbal Fluency (r = -.55).

The final exploratory analyses involved calculating *t*-tests of correlations for dependent samples (Cohen & Cohen, 1975, p. 53) to determine whether the significant correlations between subcortical atrophy and neuropsychological functioning were statistically different from those between cortical atrophy and neuropsychological functioning. Results can be found in Table 30 for all subjects, and for the AD group in Table 31.

Insert Tables 30 and 31 here

None of the t-tests resulted in significant mean differences between the correlations, indicating that neither type of atrophy could be described as more strongly associated with neuropsychological functioning, for pairs of significant correlations. These findings were true for all subjects, as well as when the AD group was analyzed separately. No comparisons were made for the MCI or NE group because there were no significant pairs of correlations.

CHAPTER NINE: DISCUSSION

Leukoaraiosis is a descriptive term for white matter changes that are evident neuroradiologically and are associated with normal aging as well as dementing conditions. The etiological roots of LA are not entirely clear, but many studies suggest that a cerebral ischemic process is probable, predicated on the fact that LA is often associated with cerebrovascular risk factors and is prevalent among people with vascular dementia (Filley, 2001; Hogervorst et al., 2002; Sawada, 2000). Studies suggest that the prevalence rates of LA are highest in vascular dementia compared to other forms of dementia (Pantoni & Garcia, 1995), but LA is also common in AD (Diaz et al., 1991; Mirsen, 1991; Tsiskaridze et al., 1998) and in nondemented elderly individuals (de Groot et al., 2000; Schmidt et al., 1999). Research has demonstrated that LA increases with age and is often associated with neurological, cerebrovascular, and cognitive concomitants. However, aside from the clear association to age (Longstreth et al., 1996), the risk factors associated with LA are not clearly understood. In addition, the relationship between LA and cognition in AD and nondemented elderly is a source of controversy in the literature.

While many studies have demonstrated that LA is associated with cognitive impairment in nondemented elderly (Fukui et al., 1994; Skoog et al., 1996; Ylikoski et al., 1993) and AD (Alkvist et al., 1992; Diaz et al., 1991; Tsiskaridze et al., 1998) other studies contradict these findings, and argue that LA does not detrimentally impact cognition (Kozachuk et al., 1990; Whitman et al., 2001). Factors such as

differences in imaging techniques and neuropsychological tests used, have been identified as contributors to the variability in findings. Additionally, the impact of LA on cognition in MCI is unknown, as very few studies have examined associations between LA and cognition among individuals with MCI (DeCarli et al., 2001; DeCarli et al., 2004). The primary goal of the current study was to examine the relationship between neuropsychological functioning and LA across and within the three groups (AD, MCI, and NE) to explore the impact of LA on the cognitive deficits found in AD and MCI.

Three primary aims were addressed in the current study in order to achieve the above goal: 1) to examine the presence and severity of LA in AD, MCI, and NE, 2) to determine the risk factors associated with LA, and 3) to identify the relationships between LA and neuropsychological functioning across and within the three groups. In addition, exploratory analyses were addressed to examine two main goals: 1) to examine the relationship between LA and cognitive functioning within the MCI group through a more extensive neuropsychological battery, which was not utilized with the other two groups, and 2) to explore the relationship among LA, neuropsychological functioning, and semiquantitative measures of cerebral atrophy.

To examine the study aims, ninety individuals (30 AD, 30 MCI, and 30 NE) who underwent MRI and neuropsychological testing were included. The MRI scans of the 90 subjects were evaluated with a semiquantitative measure to assess the severity of LA and cerebral atrophy, and these scores were compared to performance

on neuropsychological measures. In the following section, the findings and limitations of the current study will be discussed, followed by potential directions for future research.

Discussion of Hypotheses

Severity of LA in the Sample

The AD group demonstrated greater total LA scores than the MCI and NE samples, and had greater periventricular LA and subcortical LA than the MCI group, which provided partial support for the first hypothesis. The finding supported previous studies that have found LA to be more severe among individuals with AD than nondemented elderly controls (Barber et al., 1999; Hogervorst et al., 2002; Mirsen et al., 1991; Pantoni & Garcia, 1995). Counter to the hypothesis, the NE group emerged with significantly greater periventricular LA than the MCI group and also had slightly higher subcortical and total LA scores, though not significant, than the MCI group. The literature on the relationship between MCI and LA is particularly limited. At least one study showed that subjects with MCI had significantly greater LA volumes than nondemented elderly controls (DeCarli et al., 2001). In addition, MCI is widely conceptualized as a cognitive category between normal aging and dementia that significantly increases the risk of progression to AD (DeCarli, 2003; Petersen et al., 2001). Thus, based on theory, and the findings of DeCarli et al. (2001), it was predicted that LA scores of the MCI group would fall between the AD and NE

groups. It is possible that LA is not more prevalent or extensive in MCI than in elderly without cognitive impairment.

Another possible explanation for the unexpected findings of the MCI and NE groups pertains to sample characteristics. Regarding the MCI sample, 10 of the 30 subjects had a diagnosis of "Possible MCI," while the remainder of the subjects met criteria for "Probable MCI." There was some variability in the extent and type of cognitive complaints and impairments in the Possible MCI group. To determine if the "Possible" subjects had different LA scores than the Probable MCI subjects, *t*-tests were computed and no significant differences were found between the mean LA scores of the two groups. An alternative explanation for the unexpected findings could also pertain to the sampling characteristics of the NE sample. Many of the NE subjects were spouses and family members of the AD group, which may have introduced sampling bias. To elaborate, family members of subjects in the AD group may have certain unique confounding characteristics that the general population does not have. The NE group did not demonstrate any significant differences from the MCI group in demographic variables or vascular risk factors (Tables 4 and 5). However, the cognitive screen used for the NE group may have lacked sufficient sensitivity to differentiate between normal cognition and mild impairment associated with MCI.

The MMSE was the primary cognitive screening measure for the study, and NE individuals with a score of at least 28, who met other inclusion criteria, were included. Studies have demonstrated that the MMSE lacks sensitivity in

discriminating between MCI and normal cognition (Chandler, 2004; Malloy et al., 1997). Furthermore, Chandler (2004) found that individuals with a CERAD total score of <85 were three times more likely to have MCI. The mean total CERAD performance of the NE sample in the current study was 80.2, which fell below the cut-off score of 85 that was found to discriminate NC from MCI by Chandler (2004). However, it is important to note that Chandler's score was demographically corrected, while the total CERAD score of the current study was not. The mean total CERAD score of the MCI sample in the current study was 73.4 and was not statistically different from the NE group, providing more evidence that the two groups were similar cognitively. This is further substantiated by the fact that the two groups had identical, or nearly identical, means on other neuropsychological measures such as a language task, memory tasks, visuospatial measures, and other variables assessing attention, processing speed, and mental flexibility (see Table 10).

The majority of studies in the literature that have explored periventricular LA and subcortical LA separately have found that periventricular LA is more prevalent and severe in AD than controls (Barber et al., 1999; Campbell & Coffey, 2001; Kobari et al., 1990). The current study failed to support those previous findings. Although the mean periventricular LA of the AD group was larger than the NE group, the difference was small and not significant (M = 6.2 vs. M = 5.4, respectively). Literature regarding the prevalence and severity of subcortical LA in AD versus normal elderly is less definitive. Several studies have found greater severity of

subcortical LA in AD compared to normal elderly (Barber et al., 1999; Bowen et al., 1990; Schmidt et al., 1992) while others have not (Harrell et al., 1991; Kozachuk et al., 1990; Mirsen et al., 1991). The current study failed to support the hypothesis, as no significant difference was found between the AD and NE groups on the measure of subcortical LA, although the AD group mean was larger than the NE group (M = 2.5 vs. M = 1.4, respectively). While the data give support to studies that find no differences in the severity of subcortical LA between AD and normal elderly, it must also be noted again that possible sampling bias in the groups could have interfered with the findings. For example, the NE group resembles the MCI group on neuropsychological testing, and had more LA than the MCI group, which suggests that despite screening efforts, the NE group may have included individuals that had some degree of cognitive impairment. It is also possible that in the AD group, individuals with comorbid vascular issues were screened out in an effort to only include individuals with pure AD, potentially reducing the number of people with severe LA. This could explain the lack of significant findings in extent of periventricular and subcortical LA between the AD and NE groups, but would not account for the lack of differences between the MCI and NE groups.

Risk Factors Associated with LA

There were no differences among the groups (AD, MCI, and NE) with respect to risk factors associated with LA, such as age, hypertension, smoking, or

hyperlipidemia. The mean homocysteine (HCY) value was significantly greater for the MCI group than the other groups. Since deficiencies in folate and vitamins B6 and B12 have been associated with hyperhomocysteinemia (e.g., Reutens & Sachdev, 2002), additional analyses were computed to ascertain whether the MCI group was different from the other groups in terms of vitamin use. No significant differences were found. Age is widely regarded as the most significant risk factor associated with severity of LA in the literature (Capizzano et al., 2004; Longstreth et al., 1996; Merino & Hachinski, 2000). Although age emerged as a significant predictor of periventricular LA (Hypothesis 2A) and subcortical LA (Hypothesis 2B) in all regression models (see Tables 7 and 8) in the current study, it only accounted for a small amount of the variance.

Contrary to the hypotheses, hypertension did not contribute significantly to the variability of either type of LA. A study by deLeeuw et al. (1999) examined the association of periventricular and subcortical LA separately with blood pressure and found increased diastolic and systolic pressures were associated with both types of LA, even when controlling for the effects of other vascular risk factors. A possible explanation for the discrepancy in the findings of the current study compared to deLeeuw et al. may be attributed in part to the method by which blood pressure was quantified. In the current study, blood pressure was assessed and entered into the regression equations dichotomously, while deLeeuw et al. used continuous blood pressure measurements, which provided a greater range for statistical comparisons.

Based on the findings of two recent studies (e.g., Hogervorst et al., 2002; Sachdev et al., 2004), it was predicted that the total homocysteine (tHCY) level would be associated with severity of subcortical LA, following age and hypertension (Hypothesis 2B). In addition, it was expected that tHCY would be associated with severity of periventricular LA, although no specific prediction was made regarding the strength of the association compared to other factors (Hypothesis 2A). The results of the regression analyses demonstrated that HCY was not a significant predictor for either type of LA. However, it is important to note that the studies by Hogervorst et al. (2002) and Sachdev et al. (2004) had higher levels of tHcy present in the samples than in the current study. For example, 60% of the sample in the study done by Sachdev et al. (2004) had tHcy levels over 15 umol/L, while the mean levels in the current study ranged from 8.4 umol/L (NE) to 11.0 umol/L (MCI). Therefore the relationship between tHcy and subcortical LA may be found with higher levels of tHcy.

The other vascular risk factors entered into the regression equations included gender, group membership (AD, MCI, or NE), duration of disease, smoking, hyperlipidemia, diabetes, and a combined sum of additional cerebrovascular factors (stroke, myocardial infarction, coronary artery bypass graft/angioplasty, peripheral arterial disease, and deep venous thrombosis). The linear combination of those factors was significantly related to the severity of periventricular LA.

Neuropsychological Performance and Total LA

Hypotheses 3A and 3B addressed the relationship between LA and neuropsychological functioning. Based on findings of prior studies, it was hypothesized that increased severity of LA would be associated with lower neuropsychological performance, particularly with respect to measures that assess frontal and subcortical functioning. The domains that were expected to demonstrate greatest decline relative to LA included general cognitive functioning (deGroot et al., 2000; Longstreth et al., 1996), attention and processing speed (Fukui et al., 1994; Ylikoski et al., 1993), and executive functioning (DeCarli et al., 1995; Tsiskaridze et al., 1998). Although many studies have found a relationship between LA and cognition, the issue remains a source of controversy, particularly regarding the contribution of LA to the course of cognitive decline in demented elderly. Many studies have relied on limited cognitive screens and small sample sizes. The current study was designed to address these issues by expanding the sample to include individuals with MCI in addition to AD and nondemented elderly (n = 90), and by incorporating testing that would target the areas relevant to both AD and LA.

As predicted, increased severity of total LA was associated with greater impairment on neuropsychological measures for all subjects combined (Hypothesis 3A). Although all correlations were inverse, and the majority were statistically significant, the correlations were low (r = -.23 to r = -.36). Therefore, while statistical significance was reached in the majority of correlations, the clinical significance of

those findings is questionable, as LA contributed to only 5% to 10% of the variance in neuropsychological performances. Furthermore, multiple correlations were conducted, which increased the likelihood of detecting relationships that were due to chance.

When all subjects were analyzed as one group, the CERAD Total score, MMSE, Verbal Fluency, and Trails B scores were among the measures that correlated significantly with total LA, providing partial support for the hypothesis. Measures of verbal and nonverbal memory were also significantly correlated. Contrary to the prediction, performance on Digit Span was not related to total LA. This was not consistent with findings of Boone et al. (1992) who found, in a sample of 100 healthy elderly, that Digit Span performance was poorer in subjects with more severe total LA (>10 cm^2). The current study utilized LA values that were not directly comparable to the aforementioned study by Boone and colleagues. It is possible that the difference in findings between the studies is attributable to differences in severity of LA between the studies. In addition, Boone et al. (1992) did not analyze digit span backwards separately, while the current study included only digit span backwards. The difference in findings could therefore also be related to differences in the neuropsychological measure.

The low strength of the correlations between total LA scores and neuropsychological functioning across all subjects may have been a consequence of findings among the within-group comparisons. Controlling for age and atrophy

significantly reduced the magnitude of the correlations, such that no significant correlations remained between total LA and neuropsychological functioning across all subjects. The correlations in the AD group were primarily positive, though after controlling for age, the majority of the correlations in the AD group were reduced below $r = .20$, suggesting that the relationship between total LA and neuropsychological functioning was largely dependent upon age. However, the majority of the correlations remained in the positive direction, suggesting that even after controlling for age, individuals with greater severity of LA actually showed a tendency toward better performance on neuropsychological measures. Controlling for the effect of age and atrophy in the AD group did not significantly change the correlations, beyond what was found when controlling for the effects of age. The correlation coefficients for total LA and most measures of neuropsychological functioning were inverse within the MCI and NE groups, although the range of the correlations was from very low to moderate ($r = -.04$ to $r = -.41$). Only one correlation was significant in the NE group before controlling for age (Digit Span longest digits backward, $r = -.41$), and none were significant after the age effect was removed. There were no significant correlations in the MCI group.

T-test comparisons for high and low total LA scores were performed across and within the groups. The power of the within-group correlations may have been limited by small sample sizes and restricted range of data within the groups, and the *t*-tests were included to compensate for those potential limitations. Neuropsychological

performance was better in the low versus high LA group when all subjects were analyzed together. The mean differences were significant for measures of general cognitive functioning, language, verbal memory, and a measure of executive functioning. Within-group *t*-tests produced varied results. The AD group results were opposite from the expected direction, as the high LA group had higher means on neuropsychological functioning across all tests, which was in accordance with the positive correlations found within the AD group. While the high LA group was significantly older ($M = 75$, $SD = 7.5$) than the low LA group ($M = 66$, $SD = 1.8$), $t(28) = -3.19$, $p = .004$, and predominately male (75%, $n = 15$), there were no differences between the groups for years of education or duration of disease that could account for the neuropsychological findings.

Although the AD sample had more severe LA than the other groups, severity of total LA was not associated with impairment on neuropsychological performance. However, the MCI and NE groups did show associations between increased severity of LA and worse performance on neuropsychological measures, although the correlations did not reach statistical significance. One possibility for the discrepancy in the findings is that while LA may have a negative, albeit mild, impact on cognition in normal elderly, and in milder forms of dementia, the disease process (i.e., AD) may override the impact of LA in AD. Although a presumably less severe, "Early" AD sample was recruited in order to avoid this potential confound, it is possible that the disease process had advanced beyond the early stages in some of the sample. It is also

possible that the AD group has more extensive cerebral atrophy than the other groups that is interfering with the ability to detect a relationship between LA and cognition. However, controlling for cerebral atrophy, in addition to age, did not affect the findings. In addition, it is simply possible that the AD group is unusual in the current study and has a group of older individuals who performed better than the younger subjects. This could explain the reason age was so highly associated with the results among the AD group. An alternative explanation resides on a possible limitation of the measure used to quantify LA in the current study. The measure was modified slightly from the scale used in the Rotterdam Scan Study (deGroot et al., 2000; deLeeuw et al., 1999), which was a study of nondemented elderly. The scale has not been validated in AD patients, and furthermore, the total LA score derived for the current study has also not been previously validated. It is possible that the scale is sensitive enough to differentiate severity of LA in normals, and even the MCI population, but lacks adequate range at the upper end of the scale to account for the more severe white matter changes found in AD.

To summarize, severity of total LA was associated with poorer neuropsychological performance when all subjects were analyzed together. The strength of the correlations was low to moderate, and the clinical relevance of the associations is questionable. As predicted, the CERAD Total score, MMSE, Verbal Fluency, and Trails B score were significantly correlated with total LA. Also significant were measures of verbal and nonverbal memory. Within group

comparisons revealed that severity of total LA in the AD group was not associated with greater impairment in neuropsychological functioning, which likely reduced the strength of the correlations for the all subject comparisons. In the MCI group, higher total LA was associated with worse performance on a measure of executive functioning, and in the NE group, higher total LA was associated with worse performance on measures of general cognitive functioning, language, immediate verbal memory, and attention.

Neuropsychological Performance, Periventricular and Subcortical LA

It was hypothesized that increased severity of both periventricular and subcortical LA would be associated with poorer neuropsychological performance (Hypothesis 3B). The periventricular LA results parallel those described above for total LA, which was not surprising as the measures were highly correlated ($r = .86$, $p < .001$). Severity of periventricular LA was thus associated with poorer neuropsychological performance across the measures when all subjects were collapsed into one group. As predicted, measures of general cognitive functioning (CERAD Total, MMSE), Verbal Fluency, and executive functioning (Trails B) correlated significantly with periventricular LA ($r = -.28$ to $r = -.32$). However, measures of verbal memory (Word List Learning, Recall, and Recognition) and nonverbal memory (Constructional Praxis Recall) were of equal statistical significant, which was counter to the hypothesis, as the former measures were expected to be more highly related to

periventricular LA severity. Digit Span and Trails A were not significantly correlated, which was also counter to the hypothesis. Controlling for the effect of age and atrophy significantly reduced the magnitude of the correlations between periventricular LA and neuropsychological functioning across all subjects; no significant correlations remained after controlling for both age and atrophy.

After controlling for age, the AD group correlations decreased across the measures, and only Digit Span longest digits backwards remained significant (r = .43), although the majority of correlations remained positive. As with the total LA findings, *t*-test comparisons revealed that in the AD group, those with more severe periventricular LA also had higher mean performances on neuropsychological measures. The significant mean differences were in the domain of verbal memory and attention. As expected, in the MCI and NE groups, increased periventricular LA severity showed a trend towards poorer performance on neuropsychological tests, although the correlation coefficients were low to moderate, and only Word List Learning was significant (NE group, r = -.45). T-test data revealed that for both the MCI and NE groups, those with better performances on the CERAD Total score had less periventricular LA. The Verbal Fluency results also showed this pattern in the MCI group.

Subcortical LA volume did not correlate significantly with the majority of neuropsychological measures across subjects, or within groups. Although the correlation coefficients were inverse for all of the measures across all subjects, only

four were statistically significant (CERAD Total score, MMSE, Word List Learning, and Recall, r = -.24 to r = -.29). The significant findings on the CERAD Total score and MMSE provided partial support for the hypothesis, although the clinical relevance of the findings is questionable, due to the low strength of the correlations. As with the periventricular and total LA comparisons, the AD group correlations were opposite from the expected direction, although correcting for age reduced the strength for the majority of the coefficients. The MCI and NE groups also showed inverse correlation coefficients between subcortical LA severity and neuropsychological functioning, although almost none were significant. T-tests further confirmed that those with greater severity of subcortical LA had poorer neuropsychological performance, as expected.

The severity of periventricular LA was associated with poorer neuropsychological performance across most measures when all subjects were collapsed into one group. However, increased severity of subcortical LA was significantly correlated with fewer neuropsychological measures across all subjects than periventricular LA. This finding supported Hypothesis 3B, which predicted that severity of periventricular LA would be more strongly associated with neuropsychological functioning than subcortical LA, specifically the CERAD Total score, MMSE, Verbal Fluency, Digit Span backwards, and Trails A and B. The test of correlations failed to detect a difference between the correlations for the CERAD Total score and MMSE. However, Verbal Fluency, Trails B, and Digit Span total

digits backward (age-corrected) were significantly correlated with periventricular LA but not subcortical LA. Furthermore, periventricular LA was correlated with additional measures of memory that were not significant for subcortical LA. This provides partial support for the hypothesis and suggests that, although the strength of the correlations were low, periventricular LA was more associated with neuropsychological functioning than subcortical LA. The positive correlations of the AD group again likely reduced the strength of the inverse correlations across all subjects, particularly for periventricular LA, as there was a consistent trend for inverse correlations in both the MCI and NE groups.

Examining Neuropsychological Functioning and LA in MCI with Additional Measures

Few studies have explored the relationship between LA and cognitive functioning in MCI. MCI was included in the current study to expand the range of cognitive impairment in the sample in order to examine the impact of LA on cognitive functioning in dementia (AD), and earlier stages of cognitive decline (MCI). The MCI sample that was examined in the current study underwent more extensive neuropsychological testing than the AD and NE samples, due to participation in prior studies. Leukoaraiosis (total, periventricular, and subcortical) and neuropsychological test performance were examined in the MCI group with correlations and *t*-test comparisons. The additional neuropsychological measures included the WCST, BNT, FAS, CVLT, and the Rey-Osterrieth Complex Figure Task. Only one significant

Pearson correlation was found among the tests, and no consistent trend for the direction of the means (e.g., high LA with lower test performance mean) emerged across the majority of *t*-tests. This is surprising in light of some of the findings from testing Hypothesis 3A. In the previous hypothesis, those with better mean performance on Verbal Fluency (animals) had less severe periventricular LA, which suggested a similar relationship could have been expected with the FAS test. The means of the high and low groups (total, periventricular, and subcortical) were all within normal limits and ranged from $M = 34.8$ to $M = 39.0$ for the FAS Total fluency score. In addition, the Pearson correlations between all types of LA and FAS Total fluency scores were in the expected inverse direction, but the coefficients were close to zero. Similarly, those with better performance on the CERAD BNT had less severe subcortical LA, but no mean differences were found with the 60-item BNT. The 60-item BNT T-score means were also average and ranged from $M = 49.38$ to $M = 55.31$ across the high and low LA groups. No significant mean differences were found (though they were generally in the expected direction) nor did the correlations follow a specific trend.

Significant findings did emerge from the WCST. First, Pearson correlations were computed for LA and the WCST Perseverative T-Score and total categories completed variables. A significant positive correlation was found for total LA and the WCST perseverative errors T-score ($r = .55$), which was in the opposite direction from what would be expected. However, when the MCI group was divided into high versus

low total and subcortical LA groups (by Method 1), the low LA groups had significantly higher mean perseverative error T scores than the high LA groups, as expected. The correlations should likely be interpreted with caution as the ability to detect significant correlations may have been limited by the relatively small sample size (n = 30) and limited range of scores of the MCI sample, which were within normal limits.

Relationship between Cerebral Atrophy, LA and Neuropsychological Functioning

Cerebral atrophy has been identified as a contributor to impairment in neuropsychological performance in demented and nondemented elderly (Soderlund et al., 2004; Swan et al., 2000). Studies have shown that subcortical and cortical atrophy appear to impact different aspects of cognition, although findings are mixed (Soderlund et al., 2004). Leukoaraiosis has also been associated with both neuropsychological impairment and cerebral atrophy in aging populations (Capizzano et al., 2004). To examine the potential associations between cerebral atrophy, LA, and neuropsychological functioning, semiquantitative subcortical and cortical atrophy measures were conducted on the MRI scans of all 90 subjects. Subcortical atrophy was assessed with ventricle to brain ratios at the level of the frontal horns, caudate nucleus, and occipital horns. Cortical atrophy was determined with visual ratings of severity (range = 0-3) for the temporal horns, Perisylvian cistern, and convexity sulci.

The AD group demonstrated significantly more subcortical and cortical atrophy than the MCI and NE groups. This finding is consistent with other studies that have shown that the brains of individuals with Alzheimer's Disease have greater cerebral atrophy than controls in both cortical and subcortical gray matter (Capizzano et al., 2004; Meyer et al., 2000). The AD group had more atrophy than the other groups in the specific subcortical regions, and surprisingly, atrophy at the level of the occipital horns was more substantial than other areas in all three groups. The cortical areas that have been shown to demonstrate the most significant atrophy in AD are the frontal, temporal, and parietal areas with less atrophy in the occipital region of the brain (Rosenzweig et al., 2002). Further evidence was documented by Capizzano et al. (2004), who compared the gray and white matter volumes of patients with moderate to severe AD (CDR > 1), mild AD (CDR = 1), very mild AD (CDR = 0.5), and normal controls. They found that the gray matter volumes of the frontal, temporal, and parietal lobes of the moderate to severe and mild AD groups were significantly lower than the normal controls, and found no differences in occipital volumes. Alternatively, the white matter volumes of the frontal, temporal, parietal, and occipital lobes were significantly lower in all of the AD groups compared to normal controls (Capizzano et al., 2004). Parietal atrophy is a common finding in AD, and the occipital and parietal regions may overlap or converge at the point where the ventricle to brain ratio was measured. Thus, the greater extent of atrophy found in the occipital region of the current study could be attributable in part to parietal atrophy.

Leukoaraiosis has been associated with cortical atrophy in AD, and may contribute to the process of degeneration. In the current study, all three measures of LA (total, periventricular, and subcortical) correlated with subcortical and cortical atrophy scores when all subjects were analyzed together. Age was significantly correlated with all three measures of LA (r = .40 to r = .44) and both measures of atrophy (subcortical, r = .27 and cortical, r = .34) for all subjects, and therefore was partialled out. Controlling for the effect of age resulted in decreased correlations between LA and atrophy, but only the correlations between subcortical LA and both atrophy measures for all subjects were no longer statistically significant.

Within-group correlations in the AD group revealed that total LA correlated significantly with subcortical atrophy before and after controlling for age (r = .43, p < .05), but not with cortical atrophy (r = .03, p = .89) either before or after partialling out the effect of age. The lack of relationship with cortical atrophy was unexpected, as LA has been cited as a significant predictor of cortical atrophy in AD. For example, Capizzano et al. (2004) found that in a group of AD patients (n = 81), LA was significantly associated with cortical gray matter volume loss in the frontal, temporal, parietal, and occipital lobes, and with white matter volume loss in the frontal and parietal lobes. One possible explanation for the finding could relate to an interaction between homocysteine levels and subcortical atrophy. Sachdev (2004) found an association between high serum levels of homocysteine and subcortical atrophy in a sample of 81 normal controls. In addition, gender differences may also relate to

subcortical atrophy, as literature has shown that men may have more severe atrophy than women, with faster progression of cortical atrophy and earlier development of subcortical atrophy than women (Soderlund et al., 2004). In the current study, there were more males in the AD group (males, n = 20/30), and there was a significantly higher level of homocysteine in the male subgroup (M = 9.5, SD = 2.2) than the female subgroup (M = 7.5, SD = 2.9), t (28) = 2.07, p = .048. However, gender and homocysteine were not significantly correlated with LA and thus did not appear to account for the findings between atrophy and LA.

Interestingly, the MCI group had significant positive correlations between total LA and cortical atrophy (r = .40), and periventricular LA and cortical atrophy (r = .51). These correlations were no longer significant after controlling for the effect age (r = .08 and r = .24, respectively). Alternatively, the NE group had primarily inverse correlations for LA and atrophy, and larger negative correlations with subcortical atrophy, after age corrections. Although there were no significant differences between the MCI and NE groups in severity of LA, with the exception that the NE group had significantly more periventricular LA, or total subcortical and cortical atrophy, the MCI group showed positive correlations between LA and atrophy, while than the NE group did not. At the same time, the AD group demonstrated no relationship between LA and cortical atrophy. Perhaps the AD group encountered a ceiling effect with cortical atrophy in terms of how atrophy was classified in this study (i. e., sum of atrophy for Temporal Horns, Perisylvian Cistern, and Convexity Sulci, range = 0-9)

thereby lowering possible correlations. The correlations between cortical atrophy and LA in the AD group ranged from r = -.01 for periventricular LA to r = .10 for subcortical atrophy. Another possible explanation for the lack of findings is that the extent of subcortical atrophy may have reduced amount of brain tissue available for developing LA. Alternatively, the relationship between LA and cortical atrophy may have been better captured in the MCI group, before age corrections, and before the extent of atrophy progressed to the point that it cancelled out the effect of LA, as in the AD group.

Relationships between cerebral atrophy and neuropsychological functioning were also explored in the current study. Prior research suggested that subcortical and cortical atrophy may impact different domains of cognitive functioning, although results have been contradictory (Soderlund et al., 2004). For example, Soderlund et al. (2004) found that in nondemented men, frontal cortical atrophy was related to impairment in verbal fluency and processing speed, while occipital cortical atrophy was associated with impairment in motor speed. Alternatively, subcortical atrophy in the region of the caudate nucleus was related to impaired motor speed in women in their study (Soderlund et al., 2004).

In the current study, both subcortical atrophy and cortical atrophy were significantly correlated with all measures of neuropsychological functioning when all subjects were analyzed together. All correlations suggested that increased atrophy was associated with decreased performance on testing. Cortical atrophy had strongest

inverse correlations with tests of general cognitive functioning, verbal fluency, verbal memory (immediate, delayed, and recognition memory), processing speed, and executive functioning. Subcortical atrophy demonstrated similar relationships, although a test of naming was also among the strongest inverse correlations. T-tests of correlations for dependent samples revealed no significant differences among the strengths of the correlations and neuropsychological functioning for either type of atrophy for all subjects combined. The AD group also demonstrated significant inverse correlations between both cortical and subcortical atrophy and neuropsychological performance on measures of global cognitive functioning, verbal fluency, confrontational naming, and verbal list learning. The t-test of correlations for dependent samples revealed no significant differences in the strengths of the correlations, indicating that both cortical and subcortical atrophy were associated to a similar extent with impairment in cognitive performance. However, recognition memory was significantly more impaired with increased subcortical atrophy, but not cortical atrophy, in the AD group, as expected. The MCI and NE groups had no significant correlations between atrophy and cognitive performance, suggesting that atrophy was not extensive enough in either of those groups to impact cognition.

Limitations of the Current Study

The current study was carefully designed to address some of the limitations of prior research in this area; however, the study was not without limitations. One

limitation may have pertained to the characteristics of the sample. Due to the archival nature of the study, the ability to screen individuals was limited. The NE and MCI groups did not demonstrate expected differences in extent of LA, vascular risk factors, cognitive functioning, or atrophy. In fact, the NE group had higher means on many of those factors than the MCI group. The MMSE was used to screen for dementia in the NE group, but it may not have been sensitive enough to eliminate some individuals with milder deficits indicative of MCI. Additionally, there was diagnostic heterogeneity within the MCI group that may have resulted in overlap with the NE group. Ten individuals were included that were considered "possible MCI" patients, but did not meet the criteria for MCI as explicitly as the "probable MCI" group. However, *t*-test comparisons between probable and possible MCI subjects revealed no significant differences between the groups in LA or neuropsychological functioning, although trends were found for higher homocysteine and hyperlipidemia in the probable MCI group. It is important to note that the AD and NE groups came from a different source than the MCI group. While the subjects in the MCI group had extensive clinical evaluations, the other groups were screened and recruited as part of a research protocol for hyperhomocysteinemia. This distinction may have created variability in the characteristics of the sample (i.e., differences in individuals volunteering for a research study on homocysteinemia compared with individuals presenting for a clinical exam who also agree to participate in a study). It is also possible that, based on the research protocol, the AD and NE groups may have been

more extensively screened for vascular disease, thereby reducing the likelihood of finding associations with vascular risk factors in the study.

The generalizability of the study may also be limited by the fact that the vast majority of the sample was Caucasian and of a higher educational level than the average population. The issue of race should be examined in future studies as it is possible that differences exist, particularly with respect to African American male populations, which may be at higher risk for LA due to higher prevalence of vascular risk factors such as hypertension. Although the literature does not discuss educational differences with respect to LA, it is possible that there is a relationship. Individuals with higher education levels would be expected to have more education about the adverse health effects of vascular risk factors, and as such, might have less LA, although this is speculative. Furthermore, the literature does not suggest that there are racial differences associated with severity of LA, but differences may exist.

The semiquantitative scale used to measure LA on MRI was also not without limitations. The use of a more sensitive, quantitative method that relies upon volumes may have increased the ability to find relationships between LA and the other factors assessed in the study. The semiquantitative scale was validated with nondemented elderly individuals, but not with a demented population. It is possible that the scale is adequate in detecting and quantifying LA for nondemented individuals with relatively mild extent of LA. However, it is also possible that the scale is not adequate in assessing the severity of LA in more severely demented populations, thereby reducing

the ability to detect relationships between LA and cognition. To elaborate, there may not be a broad enough range at the high end of the scale to adequately capture the full extent of LA, particularly when it is severe.

Another limitation of the current study was the retrospective nature of the design. The use of a retrospective design limited the ability to select neuropsychological measures tailored specifically to the project. However, the use of the CERAD battery was considered a strength as it incorporated measures of relevant cognitive domains in addition to a total score. Nonetheless, the addition of more detailed measures of general processing speed, motor performance, attention, and verbal and nonverbal memory may have detected more subtle differences associated with LA that could not be detected by the CERAD. In addition, it would have been useful to have gathered more detailed data on vascular risk factors, such as quantitative measures of blood pressure, hyperlipidemia, and smoking (packs per year). The use of more continuous variables in the regression analyses may have improved the ability to detect relationships among the variables and LA.

Conclusions and Future Directions

The primary purpose of the current study was to examine the impact of LA on cognition in AD and MCI. It was predicted that LA would be more extensive in patients with AD and MCI, in that order, than in nondemented elderly. Furthermore, neuropsychological functioning was expected to be inversely related to the severity of

LA, particularly on measures assessing general cognition, verbal fluency, attention, processing speed, and executive functioning. Periventricular LA was predicted to be more strongly correlated with those aspects of cognition than subcortical LA. Vascular risk factors were also hypothesized to increase the risk of LA across the groups.

Overall, LA was more severe in the AD group. Increased severity of LA, especially total and periventricular LA, was associated with impairment in neuropsychological functioning across all subjects, although the correlations were of low to moderate strength. Within-group correlations revealed that the strengths of the relationship between LA and cognition were likely weakened by the fact that in the AD group, increased severity of LA was associated with better performance on neuropsychological measures, while the MCI and NE groups were associated in the opposite direction. These results suggest that in the current study, LA was not associated with worse cognitive impairment in AD, or if an association was present, other factors may have overshadowed that relationship. Examples of other factors that may have interfered include the process of the dementing illness itself or severity of cerebral atrophy. The extent of both cortical and subcortical atrophy was more severe in AD than the other groups, and was significantly associated with cognitive impairment, across all subjects, and within the AD group. Subcortical atrophy, but not cortical atrophy was significantly associated with increased total LA in the AD group. This suggests that the extent of atrophy was probably not so severe that it accounted

for the lack of association between LA and cognitive factors in the AD group. However, no relationship was found between cortical atrophy and LA, which might suggest again that the extent of cortical atrophy was so severe in the AD group that any association that might have existed with LA was overshadowed by the atrophy. Future studies should examine these relationships more extensively to determine if these findings are replicable. In addition, the semiquantitative measure used to assess LA was not validated on individuals with dementia, and may have been less sensitive in measuring LA and atrophy in that population. Thus, it is important that future studies validate this measure in dementia populations to determine if it is as adequate as other quantitative measures of LA. In addition, future studies should consider the inclusion of diffusion tensor MRI measurements as an alternative to the FLAIR MRI images used in the current study, as diffusion tensor may improve the ability to quantify LA and detect relationships between LA and cognitive function (O'Sullivan et al., 2004). Diffusion tensor MRI yields quantitative information about damage to white matter projections and may be more sophisticated than other MRI techniques (such as FLAIR) in identifying the relationships between white matter damage and cognitive functioning (O'Sullivan et al., 2004).

Periventricular and subcortical LA were examined separately in the current study, and overall, severity of periventricular LA was more strongly associated with impairment on neuropsychological measures than subcortical LA. It is possible that the extent of subcortical LA remained below a threshold of severity that is necessary

in order to detect a more significant relationship with cognition (Boone et al., 1992). Furthermore, future studies should include populations with more extensive vascular disease, as well as more extensive neuropsychological measures (e.g., processing speed, attention, verbal and nonverbal memory) to assist in determining whether more subtle connections exist that were not captured in the current study.

The results of the current study did not find that individual vascular risk factors were significantly associated with predicting severity of periventricular and subcortical LA. Age was significantly associated with predicting both subtypes of LA, but hypertension and homocysteine were not independently related to LA. However, the combined sum of vascular risk factors was related to predicting severity of both types of LA. Future studies should explore the relationship of vascular factors with more extensive quantitative data, in order to increase the ability to find relationships among the variables. Many of the vascular risk factors were entered into the regression models as dichotomous variables, which provided less range of variability in the data. In addition, future studies could benefit from the inclusion of individuals with vascular dementia for comparison.

The implications of the current study suggest that age and cerebral atrophy are highly associated with the relationships between LA and cognition. In addition, LA may be more directly related to impairment in cognition before dementing illness develops, and in individuals with AD, the dementing illness may obscure the impact of LA on cognition. Alternatively, limitations of the current study, as described above,

may have interfered with the ability to detect the relationship between LA and cognition in AD if it exists. In order to explore these relationships more extensively, future studies should consider using larger sample sizes, a quantitative LA assessment method, and longitudinal designs to follow changes in LA and neuropsychological functioning over time.

Table 1

NINCDS-ADRDA Criteria for the Diagnosis of Probable Alzheimer's Disease

Probable Alzheimer's Disease

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

Table 2

Diagnostic Criteria for Mild Cognitive Impairment

Probable MCI (n = 20)	Possible MCI (n = 10)
Memory complaint, corroborated by informant.	Memory complaint, corroborated by informant.
CDR = 0.5	CDR = 0.5
Objective memory impairment for age and education.	May or may not have objective memory impairment on neuropsychological testing.
Largely intact general cognitive function.	Largely intact general cognitive function.
Essentially preserved activities of daily living.	Essentially preserved activities of daily living.
Not demented.	Not demented.

Table 3

Demographic Characteristics of Total Sample (n =90)

Variable	All Subjects		
	M	*SD*	Range
Age (years)	71.2	7.3	57 - 88
Education (years)	14.8	2.9	4 - 21
	n	*%*	
Gender (Male)	51	56.7	
Race			
Caucasian	83	92.2	
Hispanic	5	5.6	
African American	2	2.2	

Table 4

Demographic Characteristics of AD, MCI, and NE Samples

Variable	Group				
	AD *M (SD)*	MCI *M (SD)*	NE *M (SD)*	Statistic	*p* value
Age	72.1 (8.0)	71.2 (7.4)	70.3 (6.5)	F (2, 87) = .47	.63
Education	14.9 (3.2)	14.9 (3.1)	14.8 (2.4)	F (2, 87) = .03	.97
Duration of Illness	5.1 (2.7)	3.8 (2.0)	-	t (58) = -2.15	.04
	n (%)	*n* (%)	*n* (%)	Statistic	*p* value
Male	20 (67.0)	16 (53.0)	15 (50.0)	X^2 (2, N = 90) = 1.90	.39
Race					
Caucasian	26 (87.0)	29 (97.0)	28 (93.0)	-	-
Hispanic	3 (10.0)	0 (0.0)	2 (7.0)	-	-
African American	1 (3.0)	1 (3.0)	0 (0.0)	-	-

Table 5

Means, Standard Deviations, and Significance Levels for Leukoaraiosis (LA)

	AD *M (SD)*	MCI *M (SD)*	NE *M (SD)*	Statistic	*p* value	Bonferroni	*p* value
Periventricular LA[a]	6.2 (1.3)	4.3 (1.8)	5.4 (1.5)	F (2, 87) = 11.27	<.001	AD vs. MCI NE vs. MCI	<.001 .03
Subcortical LA[b]	2.5 (2.7)	1.0 (1.8)	1.4 (1.9)	F (2, 87) = 3.67	.03	AD vs. MCI	.03
Total LA[c]	4.8 (1.3)	3.2 (1.3)	3.8 (1.2)	F (2, 87) = 11.81	<.001	AD vs. MCI AD vs. NE	<.001 .01

[a] Values represent total periventricular score (range = 0-9).
[b] Subcortical values represent volumes (range = 0 – 11.1 cm^3).
[c] Total LA was calculated by regrouping periventricular and subcortical scores into low, medium, and high categories (range = 1-3, respectively) and summing the scores (range = 2-6).

Table 6

Descriptive Data of Vascular Risk Factors in AD, MCI, and NE

Vascular Variable	Group				
	AD *M (SD)*	MCI *M (SD)*	NE *M (SD)*	Statistic	*p* value
Homocysteine (μmol/L)	8.8 (2.5)[b]	11.0 (3.1)[a]	8.4 (2.7)[c]	F (2, 73) = 4.98	.01
Males	9.5 (2.2)	11.1 (3.3)	9.3 (2.1)		
Females	7.5 (2.9)	10.9 (3.1)	7.4 (3.0)		
	n (%)	*n (%)*	*n (%)*		
Hypertension	10 (34.5)	14 (48.3)	15 (50.0)	X^2 (2, N = 88) = 1.71	.43
Smoking	13 (44.8)	10 (37.0)	17 (56.7)	X^2 (2, N = 88) = 2.25	.33
Hyperlipidemia	14 (48.3)	21 (70.0)	12 (40.0)	X^2 (2, N = 89) = 5.77	.06
Diabetes	4 (13.8)	3 (10.0)	1 (3.3)	-	-

(table continues)

Table 6 cont.

	AD *n (%)*	MCI *n (%)*	NE *n (%)*	Statistic	*p* value
Cardiovascular Disease History					
Stroke	1 (3.4)	1 (3.3)	0 (0.0)	-	-
Myocardial Infarction	2 (6.9)	0 (0.0)	0 (0.0)	-	-
CABG/Angioplasty	2 (6.9)	5 (16.7)	1 (3.3)	-	-
CHF	1 (3.4)	1 (3.3)	1 (3.3)	-	-
PAD	0 (0.0)	0 (0.0)	0 (0.0)	-	-
DVT	0 (0.0)	2 (6.7)	0 (0.0)	-	-

Note. CABG = coronary artery bypass graft, CHF = congestive heart failure, PAD = peripheral arterial disease, DVT = deep venous thrombosis.
[a] N = 16 for MCI group, N = 30 for AD and NE.
[b] Score significantly different from the MCI group, Bonferroni post hoc test, $p = .04$.
[c] Score significantly different from the MCI group, Bonferroni post hoc test, $p = .01$

Table 7

Prediction of Periventricular LA Using Multiple Regression

	Total R^2	*df*	*F*	*p*	ß	*p*	R^2 Change
Model 1	.13	1, 71	10.16	<.01	.35	<.01	
Age	.13	1, 71	10.16	<.01	.35	<.01	
Model 2	.13	2, 70	5.03	.01			.00
Age					.35	<.01	
Hypertension					.02	.85	
Model 3	.34	8, 64	4.05	<.01			.21
Age					.32	.01	
Hypertension					-.06	.59	
Homocysteine[a]					-.04	.77	
Gender					-.03	.80	
AD Group					.28	.14	
MCI Group					-.29	.06	
Duration of Diagnosis					-.07	.68	
Additional Vascular Factors					-.03	.78	

Note. Additional Vascular Factors variable includes sum of history of smoking, hyperlipidemia, diabetes, stroke, myocardial infarction, coronary artery bypass graft, congestive heart failure, peripheral arterial disease, deep venous thrombosis.

[a] $n = 16$ for homocysteine in MCI

Table 8

Prediction of Subcortical LA Using Multiple Regression

	Total R^2	*df*	*F*	*p*	ß	*p*	R^2 Change
Model 1	.09	1, 71	6.80	.01	.30	.01	
Age	.09	1, 71	6.80	.01	.30	.01	
Model 2	.09	2, 70	3.38	.04			<.01
Age					.30	.01	
Hypertension					-.02	.84	
Model 3	.088	3, 69	2.22	.09			<.001
Age					.30	.02	
Hypertension					-.03	.82	
Homocysteine					.10	.91	
Model 4	.177	8, 64	1.72	.11	.09		.09
Age					.25	.04	
Hypertension					-.02	.87	
Homocysteine[a]					-.05	.74	
Gender					-.11	.37	
AD Group					.42	.05	
MCI Group					.09	.60	
Duration of Diagnosis					-.29	.14	
Additional Vascular Factors					-.03	.79	

Note. Additional Vascular Factors variable includes sum of history of smoking, hyperlipidemia, diabetes, stroke, myocardial infarction, coronary artery bypass graft, congestive heart failure, peripheral arterial disease, deep venous thrombosis.

[a] $n = 16$ for homocysteine in MCI

Table 9

Cognitive Domain and Measure Selected for Analysis

Cognitive Domain	Selected Measure
General Cognitive Functioning	CERAD Total Score
	Mini Mental State Exam
Attention/ Concentration	Trail Making Test, Part A and Part B
	Digit Span Backward – adapted from WAIS-R
Processing Speed	Trail Making Test, Part A
Executive Functioning	Trail Making Test, Part B
Language	CERAD Modified Boston Naming Test
	CERAD Verbal Fluency (Animal Category)
Memory	CERAD Word List Learning, Recall, and Recognition
Visuospatial Construction	CERAD Constructional Praxis

(table continues)

Table 9 cont.

Cognitive Domain	Selected Measure
Exploratory Analyses:	
Language	Boston Naming Test
	Phonemic Fluency (FAS)
Executive Functioning	Wisconsin Card Sorting Test
Verbal Learning and Memory	California Verbal Learning Test
Visuospatial Ability	Rey-Osterrieth Complex Figure, Copy
Nonverbal Memory	Rey-Osterrieth Delayed Recall

Table 10

Means and Standard Deviations of Neuropsychological Scores Across and Within Groups

Measure	All Subjects	AD	MCI	NE	Statistic	*p* value
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*		
CERAD Total	64.7 (21.7)	40.9 (17.3)[a]	73.4 (9.9)	80.2 (10.6)	*F* (2, 82) =73.94	<.001
MMSE	24.9 (6.8)	17.3 (6.7)[a]	28.7 (1.3)	29.1 (0.8)	*F* (2, 85) = 82.78	<.001
Verbal Fluency	14.9 (7.1)	8.4 (5.1)[a,b]	16.3 (4.6)	20.2 (5.2)	*F* (2, 83) = 44.16	<.001
CERAD BNT	13.2 (3.0)	10.9 (4.1)[a]	14.4 (0.9)	14.5 (0.8)	*F* (2,83) = 20.00	<.001
Word List Learning	15.3 (7.2)	7.9 (5.0)[a]	18.2 (4.6)	19.9 (4.9)	*F* (2, 82) = 52.49	<.001
Word List Recall	4.7 (3.2)	1.3 (1.8)[a]	6.0 (2.1)	7.0 (2.0)	*F* (2, 83) = 72.53	<.001

(table continues)

Table 10 cont.

Measure	All Subjects	AD	MCI	NE	Statistic	*p* value
	M (SD)	*M (SD)*	*M (SD)*	*M (SD)*		<.001
Word List Recognition	8.1 (2.9)	5.3 (3.3)[a]	9.5 (0.9)	9.6 (1.1)	F (2, 82) = 37.90	<.001
Constructional Praxis	8.6 (2.1)	6.6 (2.4)[a]	9.6 (1.1)	9.6 (1.0)	F (2, 82) = 32.63	<.001
Constructional Praxis Recall	5.9 (3.9)	2.0 (2.6)[a]	7.3 (2.1)	8.5 (2.9)	F (2, 82) = 51.20	<.001
Total Digit Span Backwards	5.4 (2.6)	3.5 (2.1)[a]	6.8 (1.3)	6.8 (2.1)	F (2, 66) = 23.21	<.001
Longest Digits Backwards	4.1 (1.6)	3.0 (1.6)[a]	5.0 (1.1)	4.9 (1.2)	F (2, 67) = 18.12	<.001
Trails A T Score	41.1 (20.5)	19.0 (17.7)[a]	50.1 (10.3)	54.3 (9.8)	F (2, 86) = 64.14	<.001
Trails B T Score	36.5 (23.0)	9.1 (16.1)[a]	47.8 (8.0)	52.9 (10.0)	F (2, 86) = 120.5	<.001

Note. Values represent raw scores unless otherwise indicated.
[a] AD group differs from MCI and NE groups, $p < .001$.
[b] MCI differs from NE group, $p = .01$

Table 11

Pearson Product-Moment Correlations (except where noted) for Total LA and Neuropsychological Scores Across and Within Groups

Measure	All Subjects	AD	MCI	NE
CERAD Total	-.31**	.35	-.36	-.30
MMSE	-.36**[a]	.33	-.18[a]	-.12[a]
Verbal Fluency	-.34**[a]	.15	-.31	-.23
CERAD BNT	-.30**[a]	.12	-.18[a]	-.12[a]
Word List Learning	-.32**	.34	-.17	-.35
Word List Recall	-.32**	.51**[a]	-.19	-.34
Word List Recognition	-.23*	.20	-.28[a]	.04[a]
Constructional Praxis	-.12	.36	-.14	.32
Constructional Praxis Recall	-.27*	.43*[a]	-.13	-.24
Total Digit Span Backwards	-.17[c]	.52**	-[b]	-.15
Longest Digits Backwards	-.16[d]	.59**	-[b]	-.41*[a]
Trails A T Score	-.20	.36	-.02[a]	.30
Trails B T Score	-.29**	.31[a]	.10	-.18

Note. Values are raw scores unless otherwise indicated.
[a] Spearman *rho* correlation coefficient
[b] $n = 10$; measure not given consistently to MCI group
[c] $n = 69$; [d] $n = 70$
* $p < .05$, ** $p < .01$

Table 12

Pearson Product-Moment Partial Correlations for Total LA and Neuropsychological Scores Controlling for Age

Measure	All Subjects	AD	MCI	NE
CERAD Total	-.31**	.10	-.21	-.27
MMSE	-.27*	.07	.01	-.02
Verbal Fluency	-.28*	-.04	-.22	-.19
CERAD BNT	-.20	-.02	<.01	-.03
Word List Learning	-.32**	.17	-.07	-.35
Word List Recall	-.29**	.38*	-.06	-.32
Word List Recognition	-.24*	.14	-.22	-.05
Constructional Praxis	-.16	.04	-.08	.35
Constructional Praxis Recall	-.28*	.30	-.14	-.26
Total Digit Span Backwards	-.23[b]	.28	-[a]	-.13
Longest Digits Backwards	-.21[c]	.37*	-[a]	-.26
Trails A T Score	-.17	.25	-.02	.30
Trails B T Score	-.30**	.13	.03	-.22

Note. Values are raw scores unless otherwise indicated.
[a] $n = 10$; measure not given consistently to MCI group
[b] $n = 69$; [c] $n = 70$
* $p < .05$
** $p < .01$

Table 13

Ranges and Frequencies of High and Low Total LA Scores Across and Within Groups

Group	Low Total LA		High Total LA	
	Score/Range	*n*	Score/Range	*n*
All Subjects Method 1	2-3	38	4-6	52
All Subjects Method 2	2	20	6	17
AD Method 1	2-4	10	5-6	20
AD Method 2	2-3	6	6	12
MCI Method 1	2-3	19	4-6	11
MCI Method 2[a]	-	-	-	-
NE Method 1	2-3	13	4-6	17
NE Method 2[a]	-	-	-	-

Note. In Method 1 subjects were divided in half (or approximately half), based on the frequency distribution of total LA, to form low and high total LA groups. In Method 2 subjects were divided in thirds, based on the frequency distribution of total LA, and the highest and lowest thirds were compared in *t*-tests.

[a] Frequencies of scores in low and high thirds were too small to make comparisons based on Method 2.

Table 14

T-test Comparisons of High and Low Total LA Scores with Neuropsychological Performance Across and Within Groups

Group and Measure	Low Total LA	High Total LA			
	M (SD)	*M (SD)*	*df*	*t*	*p*
All Subjects Method 1[a]	*n* = 38	*n* = 52			
CERAD Total	71.5 (21.8)	60.2 (20.7)	83	2.41	.02
Verbal Fluency	17.5 (7.1)	13.2 (6.6)	84	2.87	.01
Word List Learning	17.6 (7.4)	13.8 (6.7)	83	2.43	.02
Word List Recall	5.8 (3.1)	4.0 (3.1)	84	2.61	.01
Trails B T Score	42.4 (21.1)	32.3 (23.5)	87	2.10	.04
All Subjects Method 2[b]	*n* = 20	*n* = 17			
CERAD BNT	14.5 (0.8)	12.3 (3.8)	17	2.29	.04
Word List Recognition	9.4 (1.5)	7.1 (3.8)	19	2.28	.03

(table continues)

Table 14 cont.

Group and Measure	Low Total LA	High Total LA			
	M (SD)	*M (SD)*	*df*	*t*	*p*
AD Group Method 1[a]	*n* = 10	*n* = 20			
Constructional Praxis	5.2 (2.3)	7.4 (2.1)	27	-2.17	.02
Word List Recall	0.3 (0.7)	1.8 (2.0)	26	-1.45	.01
Digit Span (Longest Backward)	1.8 (1.8)	3.6 (1.1)	28	-1.75	<.01
Digit Span (Total Backward)	2.1 (2.4)	4.2 (1.7)	28	-2.05	.01
AD Group Method 2[b]	*n* = 6	*n* = 12			
CERAD Total	30.7 (16.6)	49.2 (16.6)	15	-2.20	.04
MMSE	12.2 (8.0)	19.4 (5.9)	16	-2.20	.04
Word List Learning	4.6 (4.3)	10.0 (4.7)	16	-2.32	.03
Trails A	6.8 (11.6)	26.8 (18.1)	16	-2.44	.03

(table continues)

Table 14 cont.

Group and Measure	Low Total LA	High Total LA			
	M (SD)	*M (SD)*	*df*	*t*	*p*
MCI Group Method 1 [a]	*n* = 19	*n* = 11			
None Significant					
NE Group Method 1[a]	*n* = 13	*n* = 17			
CERAD Total	84.9 (7.3)	76.7 (11.6)	28	2.23	.03
Verbal Fluency					
(Animal Category)	22.4 (4.3)	18.6 (5.3)	28	2.11	.04
Word List Learning	22.1 (4.1)	18.3 (4.9)	28	2.25	.03
Digit Span (Longest					
Backward)	5.5 (1.1)	4.4 (1.0)	28	2.89	.01

Note. Only significant *t*-test results are reported. Values are raw scores unless otherwise indicated.
[a] In Method 1 subjects were divided in half (or approximately half), based on the frequency distribution of total LA, to form low and high total LA groups.
[b] In Method 2 subjects were divided in thirds, based on the frequency distribution of total LA, and the highest and lowest thirds were compared in *t*-tests

Table 15

Pearson Product-Moment Correlations (except where noted) for Periventricular LA and Neuropsychological Scores Across and Within Groups

Measure	All Subjects	AD	MCI	NE
CERAD Total	-.29**	.28	-.24[a]	-.36
MMSE	-.32**[a]	.28	-.10[a]	-.15
Verbal Fluency	-.28*	.16	-.25[a]	-.25
CERAD BNT	-.16	.23	-.34	-.19
Word List Learning	-.29**	.32	-.09	-.45*
Word List Recall	-.28**	.42*[a]	-.03[a]	-.38*
Word List Recognition	-.26*[a]	-.00	-.32	.02
Constructional Praxis	-.17[a]	.20	-.21	.22
Constructional Praxis Recall	-.28**	.17	-.12	-.19[a]
Total Digit Span Backwards	-.19[c]	.50**	-[b]	-.15[a]
Longest Digits Backwards	-.13[d]	.60[§]	-[b]	-.29
Trails A T Score	-.20	.29	-.08	.16
Trails B T Score	-.29**	.30	-.18	-.18

Note. Values are raw scores unless otherwise indicated.
[a] Spearman *rho* correlation coefficient
[b] $n = 10$; measure not given consistently to MCI group
[c] $n = 69$; [d] $n = 70$
* $p < .05$, ** $p < .01$, § $p < .001$

Table 16

Pearson Product-Moment Partial Correlations for Periventricular LA and Neuropsychological Scores Controlling for Age

Measure	All Subjects	AD	MCI	NE
CERAD Total	-.27*	.07	-.09	-.34
MMSE	-.24*	.02	.08	-.11
Verbal Fluency	-.22*	.01	-.16	-.22
CERAD BNT	-.17	.13	-.19	-.16
Word List Learning	-.28*	.14	.05	-.45*
Word List Recall	-.26*	.26	.09	-.36
Word List Recognition	-.29**	-.12	-.31	.01
Constructional Praxis	-.23*	-.15	-.18	.24
Constructional Praxis Recall	-.30**	.03	-.12	-.30
Total Digit Span Backwards	-.24*[b]	.30	-[a]	-.20
Longest Digits Backwards	-.17[c]	.43*	-[a]	-.23
Trails A T Score	-.19	.13	-.13	.15
Trails B T Score	-.29**	.12	-.34	-.20

Note. Values are raw scores unless otherwise indicated.
[a] $n = 10$; measure not given consistently to MCI group
[b] $n = 69$; [c] $n = 70$
* $p < .05$
** $p < .01$

Table 17

Ranges and Frequencies of High and Low Periventricular LA Scores Across and Within Groups

Group	Low Total LA		High Total LA	
	Score/Range	*n*	Score/Range	*n*
All Subjects Method 1	2-5	49	6-9	41
All Subjects Method 2	2-4	32	7-9	26
AD Method 1	4-6	15	7-9	15
AD Method 2	-	-	-	-
MCI Method 1	2-4	20	5-8	10
MCI Method 2	2-3	10	5-8	10
NE Method 1	3-5	15	6-9	15
NE Method 2[a]	-	-	-	-

Note. In Method 1 subjects were divided in half (or approximately half), based on the frequency distribution of total LA, to form low and high total LA groups. In Method 2 subjects were divided in thirds, based on the frequency distribution of total LA, and the highest and lowest thirds were compared in *t*-tests.

[a] Frequencies of scores in low and high thirds were too small to make comparisons based on Method 2.

Table 18

T-test Comparisons of High and Low Periventricular LA Scores with Neuropsychological Performance Across and Within Groups

Group and Measure	Low PV LA	High PV LA			
	M (SD)	*M (SD)*	*df*	*t*	*p*
All Subjects Method 1[a]					
CERAD Total	75.9 (15.4)	59.0 (20.1)	52	3.49	.001
MMSE	27.8 (4.8)	23.5 (6.3)	46	2.87	.01
Verbal Fluency	18.5 (5.9)	12.4 (6.2)	53	3.77	<.001
CERAD BNT	14.5 (0.9)	12.8 (3.3)	28	2.59	.02
Word List Learning	18.9 (6.3)	13.8 (6.8)	52	2.88	.01
Word List Recall	6.1 (2.7)	3.7 (3.0)	53	3.06	<.01
Word List Recognition	9.2 (1.4)	7.1 (3.4)	31	2.86	.01
Constructional Praxis					
Recall	7.2 (3.1)	4.4 (3.7)	52	3.06	<.01
Trails A T Score	47.5 (16.6)	36.0 (21.5)	55	2.28	.03
Trails B T Score	45.7 (18.2)	28.6 (23.2)	47	3.05	<.01

(table continues)

Table 18 cont.

Group and Measure	Low PV LA	High PV LA			
	M (SD)	*M (SD)*	*df*	*t*	*p*
AD Group Method 1					
Word List Learning	6.1 (4.9)	9.8 (4.5)	27	-2.10	.045
Word List Recall	0.4 (0.7)	2.1 (2.2)	17	-1.73	.01
Digit Span (Longest Backward)	2.0 (1.5)	3.9 (1.0)	28	-4.28	<.01
Digit Span (Total Backward)	2.3 (2.0)	4.6 (1.6)	28	-3.37	<.01
MCI Group Method 1					
CERAD Total	76.4 (8.2)	67.8 (11.0)	24	2.26	.03
Verbal Fluency (Animals)	17.8 (4.3)	13.6 (4.0)	24	2.43	.02
NE Group Method 1					
CERAD Total	84.0 (7.4)	76.4 (12.2)	28	2.06	.05

Note. Only significant *t*-test results are reported. Values are raw scores unless otherwise indicated.

[a]In Method 1 subjects were divided in half (or approximately half), based on the frequency distribution of total LA, to form low and high periventricular LA groups. Comparisons by Method 2 revealed no additional significant differences.

Table 19

Pearson Product-Moment Correlations (except where noted) for Subcortical LA and Neuropsychological Scores Across and Within Groups

Measure	All Subjects	AD	MCI	NE
CERAD Total	-.24*[a]	.38*	-.30[a]	-.19[a]
MMSE	-.24*[a]	.31[a]	-.34[a]	.08[a]
Verbal Fluency	-.17[a]	.17[a]	-.09[a]	-.03[a]
CERAD BNT	-.20[a]	.22[a]	-.36[a]	.07[a]
Word List Learning	-.29**[a]	.30	-.25[a]	-.33
Word List Recall	-.24*[a]	.57**	-.24[a]	-.36*
Word List Recognition	-.18[a]	.29[a]	-.21[a]	-.16[a]
Constructional Praxis	-.06[a]	.38*[a]	-.08[a]	.27[a]
Constructional Praxis Recall	-.17[a]	.40*	-.30[a]	-.06[a]
Total Digit Span Backwards	-.15[ac]	.40*	-[b]	-.07[a]
Longest Digits Backwards	-.23[ad]	.41*[a]	-[b]	-.35[a]
Trails A T Score	-.06[a]	.48**[a]	.11[a]	.32
Trails B T Score	-.18[a]	.35[a]	.19[a]	-.18[a]

Note. Values are raw scores unless otherwise indicated.
[a] Spearman *rho* correlation coefficient
[b] n = 10; measure not given consistently to MCI group
[c] n = 69; [d] n = 70
* $p < .05$
** $p < .01$

Table 20

Pearson Product-Moment Partial Correlations for Subcortical LA and Neuropsychological Scores Controlling for Age

Measure	All Subjects	AD	MCI	NE
CERAD Total	-.09	.27	-.15	.03
MMSE	-.08	.24	.09	.20
Verbal Fluency	-.03	.21	.09	.10
CERAD BNT	.01	.24	-.02	.07
Word List Learning	-.14	.19	-.07	-.10
Word List Recall	-.06	.51**	-.03	-.09
Word List Recognition	-.07	.14	.07	.10
Constructional Praxis	-.04	.13	-.03	.25
Constructional Praxis Recall	-.13	.34	-.32	-.13
Total Digit Span Backwards	-.05[b]	.27	-[a]	-.00
Longest Digits Backwards	-.06[c]	.27	-[a]	-.15
Trails A T Score	.08	.47*	-.02	.50**
Trails B T Score	-.09	.33	.11	-.07

Note. Values are raw scores unless otherwise indicated.
[a] n = 10; measure not given consistently to MCI group
[b] n = 69; [c] n = 70
* $p < .05$
** $p < .01$

Table 21

Ranges and Frequencies of High and Low Subcortical LA Scores Across and Within Groups

Group	Low Total LA[a]		High Total LA[a]	
	Score/Range	*n*	Score/Range	*n*
All Subjects Method 1	0 - 0.64	45	>0.64 – 11.1	45
All Subjects Method 2	0 – 0.26	30	1.37 – 11.1	30
AD Method 1	0 – 1.81	15	>1.81 – 11.1	15
AD Method 2	0 – 0.48	10	2.67 – 11.1	10
MCI Method 1	0 – 0.25	15	>0.25 – 8.8	15
MCI Method 2	0 – 0.23	10	>0.83 – 8.8	10
NE Method 1	0 – 0.64	15	>0.64 – 6.6	15
NE Method 2	0 – 0.31	10	> 1.11 – 6.6	10

Note. In Method 1 subjects were divided in half (or approximately half), based on the frequency distribution of total LA, to form low and high total LA groups. In Method 2 subjects were divided in thirds, based on the frequency distribution of total LA, and the highest and lowest thirds were compared in *t*-tests.

[a] Scores represent volumes (cm^3).

Table 22

T-test Comparisons of High and Low Subcortical LA Scores with Neuropsychological Performance Across and Within Groups

Group and Measure	Low SC LA	High SC LA			
	M (SD)	*M (SD)*	*df*	*t*	*p*
All Subjects Method 1[a]					
Word List Learning	17.2 (7.5)	13.5 (6.5)	83	2.44	.02
Word List Recall	5.5 (3.3)	3.9 (2.9)	84	2.44	.02
AD Group Method 1[a]					
Word List Recall	0.4 (0.6)	2.1 (2.1)	18	1.71	.01
Constructional Praxis	5.6 (2.6)	7.5 (1.8)	27	2.33	.03
Constructional Praxis Recall	0.7 (1.1)	3.2 (3.1)	17	2.49	.01
Trails A	12.1 (16.4)	25.1 (17.1)	28	2.13	.04
AD Group Method 2[b]					
CERAD Total	33.8 (18.2)	48.3 (11.7)	18	-2.12	.048

(table continues)

Table 22 cont.

Group and Measure	Low SC LA	High SC LA			
	M (SD)	*M (SD)*	*df*	*t*	*p*
MCI Group Method 1[a]					
MMSE	29.4 (0.7)	28.3 (1.3)	15	2.47	.03
CERAD BNT	15.0 (0.0)	14.2 (1.0)	8	2.40	.04
NE Group Method 1[a]					
CERAD Total	84.0 (7.0)	76.4 (12.4)	28	2.06	
.049					
Word List Learning	22.0 (3.8)	17.9 (5.1)	28	2.52	.02
Word List Recall	8.0 (1.2)	6.0 (2.1)	28	3.16	<.01

Note. Only significant *t*-test results are reported. Values are raw scores unless otherwise indicated.

[a] In Method 1 subjects were divided in half (or approximately half), based on the frequency distribution of subcortical LA, to form low and high total LA groups.

[b] In Method 2 subjects were divided in thirds, based on the frequency distribution of subcortical LA, and the highest and lowest thirds were compared in *t*-tests.

Table 23

Comparison of Significant Periventricular and Subcortical LA Correlations with Neuropsychological Functioning for All Subjects: T-test of Correlations for Dependent Samples

Measure	PVLA	SCLA	t	p
CERAD Total	-.32**	-.24*	.91	.37
MMSE	-.32**	-.24*[a]	.91	.37
Word List Learning	-.32**	-.29**	.34	.74
Word List Recall	-.28**	-.24*	.45	.66

Note. Comparisons were made with Spearman correlation coefficients.
* $p < .05$
** $p < .01$

Table 24

Means, Standard Deviations, and Significance Levels for Cortical and Subcortical Atrophy

Brain Atrophy	Group						
	AD *M (SD)*	MCI *M (SD)*	NE *M (SD)*	Statistic	*p*	Bonferroni post hoc	*p*
Subcortical							
Atrophy (Total Mean)[a]	.36 (.04)	.31 (.03)	.31 (.03)	F (2, 87) = 18.73	<.001	AD vs. MCI AD vs. NE	<.001 <.001
Frontal[a]	.36 (.04)	.33 (.04)	.34 (.04)	F (2, 87) = 5.67	.005	AD vs. MCI AD vs. NE	.01 .02
Caudate[a]	.23 (.03)	.19 (.03)	.20 (.03)	F (2, 87) = 13.63	<.001	AD vs. MCI AD vs. NE	<.001 <.001
Occipital[a]	.48 (.08)	.40 (.06)	.39 (.05)	F (2, 87) = 17.04	<.001	AD vs. MCI AD vs. NE	<.001 <.001

(table continues)

Table 24 cont.

Brain Atrophy	Group						
	AD *M (SD)*	MCI *M (SD)*	NE *M (SD)*	Statistic	*p*	Bonferroni	*p*
Cortical Atrophy (Total)[b]	7.03 (1.10)	4.73 (1.48)	5.20 (1.00)	F (2, 87) = 30.23	<.001	AD vs. MCI AD vs. NE	<.001 <.001
Temporal Horns[c]	2.10 (.76)	1.23 (.63)	1.20 (.48)	F (2, 87) = 19.49	<.001	AD vs. MCI AD vs. NE	<.001 <.001
Perisylvian Cistern[c]	2.73 (.45)	2.00 (.59)	2.20 (.41)	F (2, 87) = 18.15	<.001	AD vs. MCI AD vs. NE	<.001 <.001
Convexity Sulci[c]	2.20 (.41)	1.50 (.51)	1.80 (.48)	F (2, 87) = 16.85	<.001	AD vs. MCI AD vs. NE MCI vs. NE	<.001 .004 .045

Note. Higher scores indicate greater atrophy. See Appendix B for atrophy calculations.
[a] Subcortical atrophy values represent ventricle to brain ratios.
[b] Atrophy values range from 0-9.
[c] Atrophy values range from 0-3.

Table 25

Pearson Product-Moment Correlations (except where noted) for Brain Atrophy and LA Across and Within Groups

LA	Subcortical Atrophy				Cortical Atrophy			
	All Subjects	AD	MCI	NE	All Subjects	AD	MCI	NE
Total LA	.39**	.38*	.33	-.16	.43**	.08	.40*	.03
Partial correlation (age)	.32**	.43*	.12	-.30	.33**	.03	.08	-.05
Periventricular LA	.31**	.24	.30	-.19	.45**	-.01	.51**	.09
Partial correlation (age)	.23*	.24	.08	-.28	.36**	-.06	.24	.03
Subcortical LA	.30**[a]	.15	.32	-.20	.34*[a]	.10	.28	.03
Partial correlation (age)	.16	.14	.17	-.27	.20	.08	.01	-.01

Note. Higher scores indicate greater atrophy. See Appendix B for atrophy calculations.
[a] Spearman *rho* correlation coefficient
* $p < .05$
** $p < .01$

Table 26

Pearson Product-Moment Correlations (except where noted) for Subcortical Atrophy Regions and LA Across and Within Groups

Subcortical Region	Total LA				Periventricular LA				Subcortical LA[a]			
	All Subjects	AD	MCI	NE	All Subjects	AD	MCI	NE	All Subjects	AD	MCI	NE
Frontal Horn	.24*	.24	.21	-.16	.17	.09	.22	-.23	.23*	.31	.01	.08
Partial correlation (age)	.12	.23	.03	-.37*	.05	.04	.04	-.40*	.14	.23	.13	-.21
Caudate Nucleus	.40**	.37*	.23	.10	.37**	.35	.29	.03	.31**	.34	.17	.17
Partial correlation (age)	.29**	.39*	-.06	-.07	.27*	.35	.02	-.10	.16	.19	-.15	-.01
Occipital Horns	.35**	.36*	.28	-.26	.26*	.22	.20	-.21	.23*	.16	.24	-.19
Partial correlation (age)	.34**	.43*	.19	-.26	.23*	.24	.08	-.21	.13	.04	.24	.35

Note. Higher scores indicate greater atrophy. See Appendix B for atrophy calculations.
[a] Spearman *rho* correlation coefficients are given.
* $p < .05$, ** $p < .01$

Table 27

Pearson Product-Moment Correlations (except where noted) for Cortical Atrophy Regions and LA Across and Within Groups

Cortical Region	Total LA				PV LA				SC LA[a]			
	All Subjects	AD	MCI	NE	All Subjects	AD	MCI	NE	All Subjects	AD	MCI	NE
Temporal Horns	.39**	.37*	.36	-.28	.37**	.25	.49**	-.20	.27*	.38*	.26	-.27
Partial correlation (age)	.30**	.33	.15	-.34	.29**	.19	.31	-.24	.22*	.25	.14	-.27
Perisylvian Cistern	.26*	-.33	.22	.08	.34**	-.20	.33	.16	.16	-.24	.21	.03
Partial correlation (age)	.19	-.39*	-.04	.08	.29**	-.22	.08	.16	.10	-.11	-.14	.10
Convexity Sulci	.42**	-.12	.46*	.28	.41**	-.27	.51**	.24	.38**	-.11	.48**	.29
Partial correlation (age)	.30**	-.10	.10	.18	.31**	-.28	.16	.19	.15	-.13	.03	.19

Note. Higher scores indicate greater atrophy. See Appendix B for atrophy calculations.
[a] Spearman correlation coefficients are given.
* $p < .05$
** $p < .01$

Table 28

Pearson Product-Moment Correlations for Subcortical Brain Atrophy and Neuropsychological Scores Across and Within Groups

Measure	All Subjects	AD	MCI	NE
CERAD Total	-.57**	-.47**	-.11	-.02
MMSE	-.54**	-.28	.10	-.15
Verbal Fluency	-.47**	-.46**	-.00	.10
CERAD BNT	-.55**	-.51**	.01	.02
Word List Learning	-.53**	-.44*	-.07	-.02
Word List Recall	-.54**	-.27	-.28	-.04
Word List Recognition	-.60**	-.48**	-.28	-.19
Constructional Praxis	-.40**	-.18	.32	-.10
Constructional Praxis Recall	-.43**	-.27	.04	.10
Total Digit Span Backwards	-.43**[b]	-.23	-[a]	.09
Longest Digits Backwards	-.36**[c]	-.11	-[a]	.02
Trails A T Score	-.51**	-.23	-.08	-.06
Trails B T Score	-.52**	-.26	.05	.20

Note. Values are raw scores unless otherwise indicated.
[a] n = 10; measure not given consistently to MCI group
[b] n = 69; [c] n = 70
* $p < .05$
** $p < .01$

Table 29

Pearson Product-Moment Correlations for Cortical Brain Atrophy and Neuropsychological Scores Across and Within Groups

Measure	All Subjects	AD	MCI	NE
CERAD Total	-.60**	-.48**	-.13	-.03
MMSE	-.57**	-.30	.19	.06
Verbal Fluency	-.56**	-.55**	-.23	-.10
CERAD BNT	-.49**	-.36*	-.04	-.13
Word List Learning	-.53**	-.41*	.02	-.06
Word List Recall	-.52**	-.21	-.04	.00
Word List Recognition	-.52**	-.25	-.21	.11
Constructional Praxis	-.44**	-.31	.27	.17
Constructional Praxis Recall	-.47**	-.33	.11	.05
Total Digit Span Backwards	-.43**[b]	.02	-[a]	-.01
Longest Digits Backwards	-.37**[c]	.06	-[a]	-.01
Trails A T Score	-.52**	-.15	-.14	.07
Trails B T Score	-.51**	-.08	.07	.29

Note. Values are raw scores unless otherwise indicated.
[a] n = 10; measure not given consistently to MCI group
[b] n = 69; [c] n = 70
* $p < .05$
** $p < .01$

Table 30

Comparison of Significant Cortical and Subcortical Atrophy Correlations with Neuropsychological Functioning for All Subjects: T-test of Correlations for Dependent Samples

Measure	Cortical Atrophy	Subcortical Atrophy	t	p
CERAD Total	-.60**	-.57**	.43	.67
MMSE	-.57**	-.54**	.42	.68
Verbal Fluency	-.56**	-.47**	1.20	.23
CERAD BNT	-.49**	-.55**	.80	.43
Word List Learning	-.53**	-.53**	.00	1.00
Word List Recall	-.52**	-.54**	.27	.79
Word List Recognition	-.52**	-.60**	1.11	.27
Constructional Praxis	-.44**	-.40**	.49	.63
Constructional Praxis Recall	-.47**	-.43**	.50	.62
Total Digit Span Backwards	-.43**[a]	-.43**[a]	.00	1.00
Longest Digit Span Backwards	-.37**[a]	-.36**[a]	.11	.92
Trails A T Score	-.52**	-.51**	.13	.89
Trails B T Score	-.51**	-.52**	.13	.89

Note. Values are raw scores unless otherwise indicated.
[a] Comparisons were made with Spearman *rho* correlation coefficients.
* $p < .05$
** $p < .01$

Table 31

Comparison of Significant Cortical and Subcortical Atrophy Correlations with Neuropsychological Functioning for AD Group: T-test of Correlations for Dependent Samples

Measure	Cortical Atrophy	Subcortical Atrophy	t	p
CERAD Total	-.48**	-.47**	.06	.95
Verbal Fluency	-.55**	-.46**	.57	.57
CERAD BNT	-.36*	-.51**	.91	.37
Word List Learning	-.41*	-.44*	.17	.86

Note. Values are raw scores.
* $p < .05$
** $p < .01$

APPENDIX A

Neuropsychological Measures

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Neuropsychological Battery (Morris et al., 1989)

The CERAD developed a brief battery of neuropsychological tests to assist in diagnosing AD, and in measuring progression of dementia over time (Morris et al., 1989). The neuropsychological battery includes six measures that assess memory, language, and praxis, in addition to a slightly modified verson of the original MMSE. The entire battery requires approximately 20 to 30 minutes to administer. Preliminary normative data for the battery has been published (Welsh et al., 1994). The battery has high interrater agreement (r = .92 to 1.0), high test-retest reliability over 1-month, and is sensitive to change over longer time periods (Morris et al., 1989). The current study incorporates individual scores from each of the tests in the battery in addition to a CERAD Total Score. The Total Score is based on the method of Chandler et al. (2005) and is calculated by summing the following subtests of the CERAD: Verbal Fluency, CERAD BNT, Constructional Praxis, and Word List Learning, Recall, and Recognition Discriminability. Recognition Discriminability is calculated by subtracting the number of false positives from the number of true positive responses. The Constructional Praxis Recall subtest is not included in the Total Score because it was not included as part original CERAD registry data that were used to derive and

validate the Total Score (Chandler, 2004). A description of each subtest of the CERAD battery follows.

MMSE (Folstein, Folstein, & McHugh, 1975).

The MMSE is a brief general cognitive screening test that was developed to assess key cognitive domains of the mental status exam in a structured, scorable format. The MMSE is comprised of 22 items that assess orientation, immediate and delayed memory, concentration, language, and praxis. The MMSE used in the CERAD is slightly modified from the original measure developed by Folstein et al. (1975). The test was modified by replacing the original serial seven subtraction item with spelling the word "world" backwards. The highest attainable score is 30. The measure takes approximately 5 to 10 minutes to administer and score. The test requires subjects to verbally respond to questions that assess orientation, memory, and attention. Subjects are also asked to name objects, follow verbal and written commands, write an original sentence, and copy a design of intersecting polygons. In general, those with scores of 24 and below are considered to have cognitive impairment (Welsh, Butters, Hughes, Mohs, & Heyman, 1992).

Folstein et al. (1975) reported good inter-rater reliability for the MMSE ($r >$ .65). Test-retest reliability for the MMSE is also high ($r = .80$ to $r = .99$) for short intervals of 24 hours to one month in demented and nondemented individuals. Longer test-retest intervals have produced variable results. Studies examining one year intervals have found reliability coefficients ranging from $r = .45$ to $r = .86$ (Lacritz,

1995). They examined the convergent validity of the MMSE with the WAIS Verbal and Performance IQ scores and reported correlation coefficients of $r = .78$ and $r = .66$, respectively, with a population of mixed psychiatric disorders.

Verbal Fluency.

Category Fluency is a test of verbal fluency within a semantic category. The category "animals" is used, wherein the subject is asked to name as many animals as they can within one minute. Subjects' scores are calculated by summing the number of words produced for the category . Perseverations (repetitions of the same word) and losses of set (production of words that do not fit the category) are excluded.

Modified Boston Naming Test.

The CERAD BNT is a measure of confrontation naming that was modified from the original Boston Naming Test (see below, Kaplan, Goodglass, & Weintraub, 1983). It includes 15 objects that are presented as line drawings. A maximum of 10 seconds is allowed for each picture presented, and the subject is asked to name each picture. The task includes three groups of five items, and the groups have high, medium, and low frequency of occurrence in the English language (Morris et al., 1989).

Word List Learning.

Word List Learning is a verbal list-learning test that is composed of 10 printed words, presented at a rate of one word every two seconds. For each of 3 trials, the list is presented in a random order and the subject is asked to recall as many words as they

can. Subjects can earn a maximum of 30 points for all three trials (Morris et al., 1989).

Word List Recall – Delay.

This task examines delayed verbal memory and involved recall of the 10-item Word List Learning test after a 5-minute delay. Subjects can earn a maximum of 10 points on this task. A savings score is computed and presented as a percentage to represent the amount of information retained over the delay ([Delay/Trial 3] × 100 = Savings) (Welsh et al., 1994).

Word List Recognition Discriminability.

The Recognition test assesses subjects' ability to recognize the 10 words presented in the Word List Memory test when presented with 10 additional distractor words (Morris et al., 1989). The Recognition Discriminability score is derived by subtracting the total number of false positive responses from the total number of true positives (Chandler, 2004).

Constructional Praxis.

The Constructional Praxis subtest is a measure of visuospatial constructional ability (Morris et al., 1993; Welsh et al., 1994). It includes the presentation of four line drawings of figures of increasing complexity. A circle, diamond, intersecting rectangles, and a cube are presented to the subject to copy. Subjects are given 2 minutes per item to complete each copy, and they can earn a maximum of 11 points on the test.

Constructional Praxis Recall.

This task was not included in the original CERAD neuropsychological battery but was added to include a measure of visuospatial memory. Researchers have examined the utility of including a recall measure of Constructional Praxis to assess visuospatial memory. The subtest is administered by presenting items from Constructional Praxis. Following a delay of several minutes, subjects are asked to redraw the items from memory, and then a recognition task is administered (Yuspeh, Vanderploeg, & Kershaw, 1998). Scores were compared with the Visual Reproduction subtests (VR I and VR II) of the Wechsler Memory Scale – Revised (WMS-R; Wechsler, 1987) and determined that the Constructional Praxis Free Recall and Recognition procedures had strong concurrent validity (for free recall, $r = .70$ and $r = .50$, respectively; recognition, $r = .49$ and $r = .46$, respectively). Yuspeh et al. (1998) also found that Constructional Praxis Free Recall predicted diagnosis of Alzheimer's disease versus controls with high sensitivity (90%) and specificity (86%) and an overall hit rate of 88%.

Boston Naming Test (BNT; Kaplan, Goodglass, & Weintraub, 1983)

The BNT is a popular test of confrontation naming. It was originally published with 85 items and was revised to include 60 items. The test is administered through presentation of line drawings that depict vocabulary words ranging in difficulty. Subjects are asked to name each line drawing, and a semantic cue is provided if they do not produce the correct word within 20 seconds. Subjects are given an additional

20 seconds to respond after the semantic cue is given. If the correct response is not given, a phonemic cue is given, and the subject has another 20 seconds to produce the correct answer. A total of 60 points can be earned on the test. Age-, gender-, and education-corrected scores were transformed from the Heaton et al. (1991) normative sample.

Controlled Oral Word Association (FAS-Test; Spreen & Strauss, 1998)

Controlled Oral Word Association, is a Phonemic Fluency test (FAS Test) of spontaneous word production. The FAS-test requires subjects to produce as many words as possible in one minute that begin with the letter "F," "A," and "S." Each letter is tested individually (one minute per letter). The score is the sum of the total words for each letter. Words that violate the rules are excluded from the sum, such as proper nouns, perseverations (repetitions of the same word), and losses of set (production of words that do not fit the category). Test-retest reliability at one-year was reported to be $r = .70$ and retest reliability of 19 to 42 days was $r = .88$ (Spreen & Strauss, 1998).

California Verbal Leaning Test (CVLT; Delis et al., 1987)

The CVLT is a 16-item verbal learning and memory measure that includes 5 learning trials. The CVLT examines learning and memory by assessing immediate and delayed free recall, immediate and delayed semantically-cued recall, and recognition testing. The 16-items on the initial list ("Monday" list) comprise four semantic categories (spices and herbs, tools, fruits, and clothing). Following

presentation and free recall of the "Monday" list over five trials, an interference list of 16 words ("Tuesday" list) is presented and subsequently followed by free and category-cued recall of the "Monday list." Then a 20-minute delay occurs and is followed by free recall, cued recall, and recognition of the "Monday" list. Through this procedure, the test was designed both to quantify and qualitatively characterize learning and memory processes (Norman, Evans, Miller, & Heaton, 2000).

Delis et al. (1987) found an estimated internal reliability of $r = .92$ for the total score, and split-half reliability was $r = .63$. The reliability data in the original manual suggests that the CVLT has sound internal consistency and test-retest reliability.

Rey-Osterrieth Complex Figure (Rey-O; Corwin & Bylsma, 1993)

The Rey-O assesses visual-perceptual organization and nonverbal memory. Subjects are asked to copy the complex geometric figure and then immediately redraw it from memory. Subjects are then asked to redraw the figure from memory again after a 15-minute delay, but are not told in advance that they will do this. Loring, Martin, Meador, and Lee (1990) developed scoring criteria for each of 18 figure elements. Each element is awarded zero to two points depending on the accuracy of drawing and placement of the element. All points awarded for each element are then summed to determine the score. Interrater reliability coefficients were $r = .80$ for the copy, $r = .93$ for the immediate recall, and $r = .96$ for delayed recall (Loring et al.). Spreen and Strauss (1998) indicate that correlational and factor analyses have demonstrated that

the Rey-O measures the construct of visuoconstructional ability as well as nonverbal memory.

Trail Making Test (Reitan & Wolfson, 1993)

The Trail Making Test assesses attention, visual scanning, motor speed, and mental sequencing and flexibility (Spreen & Strauss, 1998). The test is comprised of two parts: Part A requires the subject to draw a continuous line connecting numbers from one to 25 as quickly as possible, and Part B requires the subject to draw a line connecting letters and numbers in alternating sequence. Part B is more complex and assesses mental flexibility. The tasks are completed on paper that has the appropriate numbers and letters pre-printed. Subjects are scored according to the length of time required to complete the tasks, and the number of errors made. Age-, gender-, and education-corrected scores were obtained from Heaton et al. (1991).

Digit Span Backwards.

The Digit Span subtest assesses auditory attentional functioning, and only the Digits Backward section of the test was administered for the current study. The subtest was adapted from the Wechsler Digit Span subtest, as the numbers used in the current study were modified (Wechsler, 1997). The subtest was administered by asking subjects to repeat a sequence of numbers, spoken to them verbally at a rate of one per second, in reverse order (Digits Backward). Subjects were given a series of

numbers ranging in length from two to seven digits, and earned 1 point for each correct series. Subjects could earn a maximum of 12 points.

Wisconsin Card Sorting Test (WCST; Heaton, Chelune, Talley, Kay, & Curtis, 1993)

The WCST is a test of mental flexibility and problem solving. It assesses executive functioning by asking subjects to match response cards to one of four stimulus cards. Subjects are evaluated on their ability to match the cards according to three sorting principles; however, the principles are not described to the subject. The subject is only given feedback regarding whether they matched correctly or incorrectly. Subjects must use problem solving skills to figure out the strategy, and they must match cards to each of the principles for a series of ten consecutive trials, at which point the strategy is changed, and the subject must adapt accordingly. The task is completed when the subject completes each category twice in the correct order. The test can be discontinued after the first 64 cards (total of 128 cards) if the subject has not completed any sets. Several scores are obtained including perseverative responses, perseverative errors, losses of set, and categories completed. Axelrod, Goldman, and Woodard (1992) reported interscorer reliability of $r = .88$ to $r = .92$. Age-, gender-, and education-corrected scores were obtained from the Heaton et al. (1991) norms.

APPENDIX B: Semi-Quantitative Rating Scale for Cerebral White Matter Lesions

Alzheimer's Disease Center
University of Texas Southwestern Medical Center

Semi-Quantitative Rating Scale for Cerebral White Matter Lesions

Digital MRI data available ☐ Yes ☐ No

I. **PERIVENTRICULAR WHITE MATTER LESIONS** (0-9) Circle what applies

A. Frontal horns
   0. None
   1. Pencil-thin lining
   2. Smooth halo
   3. Large confluent

B. Wall of lateral ventricles
   0. None
   1. Pencil-thin lining
   2. Smooth halo
   3. Large confluent

TOTAL = _____

C. Occipital horns
   0. None
   1. Pencil-thin lining
   2. Smooth halo
   3. Large confluent

II. **SUBCORTICAL WHITE MATTER LESIONS.** TOTAL VOL. = _____ cm^3

A. Number small WMLs (<3 mm) _____ $V = n \times 4/3\ \pi\ (0.1)^3 =$ _____ cm^3

B. Number medium WMLs (3-10 mm)_____ $V = n \times 4/3\ \pi\ (0.3)^3 =$ _____ cm^3

C. Number large WMLs (>10 mm)_____ $V = n \times 4/3\ \pi\ (0.6)^3 =$ _____ cm^3

III. CEREBRAL ATROPHY.

A. Subcortical Atrophy: Ventricle to brain ratio

Frontal _____ / _____ = _____
Caudate _____ / _____ = _____
Occipital _____ / _____ = _____
MEAN = _____

(Mean biventricular width at level of frontal horns, occipital horns, and body of the caudate divided by corresponding brain width at those levels)

B. Cortical Atrophy:
   0. None.
   1. Mild
   2. Moderate
   3. Severe

A. Temporal horns _____
B. Perisylvian cistern _____
C. Convexity sulci _____

TOTAL = _____

Ref: deGroot et al, Cerebral white matter lesions and cognitive function: The Rotterdam study. *Ann. Neurol;* **2000**:47:145-151
deLeeuw et al, A follow-up study of blood pressure and cerebral white matter lesions. *Ann. Neurol;* **1999**:46:827-833

APPENDIX C: Manual for Semi-Quantitative Scoring of MRI in Dementia and Cognitive Impairment

Manual for Semi-quantitative Scoring of MRI in Dementia and Cognitive Impairment

The Rotterdam Scan Study

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Manual for Semi-quantitative Scoring of MRI in Dementia and Cognitve Impairment

The Rotterdam Scan Study

The Rotterdam Scan Study is a population-based study designed to study causes and consequences of age-related brain changes in elderly people, based in Erasmus University in the city of Rotterdam, The Netherlands. This study has been highly influential in identifying risk factors for dementia and Alzheimer's disease, particularly factors related to vascular disease[1]. The study was started in 1995 – 1996, when 1,077 non-demented, community-dwelling residents of Rotterdam, ages 60 – 90, underwent a baseline examination which included a cranial MRI scan. A semi-quantitative scale was developed for analyzing these scans[2], which was validated by demonstrating a high inter-rater correlation, as well as high correlation with other widely-used semi-quantitative scales[3]. More recently, this scale has been used in studies of patients with mild cognitive impairment, early Alzheimer's disease, and vascular dementia by several groups of investigators throughout the world.

In the Rotterdam study, hard copies of scans (printed at a reduction factor of 2.7) were read by experienced, trained physicians. T2-weighted images were analyzed for white matter lesions (WMLs). There was a pool of 4 physicians, and each scan was read by two readers. If the readers agreed within one point, the average of the two scores was used. In case of disagreement, a consensus conference was held[2]. Weighted κ values for periventricular WML severity grades and subcortical WML volumes were between 0.79 and 0.95.

The Rotterdam Scan Scale has four components:

(1). Periventricular White Matter Lesions. Score 0 – 3 for each of three regions (frontal horns, wall of lateral ventricles, occipital horns). Total score 0 – 9.

(2). Subcortical White Matter Lesions. Subcortical WMLs are categorized as small (< 3 mm), medium (3 – 10 mm) or large (>10 mm). Total subcortical WML volume was calculated by assuming that each lesion is spherical with diameters of 2, 6, or 12 mm (on average, for each size category), and summing the volumes.

(3). Ventricle to brain ratio. Measure biventricular width at the level of the frontal horns, caudate nucleus, and occipital horns, and divide each by the corresponding brain width at those levels.

(4). Cortical atrophy. Rated visually on a 4 point scale (0 = none, 1 = mild, 2 = moderate, 3 = severe).

For UTSW ADC cohort patients, we will attempt to use this scale as closely as possible to what was done by the original developers. The major change is that the images will be axial FLAIR images, analyzed as .DICOM files on a computer monitor. These technical advances, not available at the time the Rotterdam Study started, make the work substantially easier and more likely to be accurate, although ineveitably they will lead to results that are different from that originally found by the Dutch investigators. Given that the patient population is substantially different, this failure will not significantly detract from our study goals.

Using Osiris

Osiris is free DICOM reading software, used to view and manipulate medical images as .DICOM files. A manual can be downloaded from: http://www.expasy.org/www/UIN/html1/projects/osiris/osirismanual.html. A .PDF version of the manual is also included in the accompanying CD.

Osiris supports Unix Based, Macintosh, and PCs.

1. Download Osiris from http://www.expasy.org/www/UIN/html1/projects/osiris/DownloadOsiris.html. A ZIPped version of this program is included in the accompanying CD.
2. Once the Osiris folder is downloaded, run SETUP.EXE and follow instructions. This should install the program onto the machine.
3. To open a file in Osiris, double click on the Osiris icon which should appear under program files.
4. A window labeled GET FILE will appear. Indicate in this window the drive that the scans can be found.
5. Then proceed to open the folders until coming to the 00000_ _ _.SER files. In most patients the axial FLAIR sections will be found in 00000301.SER.
6. Once this last file is clicked on, click on PATIENT LIST. A window titled DICOMDIR should open. In this window click on OPEN FILE.
7. Once the scans are loaded onto Osiris, adjust the zoom percentage to 275% in the lower left corner. This makes the caliper tool 1 cm long, and simplifies measurements.
8. Contrast and brightness can be adjusted by clicking the COLOR ADJUSTMENT BUTTON on the left side of the window. Move the curser over the image and move down to make the image lighter and up to darken the image. Click OKAY once the image is appropriate. This is not necessary in most scans.
9. Begin scoring lesions at the first scan on which leukoariosis appears. (Note: On most scans the brainstem and cerebellum will not show signs of leukoariosis, but score them if lesions appear in these areas.)

Scoring Periventricular Lesions

1. Use the line caliper found under TOOLS menu to measure lesions.
2. When measuring periventricular lesions, find the slice that has the largest lesion adjacent to the ventricle and measure the width of the lesion.

Periventricular lesion scale
Pencil thin line ≤ 3mm from ventricle
Smooth Halo > 3 mm but ≤ 10mm from the ventricle
Large confluent >10 mm from ventricle

- Lesions are scored as periventricular if the maximum diameter is adjacent to the ventricle. Otherwise it is scored as subcortical.
- If the lesions are not symmetrical, measure the larger lesion (ex: MDL #86 scan 12/25 occipital horns)
- Use caution when measuring periventricular lesions on higher frames as the higher cuts distort the size of the lesion (ex: MDL #86 scan 17/25 lateral wall of ventricle)

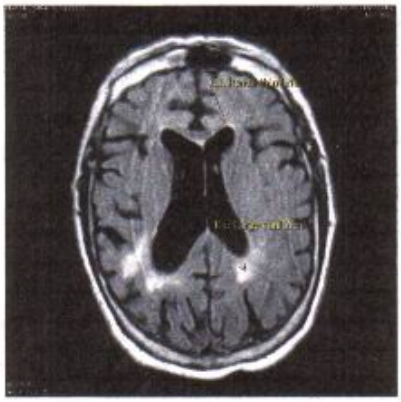

Figure 1 WLD #55 scan 16/25

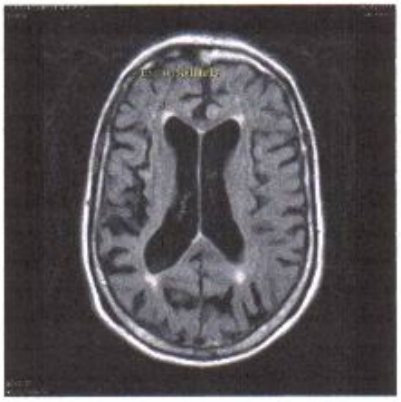

Figure 2RPH #91 scan 14/25

Subcortical White matter lesions

1. Small lesions are scored on each new section.
2. Medium lesions are scored on every other section (allowed to go on for two frames).
3. Large lesions are scored on every third section (allowed to go on for three frames).

- Multipunctate lesions can be counted as a single medium or large lesion if they appear to coalesce. This does not affect the volume calculations.
- The border between gray and white matter naturally appears brighter on FLAIR images than normal brain so be wary of counting lesions along this border.
- Certain gray matter structures appear brighter on FLAIR images (hippocampus, thalamus, striatum). Avoid lesions in gray matter.
- Blood vessels may also appear brighter then normal brain matter, but it will be fainter than actual lesions.
- For any lesions that are elongated, imagine it condensed into a sphere and then estimate a measurement.
- Usually if hyper-intensities are symmetrical, they are not lesions.(ex: RPR #102 scan 6/25)
- Count any lesions that are along the ventricle border only if there is a distinct separation from the ventricle or periventricular lesion.
- Do not count any lesions in the early scans that appear to develop into periventricular lesions in the following scans. (ex: MDL #86 scan 9/25 early periventricular lesion; see also figure 6)

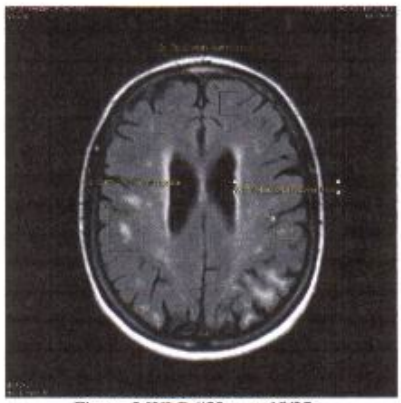

Figure 3 WLD #55 scan 18/25

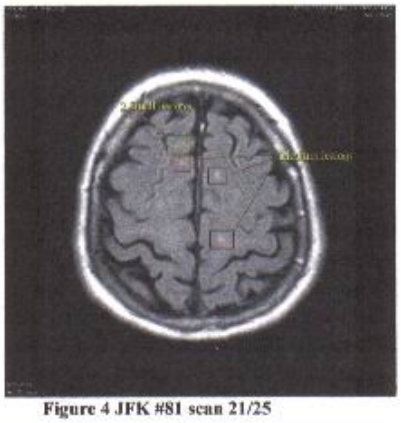

Figure 4 JFK #81 scan 21/25

Ventricle to Brain Ratio measurement

1. Find a frame that shows the caudate most clearly.
2. Use the line caliper to draw a line across the widest distance between the frontal horns.
3. Use the ventricle distance line as a guide to measure the distance across the brain.
4. Also, take similar measurements at the level of the caudate and repeat at the widest distance between the occipital horns.

- If indentions due to imaging artifact appear on either side of the brain at the point you are measuring, estimate where the outline of the brain would be and measure from there

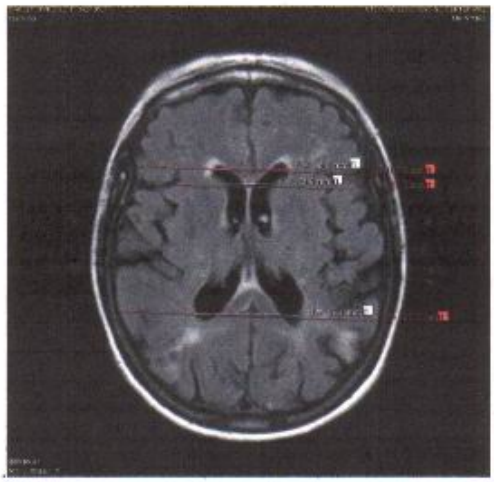

Figure 5 WLD #55 scan 16/25

Qualitative Atrophy measure

Use the following guidelines. Two out of three criteria are enough to score for a particular grade.

a. No Atrophy (score = 0)

Temporal horns are not visible
Sulci are pencil thin
Perisylvian cistern is pencil thin

b. Mild Atrophy (score = 1)

Temporal horns visible in no more than 2 frames
Sulci ≤3 mm
Perisylvian cistern ≤ 3mm wide

c. Moderate Atrophy (score = 2)

Temporal horns are visible in 3 frames
Sulci > 3mm but ≤ 10 mm
Perisylvian cistern > 3 mm ≤ 10

d. Severe Atrophy (score = 3)

Temporal horns are visible in >3 frames and coalesce with occipital horns
Sulci are > 10mm
Perisylvian cistern > 10mm wide

- Assign the grade of the width of the sulci, according to the appearance of the majority
- Total score is a sum of the scores by all three criteria (thus total score will range 0 – 9)

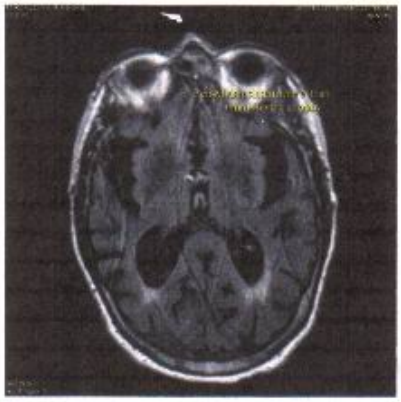

Figure 6 JHF#72 scan 13/25

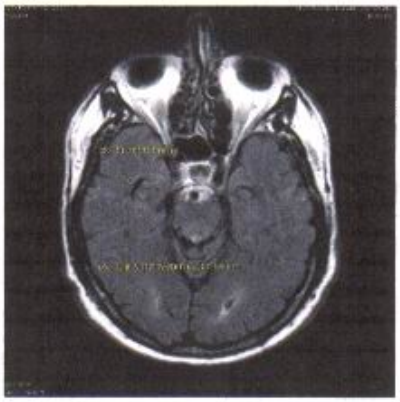

Figure 7 JFK #81 scan 9/25

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