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Understanding the Contributions of Alzheimer's Disease & Cardiovascular Risks to Cerebral Small Vessel Disease Manifest as White Matter Hyperintensities on Magnetic Resonance Imaging (MRI)

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Understanding the Contributions of Alzheimer's Disease & Cardiovascular Risks to Cerebral Small Vessel Disease Manifest as White Matter Hyperintensities on Magnetic Resonance Imaging (MRI)

Dissertation

A dissertation submitted in partial fulfillment of the
requirements for the degree of Doctor of Philosophy in the College of Medicine
at the University of Kentucky

By

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2019

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ABSTRACT OF DISSERTATION

Understanding the Contributions of Alzheimer's Disease & Cardiovascular Risks to Cerebral Small Vessel Disease Manifest as White Matter Hyperintensities on Magnetic Resonance Imaging (MRI)

Introduction: Alzheimer's Diseases (AD) & cerebral small vessel disease associated with cardiovascular risk factors (cSVD) frequently coexist, differentially affecting both imaging and clinical features associated with aging and dementia. We hypothesized that Magnetic Resonance Imaging (MRI) can be used in novel ways to identify relative contributions of AD & cardiovascular risks to cSVD and brain atrophy, generating new biomarkers & insights into mixed disease states associated with cognitive decline and dementia.

Methods: Three experiments were conducted to address the overarching hypothesis. First, we visually rated the clinical MRI of 325 participants from a community-based cross-sectional sample to elucidate the relative association of age, AD (visualized as hippocampal atrophy) and cSVD (visualized as white matter hyperintensities; WMH) with global brain atrophy in experiment 1. In experiment 2, we analyzed cross-sectional MRI scans from 62 participants from the University of Kentucky Alzheimer's Disease Center (UKADC) with available clinical data on cardiovascular risk and cerebrospinal fluid (CSF) beta-amyloid levels as a marker of AD. Voxel wise regression was used to examine the association of white matter hyperintensities with AD and/or cardiovascular risk (hypertension). Experiment 3, examined longitudinal MRI changes in WMH volumes in 377 participants from the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI 2). Subjects were categorized into three groups based on WMH volume change, including those that demonstrated regression (n=96; 25.5%), stability (n=72; 19.1%), and progression (n=209; 55.4%) of WMH volume over time. Differences in brain atrophy measures and cognitive testing among the three group were conducted.

Results: In the first experiment, logistic regression analysis demonstrated that a 1-year increase in age was associated with global brain atrophy (OR = 1.04; $p = .04$), medial temporal lobe atrophy (MTA; a surrogate of AD) (OR = 3.7; $p < .001$), and WMH as surrogate of cSVD (OR = 8.80; $p < .001$). Both MTA and WMH were strongly associated with global brain atrophy in our study population, with WMH showing the strongest relationship after adjusting for age. In the second experiment, linear regression as well as mediation and moderation analyses demonstrated significant main effects of hypertension

(HTN; the strongest risk factor associated with cSVD) and CSF Aβ 1-42 (a surrogate of AD) on WMH volume, but no significant HTN×CSF Aβ 1-42 interaction. Further exploration of the independence of HTN and Aβ using a voxelwise analysis approach, demonstrated unique patterns of WM alteration associated with either hypertension or CSF Aβ 1-42, confirming that both independently contribute to WMH previously classified as cSVD. Extending this work into a longitudinal model rather than focusing on purely cross-sectional associations, we demonstrated that spontaneous WMH regression is common, and that such regression is associated with a reduced rate of global brain atrophy (p = 0.012), and improvement in memory function over time (p = 0.003).
Conclusion: These data demonstrate that both AD and cSVD frequently coexist in the same brain, contributing differentially to alterations in brain structure, subcortical white matter injury, and cognitive function. These effects can be disentangled using MRI, and while we currently lack therapeutic interventions to halt or reverse AD, the dynamic WMH change evident in our data clearly suggests that the ability to reverse cSVD exists today.

KEYWORDS: Cerebral Small Vessel Disease, Alzheimer's Disease, Magnetic Resonance Imaging, White Matter Hyperintensity, Brain Atrophy

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02-18-2019
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DEDICATION

This work is dedicated to all patients who fight Alzheimer's Disease and vascular dementia and for their outstanding families. Also, to those who participate in research to help us finding a cure for these devastating conditions.

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I would like to express my sincere gratitude to my great mentor Dr. Gregory A. Jicha. I am thankful for having the opportunity to work with such a brilliant physician scientist who pave the road to me to start my career as a clinical and translational scientist. His unique approach in mentoring his trainees including myself, together with his generosity in sharing his years of experience as a successful physician scientist has shaped my mind as a future clinical and translational scientist and a critical thinker in the field of vascular and behavioral neurology.

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TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

List of Abbreviations

Aβ …… Amyloid Beta protein

AD …… Alzheimer's disease

AF ……... Atrial Fibrillation

BBB …… Blood Brain Barrier

CDR …… Clinical Dementia Rating

CVD …… Cerebrovascular Disease

cSVD …… Cerebral Small Vessel Disease

DM …… Diabetes Mellitus

FRS ……...…… Framingham Risk Score

HLD ...……. Hyperlipidemia

HTN ……..…… Hypertension

MCI ……. Mild Cognitive Impairment

MMSE …… Mini Mental State Exam

VaD ……. Vascular Dementia

WMH …… White Matter Hyperintensity

WML ……...…. White Matter Lesion

CHAPTER 1. INTRODUCTION

1.1 Introduction

Alzheimer's Disease (AD) and Cerebral Small Vessel Disease (cSVD), are the two major pathologies associated with cognitive decline dementia in the aging population today.[1-4] They are often found to coexist in the same individual.[5, 6]

Recent data from several large-scale, community-based, autopsy cohorts have demonstrated that mixed AD and vascular dementia (VaD) caused by cSVD is the norm rather than the exception, especially as one ages. Trends for mixed pathology increase with advancing age, reaching as high as 90% by the tenth decade of life.[7-10] It remains unclear if the association of AD and VaD is mediated purely by age or if synergistic or additive effects exist between these pathological mechanisms of degeneration allowing each disease process to feed into the other.[9, 11, 12] Despite a high level of current interest in elucidating mechanisms of synergistic interplay between AD and VaD, the field recognizes that "pure" AD and "pure" VaD exist, suggesting that despite potential shared risk factors and mechanisms, neither AD nor VaD are necessary or sufficient to cause the other.

1.2 Definition of Terms:

In this dissertation I am going to discuss several terms including cSVD, white matter hyperintensity (WMH), cerebrovascular risk factors (CVR), AD and VaD.

Understanding the meaning attributed to each of these terms is critical for an in-depth understanding of the work I will present.

cSVD is a term that is being used to define a syndrome of neuropathological, and neuroimaging findings that are thought to be secondary to the effect of uncontrolled CVR

(i.e. hypertension, hyperlipidemia, diabetes, smoking and atrial fibrillation) on perforating cerebral arterioles and capillaries. These arterioles are essential to maintain a healthy brain perfusion in the white matter in particular, which is enriched in small arterioles affected most prominently by cSVD.[13]

cSVD can be visualized using structural magnetic resonance imaging (MRI). Damage to the cerebral white matter that occur secondary to the cSVD can be seen using both T2 and fluid attenuated inversion recovery (FLAIR) sequences on MRI, and appear as areas of hyperintensities referred to as WMH. In addition, cSVD can be seen on T2, FLAIR, and gradient echo sequences of the MRI as lacunar infarcts and cerebral microbleeds that represent overt small vessel stroke and microhemorrhage, often related to cerebral amyloid angiopathy (CAA) seen in conjunction with or independent of AD.[14, 15]

Late-life WMH largely represent cerebrovascular injury resulting from cSVD.[16] In addition, WMH also occur in the pre-dementia stage of familial AD, including in those with no appreciable CVR.[17, 18] It remains unclear whether these imaging findings should be attributed to AD, cSVD, or to a combination of these pathological processes. This question will be fully addressed in chapter 3.

There are five common mechanisms that lead to WMH:

I. **Ischemia**:

A. Chronic ischemia: reduction in cerebral blood flow due to narrowing or obstruction of small arteries and arterioles in subcortical and deep white matter regions results in ischemia especially if those arterioles have only a single source of blood.[19] Chronic ischemia leads to the death of oligodendrocytes contributing

to myelinolysis.[13, 20, 21] This chronic ischemic injury will lead to the formation of incomplete lacunar infarcts.[13] Incomplete lacunae are defined as areas of selective neuronal or axonal necrosis. These lesions spare the vascular tissue and the glial components of the affected areas.[22]

B. Acute ischemia: this will result from acute obstruction of cerebral small arteries and arterioles. Acute ischemia results in the formation of complete lacunar infarcts.[13] Deep white matter lacunes can occur in regions of WMH.

II. **Disruption of Blood-Brain Barriers (BBB)**: The most accepted non-ischemic theory explaining WMH focuses on damage to the BBB. BBB breakdown results in white matter damage caused by the toxic effect of extravasated proteins such as fibrinogen, albumin and IgG and resultant inflammatory changes. Ischemic changes may occur simultaneously with BBB damage, but the relative causality is poorly understood.[13, 20, 21]

III. **Endothelial Damage**: Both ischemia due to hypoperfusion and BBB disruption can lead to the loss of endothelial integrity.[20] Also, toxic effects of homocysteine on endothelial cells may contribute to endothelial damage.[23] As a result of endothelial damage, nitric oxide is reduced, which negatively affects cerebral blood flow through interference with autoregulatory mechanisms of cerebral white matter small vessels.[24-26] Supporting evidence for this mechanism include observed elevated levels of endothelial dysfunction markers such as intercellular adhesion molecule 1 (ICAM1), thrombomodulin (TM), tissue factor (TF) and tissue factor pathway inhibitor (TFPI).[27]

IV. **Amyloid β**: The Aβ deposition and level correlates with the severity of arteriosclerotic disease.[20] Cerebral Amyloid Angiopathy (CAA) is characterized by the accumulation of Aβ protein in the walls of small to medium sized blood vessels and capillaries. In severe CAA, blood vessels' walls may be damaged causing leakage of blood into the surrounding brain tissue.[13] CAA was found to be associated with intracerebral hemorrhage, and subcortical white matter injury, and can be commonly seen in elderly subjects with Alzheimer's disease, Down's syndrome and cSVD.[28, 29]

V. **Genetics**: Many genetic risk factors may play a role in cSVD such as cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL).[21] Many other hereditary diseases lead to cerebral small vessel disease, including cerebral autosomal recessive arteriopathy with subcortical infarct and leukoencephalopathy (CARASIL), Fabry's disease, hereditary extensive vascular leukoencephalopathy (HEVL), and mitochondrial encephalopathy with lactic acidosis and stroke-like episodes (MELAS).[13] Furthermore, ABCC9 Hippocampal Sclerosis-Aging risk genotype has been found to be associated with a reduction in the cerebral blood flow.[30] Finally, APOE ε4 was found to have a role in the microvascular changes of the brain that ultimately lead to arteriolosclerosis.[31] There is a strong association between the APO E ε4 genotype and atherosclerosis in addition to cerebral blood vessel structural changes such as amyloid angiopathy (due to increased Aβ deposition). The latter is found to be associated with increased risk of white matter injury. The ultimate associated

effect of APO E ε4 is decreased cerebral blood flow which results in ischemic damage to vulnerable areas and cognitive decline.[32]

It is important to note that WMH can be seen in several other neurological diseases such as multiple sclerosis,[33] posterior reversible encephalopathy syndrome,[34] dysmyelinating diseases such as metachromatic leaukodystrophy,[35] and epilepsy,[36] as well as in a variety of other infectious, inflammatory or neoplastic disease states. However, such diseases are rare in the aging population in contrast to AD and cSVD which are quite common. As such, WMH resulting from both AD and cSVD are the focus of our dissertation.[17, 37]

AD is a widely used abbreviation for Alzheimer's disease, which is a clinical syndrome of progressive cognitive impairment and functional decline over a period of 8-10 years.[38, 39] In this dissertation, "AD pathology" will be defined using different imaging and cerebrospinal fluid (CSF) markers. Medial temporal lobe atrophy (MTA) is one of the most commonly used surrogate imaging markers for AD that can be visualized best on coronal T1-weightedMRI images.[40] Recently, young patients with familial AD were found to have more WMH on the posterior part of the brain, which may prove useful as an additional imaging marker for AD.[17, 18] In addition, CSF amyloid beta (Aβ) levels and Aβ-PET imaging can be also used as biomarkers for AD.[41]

Finally, it is important to explain the stages or progression of cognitive decline for both AD and VaD in their "pure forms", while recognizing that conclusions arising from the existing literature may in many cases be derived from "mixed" rather than "pure" pathologic disease states.

VaD refers to an impairment of memory resulting in functional decline secondary to cerebrovascular disease including cSVD.[42, 43] Clinical VaD can be divided into three stages: 1) the preclinical stage has been described by Hachinski V.C. et al.,[44] as the stage wherebrain damage occurs but without significantcognitive impairment, 2) the mild cognitive impairment stage (MCI) is characterized by cognitive impairment with intact Activities of Daily Living (ADL), 3) A Major Neurocognitive Impairment stage (defined in the DSM-V), also recognized as the stage of dementia with decline in ADL.[45]

It is widely recognized that at the stage of advanced dementia, the brain has suffered significant irreversible injury. As such, the field has moved towards earlier detection of disease. Targeting, diagnosis and secondary prevention in the preclinical and MCI stages is reasonably believed to be the best way to impact the disease process. In addition, focusing on these early predementia stages of VaD allows planning for future needs for both the patient and potential caregiver.[46] As such the focus of this dissertation and the patient population studied largely focus on the preclinical and MCI stages of VaD.

Preclinical VaD is a term used to describe a state of normal cognition characterized by early pathological changes of the cardiovascular system that are likely to lead to future cSVD and clinical cognitive decline if allowed to continue to progress.[47]

The Framingham Risk Score (FRS) is used as a primary risk assessment tool for cerebrovascular disease in asymptomatic healthy persons, as well as risk for cognitive decline in those that are already symptomatic. Traditional CVR included in the FRS are patient age, history of smoking and HTN, total serum cholesterol and high density lipoprotein (HDL). Ten-year risk scores are expressed as a percentage stroke risk. A

percentage between 0-10% is considered low risk, moderate risk falls between 11-20%, and a high risk occurs when the ten-year risk is greater than 20%.[48]

MCI was developed as a concept to identify individuals at risk for the future development of dementia. While initially developed as a construct to identify prodromal Alzheimer's disease dementia, the concept was broadened in 2004 to include categorization based on cognitive domain involvement in order to predict the underlying pathologic event responsible for the cognitive decline which may include pathologic disease states disparate from Alzheimer's alone, such as VaD.[49] These criteria are as follows:

I. Global cognition should be preserved;

II. A cognitive deficit that is reported by self or caregiver with an evidence of such complaint; (typically set at > 1.5 s.d. below age and education adjusted means)

III. Not demented by DSM-IV criteria;

IV. No, or minimal functional impairment.

This schema includes diagnosis of MCI into four major subtypes based on presence vs. absence of memory involvement and further on the presence of involvement of a single vs. multiple cognitive domains as described below in Figure 1.1.

The schema in Figure 1.1 has been developed to allow clinical determination of the potential causes for the cognitive impairment noted. Practical application of the schema for predicting underlying cause of cognitive decline is illustrated in Figure 1.2. It should be noted that this diagnostic schema has not been fully validated and ongoing work is needed to fully delineate the specific features of MCI due to specific underlying or mixed

Figure 1.1 Diagnosis of Mild Cognitive Impairment.

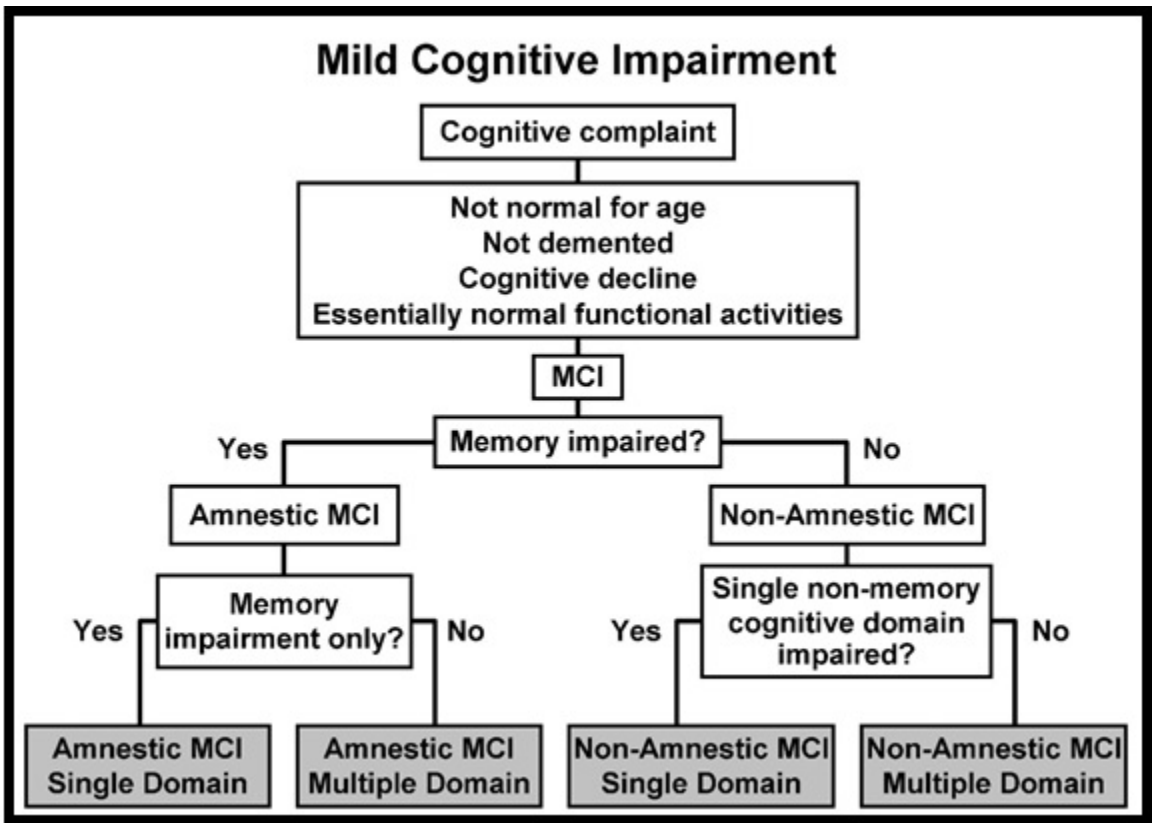
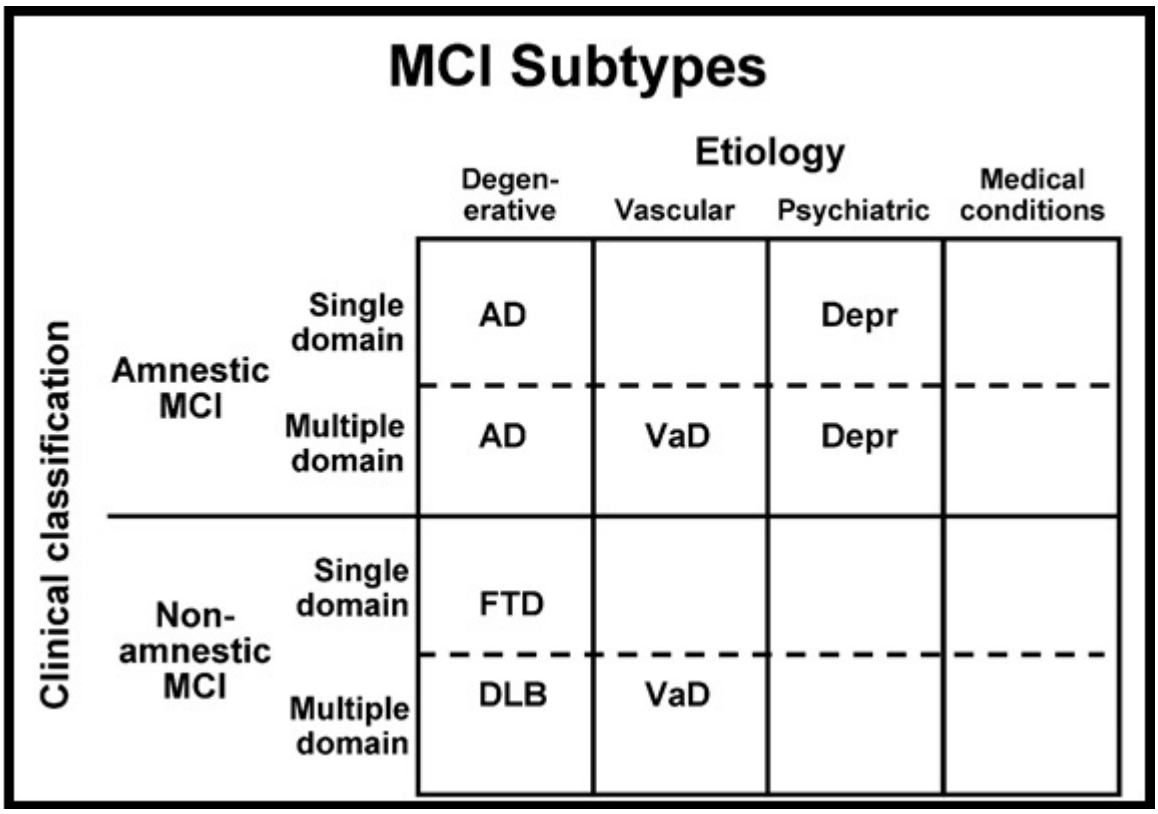


Figure 1.2 Mild Cognitive Impairment subtypes.



pathologies. This is a practical working clinical and conceptual classification at the present time.

1.3 The Role of Imaging in the Diagnosis of AD & cSVD:

Much work has gone into describing the unique cognitive sequelae associated with both prototypical AD and VaD secondary to cSVD (Table 1.1). Descriptions however are often contradictory or overlapping given the extent of shared pathology in each of these disease states. Prototypical early changes in AD include deficits in episodic memory followed by later decline in language, executive, and visuospatial function.[50]

Descriptions of prototypical changes in VaD have been more complex as a result of the pathologic and neuroanatomic heterogeneity inherent in this disease state. Cognitive

Table 1.1 Specific cognitive domain involvement associated with aging and/or cerebrovascular risk factors across cohort studies.

Study	CVD risk factor studied	Design	Affected cognitive domain
Type 2 diabetes mellitus, hypertension, dyslipidemia and obesity [51].	Type-2 DM, HTN, HLD and Obesity	Systematic Review	memory, processing speed and cognitive flexibility
The cognitive correlates of white matter abnormalities in normal aging [52]	Aging	Quantitative review	Executive functions (explained by reduced volume of prefrontal cortex), processing speed and working memory.
The Aging Brain [53]	Aging	Review	Delay recall of verbal memory
Cognitive impairment in heart failure [54]	Heart Failure	Systematic review	Memory, processing speed and attention
Cognitive outcomes after acute coronary syndrome [55]	Myocardial infarction	Prospective population based cohort study	Mostly memory and language. Executive function was affected to a lesser extent
Atrial Fibrillation Is an Independent Determinant of Low Cognitive Function [56]	Atrial Fibrillation	Cross-Sectional study	Memory, processing speed and possibly executive function
Homocysteine and the brain in midadult life: Evidence for an increased risk of leukoaraiosis in men [57]	Homocysteine	Cross-Sectional study	Verbal memory

domain involvement can vary due to the primary vascular insult contributing to VaD, such as multi-infarct dementia, isolated strategic infarcts, and cSVD. Of these varied causes, the latter may have a more uniform pattern of cognitive impairment given the more uniform distribution of vascular lesions between cases that conform largely to end arterial watershed zones in the subcortical white matter. In VaD related to cSVD, a decline in executive function may be the earliest clinical sign of disease although memory can frequently be affected again creating confusion in distinguishing AD from VaD or mixed dementia on the basis of clinical presentation alone.[50]

In general, many believe that VaD patients tend to have relatively preserved verbal long term memory in the setting of markedly impaired executive function compared to the reverse seen for AD patients in the early stages of disease.[58] We do note however that as the disease progresses to the moderate to severe stages a distinction based on clinical presentation becomes less clear.[59]

Given the difficulty in distinguishing AD from cSVD or mixed dementia clinically, the field has largely relied on imaging evidence for either AD or cSVD changes to diagnose specific or mixed disease states. Advances in neuroimaging techniques that can guide the diagnosis of dementia has revolutionized the field. Such techniques include structural, functional, and molecular neuroimaging.

Structural neuroimaging, such as routine MRI and CT-scan, can delineate anatomical structure of the brain due to the high spatial resolution of these biomarkers, allowing and evaluation of specific tissue injury as well as patterns of cerebral atrophy that are specific for distinct disease states. Functional neuroimaging including Fluoro-Deoxyglucose Positron Emission Tomography (FDG-PET), functional MRI (fMRI) and

Single Positron Emission Computed Tomography (SPECT), can delineate metabolic activity in specific brain regions that are affected in distinct disease states.[60, 61] Molecular imaging techniques such as Amyloid-PET, tau-PET, DaTscan (Dopamine Transporter (DAT) used with SPECT), and many other techniques and development can actually visualize the cellular, molecular, and pathologic changes that are distinct between subtypes of dementia. The following section focuses on these imaging advances and their role in accurately diagnosing and tracking disease progression in AD, VaD, and mixed dementia. An overview of currently used imaging modalities and specific findings in AD and VaD is presented in Table 1.2.

The current American Academy of Neurology practice parameter on the diagnosis of dementia requires the use of structural neuroimaging to evaluate non-neurodegenerative contributors to dementia such as vascular injury, intrinsic brain abnormalities, neoplasm, normal pressure hydrocephalus, brain contusions and other structural lesions that may be causative of cognitive decline and dementia.[62] The practice parameter does not specifically recommend one type of structural neuroimaging over another and yet each vary in practical application and extent of data derived in order to facilitate identification of underlying pathologic mechanisms responsible for any clinical cognitive decline seen in AD. The most recent iteration of diagnostic criteria for AD, includes structural imaging as a supportive biomarker that can demonstrate disease state specific neuronal injury, and molecular imaging techniques such as amyloid-PET, as ancillary criteria for the diagnosis of AD irrespective of the presence of comorbid CVD.[63]

CT-scans are primarily used to exclude other pathologies such as tumors and strokes. In addition, measuring hippocampal atrophy is also possible using CT-scans by

Table 1.2 Neuroimaging biomarker modalities and protocols that are commonly used for the diagnosis and tracking of Alzheimer's and cerebrovascular disease.

Technique	Protocol		Pathology studied	Characteristics
MRI	MPRAGE		Size and shape of brain regions, tumors, atrophy	Demonstrates specific structural abnormalities
	FLAIR		WMH, hemorrage, CSF	Demonstrates evidence for vascular injury
	ASL		Blood perfusion	Identifies reduced perfusion in both AD & cSVD
	BOLD (fMRI)		Oxygen concentration	Identifies coactivated brain regions establishing functional connectivity
	DTI	FA	Longitudinal water molecule movement inside the fibers	Identifies disruted Myelination of fiber tracts
		DM	average of water diffusion in all directions	
		ADC	The axial diffusion of water	
PET	^{11}C-PiB-PET		Presence of cerebral Aβ	Ligand binds Aβ, ^{11}C isotope requires cyclotron near facility, limiting broad use of this agent
	^{18}F-amyloid tracers		Presence of cerebral Aβ	Ligand binds Aβ, ^{18}F isotope stability allows more widespread use of this agent
	^{18}F-FDG		Glucose metabolism	Ligand is substrate for TCA cycle glucose utilization
SPECT	^{99m}Tc-ECD		Blood perfusion	Identifies reduced perfusion in both AD & cSVD

specialists, however these techniques are inferior to the analysis afforded by MRI given its ability to visualize the brain in multiple planes that are devoid of bony artifact.[64] CT-scans can also identify overt areas of ischemic injury and provide evidence for subcortical small vessel disease that could be responsible for cSVD or mixed disease.

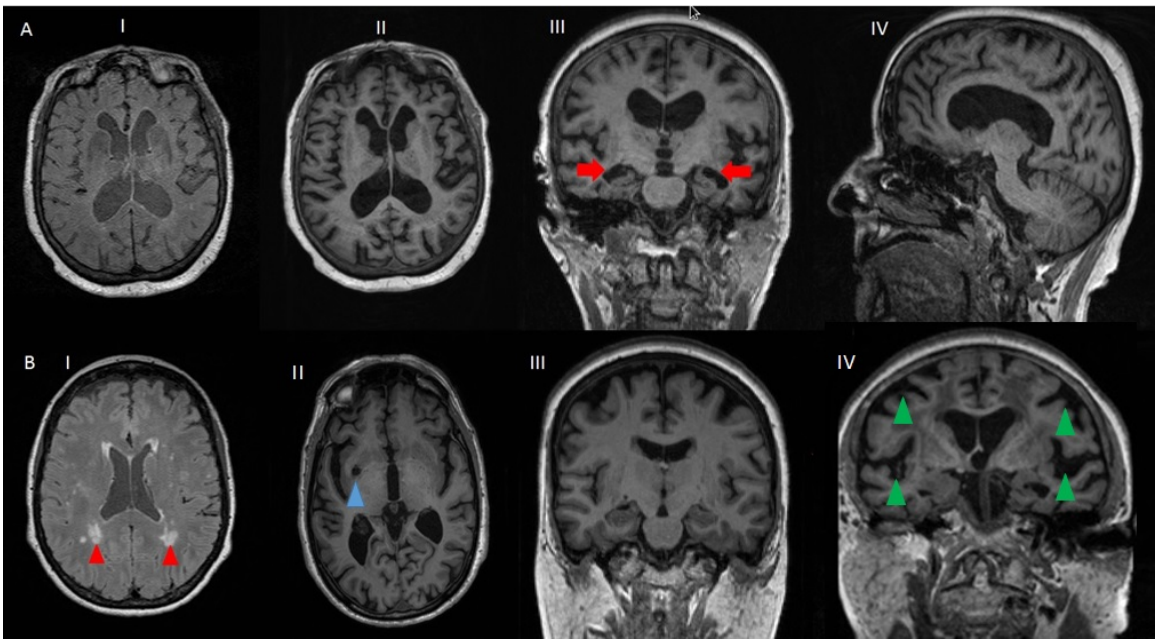
Brain MRI is being used in most centers to guide the diagnosis of AD, with the exception of use in patients with implanted or injury associated ferrous metal that would preclude the use of a high field magnet.[65] MRI is essentially contraindicated in any patient with an implanted metallic device such as pacemaker, brain or spinal cord stimulator, or implanted infusion pump. In addition, while the availability of MRI scanners has increased dramatically over the last several decades there are still many smaller and rural medical centers that do not have access to MRI for routine diagnostic purposes.

Brain MRI is the most widely used tool for the diagnosis of cSVD as recommended by the STandard for ReportIng Vascular changes on nEuroimaging (STRIVE).[15] cSVD is to some extent ubiquitous in VaD, irrespective of overt large vessel ischemic or hemorrhagic stroke and is characterized by imaging findings including increased T2 signal abnormalities in the subcortical white matter (WMH), lacunar infarcts, small subcortical infarcts, and cerebral microbleeds). There is a general consensus that such T2 signal abnormalities affecting more than 25% of the white matter are indicative of cSVD.[66] Figure 1.3 illustrates MRI characteristics that can discriminate between AD and cSVD.

T1-weighted Magnetization Prepared Rapid Acquisition Gradient Echo (MPRAGE) imaging sequence has high special resolution, affording 3-dimensional reconstructions of the brain that can be visualized in any plane, that can evaluate changes in cortical sulci and atrophy in hippocampus, parahippocampal gyrus, entorhinal cortex,

Figure 1.3 Descriptive structural imaging findings in Alzheimer's (AD) and vascular (VaD) or mixed dementia.

Panel A demonstrates typical medial temporal lobe atrophy seen in AD (red arrows). Panel B illustrates typical white matter hyperintensities (red arrow head), lacunar infarcts (blue arrow head), and cerebral atrophy (green arrow head) associated with VaD or mixed dementia. Note: global cerebral atrophy may be seen in both AD and VaD and does not distinguish these disease states.



posterior cortex, subcortical nuclei and amygdala, which are affected earliest in the course of disease for AD patients.[67, 68] T1-weighted sequences in particular, can aid the clinician and researcher in estimating Medial Temporal lobe Atrophy (MTA) as an early neuroimaging marker of AD.[69] Semi-quantitative visual rating scale such as the Scheltens' scale, can be easily taught and assessed with routine clinical imaging in either two-dimensional or 3-dimensional sequences.[70] Evaluation of medial temporal lobe atrophy is best performed in the coronal plane which allows more accurate visualization of

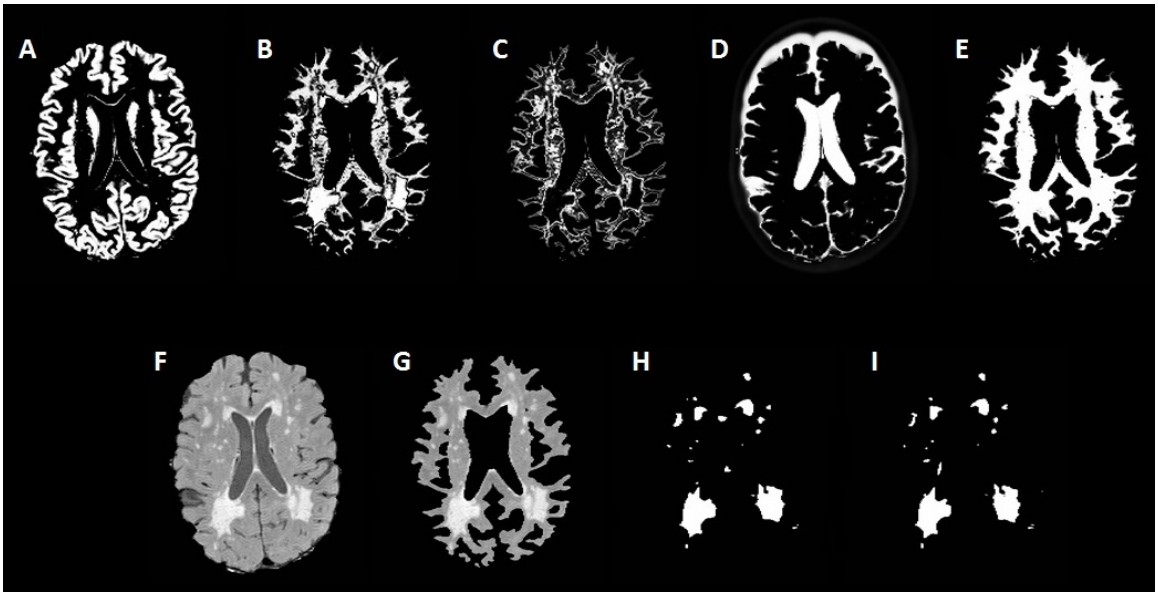
medial temporal lobe volumes that are not affected by tangential slicing of these structures as can occur with axial and/or sagittal acquisitions. In addition, there are a number of automated and semi-automated post acquisition processing software programs that can provide voxel by voxel volumes allowing quantitative assessment of these and other discrete structures within the brain. Several of these software programs, such as *FreeSurfer*, are open access and represent the state-of-the-art tools for researchers in the field. Such automated segmentation software can provide accurate volumetric measurements that can be used to estimate diagnostic probabilities for the presence of AD pathology in the antemortem state.

T2-weighted imaging is highly sensitive to tissue water content changes that are a marker for ischemic cerebrovascular disease injury. FLAIR imaging sequences null the signal derived from pure fluid compartments such as the ventricular system, allowing accurate evaluation of periventricular and cortical surface hyperintensities that would not be seen in routine T2 imaging sequences.[71, 72] These developments have dramatically improved our ability to assess contributions of vascular injury in relation to the clinical presentation of each unique patient imaged. There are many sophisticated methods to quantify the volume of WMH using FLAIR sequence of the brain MRI (Figure 1.4). However, simple visual rating such as Fazekas' scale [14] can be used by clinicians and researchers to estimate the WMH burden and guide the diagnosis of cSVD in routine clinical practice.

Diffusion Tensor Imaging (DTI) sequence can evaluate the integrity of axonal pathways forming large fiber tracts that connect often remote brain structures and regions.

Figure 1.4 Sophisticated WMH volume quantification.

Upper row: *Segmentation steps* to classify brain grey matter (GM), white matter (WM), and CSF. A. GM segment, B. first WM segment, C. second WM segment, D. CSF segment, E. total WM (C2+C3). Lower row: *Extraction of white matter (WM) hyperintensities for quantitation*. F. FLAIR image, G. extracted FLAIR WM image, H. result of thresholding FLAIR WM image (F), I. Gaussian smoothed extracted WM hyperintensities. WM hyperintensity volume is volume sum of voxels in I.

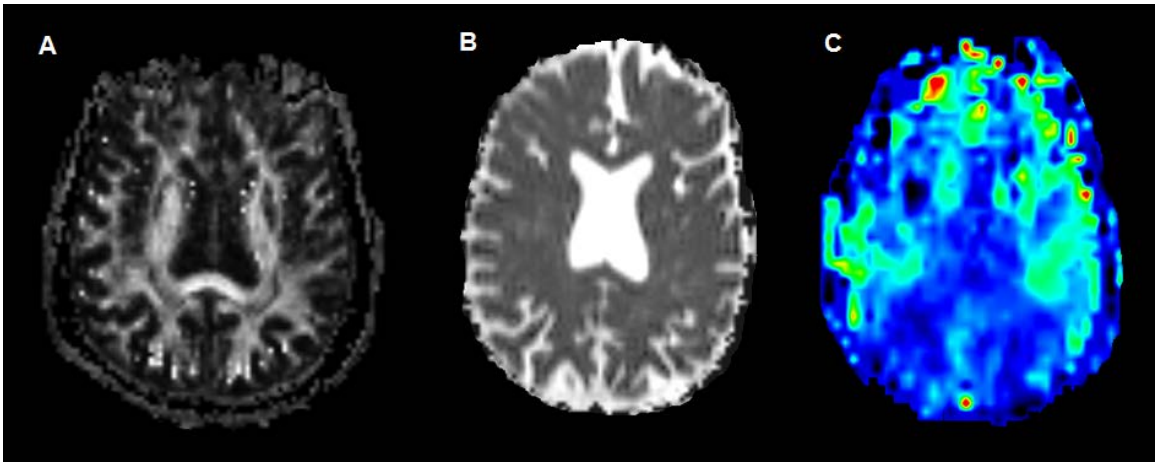


DTI can detect the microstructural changes in AD in the early stage before these changes appear anatomically.[73, 74] DTI parameters that are typically measured include Fractional Anisotropy (FA), Axial Diffusion Coefficient (ADC) and Mean Diffusivity (MD) (Figure 1.5 A and B). These parameters are based on our understanding of water movement in relation to myelinated parallel fiber pathways. Typically, water molecules move (diffuse) more rapidly in the fiber tracts longitudinally parallel to the axonal wall compared to more

slowly diffusing water molecules perpendicular to the wall. FA tracks the water molecule movement inside and parallel to the fibers.[75]

Figure 1.5 A representative brain MRI of 80 years old female showing DTI and ASL.

A. DTI-FA (highest FA is brightest), B. DTI-MD and C. PASL-Perfusion images (pseudo color, blue lowest and red highest perfusion).



For AD patients FA decreases throughout many pathways in the superior-inferior part of the brain.[76, 77] MD reflects the average of molecule diffusion in all directions per voxel depending on the membrane or barrier permeability of the axon and is elevated in AD patients. ADC demonstrates the diffusion of molecules in the axial direction of the fiber.[78] ADC reductions are associated with axonal damage and increases in AD subjects.[79] These changes appear quite distinct in both neuroanatomic specificity as well as extent in AD vs. cSVD subjects. Compared to the WMH quantification, DTI measures are less vulnerable to error attributed to using one's judgment and manual editing when using automated and semi-automated quantitative methods.[80] Haller et al. reported that DTI and more specifically the MD measures represent the most accurate imaging

biomarker for cSVD, even in the presence of AD.[80] Similarly, another study found that DTI measures were effective in distinguishing between early stage AD and cSVD.[81] It remains uncertain if overlap in DTI measures between AD and cSVD can reliably detect mixed disease states.

MRI can also be quite useful in detecting Cerebral Microbleeds (CMB), which are frequently related to the presence of cerebral amyloid angiopathy. CMBs can be visualized using MRI T-2 echo gradient, and are visualized as small hypointensities range in size from 2-10 mm. CMB can be seen in up to two thirds of AD and cSVD patients and so may be less useful in distinguishing between AD, cSVD, and mixed dementia than other modalities.[66, 82] In extreme cases however brain injury secondary to cerebral amyloid angiopathy and widespread CMBs can be a major contributor to cognitive decline that can involve both AD as well as cerebrovascular tissue injury.

Amyloid Positron Emission Tomography (Amyloid-PET) is the only imaging technique that can visualize amyloid deposition in the living brain. Multiple amyloid-PET tracers have been developed for research purposes and have eventually garnered FDA approval including Pittsburg Compound B (PiB), Florbetapir, Florbetaben, and Flumetamol. The former made the availability of the amyloid PET difficult due to its C-11 component's short half-life. This issue was resolved using other longer half-life compounds such as 18F (for example Florbetapir, Florbetaben, and Flumetamol), which made amyloid-PET widely available.[66]

Amyloid PET scans are approved by the FDA for the detection of cerebral amyloid deposition and are not specific to any individual disease state. They can be useful in differentiating dementia such as AD from other forms of dementia that do not include

amyloid deposition asa pathologic feature such as Frontotemporal Dementia (FTD).[83, 84] The specificity of amyloid PET scans for Alzheimer's disease is low and positive scans are also frequently seen in cases of Dementia with Lewy Bodies (DLB).[85, 86] Similarly, cases with mixed dementia were found to have a positive amyloid PET scan although this is related to the comorbid Alzheimer pathology rather than direct visualization of vascular amyloid.[87] While the PET ligands do bind vascular amyloid, this is found in much lower abundance in the brain than plaque associated amyloid and it is unclear how the presence or absence of cerebral amyloid angiopathy may influence the PET scan results. It should also be noted that amyloid PET scans are positive in about 20-30% of people with normal cognition,[88] and are used to detect the pre-clinical stage of AD.[89] This has opened up new possibilities for secondary prevention trials in the area of AD.

Functional MRI (fMRI) can detect oxygen consumption in specific brain regions during rest and activity dependent stimulation by measuring the ratio of oxy- to deoxy-hemoglobin. Blood-Oxygen-Level Dependent contrast imaging (BOLD) can demonstrate abnormalities in the hippocampus, inferior parietal lobe, medial temporal lobe and cingulate cortex in AD that may provide clues to a pure and/or mixed state.[90, 91] Work investigating BOLD signal changes in subjects with cerebrovascular disease can produce heterogeneous results again secondary to the heterogeneity of pathologic cause and neuro anatomic involvement seen in cSVD.

Metabolic activity in the brain can also be visualized using Fluoro-Deoxyglucose Positron Emission Tomography (FDG-PET). Radiolabeled glucoses up taken in metabolically active tissues (mainly synapses in the brain), leading to increased signal in such regions. In AD patients, FDG-PET typically shows a decrease in glucose metabolism

localized to the superior and posterior temporal lobe in addition to the parietal lobe with the medial portion of it being affected earlier in AD.[89, 92] FDG-PET results can be variable again in cSVD, and lack specificity for this disease entity.

Single-photon emission computed tomography (SPECT) is sensitive to blood perfusion (hypoperfusion) and chemical changes in the brain [93] and it could prognosticate the change of MCI to AD early. [73] ^{99m}Tc-ethylcysteinate dimer (^{99m}Tc-ECD) is commonly used with SPECT for cerebral blood perfusion imaging.[94] Patients with early stages of AD usually have hypoperfusion or hypometabolism in the posterior cingulate and precuneus,[66, 95] which then extended to the temporoparietal region bilaterally that could be either symmetrical or asymmetrical. In general, SPECT is less sensitive but more specific than FDG-PET for AD changes.[96, 97] While changes in cerebral blood flow can be greatly influenced by cerebrovascular disease, specific patterns of SPECT abnormalities cannot be predicted in subjects with cSVD.

Arterial Spin Labeling (ASL) is a noninvasive MRI sequence that allows evaluation of tissue perfusion using magnetized protons within water molecules in the brain circulatory system (Figure 1.5 C). AD patients' ASL showed areas of hypoperfusion as bilateral temporoparietal lobe similar to that seen in FDG-PET and SPECT. More specifically inferior parietal, bilateral posterior cingulate and middle frontal gyrus showed reduced perfusion in AD patients.[98, 99] ASL can be used to quantify the reduction of cerebral blood perfusion in brain regions affected by microvascular disease.[100] ASL consistently demonstrates a decrease in CBF in brain regions that have been affected by microvascular change, apparent as increased T2 signal hyperintensities on FLAIR imaging sequences. in contrast to AD, cSVD is associated with decreased perfusion and metabolism

of the sensorimotor cortex and subcortical white matter with preservation of the association cortices.[66]

Each neuroimaging technique can contribute information in unique ways that can be used to support the clinical diagnoses of AD, VaD, or other forms of dementia not addressed in this thesis (see Table 1.1). Combining more than one technique may provide more details about the future progression or prediction of the underlying disease state than can be afforded through the use of a single imaging modality or fluid biomarker alone. For instance, CSF results combined with other imaging techniques such as MRI, PET, SPECT can provide a combination of structural, functional, and molecular information, which can greatly enhance the specificity of clinical diagnoses and can be useful for differentiating AD from other causes of dementia such as cSVD.[68, 73, 101]

1.4 CSF biomarkers of AD and cSVD

One of the most widely used biomarkers to diagnose AD is CSF, in which reduced levels of Aβ have been found to be strongly associated with the accumulation of parenchymal amyloid plaques. CSF Aβ levels have been found to be low even at the pre AD stage of disease. However, absolute change in CSF Aβ levels are not correlated with the rate of change in cognitive decline and/or the progression of dementia but instead appear to represent a static state once the disease process is initiated.[102-104]

CSF can also be used to examine elevated levels of tau, total tau protein levels and/or specific phosphorylated protein levels, which have a 79% specificity of identifying subjects with AD. Combining CSF Aβ1-42 and tau levels increases the specificity for identification of AD subjects to approximately 86%, and has proven to be

the measurement of choice for diagnostic accuracy in determining an underlying pathologic disease state of AD.[104]

There is still no consensus on whether specific CSF biomarkers may help identify cSVD in either clinical or preclinical disease states.[105] Some studies showed have demonstrated elevations in neurofilament light chain proteins, which presumably reflect the extent of axonal damage secondary to cSVD.[105, 106] Other studies have shown that cSVD subjects may have an elevated albumin CSF/serum ratio due to disruption of the BBB.[105, 107] Both neurofilament light chain protein and the elevated albumin ratio represent nonspecific, although potentially highly sensitive markers of cSVD, even in normal control subjects.[108]

1.5 Hypotheses and Specific Aims:

Three experiments were developed as the core of this dissertation to address these hypotheses:

1. Hypothesis 1: cSVD visualized as WMH on FLAIR imaging are related to global cortical atrophy (GCA). (Increased WMH-> increased atrophy)

   Specific Aim 1: Examine the relationship of cSVD, visualized as WMH on FLAIR imaging, with GCA.

2. Hypothesis 2: AD is related to WMH seen on FLAIR imaging

   Specific Aim 2: Investigate the association of the CSF Aβ (a surrogate of AD) with WMH seen on FLAIR imaging. Further determine if the WMH associated with AD vs. cSVD represent independent or dependent (additive or synergistic) processes.

3. Hypothesis 3: WMH are subject to dynamic change that may be related to modulation by CVR and or to progressive AD changes.

   Specific Aim 3: Determine the extent of dynamic WMH change overtime and examine the association of WMH progression or regression with CSF Aβ (surrogate for AD), and specific CVR.

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CHAPTER 2. BRAIN ATROPHY DETECTED BY ROUTINE IMAGING: RELATIONSHIP WITH AGE, HIPPOCAMPAL ATROPHY, AND WHITE MATTER HYPERINTENSITIES

Summary:

Background and Purpose: Interpreting the clinical significance of moderate to severe global cortical atrophy (GCA) is a conundrum for many clinicians, who visually interpret brain imaging studies in routine clinical practice. In the absence of clinical signs of specific neurological conditions, GCA may be attributed to normal aging, Alzheimer's disease (AD), or cerebral small vessel disease (cSVD). Understanding the relationships of GCA with aging, AD, and cSVD is important for accurate diagnosis and treatment decisions for cognitive complaints.

Methods: To elucidate the relative associations of age, white matter hyperintensities (WMH), and medial temporal lobe atrophy (MTA), with GCA, we visually rated clinical brain imaging studies of 325 participants from a community based sample. Logistic regression analysis was conducted to assess the relations of moderate-to-severe GCA with age, WMH, and MTA.

Results: The mean age was 76.2 (± 9.6) years, 40.6% were male, and the mean educational attainment was 15.1 (± 3.7) years. Logistic regression results demonstrated that while a 1-year increase in age was associated with GCA (OR=1.04; p=0.04), the effects of moderate-to-severe MTA (OR=3.38; p<0.001) and moderate-to-severe WMH (OR=9.79; p<0.001) showed much stronger associations with moderate-to-severe GCA in our study population.

Conclusions: Moderate-to-severe GCA should not be solely attributed to age when evaluating clinical imaging findings in the workup of cognitive complaints. Moderate to severe GCA is likely occur in the presence of AD or cSVD. Developing optimal diagnostic

and treatment strategies for cognitive decline in the setting of moderate to severe GCA requires an understanding of the contributors to moderate-to-severe GCA in the aging population.

2.1 Introduction:

Interpreting the diagnostic significance of moderate to severe global cerebral atrophy (GCA) is a conundrum for many clinicians, who visually interpret structural brain magnetic resonance imaging (MRI) in routine clinical practice. Many clinicians attribute GCA to the normal aging process.[109] Others may invoke degenerative processes such as Alzheimer's disease (AD), and yet others may relate these changes to cerebrovascular insults and disease (CVD).[110, 111] Understanding the relationship of GCA with aging, AD, and CVD would help inform accurate diagnosis and selection of appropriate interventions to maintain brain volume, cognition, and function.

Irrespective of the cause of GCA, strong associations across multiple studies argue that it is a reliable marker of cognitive and functional impairment seen in the aging population.[112, 113] GCA can be readily identified using conventional imaging techniques, such as MRI and computed tomography (CT) scans, and so is evaluated by examining clinicians in virtually every case presenting with cognitive impairment.[114] GCA can be reliably scaled on a semi-quantitative basis using standardized protocols [115] and further quantified using volumetric analysis techniques. In routine clinical practice, however, it is uncommon to use sophisticated volumetric techniques and instead qualitative assessment prevails. Similarly, vascular changes—such as white matter hyperintensities (WMH)[14, 116]—and medial temporal lobe atrophy (MTA) can be graded semi-quantitatively using visual rating scales.[40] These features may also be analyzed using

more sophisticated quantitative volumetric measures, which again are not commonly relied on by clinicians for making diagnostic or therapeutic decisions in routine clinical practice.

Potential contributors to GCA include age,[117] WMH associated with CVD,[110] and AD.[111] Many studies have shown that the severity of GCA is associated with increased age.[109, 117-121] Resnick et al. showed no detectable GCA over one year, but reported 1.5 cubic centimeter increase in ventricular volume over the same period longitudinal data analyses.[122] A subsequent analysis of two and four year follow-up data from the cohort later revealed a significant association between GCA and age.[114] In summary, although the literature is ambiguous, the hypothesis that GCA is associated with age per se has become strongly fortified for many practicing clinicians and radiologists

MTA can be associated with both AD and to a lesser extent with normal aging.[119, 123] A recent report from Alzheimer's Disease Neuroimaging Initiative (ADNI) showed that absolute MTA two years after the baseline MRI scan ranges from a 1-7% loss of medial temporal lobe volume in addition to a 10% increase in ventricular size.[124] While ventricular changes may be readily discernable to the naked eye, MTA at a rate of only 1-7% per / year is difficult to detect in routine qualitative clinical evaluation of patient scans.

GCA has also been shown to be associated with CVD, and both share many common risk factors.[110] Prior studies examining healthy participants found that subcortical T2 signal changes in the white matter (i.e. WMH) were strongly associated with GCA.[125-129] These studies suggested that the magnitude of the association between WMH and GCA in cognitively intact subjects may be double that associated with aging in the absence of WMH.[112] However, these findings have been disputed in several other studies that reported no association between GCA and WMH.[130, 131]

In order to further elucidate the relative associations of age, WMH (as a surrogate for CVD), and MTA (as a surrogate for AD), with GCA, we examined MRI and CT with semi-quantitative metrics of each from 325 participants in a community-based longitudinal study of aging and cognition. Participants in the current study span the cognitive continuum.

2.2 Methods:

2.1.1 Subjects:

Both MRI and CT scans were acquired during routine clinical evaluation of study participants in the University of Kentucky Alzheimer Disease Center Cohort (n=325). 65% of scans were MRI. Details of the recruitment and longitudinal evaluation of these participants have been published previously.[132] This study was approved by the University of Kentucky Institutional Review Board.

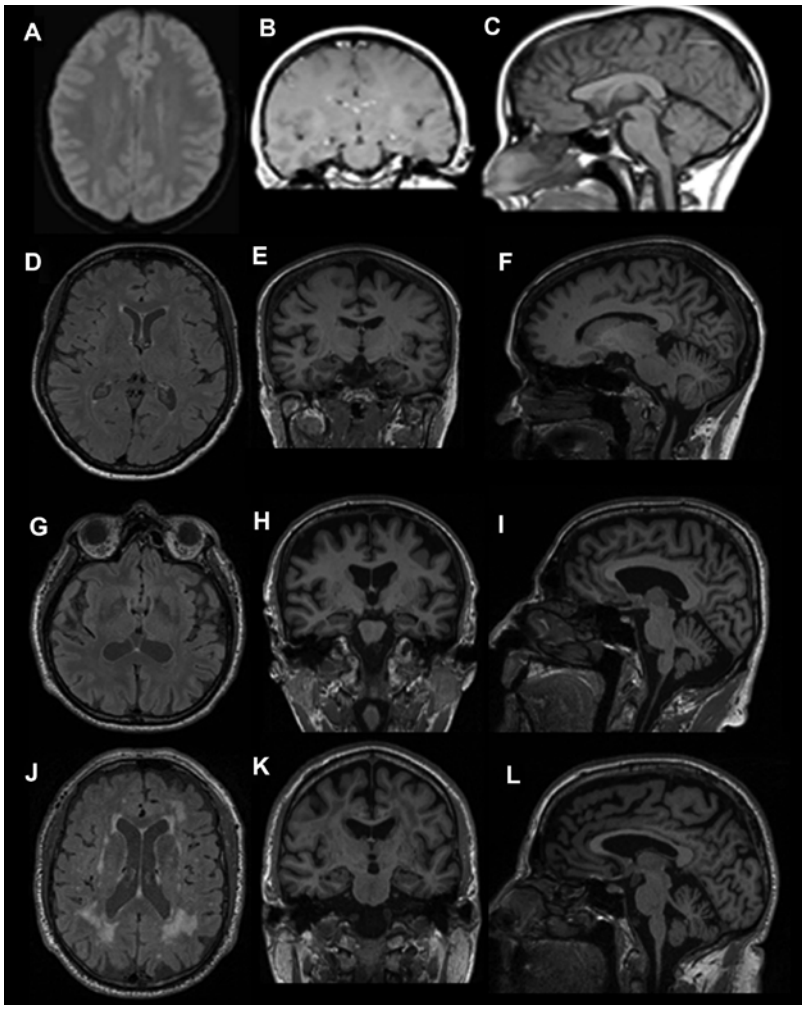
2.1.2 Visual rating of brain images:

Visual rating of clinical brain images was performed independently by three physicians including a general neurologist (PP), neuroimaging specialist (CDS), and a behavioral neurologist (GAJ) using the standardized visual rating scales described below. Discrepant rating scores were adjudicated in a consensus conference including all three raters.

Representative images from a young normal and elderly normal subjects with and without imaging findings of WMH, MTA, and GCA are presented in Figure 2.1.

Global cerebral atrophy: GCA was visually rated on scale of (0-3) using T1 MRI or CT structural images based on the semi-quantitative rating scale due to Pasquier and colleagues.[115] The raw data were then dichotomized with scores of 0 and 1 considered

Figure 2.1 Descriptive figure showing representative magnetic resonance imaging images. From (A-C) a young normal, (D-F) an elderly subject without significant white matter hyperintensity (WMH), medial temporal lobe atrophy (MTA), or global cerebral atrophy (GCA), (G-I) an elderly subject with significant MTA and GCA without WMH, and (J-L) an elderly subject with significant WMH and GCA without significant MTA.



(A), (D), (G), and (J) are axial fluid-attenuated inversion recovery images. (B), (E), (H), and (K) are coronal T1 images. (C), (F), (I), and (L) are sagittal T1 images.

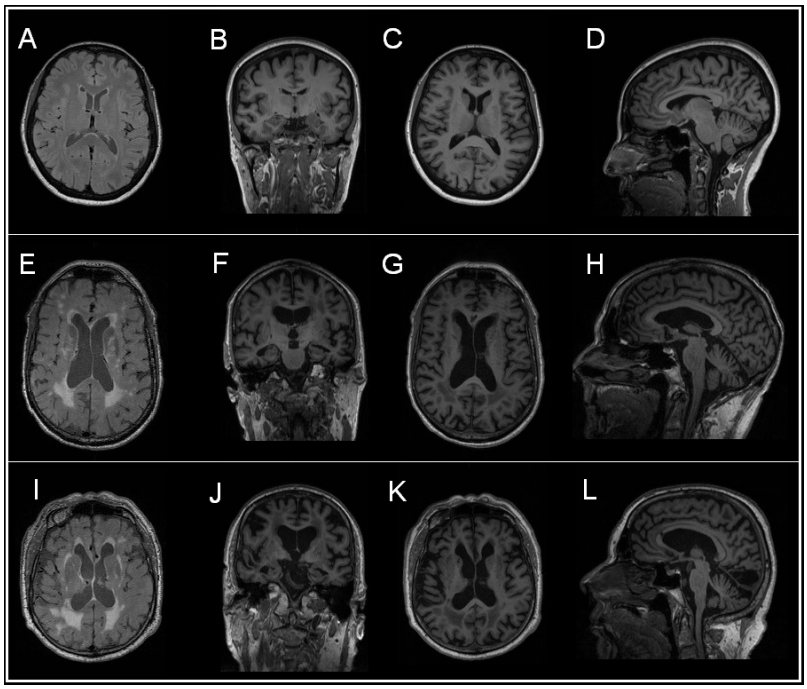
as negative for significant atrophy (see figure 2.2 panel C and D), and scores of 2 and 3 considered as positive for moderate to severe atrophy (see figure 2.2 panel G, H, K and L). Medial temporal lobe atrophy (MTA): MTA was rated based on the 5-point semi-quantitative scale developed by Scheltens and colleagues [40] using T1 MRI or CT structural images. The raw data were dichotomized as follows: scores of 0, 1 and 2 were considered negative for significant atrophy, demonstrating only no or mild atrophy (see figure 2.2 panel B), while scores of 3 and 4 were considered positive for moderate to severe atrophy (see figure 2.2 panel F and J).

White Matter Lesions: We visually rated WMH using a modified Longstreth scale [116] using CT scan or fluid attenuated inversion recovery (FLAIR) sequence of the MRI. The Longstreth scale was compressed by mapping the 0-9 Longstreth score into a 1-4 scale, using the mapping 1 = 0-2, 2 = 3-4, 3 = 5-6 and 4 = 7-8. The ends of the Longstreth scale, 0 and 9 are extreme values to account for extraordinary, rarely encountered instances of either no periventricular hyperintensity rim at all (0) or extremely severe global white matter hyperintensity exceeding even the severe 8 Longstreth rating (9). These extreme ratings were incorporated for completeness into our 1 and 4 ratings respectively, but were not in fact encountered in our images. The raw data were then dichotomized with scores of 1 and 2 considered as negative for significant WMH volume (see figure 2.2 panel A), and scores of 3 and 4 considered as positive for moderate to severe WMH volume (see figure 2.2 panel E and I).

2.1.3 Statistical Analysis:

Descriptive statistics were used to summarize the study sample. A Spearman analysis was conducted prior to multivariable analysis to assess the degree of correlation

Figure 2.2 Descriptive figure showing the contribution of vascular damage (represented as white matter hyperintensity; WMH) and Alzheimer's Disease (represented as medial temporal lobe atrophy; MTA) to global cerebral atrophy (GCA).



The upper row is an example of a subject with no-mild WMH on the fluid attenuated inversion recovery (FLAIR) image (A) and MTA on the coronal T1 image (B). Note that the subject with no-mild WMH and MTA has no-mild GCA as shown in the transverse and sagittal T-1 image in the upper row (C and D respectively). The middle row is an example of a subject with moderate-severe WMH on the FLAIR image (E) and MTA on the coronal T1 image (F), which is associated with moderate-severe GCA seen on the transverse and sagittal T-1 image (G and H respectively). The lower row represents a second example of moderate-severe WMH on the FLAIR image (I) and MTA on the coronal T-1 image (J). Note that this subject also has moderate-severe GCA as shown in the transverse and sagittal T-1 image in the lower row (K, and L respectively).

among the study measures. Simple and multivariate logistic regression models using dichotomous measures for GCA (as described above) were performed to examine the association with age, WMH, and MTA. A separate ordinal logistic regression model was run using an ordinal measure of GCA (0-1 = no or mild GCA, 2 = moderate GCA and 3 = severe GCA). The proportional odds assumption was checked with the Score test. Potential two-way interaction between WMH and MTA in relation to GCA was included in the adjusted models. Statistical analyses were performed using Stata 14.

2.3 Results:

Demographic and clinical features of the research participants are presented in Table 2.1 The mean participant age was 76.2 years (± 9.6 years, range 41-96 years), 40.6% were male, and the mean number of years of formal education was 15.1 years (± 3.7 years). Spearman correlation analysis showed that age, WMH and MTA were all positively and significantly correlated with GCA, with the strongest correlation between WMH and GCA (rho=0.54) (table 2.2). In addition, WMH, MTA, and GCA severity were found to be positively and significantly correlated with age in the Spearman correlation analysis (table 2.2).

Simple logistic regression models using the dichotomized GCA variable (GCA of moderate-to-severe atrophy vs. no or mild atrophy) showed that the odds of having moderate-to-severe GCA increased 7.5% with each one-year increase in age (Model 1, table 2.3). Participants with moderate-to-severe MTA had 5.3 times the odds of moderate-to-severe GCA than those with no or mild MTA (Model 2, table 2.3). Similarly, the odds of having moderate-to-severe GCA were 13.6 times higher in participants with moderate-to-severe WMH than those with no or mild WMH (Model 3, table 2.3).

Table 2.1 Participant demographic, clinical, and imaging characteristics.

Participant Characteristics	Total
Age (mean ± SD)	76.2 ± 9.6
Sex (male n [%])	132 (40.6)
Education (mean ± SD)	15.1 ± 3.7
Cognitive Diagnosis	
Normal n (%)	87(26.8)
Mild Cognitive Impairment n (%)	129 (39.7)
Dementia n (%)	109 (33.5)
Imaging Results	
GCA (n [% of subjects with moderate-to-severe])	198 (60.9)
MTA (n [% of subjects with moderate-to-severe])	115 (35.4)
WMH (n [% of subjects with moderate-to-severe])	155 (47.7)

SD = standard deviation; n = number of subjects; GCA = global cerebral atrophy; MTA = medial temporal lobe atrophy; WMH = white matter hyperintensity burden.

Table 2.2 Correlations among age (in years), white matter hyperintensity burden (WMH, rated 1-4), medial temporal lobe (MTA, rated 0-4) and global cerebral atrophy (GCA, rated 0-3).

	Age	MTA		WMH		GCA	
		*r*s	*P*	*r*s	*P*	*r*s	*P*
Age	--	0.23	0.0000*	0.41	0.0000*	0.32	0.0000*
MTA	--	--		0.29	0.0000*	0.34	0.0000*
WMH	--	--		--		0.54	0.0000*

GCA = global cerebral atrophy; MTA = medial temporal lobe atrophy; WMH = white matter hyperintensity burden; *r*s = Spearman correlation coefficient.

*P <0.0001

In the multivariable logistic regression model, age remained significantly associated with the risk of having moderate-to-severe GCA and showed that the odds of having moderate-to-severe GCA increased 3.5% with each one-year increase in age, after adjustment for WMH and MTA scores (Model 4, table 2.3). Furthermore, participants with moderate-to-severe WMH had 9.76 times the odds of having moderate-to-severe GCA than those with no or mild WMH. Additionally, subjects with MTA scores in the moderate-to-severe range had 3.47 the odds of moderate-to-severe GCA than those with no or mild MTA (Model 4, table 2.3). The interaction of WMH and MTA was not significant in the adjusted model and was not retained (p=0.79).

The ordinal logistic regression model showed that with each one-year increase in age the odds of more severe GCA increased by 3.5% (Model 5, table 2.3), similar to the

results obtained in the binary logistic regression model. However, the effect of WMH was attenuated in the ordinal model, where participants with moderate-to-severe WMH scores had 6.7 times the odds of more severe GCA compared to participants with no or mild WMH (Model 5, table 2.3). On the other hand, participants with MTA scores indicating moderate-to-severe ratings had 4.1 times the odds of more severe GCA compared to participants with no or mild MTA (Model 5, table 2.3), which was comparable to the effect observed in the binary models (Models 2 and 4, table 2.3). The interaction term between WMH and MTA was not significant in this model and was not retained (p=0.64).

Table 2.3 Odds ratios (95% CI) for moderate-to-severe global cerebral atrophy (GCA) based on participant age, white matter hyperintensity (WMH), and medial temporal lobe atrophy (MTA). Models 1-3 are simple binary logistic regression, and Model 4 is multivariable binary logistic regression. Model 5 is ordinal logistic regression.

Comparison	Model 1	Model 2	Model 3	Model 4	Model 5
Age (1 year)	1.075 (1.05-1.10)	--	--	1.03 (1.00-1.07)	1.03 (1.00-1.06)
MTA (moderate-to-severe vs. no or mild)	--	5.35 (3.05-9.38)	--	3.47 (1.83-6.60)	4.05 (2.48-6.60)
WMH (moderate-to-severe vs. no or mild)	--	--	13.60 (7.60-24.36)	9.76 (5.17-18.45)	6.66 (3.97-11.17)

GCA = global cerebral atrophy; MTA = medial temporal lobe atrophy; WMH = white matter hyperintensity burden.

2.4 Discussion:

These data argue that moderate to severe GCA seen on brain imaging studies should not be solely attributed to normal aging. Instead, CVD, and to a lesser extent AD, should be considered as the proximate cause of moderate-to-severe GCA in the majority of cases

(where the prior probability of other causes of atrophy is assumed to be relatively low).

Such understanding may help direct appropriate diagnosis and treatment strategies for those undergoing evaluation of memory complaints or more significant cognitive decline that have had structural imaging performed as part of the diagnostic workup.

In the context of potential neuropathologic injury to the brain, age appears to be only a minor contributor to the development of moderate to severe GCA, in line with the results from prior studies in the field. Fjell et al. reported that the rate of GCA progression due to normal aging is 0.5% annually.[133] Similarly, Hua et al. and Scahill et al. also found a small but significant decrease in regional and whole brain volumes and a concomitant small increase in ventricular volume with increasing age.[109, 134] The present findings suggest that more advanced GCA in the moderate to severe range should not be solely attributed to normal age-related processes, but rather suggest that more advanced GCA is most likely to be associated with specific disease states such as subcortical cerebrovascular injuries or neurodegenerative processes, such as AD, that may be more prevalent with advancing age, but are distinct from the normal aging process.

In AD, based on quantitative studies, the rate of GCA is accelerated compared to that seen in normal aging (1.25% compared to 0.5% annually), with the fastest rate of atrophy affecting the medial temporal lobe (2.5% annually).[133] Moreover, the rate of GCA and ventricular enlargement is accelerated even in young subjects (60-70 years) with MCI, reflecting the aggressiveness of neurodegenerative disease processes in young compared to old adults in even the earliest stages of cognitive decline.[134] The pattern of brain atrophy in AD also differs from that seen in normal aging. In AD, the medial temporal lobe is involved early in the disease course. Subsequently, the lateral temporal and frontal

lobes are affected, with eventual involvement of the sensorimotor and visual cortices. Such progression eventually leads to the development of moderate-to-severe GCA that is not a part of the normal aging process.[135]

Another important factor to consider as a contributor to the development of moderate-to-severe GCA is CVD. CVD may be present without evidence for GCA, but if progressive, can eventually result in moderate to severe GCA secondary to subcortical vascular damage that can lead to severe white matter atrophy.[136] In addition, progressive ischemic injury can lead to widespread neuronal atrophy and attrition in the grey matter that can be visualized on structural imaging as cortical thinning which can further contribute to the picture of moderate to severe GCA.[137] The STandard for ReportIng Vascular changes on nEuroimaging working group (STRIVE) has proposed terms and definitions to describe neuroimaging features of small vessel disease that include using GCA as an imaging correlate of CVD.[137] Few studies have failed to report an association between WMH and GCA, and those that have not found such an association have not been able to control for confounding factors such as small sample sizes or inclusion of participants with minimal to no CVD risks.[130, 131]

There are several limitations to the present study, including its cross-sectional design. While we have identified associations between age, MTA, WMH and the presence or absence of GCA, our data does not assess the temporal sequence of findings, limiting our ability to draw inferences on potential causality. We have also relied on a convenience sample drawn from a community-based cohort, enriched in highly educated Caucasian subjects that may limit the generalizability of the present findings. However, a major strength of our study also lies in our study sample, which is derived from a well

characterized community-based cohort, spanning the cognitive continuum from intact cognition to dementia. Furthermore, the wide age range (41-96 years) increases the generalizability of the findings at least in regards to lifespan. The use of visual rating scales derived from standard clinical images is also a major strength, allowing us to examine structural imaging findings that are part of the normal clinical workup for memory complaints. These assessments are directly applicable to imaging review procedures used in routine clinical practice rather than relying on advanced volumetric analysis techniques that are seldom available to the practicing clinician.

In conclusion, our study demonstrates that qualitative appraisals of structural imaging findings that are used routinely in clinical settings are an appropriate means of evaluating the differences between imaging correlates of normal aging and those related to specific disease processes. Such information may help direct accurate diagnoses and treatment strategies designed to maximally address cognitive and functional impairments that may be seen in mild forms as part of the normal aging process, or in more moderate to severe forms as the sequelae of AD or CVD. Further studies exploring other imaging features with an eye to practical clinical utility in diagnosis and care are much needed in the field.

CHAPTER 3. DISTINCT WHITE MATTER CHANGES ASSOCIATED WITH CSF AMYLOID B $_{1-42}$ & HYPERTENSION

Summary:

Background: Alzheimer's disease (AD) pathology and hypertension (HTN) are risk factors for development of white matter (WM) alterations and might be independently associated with these alterations in older adults.

Objective: To evaluate the independent and synergistic effects of HTN and AD pathology on WM alterations.

Methods: Clinical measures of CVD risk were collected from 62 participants in University of Kentucky Alzheimer's Disease Center studies who also had CSF sampling and MRI brain scans. CSF $A\beta_{1-42}$ levels were measured as a marker of AD, and fluid-attenuated inversion recovery imaging and diffusion tensor imaging were obtained to assess WM macro and microstructural properties. Linear regression analyses were used to assess the relationships among WM alterations, CVD risk and AD pathology. Voxelwise analyses were performed to examine spatial patterns of WM alteration associated with each pathology.

Results: HTN and CSF $A\beta_{1-42}$ levels were each associated with white matter hyper-intensities (WMH). Also, CSF $A\beta_{1-42}$ levels were associated with alterations in normal appearing white matter fractional anisotropy (NAWM-FA), whereas HTN was marginally associated with alterations in NAWM-FA. Linear regression analyses demonstrated significant main effects of HTN and CSF $A\beta_{1-42}$ on WMH volume, but no significant HTN $\times$ CSF $A\beta_{1-42}$ interaction. Furthermore, voxelwise analyses showed unique patterns of WM alteration. associated with hypertension and CSF $A\beta_{1-42}$.

Conclusion: Associations of HTN and lower CSF $A\beta_{1-42}$ with WM alteration were statistically and spatially distinct, suggesting independent rather than synergistic effects. Considering such spatial distributions may improve diagnostic accuracy to address each underlying pathology.

Keywords: Hypertension, Alzheimer's Disease, $A\beta_{1-42}$ and white matter alteration.

3.1 Introduction:

Over 50% of individuals who develop dementia have mixed pathologies at autopsy.[138-140] The two most prevalent contributors to mixed pathology are Alzheimer's disease (AD) and cerebrovascular disease (CVD), and intense efforts are being made to develop in vivo tests for early diagnosis.[138, 140] Antemortem identification of AD pathology has become easier since the development of *in vivo* markers of amyloid and tau using cerebrospinal fluid (CSF) or positron emission tomography (PET) scans.[41, 141-143] Accurate identification and classification of CVD *in vivo,* however, remains challenging. Markers of CVD include areas of hyper-intense signal in white matter (white matter hyper-intensities, WMH) on T2-weighted MRI of the brain, and more recently, alterations in microstructural properties of WM such as fractional anisotropy (FA) detected using diffusion tensor imaging (DTI).[144-146]

WMH also occur in the pre-dementia stage of familial AD, including in those with no appreciable CVD risks.[17, 18] It remains unclear whether these WM alterations should be attributed to AD, CVD, or both pathological processes. Further, it is unknown whether the effects of AD and CVD are independent or synergistic. The present study examined relationships between CSF beta-amyloid ($A\beta_{1-42}$) and CVD risk factors with both WMH volumes and FA values within regions of normal appearing WM. The central analysis of

the study utilized multiple linear regression to determine whether AD pathology and CVD risk are independently or synergistically associated with WM alterations. An interaction term was used to explore potential synergistic effects, while main effects explored potential independent effects of AD pathology and CVD risk. Voxelwise analyses were then used to determine the spatial distribution of WMH changes associated with CSF $A\beta_{1-42}$ levels and/or CVD risk factors.

3.2 Methods:

3.2.1 Participants:

Participants enrolled in the University of Kentucky Alzheimer's Disease Center (UK-ADC) cohort and affiliated clinical trials were included in the present study. All studies used identical imaging and cerebrospinal fluid collection protocols, and all research protocols were approved by the University of Kentucky Institutional Review Board. All participants gave written informed consent.

Inclusion criteria for the current study included a classification of cognitively normal (CN) or mild cognitive impairment (MCI), which was based on Clinical Dementia Rating (CDR)[147] global scores: CN (CDR = 0) and MCI (CDR = 0.5). Additionally, all participants were required to have MRI data that met quality control standards for motion and artifacts, available CSF $A\beta_{1-42}$ data, and clinical data regarding current or previous diagnosis of hypertension (HTN: 1=yes, 0=no), hyperlipidemia (HLD: 1=yes, 0=no), and diabetes mellitus (DM: 1=yes, 0=no). In addition, data on antihypertensive medication use, history of cardiovascular disease, atrial fibrillation, cigarette smoking, blood pressure, and lipid levels were used to calculate a modified Framingham 10-year Stroke Risk Score

(mFRS) for each participant (FRS was modified because data on left ventricular hypertrophy were not available).[148]

3.2.2 MRI Protocol and Analysis:

Data were collected on a Siemens 3 Tesla TIM TRIO scanner using a 32-channel head coil at the University of Kentucky Magnetic Resonance Imaging and Spectroscopy Center. Two high-resolution 3D T1-weighted images were obtained using a magnetization-prepared rapid acquisition gradient echo (MP-RAGE) sequence [repetition time (TR) = 2530 ms, inversion time (TI) = 1100 ms, echo time (TE) = 2.56 ms, Flip angle = 7 degrees, 1 mm isotropic voxels]. Fluid-attenuated inversion recovery (FLAIR) images were acquired using a 3D sequence [TR = 6000ms, TI = 2200ms, TE = 338ms, 1mm isotropic voxels]. DTI used an axial, double-refocused spin-echo, echo planar imaging sequence [TR = 8000ms, TE = 96ms, FOV = 224mm^2, 52 contiguous slices, 2mm isotropic voxels] with 60 non-collinear encoding directions (b = 1000 s/mm^2) and 8 images without diffusion weighting (b0, b = 0 s/mm^2).

3.2.2.1 FLAIR Sequence Analysis and WMH Mask Generation:

FLAIR image processing was performed using a previously described protocol.[149] Briefly, MP-RAGE and FLAIR images were radiofrequency inhomogeneity-corrected using the N3-correction algorithm provided in MIPAV (http://mipav.cit.nih.gov). The two MP-RAGE images were registered to each other using SPM12 (http://www.fil.ion.ucl.ac.uk/spm/software/spm12) and then averaged. The averaged MP-RAGE image was then registered to FLAIR image using SPM12. Next, the FSL (v5.0.9) brain extraction tool[150] was used to remove non-brain tissue from the average MP-RAGE image to create a binary mask of brain tissue. This mask was then

applied to the FLAIR image to remove non-brain tissue. Multimodal segmentation was performed with SPM12 using the average MP-RAGE and FLAIR image. The brain was segmented into gray matter, two separate white matter segments, CSF, and other tissues segments using a previously validated segmentation method.[151] The two WM segments were combined to form a single WM mask, which was dilated and then multiplied with the FLAIR image to form a FLAIR WM mask. Matlab 2015b was then used to determine the mean and standard deviation (SD) of the FLAIR WM in each participant by fitting a Gaussian model curve to the histogram of WM voxels intensity. The FLAIR WM images were then thresholded at 3 SDs above each participant's mean value to identify areas of WMH in that participant. The resulting WMH mask were then manually edited to remove artifacts around the interventricular septum and inferior slices.[151] The summed volume of remaining voxels in each participant was used as a measure of WMH volume.

3.2.2.2 DTI Sequence Analysis:

The goal of the DTI analyses was to compute mean FA values within regions of normal-appearing WM (NAWM) in each participant's FLAIR image. DTI image processing was performed using a previously described protocol.[152] Briefly, FSL (v5.0.9) was used to perform pre-processing for motion and eddy-current correction with outlier detection and replacement.[153, 154] Following brain extraction, the FMRIB Diffusion Toolbox (FDT v3.0) was used to fit a voxelwise diffusion tensor model, determine the eigenvalues, and calculate FA.[155] FA images were registered into FMRIB FA 1mm space, averaged to form a mean FA image to then generate a common WM skeleton, and finally project each participants FA image onto the group skeleton using tract-based spatial statistics (TBSS).[155]

The same registration parameters were then used to project the FA image to standard (MNI152 T1 1mm3) space. The common track skeleton was used together with the WMH images in the TBSS non-FA pipeline.[155] These WMH images were then subtracted from the TBSS skeleton in order to create a NAWM image for each participant that comprised only WM outside of WMH. The mean global FA was then extracted from each participant's NAWM image using fslstats FSL statistical tool.

3.2.2.3. Cerebral Microbleed Analysis:

Measures of cerebral microbleeds (CMBs) were collected from 62 participants who had CSF sampling. Gradient recalled echo (GRE) MRI sequence was obtained to assess CMBs. CMBs were visually rated using Microbleeds Anatomical Rating Scale (MARS).[156]

3.2.3 CSF Collection and Analysis:

CSF collection and analysis was performed as previously described.[157] In brief, participants underwent lumbar puncture the same day as MRI scanning. CSF was collected in the morning after fasting since midnight and stored in a − 80 °C freezer prior to shipment on dry ice to the Alzheimer's Disease Neuroimaging Initiative (ADNI) Biomarker Core laboratory at the University of Pennsylvania Medical Center. CSF levels of Aβ1-42 were measured using the multiplex xMAP Luminex Platform (Luminex Corp, Austin, TX) with Innogenetics (INNO-BIA, AlzBio3; Ghent, Belgium) immunoassay kit as previously described.[158]

3.2.4 Statistical Analysis:

A. Statistical Analysis:

Independent samples t-tests and chi-square tests were used to assess differences between CN and MCI groups in demographic and clinical measures, CSF $A\beta_{1-42}$, and measures of WM alteration. Bivariate relationships between CSF $A\beta_{1-42}$, mFRS, HTN status, HLD status, DM status, smoking status and quantitative measures of WMH volume and DTI-based FA measures were investigated using partial correlations controlling for age and sex.

As HTN was the only CVD risk factors associated with WMH volume, HTN was used as a marker of CVD risk in further analyses. Next, separate linear regression models were used to explore the association of HTN and CSF $A\beta_{1-42}$ with WMH volume and NAWM-FA. Each model included main effects of HTN and CSF $A\beta_{1-42}$, a HTN × CSF $A\beta_{1-42}$ interaction, and age, sex, and cognitive status as covariates. The interaction term was included to explore any synergistic effects of HTN and CSF $A\beta_{1-42}$ on WM alterations. If the interaction term was not significant, it was removed from the model and the model was refit to the data in order to explore the independent effects of HTN and CSF $A\beta_{1-42}$. Finally, the above models were repeated with the mFRS included as additional covariate.

In order to assess potential contributions from cerebral amyloid angiopathy (CAA), bivariate relationships of CSF $A\beta_{1-42}$ with CMBs in the frontal, parietal, temporal, occipital lobes and the basal ganglia were investigated using partial correlations controlling for age and sex. Next, linear regression was performed to explore whether WMH and significant CMBs predicted CSF $A\beta_{1-42}$ independently after controlling for age, sex, and cognitive status. SPSS 23 (IBM, Chicago, IL) was used for all statistical analyses, and significance was set at 0.05.

B. Voxelwise Regression Analysis:

FSL's *Randomise* tool was used to perform exploratory voxelwise regression analyses to examine the spatial location of WM alteration associated with CSF $A\beta_{1-42}$ and HTN. CSF $A\beta_{1-42}$ (measured in pg/ml) was treated as a continuous variable, whereas the clinical diagnosis of HTN, systolic BP >139, or diastolic BP > 89 were used as criteria indicating presence of HTN. Each analysis included either CSF $A\beta_{1-42}$ or HTN as the predictor of interest and age, sex, and education as covariates. These models were then used to identify voxels where the presence of WMH were associated with CSF $A\beta_{1-42}$ or HTN. Correction for multiple comparisons across all voxels was performed using the false-discovery rate (FDR) tool provided with FSL (https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/FDR), which uses the distribution of p-values from every voxel in order to determine an appropriate threshold to reduce false-positives.[159] Results were then compared to the ICBM-DTI-81 WM labels atlas to identify the tracts that included significant voxels.

3.3 Results:

A total of 62 participants met all criteria for inclusion, including 26 CN (CDR=0) and 36 MCI (CDR=0.5). Demographic and clinical features of the participants are presented in Table 3.1 The MCI group had higher percentages of participants with HTN and HLD than the CN group ($p < .001$). In addition, CSF $A\beta_{1-42}$ was significantly lower in the MCI group than the CN group ($p = .005$). There was no difference between CN and MCI groups in other clinical measures or in measures of WM alterations. Results of bivariate partial correlations controlling for age, sex, and cognitive status are shown in Table 3.2. The mFRS, HLD and DM were not associated with either WMH volume or FA in NAWM. HTN and lower CSF $A\beta_{1-42}$ (which is associated with higher amyloid plaque burden), however, were both correlated with higher WMH volume ($r = 0.30$, $df = 57$, $p =$

0.021 and r = - 0.30, df = 57, p = 0.021, respectively). CSF $A\beta_{1-42}$ but not HTN was associated with lower FA in NAWM (r = 0.40, df = 57, p = 0.002 and r = -0.23, df = 57, p = 0.08, respectively).

Table 3.1 Demographics, clinical, imaging and laboratory characteristics of the study cohort.

Variables	CN (N=26)	MCI (N=36)	Total (N=62)	Differences CN vs. MCI (p-value)
Age mean ± sd	76.81 ± 6.14	73.47 ± 7.98	74.87 ± 7.40	0.080
Male sex n (%)	9 (34.6)	19 (52.8)	28 (45.2)	0.156
Education mean ± sd	17.08 ± 2.18	16.83 ± 3.67	16.94 ± 3.12	0.764
mFRS mean ± sd	17.58 ± 2.8	16.56 ± 3.1	17 ± 3	0.189
Hypertension n (%)	7 (26.9)	27 (75.0)	34 (54.8)	0.001‡
SBP mean ± sd	135.77 ± 10.77	138.47 ± 16.47	137.34 ± 14.32	0.468
DBP mean ± sd	74.19 ± 9.70	73.89 ± 11.42	74.02 ± 10.65	0.913
Hyperlipidemia n (%)	2 (7.7)	25 (73.5)	27 (43.5)	0.000‡
Diabetes n (%)	4 (15.4)	10 (27.8)	14 (22.6)	0.247

Smoking n (%)	2 (7.7)	1 (2.7)	3 (4.8)	0.567
NAWM-FA mean ± sd	0.59 ± 0.41	0.59 ± 0.55	0.59 ± 0.05	0.987
$A\beta_{1\text{-}42}$ mean ± sd	320 ± 93.14	251.03 ± 90.82	279.95 ± 97.29	0.005¥
WMH volume cc mean ± sd	8.22 ± 9.98	13.30 ± 20.03	11.17 ± 16.65	0.238

CN = cognitively normal; MCI = mild cognitive impairment; mFRS = modified Framingham stroke risk score; SBP = systolic blood pressure; DBP = diastolic blood pressure; HLD = hyperlipidemia; NAWM-FA = fractional anisotropy values of the normally appearing white matter; $A\beta_{1\text{-}42}$ = Cerebrospinal fluid amyloid beta 1-42 levels; WMH = white matter hyperintensities.

‡ Pearson Chi-square ¥ T test (2 sided)

Table 3.2 Partial Correlation of hypertension, CSF amyloid β_{1-42}levels and imaging measures of micro and macrostructural white matter alteration in study subjects.

	HTN	$A\beta_{1-42}$	HLD	DM	mFRS	WMH volume	NAWM-FA
HTN	--	-0.01	0.308*	0.207	0.026	0.298*	-0.233
$A\beta_{1-42}$	--	--	0.036	0.188	-0.057	-0.300*	0.400**
HLD	--	--	--	0.083	0.078	0.056	-0.036
DM	--	--	--	--	-0.001	-0.100	0.019
mFRS	--	--	--	--	--	-0.041	-0.007
WMH volume	--	--	--	--	--	--	-0.481‡

Values are partial correlation coefficients adjusted for age, gender and cognitive status; HTN = hypertension; $A\beta_{1-42}$ = Cerebrospinal fluid amyloid beta 1-42 levels; HLD = hyperlipidemia; DM = diabetes mellitus; mFRS = modified Framingham stroke risk score; WMH = white matter hyperintensity; NAWM-FA = fractional anisotropy values of the normally appearing white matter.

* $P \leq 0.05$, ** $P \leq 0.01$, ‡ $P \leq 0.001$

Results of linear regression analysis examining the effects of CSF $A\beta_{1\text{-}42}$, HTN, the CSF $A\beta_{1\text{-}42}$ × HTN interaction on WMH volume, controlling for age, sex, and cognitive status are shown in Table 3.3 (Model 1). Results after removing the non-significant interaction term are also shown (Model 2). Models 1 and 2 were repeated with the inclusion of mFRS as an additional covariate (Table 3.3; Models 3 and 4, respectively). Results of linear regression analysis examining the effects of CSF $A\beta_{1\text{-}42}$, HTN, the CSF $A\beta_{1\text{-}42}$ × HTN interaction on NAWM-FA controlling for age, sex, and cognitive status are shown in Table 3.4 (Model 1). Results after removing the non-significant interaction term are also shown (Model 2). Models 1 and 2 were repeated with the inclusion of mFRS as an additional covariate (Table 3.4; Models 3 and 4, respectively).

Results from the voxelwise regression analyses demonstrated both HTN and CSF $A\beta_{1\text{-}42}$ were primarily associated with WMH in different areas, with 95% of HTN-related WMH voxels and 90% of CSF $A\beta_{1\text{-}42}$ -related WMH voxels being unique (i.e., non-overlapping) (Figure 3.1). WMH associated with HTN were primarily located in the right inferior fronto-occipital fasciculus, right superior longitudinal fasciculus, and bilateral periventricular WM along the body of the lateral ventricles. In contrast, WMH associated with CSF $A\beta_{1\text{-}42}$ were primarily located at the posterior corona radiata bilaterally and periventricular regions near the anterior horns of the lateral ventricles. The primary area of overlap was in the posterior portion of the right cingulum (Figure 3.1).

Table 3.3 Linear regression models to examine the effects of hypertension and Cerebrospinal fluid amyloid beta 1-42 levels on white matter hyperintensity burden.

	$A\beta_{1\text{-}42}$	HTN	$A\beta_{1\text{-}42}$ × HTN
Model 1[a] ($F_{5,56}$ = 7.7, R^2 = 0.409, p < *0.001*)	*B* = -0.28 (.026)	*B* = 0.30 (.017)	*B* = 0.03 (.829)
Model 2[a] ($F_{6,55}$ = 6.3, R^2 = 0.408, p < *0.001*)	*B* = -0.28 (.016)	*B* = 0.30 (.016)	--
Model 3[b] ($F_{7,54}$ = 5.8, R^2 = 0.432, p < *0.001*)	*B* = -0.28 (.024)	*B* = 0.32 (.012)	*B* = 0.04 (.728)
Model 4[b] ($F_{6,55}$ = 6.9, R^2 = 0.431, p < *0.001*)	*B* = -0.29 (.013)	*B* = 0.32 (.011)	--

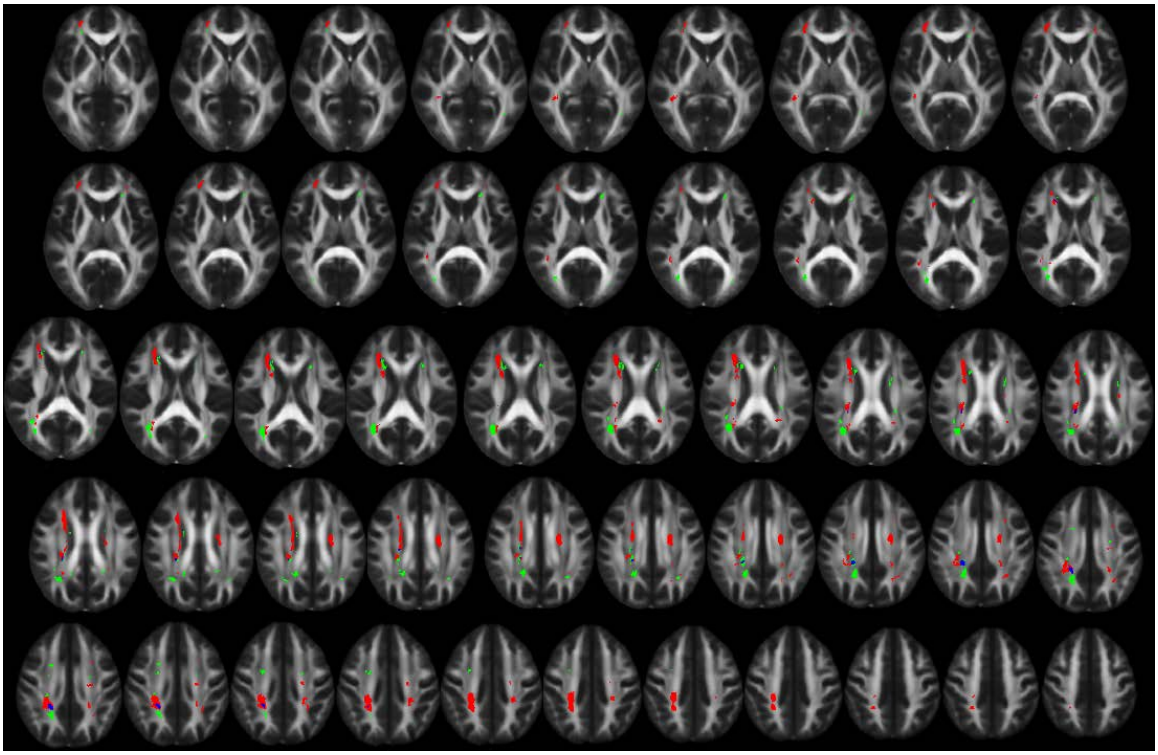
Linear regression models using white matter hyperintensity (WMH) volume as the dependent variable. Values shown are standardized β-coefficients with *p*-values in parentheses. Predictors of interest were CSF levels of $A\beta_{1\text{-}42}$, HTN, and $A\beta_{1\text{-}42}$ × HTN interaction (Models 1, 3). The analyses were repeated without the non-significant interaction term (Models 2, 4). [a]Covariates included in models 1 & 2 were age, sex, and cognitive status. [b]Covariates included in models 3 & 4 were age, sex, cognitive status, and mFRS.

Table 3.4 Linear regression models to examine the effects of hypertension and Cerebrospinal fluid amyloid beta 1-42 levels on white matter microstructural alterations.

	$A\beta_{1\text{-}42}$	HTN	$A\beta_{1\text{-}42}$ × HTN
Model 1[a] ($F_{6,55}$ = 7.0, R^2 = 0.432, p < *0.001*)	*B* = 0.016 (.007)	*B* = -0.01 (.065)	*B* = -0.01 (.143)
Model 2[a] ($F_{5,56}$ = 7.8, R^2 = 0.409, p < *0.001*)	*B* = 0.018 (.001)	*B* = -0.011 (.067)	--
Model 3[b] ($F_{7,54}$ = 5.9, R^2 = 0.434, p < *0.001*)	*B* = 0.016 (.007)	*B* = -.0011 (.063)	*B* = -0.008 (.138)
Model 4[b] ($F_{6,55}$ = 6.4, R^2 = 0.410, p < *0.001*)	*B* = 0.018 (.001)	*B* = -0.011 (.067)	--

Linear regression models using the fractional anisotropy values of the normally appearing white matter (NAWM-FA) as the dependent variable. Values shown are standardized β-coefficients with *p*-values in parentheses. Predictors of interest were CSF levels of $A\beta_{1\text{-}42}$, HTN, and $A\beta_{1\text{-}42}$ × HTN interaction (Models 1, 3). The analyses were repeated without the non-significant interaction term (Models 2, 4). [a]Covariates included in models 1 & 2 were age, gender, and cognitive status. [b]Covariates included in models 3 & 4 were age, gender, cognitive status, and mFRS.

Figure 3.1 Distinct spatial distribution of white matter hyperintensities related to hypertension and CSF amyloid β1-42 levels.



The spatial distribution of white matter hyperintensities (WMH) related to hypertension (HTN) (red) and Cerebrospinal fluid amyloid beta 1-42 levels ($A\beta_{1\text{-}42}$) (green) shows primarily distinct distributions with minimal overlapping areas (blue). WMH associated with HTN occur primarily in deep cortical white matter and along the body of the lateral ventricles. WMH associated with $A\beta_{1\text{-}42}$ occur primarily near the ventricular horns and the posterior corona radiata. Areas of WMH are displayed on the FMRIB58 FA $1mm^3$ brain. Contiguous 1mm slices are shown starting from MNI z = 0 at the top left and MNI z = 48 at the bottom right. All images are shown in radiological orientation (anatomical right is on the left side of the image).

In order to assess the impact of CMBs on the relationships observed between CSF $A\beta_{1-42}$ and WM alterations, partial correlations were performed to examine the relationships of $A\beta_{1-42}$ with basal ganglia and lobar CMBs (in frontal, parietal, temporal, and occipital lobes separately). Results of the analyses demonstrated that $A\beta_{1-42}$ was associated with parietal CMBs (r = -0.28, p = .037) but not with any other CMBs (p > 0.05). A linear regression analysis was then performed to examine whether parietal CMBs and WMH independently predicted CSF $A\beta_{1-42}$. Results demonstrated that $A\beta_{1-42}$ was significantly predicted by WMH volume (β = -0.32, p =.025) and only marginally predicted by parietal CMBs (β = -0.25, p = .06) while controlling for age, sex, and cognitive status.

3.4 Discussion:

Results from this study demonstrate that CSF levels of $A\beta_{1-42}$ and HTN are each associated with WM damage, manifesting as both overt areas of WMH and microstructural alterations in NAWM. Importantly, these processes appear to independently contribute to WM changes and affect spatially distinct areas of WM. These data demonstrate that pathologies underlying or caused by CSF $A\beta_{1-42}$ and HTN exert additive rather than synergistic effects on WM alteration. Our work also raises the question of whether the nature of white matter alteration associated with HTN is the same as that associated with CSF $A\beta_{1-42}$. Since the spatial distributions of WM changes were distinguishable (HTN vs CSF $A\beta_{1-42}$), equivalent underlying mechanisms should not be assumed, despite some similarities in their appearances on MRI. Assuming that both types of WM alteration are deleterious, it follows that treatment of mixed disease states may require interventions aimed at both processes to achieve maximal clinical efficacy.

Initial analyses sought to determine whether CVD risk factors and/or CSF $A\beta_{1-42}$ levels were associated with WM alteration as assessed by overt WMH or subtler microstructural changes within NAWM that are not detectable at the macrostructural level. The modified Framingham CVD risk score was not associated with either marker of WM alteration. Previous studies examining the relationship between the mFRS and WM alterations have been equivocal with one study finding a relationship[160] and another failing to find such a relationship in older adults.[161] These discordant findings may be due to differences in the cohorts, including clinical, environmental, and cultural characteristics. In addition, the Framingham CVD risk score is intended to predict future CVD, which may account for the lack of cross-sectional relationship between mFRS and WM alterations. Of note, a recent study failed to find a relationship between mFRS and WM but did find that mFRS predicted future cognitive decline.[161]

HTN was associated with both WMH volume and FA in NAWM, which is consistent with previous reports.[162, 163] The potential mechanisms underlying the association between HTN and WM alteration are unclear, but several explanations have been proposed. It is possible that that reduced cerebral blood flow could contribute to transient ischemic injury or that HTN-induced endothelial damage could result in extravasation of blood products into WM tissue resulting in injury.[37, 164, 165] WMH may represent areas of reduced vascular integrity,[166] whereas alteration in NAWM may include decreased myelin organization, lower axonal coherence, or decrease in axonal numbers otherwise related to reduced vascular integrity.[167]

Lower CSF $A\beta_{1-42}$ levels were also associated with both higher WMH volume and lower FA in NAWM. These findings are consistent with previous studies, which found that

WMH volume is higher[17, 18] and FA is lower[168, 169] in AD brain compared to healthy controls. The exact mechanism underlying these relationships also remains unclear, but several possibilities exist. First, we noted that soluble $A\beta_{1-42}$ oligomers were present in WM and were associated with loss of axons as well as breakdown in myelin content.[170, 171] Further, soluble $A\beta_{1-42}$ is toxic to oligodendrocytes and inhibits formation of new myelin sheaths *in vitro*.[172, 173] It is also possible that $A\beta_{1-42}$ may indirectly influence WM through increased inflammation,[174] decreased cerebral blood flow secondary to a hypocholinergic state,[175] or damage to blood vessels secondary to cerebral amyloid angiopathy.[18, 176]

The most important finding of the present study is that a history of HTN and CSF $A\beta_{1-42}$ levels are independently associated with WM alterations and have additive effects. Of note, AD and HTN often coexist in older adults.[177] However, linear regression analyses demonstrated that there was no significant interaction between CSF $A\beta_{1-42}$ levels and HTN on WM changes. Further, the main effect of CSF $A\beta_{1-42}$ and HTN were both significant when assessed simultaneously, indicating that these measures constitute independent predictors of WM changes. Several studies suggest that Aβ amyloidosis and HTN are independent predictors of cognitive outcomes,[178, 179] but this is the first evidence that CSF $A\beta_{1-42}$ levels and HTN are independently associated with WM alterations in older adults. These findings suggest that WM alterations could be viewed as the sum of effects from both AD and CVD pathology, rather than thought of as either AD or CVD modifying the effect of the other on WMH burden. This has important implications for therapeutic interventions, since treating one pathology will only address WM alteration

from that disease mechanism but may have no significant impact on WM changes related to the other condition.

After identifying statistically independent relationships of CSF $A\beta_{1-42}$ levels and HTN with WM alteration, we sought to determine if this independence was due to spatially distinct patterns of WM alteration associated with each pathology. We found minimal overlap between areas of WM alterations associated with CSF $A\beta_{1-42}$ and HTN; 95% of HTN-associated WMH and 90% of Aβ-associated WMH were unique. Consistent with previous studies in familial AD, CSF $A\beta_{1-42}$ was primarily associated with WM alteration in posterior regions.[17, 18, 176] Although much of the evidence for the relationship between $A\beta_{1-42}$ and posterior WM alteration comes from studies of dominantly-inherited AD, the present study provides support for a similar relationship in sporadic late-onset AD. In contrast to $A\beta_{1-42}$-associated WM alterations, HTN-associated WM change was primarily observed in deep WM. Many of these areas are near watershed regions between the middle cerebral artery and posterior cerebral artery distributions. These findings are consistent with previous studies that found CVD risk is associated with greater WM alteration in the watershed regions and deep WM.[164, 165]

An important possibility that must be considered is that the association between the $A\beta_{1-42}$ and WM alterations in these posterior regions is mediated by cerebral amyloid angiopathy (CAA), which has a predilection for parietal-occipital cortex. [180] In our study, we found a relationship between CSF $A\beta_{1-42}$ and CMBs in the parietal lobe, which is consistent with extensive previous work. [181, 182] However, regression analyses demonstrated that these amyloid-associated CMBs did not account for the significant relationship between amyloid and WMHs. These results suggest that CAA is likely one of

multiple mechanisms that contribute to WM alterations associated with increasing amyloid in the brain.

There are several limitations to the present study. The cross-sectional design allowed for measurement of correlations among HTN, CSF $A\beta_{1-42}$ levels and WMH/FA in NAWM, but we did not assess the temporal sequence of these changes, precluding causal inferences. In addition, the sample size may have led to insufficient power to detect small effects. Further, cardiovascular risk measures were assessed using dichotomous variables (either present or absent) and did not account for medication control or adherence, disease duration, and/or severity. This may mask potential relationships that exist between these cardiovascular risk measures and WM alterations. Additionally, our sample included only those without dementia. It is unclear whether these relationships are present in individuals with severe disease(s). Also, the present study did not examine relationships with cognition. Despite independent effects on WM, CVD risk and AD pathology may have a different relationship with cognition as demonstrated by a recent study reporting synergistic effects of CVD risk and AD pathology on cognitive decline. [26] Finally, amyloid PET scans were not collected as part of this study. Previous work has demonstrated spatial overlap between CAA and PET amyloid binding. [183, 184] Therefore, future studies should seek to include PET imaging to examine whether these areas of WM alteration found in the present study share overlap with these same regions of increased amyloid-PET binding in CAA.

In conclusion, the present study demonstrates that the effects of HTN and CSF $A\beta_{1-42}$ levels on WM alteration may be additive rather than synergistic, with each associated with distinct spatial distributions of WM alteration. Considering such spatial distributions

may improve diagnostic accuracy and optimal development of treatment paradigms that address CVD and AD, either separately or in combination. It is unclear whether the underlying pathophysiology and injurious mechanisms of these alterations are the same in the different brain regions. Further studies are needed to explore whether these distinct spatial patterns of WM alteration are associated with different cognitive processes and/or clinical outcomes.

CHAPTER 4. WHITE MATTER HYPERINTENSITY REGRESSION IS ASSOCIATED WITH DECREASED BRAIN ATROPHY AND IMPROVEMENT IN MEMORY PERFORMANCE

Summary:

Background: Subcortical white matter hyperintensities (WMH) in the aging population frequently represent vascular injury that may lead to the cognitive sequelae. The dynamic nature of WMH have been well described in the literature, although the factors underlying WMH regression remain poorly understood.

Methods: A sample of 377 participants from the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI2) were included in the analysis. Inclusion criteria required available data regarding WMH volumetric quantification, structural brain measures (i.e., brain volume), cognitive composite measures (memory and executive function), CSF tau and Aβ, and Amyloid PET data at baseline and after approximately 2 years, allowing changes in these measures (Δ) to be calculated. Subjects were categorized into three groups based on WMH change over time, including those that demonstrated regression (n=96; 25.5%), stability (n=72; 19.1%), and progression (n=209; 55.4%).

Results: There were no significant differences in age, education, sex, or cognitive status between the regression, stable, and progression groups. Analysis of variance demonstrated significant differences in changes in brain volume between the progression and regression (p = 0.004) and the progression and stable groups (p = 0.012). Memory assessments improved over time in the regression and stable groups compared to those in the progression group in whom these measures declined (p = 0.003; p = 0.018). Finally, within-groups, it was determined that Δ WMH was positively correlated with tau/Aβ in the progression, but not regression group (p = 0.036; p = 0.219).

Conclusions: WMH regression is associated with decreased brain atrophy and improvement in memory performance over two years compared to those with WMH progression. These data suggest that WMH are dynamic and directly reflect both declines and improvements in cognitive performance depending on volumetric change over time. In addition, while we currently lack therapeutic interventions to halt or reverse AD, the dynamic WMH change evident in our data clearly suggests that the ability to reverse cSVD exists today. Further work elucidating the factors associated with WMH regression, stability, and or progression may help identify targets for therapeutic intervention for cSVD related cognitive decline and dementia in the aging population.

4.1 Introduction:

Cerebral white matter hyperintensities (WMH) are non-specific, subcortical, high intensity signals found on T2 magnetic resonance imaging (MRI). Late-life WMH are thought to largely represent cerebrovascular injury resulting from cerebral small vessel disease (cSVD).[16] Such injury may lead to neuronal circuit dysfunction in affected areas that can be associated with vascular cognitive impairment and dementia. A number of previous studies have demonstrated an association between longitudinal progression of WMH lesion volume and worsening cognitive impairment.[185-188] In contrast, the cognitive sequelae of WMH volume regression has not been studied systematically, although several studies have reported cases of WMH regression without examining the relationship of such findings with cognitive outcomes. The authors of these previous reports have described the phenomena of WMH regression as both poorly understood and in need of further study.[189, 190]

It is possible that WMH regression may simply reflect imaging or methodological confounders as opposed to representing a true biological phenomenon.[191] The use of standardized imaging sequences, scanners, and head coils across longitudinal visits, along with regular scanner calibration and identical processing techniques with uniform intensity corrections, such as that used in the ADNI study, are required to overcome imaging and methodological confounders that may be related to WMH regression. ADNI was launched in 2003 as a public/private partnership designed to assess biological and clinical markers to assess AD progression, and up to date information can be found at www.afni-info.org.

As a biological phenomenon, it is possible that regression of WMH volume represents simple gliotic contraction and/or resultant microvascular encephalomalacia resulting from static ischemic injury. If WMH regression represents such a biological phenomenon, it should be associated with greater global brain atrophy and stable, or possibly improved, cognitive function as seen in many individuals post-stroke. Alternatively, WMH regression could potentially reflect a longitudinal reduction in inflammatory changes and focal edema associated with cSVD, and if so, such changes should be associated with improved cognition despite greater apparent brain atrophy associated with resolution of focal edema. Lastly, it remains possible that WMH regression represents a potentially healing or regenerative process, that would be associated with reduced brain atrophy and improvement in cognitive performance. A theoretical framework to assist with interpreting such longitudinal changes is provided in Table 4.1. The present study explored these potential hypotheses responsible for WMH regression by examining the differences in cognitive and structural brain changes (i.e. brain atrophy) that occur in the setting of WMH volume regression through the analysis of existing

Table 4.1 Possible etiologies for cerebrovascular-related white matter hyperintensities that regress over time and the expected associations with cerebral atrophy and cognitive performance.

Possible etiology for WMH	**Potential cause of regression**	**Expected association with cerebral atrophy**	**Expected association with cognitive performance**
Irreversible ischemic injury	Gliotic contraction and microscopic encephalomalacia	Increased atrophy	No change in cognitive performance
Inflammation associated with irreversible ischemic injury	Resolution of inflammation and edema with restoration of normal function in the penumbra	Increased atrophy secondary to reduced inflammatory edema	Improvement in cognitive performance
Reversible ischemic injury	Healing process	Decreased atrophy	Improvement in cognitive performance

longitudinal data collected as part of the Alzheimer's Disease Neuroimaging Initiative 2 (ADNI 2). Also, given that previous work has demonstrated that both AD and cSVD

contribute to WMH. We hypothesize that WMH progression would more likely be associated with greater AD pathology.

4.2 Methods:

4.2.1 Participants:

The study cohort was comprised of 377 ADNI 2 participants who had WMH quantification both at baseline and at 2-years +/- 3 months (UC Davis; DeCarli et al., 2013). Inclusion criteria required complete demographic information, diagnostic information within 1-year of the T2 fluid-attenuated inversion recovery (FLAIR) scan used for WMH quantification at baseline, a T1-weighted (MPRAGE) image and FreeSurfer structural segmentation[192, 193] within 1-year of the baseline FLAIR images, as well as appropriate neurocognitive metrics for assessments of memory,[194] executive function (EF)[195] and atrophy composite scores within 1-year of the baseline FLAIR images. The memory composite included the Rey Auditory Verbal Learning Test (RAVLT), the cognitive component of the Alzheimer's Disease Assessment Scale (ADAS-Cog), the Folstein Mini-Mental State Examination (MMSE), and Wechsler Logical Memory Scale scores, while the executive function composite included the Clock Drawing test, Trail Making test, Category Fluency (animal and vegetable), Wechsler Adult Intelligence Scale-Revised (WAIS-R) Digit Span and Digit Symbol tests. Participants who did not have FreeSurfer structural information or neurocognitive composite scores at follow-up were excluded from the analyses. No other subjects were excluded. Details of ADNI clinical and methodology have been published.[196, 197]

4.2.2 MRI acquisition

Due to the multi-center design of the ADNI study, the exact scanner manufacturer and model, and scanner-specific imaging protocol varied between, but not within, participants. Across participants, all FLAIR images were 2-dimensionally acquired in the axial plane with 0.9 by 0.9-millimeter voxels and 5 millimeter thickness. All scans were approximately 4-minutes in duration. Scans contained 36-42 slices with minimum matrix size of 220 by 220 millimeters (256 by 237 maximum), and a 9-11 second TR. Scanning parameters were identical within participants between the two-time points. As a result, the reported WMH progression, stability, and regression measures fulfill the criteria needed to control for radiological and methodological confounders.[191] Further information on the ADNI2 scanner protocol can be accessed on the ADNI website at www.afni-info.org.

White Matter Hyperintensity Calculations

WMH volumes were calculated using the 4-tissue segmentation method.[198] Briefly, FLAIR images were co-registered to the T1 image, inhomogeneity-corrected and non-linearly aligned to a minimal deformation template (MDT) using the T1 transformation and the FSL toolbox.[199, 200] WMHs were estimated in MDT space using Bayesian probability and prior probability maps. Binary WMH masks were created using a threshold of 3.5 SD above the mean. Volume from WMH were then calculated after back-transformation into native space. Gray, white, and CSF measurement are segmented using an expectation-maximization algorithm. WMH were ultimately subtracted from normal white matter volume and reported in cubic centimeters.

Longitudinal Change Calculations

Changes in the various measures (Δ) were calculated by subtracting the baseline value from the value at the 2-year follow-up. Positive values indicate increases whereas negative values indicate decreases between the two time points. For WMH volume change, a negative value indicates regression (i.e., less WMH volume at follow-up) whereas a positive value indicates progression (i.e., more WMH volume at follow-up).

WMH Categorization

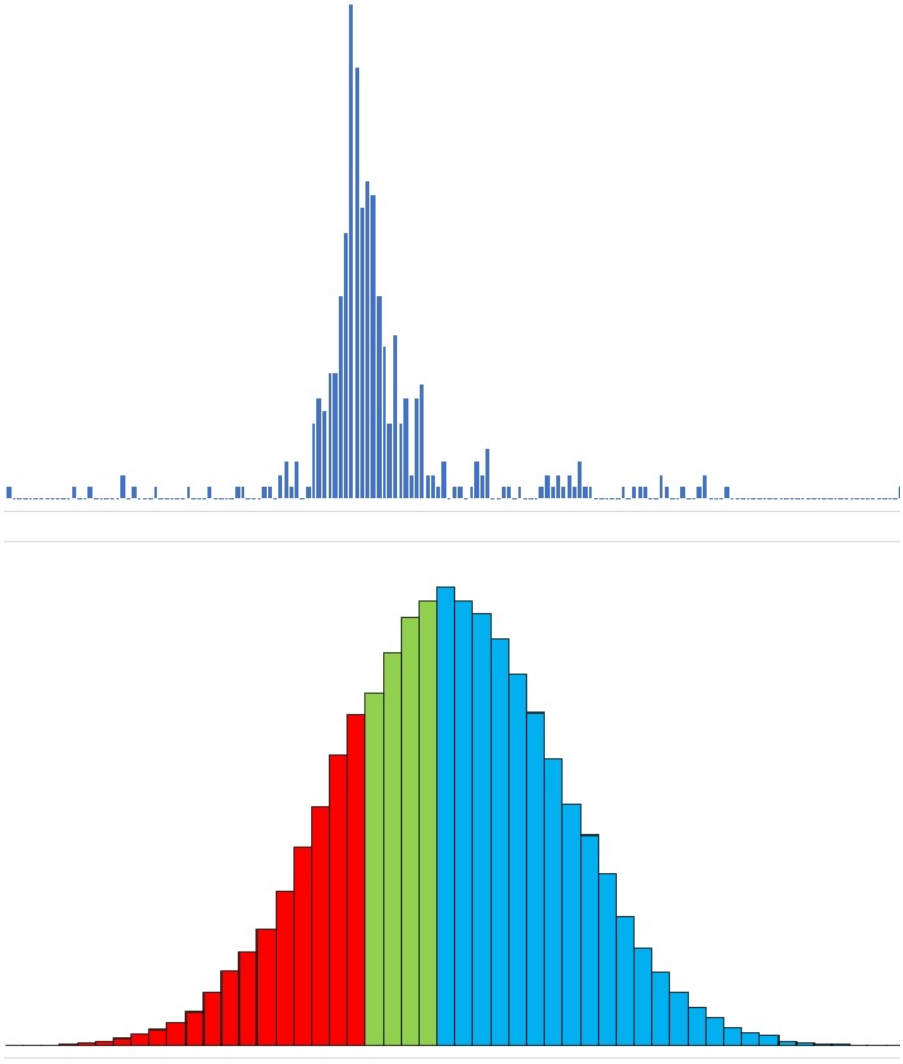
WMH net volume change between the baseline and the follow up visit was used to calculate Δ WMH. Participants were initially grouped based on Δ WMH volume (Regression, Stable, and Progression) using a percentile-based approach in which the percentile for no change was first identified (the 35th percentile). Although definitions based on standard deviations were initially considered, the notable leptokurtic distribution (Figure 4.1) of the data pre-empted such classification as only the most extreme values would be defined outside of the Stable group. Ultimately, we defined Stable the stable group as representing the 25^{th}- 45^{th} percentile of the study participant distribution. This corresponded to +/- Δ of 150 mm^3 of WMH lesion volume. Subjects classified in the regression group showed reductions in WMH volume greater than 150 mm^3 and those classified in the progression group showed increase in WMH volume greater than 150 mm^3.

Atrophy Composite Calculation

In addition, we sought to measure changes in brain and ventricular volume to estimate changes in global brain atrophy that may be related to WMH changes. Gray and white matter segmentation[198] from the four-tissue ADNI classification were combined

Figure 4.1 White matter hyperintensity distribution in the sample studied.

A) The true distribution of the data, showing notable leptokurtosis. Black arrows indicate standard deviation, demonstrating why standard deviation was not deemed an appropriate criterion for separating groups. B) Divisions of the three WMH groups. Visualization only.



to produce a total brain volume (cm^3), but this measure alone does not specifically account for the volumetric changes in the ventricles, which is associated with both WMH changes[201] and AD-related neurodegenerative processes.[202] Therefore, the volume of

the lateral ventricles (cm^3) were estimated using FreeSurfer. Although these measures were examined individually (Tables 1, 2, and 3), the final measure was a composite that used the z-scores of brain volume subtracted from the z-scores from the lateral ventricles (higher value means less brain volume and larger ventricles), which accounts for both periventricular and subcortical atrophy (ventricular volume) as well as more cortical-based whole brain atrophy (brain volume).

Cerebrospinal Fluid Amyloid beta and Amyloid PET Difference Among WMH Growth Category:

We further explore the differences in the cerebrospinal fluid (CSF) Amyloid beta (Aβ) and tau among the three WMH growth categories. In addition, we looked at the whole brain and regional Aβ deposition relationship with the WMH progression and regression.

4.2.3 Statistical Analysis:

ANOVAs were used to compare age, education, Δ WMH, Δ Memory, Δ EF, and Δ Brain Composite in WMH progression, regression, and stable groups. Chi Square was used to compare sex, marital status, cognitively normal, MCI, and AD differences. Within-groups, partial-correlation coefficients controlling for age and sex were used to examine WMH volume (as a continuous variable), Δ brain volume composite, Δ memory, and Δ EF. Between-group differences in Δ brain volume composite, Δ memory, and Δ EF between the 3 groups was examined using ANCOVA with both age and sex as covariates. In this exploratory study, we did not include correction for multiple comparisons, and so the value for statistical significance was set as an uncorrected two-tailed $p< 0.05$.

4.3 Results:

Participants were 72 ± 7.2 years old, 48.3% female, had 16.5 ± 2.6 of education with 55.7% having MCI, 37.4% being cognitively normal, and 6.9% having AD (Table 4.2). There were no significant differences between regression, stable, and progression groups in age, education, sex, marital status, diagnosis, or Δ EF.

25.5% of the participants were classified in the WMH regression group, 19.1% were classified as stable. and 55.4% were classified in the WMH progression group. ANCOVA revealed that there were differences in Δ atrophy composite between progression and regression ($p = 0.004$) and progression and stable groups ($p = 0.012$, Table 3). Longitudinally, memory improved in the regression and stable groups compared to progression ($p = 0.003$; $p = 0.018$ respectively, Table 4.3). There were no differences between any groups in Δ EF ($p = 0.306$, Table 4.3).

For all participants, Δ WMH was negatively correlated with Δ atrophy composite ($r = - 0.175$, $p< 0.001$), Δ EF ($r = -0.121$, $p < 0.021$), and Δ memory ($r = -0.165$, $p = 0.002$). Within-group analyses revealed that Δ WMH was not correlated with Δ atrophy composite or Δ memory in the WMH regression group (Table 4.4). There was a statistically significant negative correlation in the WMH regression group with Δ EF ($p = 0.041$), indicating that increased WMH regression (more negative value) was associated with increased EF performance. Δ WMH was not correlated with Δ EF in the WMH progression group but was positively associated with both the Δ atrophy composite ($p = 0.025$) and negatively associated with Δ memory ($p = 0.049$). There was no association between Δ WMH and Δ atrophy composite, Δ memory, or Δ EF in the stable group (Table 4.4).

Finally, within-groups, it was determined that Δ WMH was positively correlated with tau/Aβ in the progression, but not regression group (Table 4.5; $p = 0.036$; $p = 0.219$). The amyloid PET scans showed that Δ WMH was not positively correlated with the whole brain amyloid concentrations ($p = 0.097$), but was in the temporal region ($p = 0.049$) in the progression group. There were no significant differences found in the regression group (Table 4.5).

Table 4.2 Demographic, clinical, imaging, and change scores for subjects demonstrating progression, stability, and regression in white matter hyperintensity volumes.

Criteria	Progressors (n=209)	Regressors (n=96)	Stable (n=72)	Significance	N (P, R, S)
Age (mean, SD)	72.6 (7.1)	72.1 (7.2)	70.3 (7.2)	0.063 #	209, 96, 72
Education (mean, SD)	16.4 (2.6)	16.6 (2.5)	16.7 (2.4)	0.661 #	209, 96, 72
Female (n, %)	106 (50.7)	41 (42.7)	35 (48.6)	0.429 ^	209, 96, 72
Currently Married (n, %)	157 (75.1)	74 (77.1)	54 (75.0)	0.926 ^	209, 96, 72
Cognitively Normal (n, %)	71 (34.0)	38 (40.0)	32 (44.4)	0.250 ^	209, 96, 72
MCI (n, %)	119 (56.9)	55 (57.3)	36 (50.0)	0.555 ^	209, 96, 72
AD (n, %)	19 (9.1)	3 (3.1)	4 (5.6)	0.143 ^	209, 96, 72
Baseline WMH (mean, SD)	7.177 (10.3)	8.025 (10.5)	1.932 (1.9)	<0.001#*	209, 96, 72
Follow Up WMH (mean, SD)	9.145 (11.6)	6.737 (9.4)	1.944 (1.9)	<0.001#*	209, 96, 72
ΔWMH (mean, SD)	1.97 (2.5)	-1.29 (1.8)	0.012 (0.079)	<0.001 #*	209, 96, 72
Δ Memory (mean, SD)	-0.112 (0.38)	0.023 (0.36)	0.018 (0.35)	0.003 #*	203, 93, 69
Δ EF (mean, SD)	-0.094 (0.65)	0.011 (0.65)	-0.003 (0.58)	0.335 #	202, 94, 69

Δ Atrophy Comp (mean, SD)	0.273 (1.6)	-0.293 (1.68)	-0.335 (1.34)	0.002 #*	202, 95, 67
Δ Brain Volume (mean, SD)	-6.071 (21.1)	-0.511 (22.1)	-2.181 (19.5)	0.076 #	209, 96, 72
Δ Ventricular Vol (mean, SD)	4.160 (3.961)	3.033 (3.745)	2.619 (2.681)	0.003 #*	202, 95, 67

# indicates the p-value from ANOVA (uncorrected); ^ indicates the p-value from Pearson's Chi Square test; * indicates statistically significant

Abbreviations: SD, standard deviation; MCI, mild cognitive impairment; AD, Alzheimer's disease; WMH, white matter hyperintensities; EF, executive function composite.

Table 4.3 ANCOVA results examining brain volume composite, memory change, and EF change in all three groups. Age and gender were used as covariates.

ANCOVA				
Dependent Variable	Post-hoc Comparisons	n	Mean Difference	*p*-value
Δ Atrophy Composite		364		0.004*
	Progression/Regression	196/94	0.564	0.004*
	Progression/Stable	196/66	0.564	0.012*
	Regression/Stable	94/66	0.000	0.999
Δ Brain Volume		377		0.069
	Progression/Regression	209/96	5.684	0.030*
	Progression/Stable	209/72	4.010	0.169
	Regression/Stable	96/72	1.678	0.612
Δ Ventricular Volume		364		0.008*
	Progression/Regression	202/95	1095	0.017*

	Progression/Stable	202/67	1369	0.009*
	Regression/Stable	95/67	274	0.640
Δ Memory		365		0.004*
	Progression/Regression	203/93	0.136	0.003*
	Progression/Stable	203/69	0.123	0.018*
	Regression/Stable	93/69	0.014	0.815
Δ EF		365		0.306
	Progression/Regression	202/94	0.113	0.155
	Progression/Stable	202/69	0.087	0.330
	Regression/Stable	94/69	0.026	0.795

* indicates significant at $p < 0.05$.

Abbreviations: WMH, white matter hyperintensities; EF, executive function composite.

Table 4.4 Partial correlation between WMH change and brain volume composite, memory change, and EF change in regression, progression, and stable groups separately. The variables controlled for are age and gender.

Partial Correlations						
Regression	N=96	Δ Atrophy	Δ Brain Volume	Δ Ventricular	Δ Memory	Δ EF
Δ WMH	r	0.121	-0.001	0.202	0.033	-0.213
	P	0.248	0.991	0.052 &	0.759	0.041 *
	n	95	96	95	93	94
Progression	N=209					
Δ WMH	r	0.158	-0.125	0.122	-0.139	-0.049
	P	0.025 *	0.072 &	0.085 &	0.049 *	0.491
	n	202	209	202	202	201
Stable	N=72					
Δ WMH	r	0.131	-0.073	0.111	-0.063	-0.044
	P	0.298	0.549	0.380	0.610	0.726
	n	67	72	67	69	69

* indicates significant at $p < 0.05$; & indicates marginally significant/trend.

Abbreviations: WMH, white matter hyperintensities; EF, executive function composite.

Table 4.5 Partial correlation between WMH change and Tau/Aβ, Amyloid Total (whole brain), and regional analysis in regression, progression, and stable groups separately.

Partial Correlations							
Regression		Tau/Aβ	Amyloid Total	Frontal	Cingulate	Parietal	Temporal
Delta WMH	r	0.136	-0.046	-0.53	-0.040	-0.059	-0.027
	p	0.219	0.660	0.611	0.701	0.572	0.729
	n	85	96	96	96	96	96
Progression							
Delta WMH	r	0.151	0.116	0.126	0.096	0.096	0.137
	p	0.036*	0.097	0.070^	0.171	0.167	0.049*
	n	197	209	209	209	209	209
Stable							
Delta WMH	r	-0.041	0.074	0.098	0.111	0.061	0.011
	p	0.750	0.542	0.418	0.359	0.616	0.926
	n	64	72	72	72	72	72

The variables controlled for are age and sex. * indicates significant at $p < 0.05$, ^ indicates statistical trend.

4.4 Discussion:

Our results demonstrate that WMH regression is associated with decreased brain atrophy and improvement in memory performance over a period of 2-years compared to participants with progressive WMH changes (Table 4.3). Additionally, participants with progressive WMH changes had increased atrophy and poorer memory performance as a function of Δ WMH (Table 4.4). Consistent with prior reports, our data also show that WMH progression is associated with worsening memory[203-205] and that larger WMH volumes are associated with greater brain atrophy.[126]

Furthermore, our data showed that participants with progressive WMH changes had a strong correlation with Tau/Aβ and the amyloid deposition in the temporal lobe detected by the Amyloid PET scan.[17]

WMH progression and regression have been reported in smaller cohorts,[189, 190, 202, 206] and a stable group has also been identified in other studies.[190, 202] Several studies have reported that WMH progression is associated with greater cognitive decline,[187, 188] however, previous studies have not reported on the potential associations between WMH regression and changes in global atrophy or cognitive test performance over time.

We used the conventional net change in the WMH between the baseline and the follow up visits together with the percentile approach to categorize the dynamic changes into three groups (progression, stable and regression). We found that about 25.5% of study participants showed WMH regression, which is similar to the 21.5% reported by others.[207] In addition, 19.1% of the cohort remained stable and 55.4% showed WMH

progression over 2-years. These data add to the existing literature suggesting that WMH volume is a dynamic feature of aging and age-related neurologic disease.

There are several possible explanations for the observed WMH regression seen in this and other studies. WMH regression could be due to imaging acquisition or methodological confounders such as the use of different scanners across visits, lack of scanner calibration, lack of standardized acquisition parameters, differences in post-acquisition processing techniques such as registration or segmentation pipelines, which may all affect the accuracy of the WMH volume change calculation.[191] Use of the ADNI cohort and WMH volumes from the validated UCD 4-tissue segmentation method for this study minimized such effects, suggesting instead that the observed dynamic nature of longitudinal WMH volumes reflects meaningful biological change.

Biological causes for WMH regression could include gliotic scarring and microstructural encephalomalacia due to irreversible ischemic parenchymal injury, resolution of secondary inflammatory processes as a result of irreversible ischemic damage, or could instead reflect resolution or healing of reversible ischemic injury. The associations of WMH regression with measures of global cerebral atrophy and cognitive change over time would be expected to differ between these possibilities as highlighted in Table 4.1.

If WMH regression were the result of gliotic scarring and microstructural encephalomalacia, it would be expected that such change would be associated with increased cerebral atrophy and stable cognition. In such a scenario, acute small subcortical strokes and lacunar infarcts, which mimic WMH, could account for WMH regression through the natural course of temporal evolution. Such permanent lesions eventually

reduce in diameter over time, which could in part account for the observed WMH regression seen in this and other studies.[202, 208] The current data, however, argue against this possibility as retraction and temporal evolution of ischemic lesions would be expected to result in increased Δ brain volume which is contrary to the present findings in which WMH regression was associated with decreased Δ brain volume .

It is also possible that WMH regression may be due to resolution of inflammatory processes and focal edema related to irreversible ischemic injury. This hypothesis is supported by prior work demonstrating that parenchymal edema develops early during the WM vascular injury process.[209] Several studies supporting the concept of resolving edema as an explanation for WMH regression are based on observations in both CADASIL and stroke patients.[210] If this possibility were responsible WMH regression, one would expect that measures of atrophy would increase in the setting of WMH regression as inflammatory edema resolved, and that cognitive function would improve. Although this is a possibility for some WMH lesions, the overall lack of increased atrophy argues against this mechanism as a primary determinant of WMH regression.

Lastly, it is possible that WMH regression is most closely related to resolution of reversible ischemic changes or to healing or regenerative processes after such injury. In such a scenario, WMH regression would be associated with either no change or increased brain volume, and would also be associated with improvement in cognitive test performance. This pattern of association is exactly what is seen in the present study, supporting this hypothesis.

Our data highlight the importance of considering WMH change over time as a dynamic process which can be related to both positive and negative structural and cognitive

outcomes. The clinical implications of our findings could have a significant impact as we begin to explore the many demographic, risk and treatment variables that may have influenced longitudinal WMH change in our cohort of subjects. Much work is needed to identify associations that may serve as fertile ground for exploration of disease modifying strategies in vascular cognitive impairment and dementia.

This study does have limitations. The ADNI cohort has unique characteristics based on its inclusion/exclusion criteria which include an emphasis on earlier staged disease including normal and MCI subjects as well as criteria that excludes those with significant cerebrovascular disease and/or CVD risk factors. As such, the cohort may not be generalizable to epidemiologic and community-based cohorts that may have higher proportions of cognitively impaired individuals and/or those with increased cerebrovascular risk factors and/or WMH burden. Further, we used global net change in the WMH between the baseline and the follow up visits, limiting our ability to detect regional change in WMH progression, stability or regression compared to more detailed spatial location analyses used by others previously.[202]

Despite these limitations, the present study allowed an exploration of cognitive and brain volume changes that are associated with dynamic WMH change in a straightforward, easily-interpretable fashion. The present data demonstrate that WMH regression is not a mere imaging artifact or artifact due to methodologic procedures, but rather represents an actual biological phenomenon that may, at least in part, reflect recovery from and resolution of reversible cerebrovascular injury. The present findings demonstrating that WMH and cSVD are potentially reversible processes is not only intriguing, but also lays

the foundation for future interventional studies for subcortical vascular dementia as a highly prevalent cause of cognitive decline and dementia in the aging population.

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CHAPTER 5. CONCLUSION

5.1 Overview:

This purpose of these studies was to examine novel ways in which conventional MRI scans can identify the relative contributions of AD & cSVD to GCA and WMH in order to generate new biomarkers & insights that might prove useful in the detection of both "pure" and mixed disease states.

To do so, we first examined the relationship of cSVD visualized as WMH on FLAIR imaging in relation to GCA. Our data clearly demonstrate that WMH are more strongly associated with GCA, than CSF Aβ levels. The clinical importance of this finding should not be understated. Frequently when clinicians see extensive GCA, AD moves to the top of the differential diagnosis. This often leads to an under diagnosis of cSVD, and potentially the development of therapeutic interventions which may miss the target in regards to either reducing the rate of cognitive and functional decline or potentially halting the progression of clinical disease. In other words, when a clinician encounters a patient with significant GCA on MRI imaging, they should carefully examine for the presence of WMH, which if found, should direct them to begin to target CVD risks rather than simply attribute the GCA to AD pathology.

Second, we sought to investigate the association of the CSF Aβ (a surrogate biomarker of AD) with the WMH seen on FLAIR imaging. Specifically, we sought to determine if the WMH associated with AD vs. cSVD were spatially distinct. The findings from this 2nd study clearly demonstrate that WMH reflect contributions of both AD and cSVD processes that represent distinct, additive pathologic processes rather than a synergistic interplay between these disease entities that contribute to the eventual

development of dementia. Specifically, our data demonstrates that WMH located in the parietal and occipital periventricular region are strongly associated with CSF Aβ 1-42 levels. On the other hand, WMH in the deep frontal regions were more likely to be associated with HTN, suggesting cSVD as the underlying pathology for such findings. Finally, we sought to determine if WMH change overtime was static, progressive and/or potentially reversible in regards to pathologic etiology through an examination of the association of WMH progression or regression with the CSF Aβ, Tau and Amyloid PET (surrogates of AD). Our data clearly demonstrate that WMH are highly dynamic with many cases demonstrating regression of the WMH that appear to be largely driven by control of CVR (specifically HTN in our cohort) rather than AD, which consistently appears to lead to WMH progression rather than regression.

These findings suggest that MRI may represent a low cost non-invasive marker for both AD and cSVD that could prove useful in teasing out the relative contributions of these specific etiologies in cases representing mixed pathological disease states. These findings have broad implications for the development of effective therapeutic interventions for individuals in regards to primary prevention for asymptomatic individuals, secondary prevention for those in the earliest of clinical stages of cognitive decline, and further for halting and/or possibly reversing dementia progression, at least in those with a strong component of cSVD pathology.

5.2 HTN as the Major CVR Associated with cSVD:

The effect of HTN on the brain are mediated by many factors including patient specific characteristics, time at which the diagnosis of HTN was made, duration of disease, the degree of blood pressure elevation and severity of the disease. Chronic, uncontrolled

HTN has been shown to lead to thickening of cerebral blood vessels' basement membranes, reducing cerebral blood flow,[211] which may greatly accelerate the pathophysiological development of both AD and VaD.[212] In addition, uncontrolled HTN almost universally leads to cSVD, manifest as white matter rarefaction, widening of perivascular spaces, cerebral microbleeds, and overt ischemic infarcts.[213] cSVD can occur in conjunction with comorbid AD or can be the sole cause of cognitive decline and dementia in many cases.

Uncontrolled midlife HTN has been found to increase dementia risk in older adults, Suggesting that targeting HTN earlier in midlife may help reduce the incidence and prevalence of late the life cognitive dysfunction and dementia.[214] In addition, the Honolulu Asia Aging study (n = 7878), reported that 27% of patients with midlife HTN and 17% of patients with pre HTN, go on to develop late life cognitive decline.[215] The influence of uncontrolled HTN on the development of dementia of both the AD and cSVD type appears clear from the current literature and yet the fact that many cases of both AD and cSVD exist suggest that HTN is neither necessary nor sufficient to explain all cases of dementia and the interplay between these complex pathologic disorders.

Treatment of HTN represents an additional confound in our understanding of the complexity of the relationship between vascular pathology and AD.[212] It is clear from many studies that appropriate management of HTN can reduce the risk of late life cognitive decline and dementia. Results from the Honolulu Asia Aging Study suggest that antihypertensive treatment with a beta blocker is superior to the use of any other antihypertensive medicine in decreasing the risk of incidental cognitive impairment.[216] Yet other studies have suggested that dementia risk reduction related to the management

of HTN is not specific to the type of antihypertensive used, and that benefits can be seen with any anti-hypertensive therapy including diuretics, calcium channel antagonists, angiotensin receptor blockers and angiotensin-converting enzyme inhibitors, in addition to beta blockers.[217]

In contrast to midlife HTN, late-life HTN has not been found to be associated with cognitive decline. In fact, the opposite may be true, with some studies demonstrating an association between the late life low systolic blood pressure and cognitive decline in elderly.[218] The Rotterdam and the Gothenburg studies reported that lower diastolic blood pressure in late-life was associated with increased risk of both cSVD and AD, especially among the users of antihypertensive medications.[219] In contrast, the Bronx Aging Study found that low diastolic blood pressure was associated with AD whereas the effect of low systolic blood pressure was inconsequential.[220] Yet other studies have suggested that the association of late-life hypotension and dementia risk exists for both systolic and diastolic hypotension.[221] Still others have reported that both mid and late life blood pressure may act in conjunction to increase the risk of dementia with lower late-life diastolic pressure and midlife HTN acting in conjunction in the development of late life dementia.[222]

The data presented demonstrates that a history of hypertension is strongly associated with baseline WMH volumes. In addition, the Δ change in SBP over a period of one year is significantly associated with the Δ change in WMH volumes. These results are in line with findings from the existing, published literature, supporting our hypothesis that lowering SBP may lead to regression of WMH lesion volumes and an overall decrease in WMH burden overtime.[223]

5.3 AD Conventional Biomarkers:

5.3.1 Imaging Markers:

T1-weighted MPRAGE imaging sequences can evaluate changes in cortical sulci volume (cross-sectionally) and atrophy (longitudinally) in hippocampus, parahippocampal gyrus, entorhinal cortex, posterior cortex, subcortical nuclei and amygdala, which are affected early in the course of disease for AD patients.[67, 68] T1-weighted sequences in particular, can aid the clinician and researcher in estimating MTA as an early neuroimaging marker of AD.[69] Semi-quantitative visual rating scales such as the Scheltens' scale, can be easily taught and assessed with routine clinical imaging in either two-dimensional or 3-dimensional sequences.[70] Evaluation of MTA is best performed in the coronal plane which allows more accurate visualization of medial temporal lobe volumes that are not affected by tangential slicing of these structures as can occur with axial and/or sagittal acquisitions in addition there are a number of automated and semi-automated post acquisition processing software packages that can provide voxel by voxel volumes allowing quantitative assessment of these and other discrete structures within the brain. Using T1-weighted sequences in the diagnosis of AD is practical as it is non-invasive, relatively inexpensive, recommended currently as part of the practice parameter for a valuation of memory loss and dementia, and is almost universally covered by all insurance and other third-party payers compared to the other imaging modalities.

Amyloid PET can be useful in differentiating dementia such as AD from other forms of dementia that do not include amyloid deposition as a pathologic feature such as Frontotemporal Dementia (FTD).[83, 84] The specificity of amyloid PET scans for Alzheimer's disease is low and positive scans are also frequently seen in cases of Dementia

with Lewy Bodies (DLB).[85, 86] Despite its limitations, Amyloid PET has been widely used to detect the pre-clinical stage of AD,[89] which has opened up new possibilities for secondary prevention trials in the area of AD. In addition, it is important to note that unlike CSF Aβ, Amyloid PET scans can detect the neuroanatomic extent and distribution of amyloid deposition.[224] However, it should be noted that amyloid PET scans are expensive and often not covered by insurance and other third-party payers.

fMRI is another imaging modality that being used for the diagnosis of early stages of AD. BOLD can demonstrate abnormalities in the hippocampus, inferior parietal lobe, medial temporal lobe and cingulate cortex in AD that may provide clues to a pure and/or mixed state.[90, 91] Exploration of fMRI is led to many contradictory findings however and was not included as a methodology examined in the current set of experiments.

5.3.2 CSF Aβ:

Parenchymal and vascular deposition of Aβ occurs very early in the course of AD.[225] Aβ deposition can result in an increased thickening of blood vessels' wall, vascular tone, vasoconstriction, and reduced cerebral blood flow,[226] eventually resulting in cerebral ischemia and the development of WMH. Cerebral Amyloid Angiopathy (CAA), characterized by the accumulation of Aβ protein in the walls of small-medium sized blood vessels and capillaries may be an important contributor to deficits in nutrient and oxygen exchange as well as to resultant tissue injury occurring at the microvascular level.[13] CAA can also be associated with intracerebral hemorrhage, WMH, and cSVD, in addition to Alzheimer's disease.[28, 29]

It is important to note that CSF Aβ is being widely used for the diagnosis of AD, however, this procedure carries a more than minimal risk to the patients as it is considered an invasive procedure. In this thesis, we chose to examine whether or not noninvasive MRI could prove useful for the diagnosis of AD in regards to WMH volume and distribution that could in many cases supplant or be used as an alternative diagnostic modality for AD.

5.4 Imaging Markers Used in the Current Study:

As discussed in detail in this dissertation, many imaging markers can be reliably used to diagnose AD, cSVD or both. We used well validated MRI structural and injury-associated imaging markers, including T1-weighted and FLAIR sequences. Both sequences were analyzed using simple visual rating scales such as the Scheltens scale for the MTA, Fazekas scale for the WMH and the Pasquier scale for the GCA. In addition, we performed more sophisticated volumetric measures using the T1-weighted and the FLAIR images to quantify the WMH and further determine the differences in the spatial distribution of the WMH associated with AD vs. cSVD.

Using these MRI biomarkers in novel ways to address our hypotheses prove their utility in diagnosis and differentiation of underlying AD and cSVD pathology. Using MRI in this fashion overcomes many of the impediments to routine biomarker diagnosis of AD and mixed pathologic disease states as it is considered relatively cheap and non-invasive when compared to the more expensive imaging modalities such as Amyloid PET and Tau PET scans and to more invasive procedures such as a spinal tap to collect CSF biomarkers.

5.5 cSVD is a Greater Contributor to GCA than AD:

Our data demonstrates that moderate to severe GCA seen on brain imaging studies should not be solely attributed to normal aging or AD. Instead, cSVD should be considered as the proximate cause of moderate-to-severe GCA in the majority of cases. Such understanding may help direct appropriate diagnosis and treatment strategies for those undergoing evaluation of memory complaints or more significant cognitive decline that have had structural imaging performed as part of the diagnostic workup.

5.6 AD and HTN are Associated with Spatially Distinct WMH:

Our study demonstrates that the effects of HTN and CSF $A\beta_{1\text{-}42}$ levels on WM injury may be additive rather than synergistic, with each associated with distinct spatial distributions of WMH. Considering such spatial distributions during routine diagnostic evaluation may improve diagnostic accuracy and further contribute to optimal development of treatment paradigms that address cSVD and AD, either separately or in combination. The present studies remain largely empiric and on the basis of our data it remains unclear as to whether the underlying pathophysiology and mechanisms of cerebral injury manifest as WMH are the same in the different brain regions identified as being independently associated with either AD or cSVD.

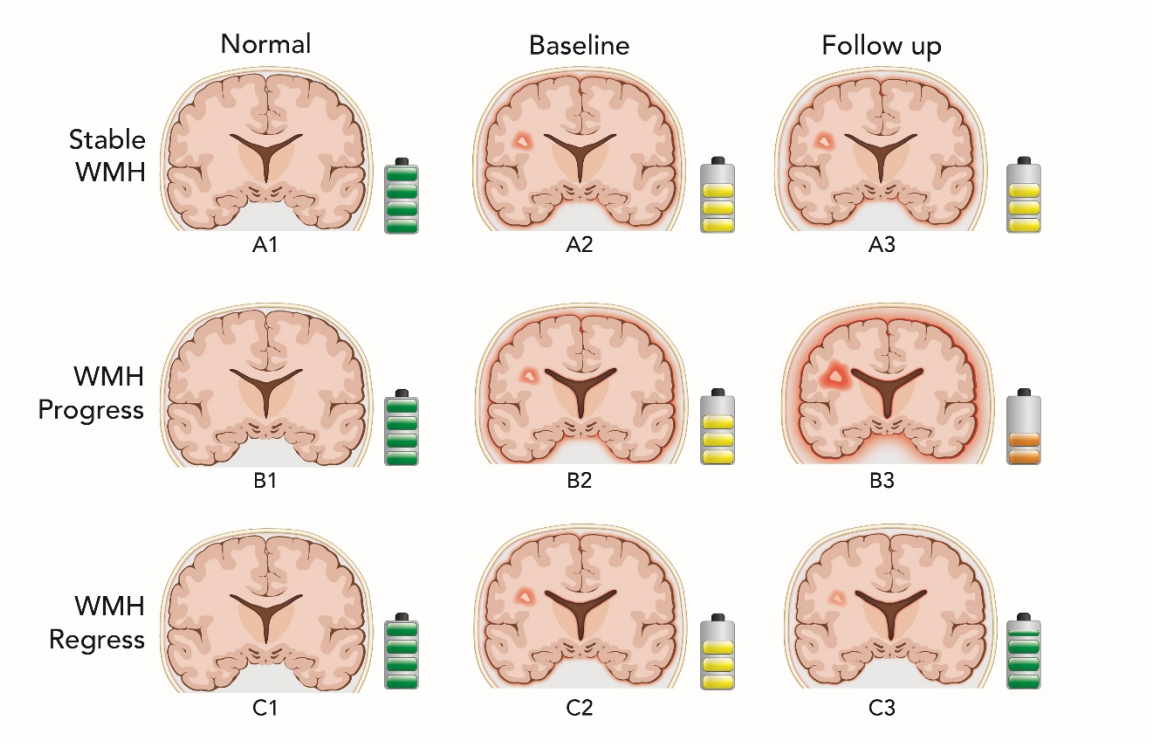
5.7 WMH are Dynamic with AD Participants Being More Likely to Progress:

Results from the third experiment in this thesis demonstrate that WMH regression is associated with decreased brain atrophy and improvement in memory performance over a period of 2-years compared to participants with progressive WMH changes (Figure 5.1).

There are several potential explanations for the WMH regression seen in this cohort. First, ischemic non reversible injury, may regress due to the process of gliotic contraction and micro- and or macroscopic encephalomalacia. In this setting one would expect increasing brain atrophy (due to encephalomalacia) in the follow up scan, but as the injury is static, one would expect no change in cognitive performance (Figure 5.2). Second, inflammation that is associated with irreversible ischemic injury, leading to WMH regression as a result of resolution of the inflammation and edema with restoration of normal function in the resolved inflammatory penumbra. If such an explanation were true, one would expect to see an increase in brain atrophy secondary to reduced inflammatory edema in such cases. However, we would expect some improvement in cognitive performance as a result of resolution of the inflammatory penumbra (Figure 5.2). Finally, it is possible that WMH regression could be the result of a healing or reparative process of ischemic injury. If such were true, one would expect to see reduced brain atrophy (no gliotic contraction or encephalomalacia in restored tissue) and improvement in the cognitive performance as a result of this healing process (Figure 5.2). The latter explanation may in part explain the characteristics associated with WMH regression seen in experiment #3 using the ADNI II cohort.

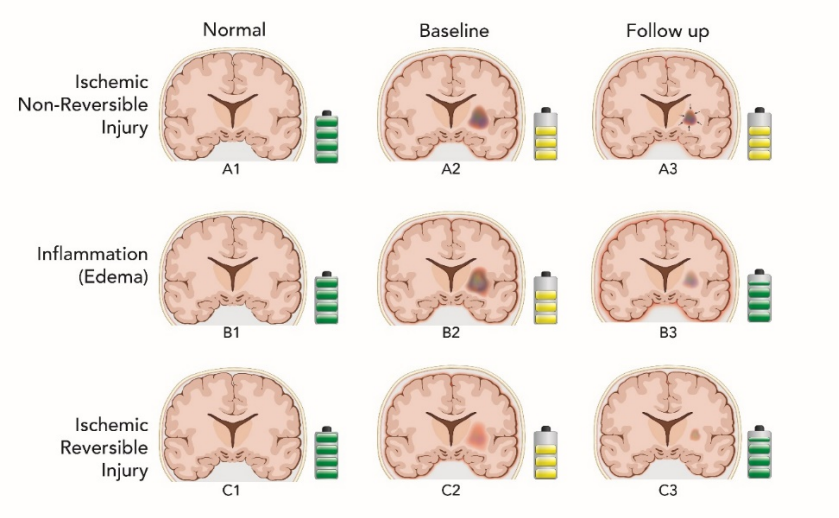
It is important to note that WMH regression was not associated with the CSF Aβ or Amyloid PET measures, suggesting that WMH regression may be primarily driven by CVR rather than AD processes. This observation suggests that aggressive management of SBP may be a possible target for future clinical trials to reduce the WMH burden and dementia that may exist independent of AD processes. In contrast, our data suggest that WMH

Figure 5.1 Descriptive figure showing the dynamic nature of the white matter hyperintensity changes overtime and the associated change in brain volume and cognitive performance.



The battery represents the memory performance. The upper row is showing a representation of how the white matter hyperintensity (WMH) remains stable in the follow up visit. Similarly, brain volume and memory remained stable in the follow up visit as shown in A2 and A3. The middle row is showing the progression of WMH over time. In B3 note how the WMH lesion is growing, the brain volume is remarkably reduced and the memory is getting worse compared to B2. Finally, the lower row is showing a representation of a WMH regression over time. In C3 note how the WMH lesion is shrinking, the brain volume is maintained or even minimally increase, and the memory is improving when compared to C2.

Figure 5.2 Decsriptive figure showing the possible mechanisms that lead to white matter hyperintensity regression overtime and their associated effect on the brain volume and the cognitive performance.



The battery represents the memory performance. The upper row is showing the first potential mechanism of white matter hyperintensity (WMH) regression, which is the ischemic non reversible injury. In A3 note how the WMH lesion contract (black arrows) and the brain volume is reducing when compared to A2. However, the memory performance did not change when compared to A2. The middle row is showing how inflammation as a potential cause of WMH regression. In B3 note that the lesion is shrinking, the brain volume is reducing and the memory is improving a little bit when compared to B2. Note that the difference between A3 and B3 is in memory performance. Finally, the lower row represents the third possible explanation of WMH regression, which is the most likely cause in our study. In C3 note that the WMH lesion is regressing, the brain volume and memory performance is increasing when compared to C2. Note that the difference between C3 and B3 is in the brain atrophy in which the latter showed more atrophy.

associated with AD processes are irreversible at present and almost universally will progress until such time as effective disease modifying therapies for AD are developed.

In support of this contention, participants with progressive WMH changes demonstrated increased atrophy, poorer memory performance, higher tau/Aβ and more temporal lobe amyloid deposition again attesting to an unrelenting AD pathologic progression (Figure 5.1). Irrespective of whether WMH progression is due to AD processes or to uncontrolled SBP, our data clearly demonstrate that WMH progression is associated with worsening memory [203-205] and greater brain atrophy.[126]

5.8 Overall Conclusion:

These data demonstrate that both AD and cSVD frequently coexist in the same brain, contributing differentially to alterations in brain structure, subcortical white matter injury, and cognitive function. These effects can be disentangled using MRI, and while we currently lack therapeutic interventions to halt or reverse AD, the dynamic WMH change evident in our data clearly suggests that the ability to reverse cSVD exists today.

5.9 Future Planned Studies:

Ongoing studies in these cohorts include an assessment of CVR and the relationship of specific CVD risks with the development and/or progression of WMH. In addition, our lab is actively exploring WMH change over time at the voxel level "WMH penumbra." This work is being done in collaboration with Ahmed Bahrani (a PhD candidate in biomedical engineering at the University of Kentucky). In brief, WMH penumbra represents areas of dynamic WMH changes over time. The penumbra surrounding the WMH core can be identified using FLAIR, diffusion tensor imaging (DTI) and arterial spin

labeling ASL sequences on MRI. While several groups have postulated the existence of a penumbra and we were able to demonstrate abnormalities in DTI and ASL in a proximal tissue sphere around WMH, we are the first to develop a precise WMH penumbra detection protocol using FLAIR images. This experiment is in its final phases and may potentially change our fundamental understanding of the WMH Penumbra phenomenon.

Further studies are needed to explore whether the distinct spatial patterns of WM alteration seen as a result of AD and or cSVD are associated with impairment of different cognitive processes, longitudinal clinical progression, and/or clinical outcomes. These data are also being used to further explore the development of an algorithmic, novel, non-invasive, neuroimaging marker for AD that includes previously identified structural determinations of medial temporal lobe and discrete cortical regional atrophy in conjunction with or novel WMH distribution patterns that are linked to Alzheimer's disease derived from experiment #2. The potential validation of such a biomarker algorithm may not only prove extremely useful for clinicians that currently lack inexpensive and noninvasive biomarkers for use in the routine clinical setting, but may also prove extremely cost-effective in identifying amyloid positive participants, irrespective of cognitive status, for participation in the burgeoning number of clinical trials for AD that are currently limited universally by an inability to reliably and cheaply identify those at risk.

Cumulative data from the experiments that comprise this thesis are also being used to help design early interventional trials in the area of cSVD. Such trials are focused on modulation of hypertension and exploration of biological change in WMH volume and distribution that will lead to more efficient clinical trials requiring fewer subjects, and less

invasive and costly means of determining pharmacodynamic effects of intervention than those currently available.

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older individuals without cognitive impairment. *Brain Structure and Function*. 2016;221:2135-46.
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late-life dementia: Perspective from the Honolulu Heart Program/Honolulu Asia Aging Study. *Hypertension*. 2010;55:1352-9.
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VITA

Name:

Omar M. Al-Janabi

Education and Degrees:

09/03 – 07/09	Bachelor of Medicine, Bachelor of Surgery (M.B.Ch. B) equivalent to the United States MD degree, College of Medicine, University of Tikrit, Tikrit, Salah Addin, Iraq.
08/14 – 05/16	Master of Science (with a major in Medical Sciences; M.S), College of Medicine, University of Kentucky, Lexington, KY.
08/16 – Present	PhD in Clinical and Translational Science, College of Medicine, University of Kentucky, Lexington, KY.

Awards and Honors:

07/09	Ranked as the second student (Distinction of Excellence) in my class at Tikrit University College of Medicine.
09/09	Received shield of top ranked Iraqi valedictorian for a distinguished performance in medicine. Office of Iraqi Vice President.
06/13	Academic Scholarship awarded by The Higher Committee for Education Development in Iraq (HCED Iraq) – Office of Iraqi prime minister, for being one of the top ranked Iraqi medical graduate in the year of 2009.
06/15	Outstanding Scientific Poster Award. Clinical Features of Mild Cognitive Impairment of the Cerebrovascular Type (MCI-CVD). Poster session presented at the 2015 Clinical and Translational Neuroscience Exposition, Lexington, KY
07/16	Awarded a scholarship to participate in the American Neurological Association's 8th Annual Translational and Clinical Research Course for Clinician-Scientists.
11/17	Outstanding Poster Award. Amyloid pathology and hypertension are associated with white matter injury through different mechanisms as assessed by FLAIR and DTI MRI. Poster number 26, presented at the Markesbery symposium on aging and dementia. Lexington, KY.

Work Experience:

1. Clinical: 4 years of clinical training including formal neurology residency training from (2009-2013) at Tikrit Teaching Hospital.

2. Research: 5 years of clinical research at Sanders-Brown Center on Aging / University of Kentucky from (2014-2019).

Publications:

- **Thesis:**
  Al-Janabi, Omar M., "Cerebrovascular Risk Factors, Arteriolar Sclerosis, and Cognitive Decline in The Kentucky Appalachian "Stroke-belt"" (2016). *Theses and Dissertations--Medical Sciences.* Paper 5.
  http://uknowledge.uky.edu/medsci_etds/5.

- **Published Articles:**
  Nelson, P. T., Trojanowski, J. Q., Abner, E. L., **Al-Janabi, O. M.**, Jicha, G. A., Schmitt, F. A., . . . Ighodaro, E. T. (2016). "New Old Pathologies": AD, PART, and Cerebral Age-Related TDP-43 With Sclerosis (CARTS). *Journal of Neuropathology & Experimental Neurology*, *75* (6), 482-498. doi: 10.1093/jnen/nlw033

  Al-Janabi, O. M., Panuganti, P., Abner, E. L., et al. Global Cerebral Atrophy Detected by Routine Imaging: Relationship with Age, Hippocampal atrophy, and White Matter Hyperintensities. *Journal of Neuroimaging*. doi: 10.1111/jon12494 https://www.ncbi.nlm.nih.gov/pubmed/29314393.

  Al-Janabi, O. M., Brown, C. A., Bahrani, A. A., et al. Distinct White Matter Changes Associated with Cerebrospinal Fluid Amyloid-β1 - 42 and Hypertension. *Journal of Alzheimer's Disease*. Doi 10.3233/JAD- 180663. https://content.iospress.com/articles/journal-of-alzheimers-disease/jad180663

- **Book Chapters:**
  Al-Janabi, Omar M., Bahrani, Ahmed A., Jicha, Gregory A (2017). Vascular Contributions to Alzheimer's Disease and Mixed Pathological Disease States. Avid Science. Alzheimer's Disease. Retrieved from http://www.avidscience.com/wp-content/uploads/2017/09/vascular-contributions-to-alzheimers-disease-and-mixed-pathological-disease-states.pdf.

- **Abstracts:**
  Omar M. Al-Janabi, Laura Hench, Erin L. Abner, Debra Moser, Gregory A. Jicha. (June 2015). Clinical Features of Mild Cognitive Impairment of the Cerebrovascular Type (MCI-CVD). Poster session at the 2015 Clinical and Translational Neuroscience Exposition, Lexington, KY.

Omar M. Al-Janabi, Ahmed Bahrani, Erin Abner, Charles Smith, Peter Nelson, Debra Moser, Gregory Jicha. (2016 April). Arteriolar Sclerosis and Cognitive Decline in the Kentucky Appalachian "Stroke-belt." Poster session (poster #35) at the 7th annual Midwest Graduate Research Symposium (MGRS), Toledo, OH.

Omar M. Al-Janabi, Ahmed Bahrani, Erin Abner, Charles Smith, Peter Nelson, Debra Moser, Gregory Jicha. (2016 April). Cerebrovascular Disease Risk Factors and Arteriolar Sclerosis in the Kentucky Appalachian "Stroke-belt." Poster session (poster #29) at the 11th annual CCTS conference, Lexington, KY.

Omar M. Al-Janabi, Charles D. Smith, Gregory A. Jicha (2016 September). Clinical impact of MRI-evident, deep vs periventricular T2 abnormalities on cognitive impairment in cerebrovascular disease and other leukopathologies. 2016 Clinical-Translational Research Symposium. Lexington, KY.

Omar M. Al-Janabi, Ahmed Bahrani, Erin Abner, Charles Smith, Peter Nelson, Debra Moser, Gregory Jicha. (2016 October). Cerebrovascular Disease Risk Factors, Arteriolar Sclerosis, and Cognitive Decline in the Kentucky Appalachian "Stroke-Belt". Poster confirmation number M208, presented at the American Neurological Association's (ANA) 2016 Annual Meeting. http://onlinelibrary.wiley.com.ezproxy.uky.edu/doi/10.1002/ana.24759/epdf.

Omar M. Al-Janabi, Ahmed Bahrani, Erin Abner, Pradeep Panuganti, Ronan Murphy, Shani Bardach, Allison Caban-Holt, Gregory Jicha. (2017 July). Cerebrovascular Disease and Alzheimer's Disease, but Not Aging, Are Associated with Moderate to Severe Global Cerebral Atrophy Seen on Clinical Brain Imaging Studies. Oral presentation #18115 at the Alzheimer's Association International Conference (AAIC). AAIC. London, England. http://www.alzheimersanddementia.com/article/S1552-5260(17)33005-4/abstract

Gregory A. Jicha, ***Omar M. Al-Janabi***, Ahmed Bahrani, Erin Abner, Ronan Murphy, Shani Bardach, Allison Caban-Holt. (2017 July). Clinical imaging, Cognitive, and Genetic Risk Profiles in Incident MCI for the Prediction of Long Term Neuropathological Outcomes at Autopsy. Poster presentation #18130 at the Alzheimer's Association International Conference (AAIC). AAIC. London, England. http://www.alzheimersanddementia.com/article/S1552-5260(17)32245-8/abstract.

Omar M. Al-Janabi, Christopher A. Brown, Ahmed A. Bahrani, Ronan Murphy, Charles D. Smith and Gregory A. Jicha. (September 2017). Cerebrovascular and Alzheimer's Disease Are Associated with Different Subcortical White Matter Microstructural Damage Mechanisms. Poster number H1, presented at Poster session at the 2017 Clinical and Translational Neuroscience Exposition, Lexington, KY.

Omar M. Al-Janabi, Christopher A. Brown, Ahmed A. Bahrani, Charles D. Smith and Gregory A. Jicha. (October 2017). Cerebrovascular and Alzheimer's contribute to subcortical ischemic injury via independent rather than synergistic mechanisms. Poster number S170, presented at the American Neurological Association's (ANA) 2017 Annual Meeting. San Diego, CA. http://onlinelibrary.wiley.com/doi/10.1002/ana.25024/epdf

Omar M. Al-Janabi, Christopher A. Brown, Ahmed A. Bahrani, Ronan R. Murphy, Donna Wilcock, Brian T. Gold, Larry B. Goldstein, Charles D. Smith and Gregory A. Jicha. (November 2017). Amyloid pathology and hypertension are associated with white matter injury through different mechanisms as assessed by FLAIR and DTI MRI. Poster number 26, presented at the Markesbery symposium on aging and dementia. Lexington, KY.

Ahmed A. Bahrani, ***Omar M. Al-Janabi***, Donna Wilcock, Charles D. Smith and Gregory A. Jicha. (November 2017). MRI volumetric quantification method: sources of variability. Poster number 35, presented at the Markesbery symposium on aging and dementia. Lexington, KY.

Omar M. Al-Janabi, Christopher A. Brown, and Gregory A. Jicha. (December 2017). Distinct spatial distribution of white matter hyperintensities associated with Alzheimer's disease pathology and hypertension. Department of Neurology's Trainee Research Day. Lexington, KY.

Omar M. Al-Janabi and Gregory A. Jicha. (December 2017). Visual rating of dementia associated features assessed by computed tomography vs. magnetic resonance imaging, is there a difference? Department of Neurology's Trainee Research Day. Lexington, KY.

Omar M. Al-Janabi, Christopher A. Brown, Ahmed A. Bahrani, Ronan R. Murphy, Donna Wilcock, Brian T. Gold, Peter T. Nelson, Larry B. Goldstein, Charles D. Smith and Gregory A. Jicha. Amyloid and hypertension are independently associated with white matter injury assessed by FLAIR and DTI MRI (poster number 174). Presented at the American Academy of Neurology 70th Annual Meeting. Los Angeles, CA. http://n.neurology.org/content/90/15_Supplement/P3.174

Omar M. Al-Janabi, Christopher A. Brown, Ahmed A. Bahrani, Ronan R. Murphy, Donna Wilcock, Brian T. Gold, Peter T. Nelson, Larry B. Goldstein, Charles D. Smith and Gregory A. Jicha. Distinct spatial distribution of white matter hyperintensities associated with Alzheimer's disease pathology and

hypertension (poster number 180). Presented at the American Academy of Neurology 70th Annual Meeting. Los Angeles, CA. http://n.neurology.org/content/90/15_Supplement/P3.180

Omar M. Al-Janabi, Ahmed A. Bahrani, Ronan R. Murphy, Peter T. Nelson, Charles D. Smith, Donna Wilcock and Gregory A. Jicha. Parietal Lobe Cerebral Microbleeds Are Associated with Lower Cerebrospinal Fluid Beta Amyloid 1-42 in Patients with Sporadic AD (poster number 40). Presented at the 13th annual CCTS conference, Lexington, KY.

Ahmed A. Bahrani, ***Omar M. Al-Janabi***, Guoqiang Yu, Donna Wilcock, Charles D. Smith and Gregory A. Jicha. Cerebral microhemorrhage volumetric method using susceptibility weighted imaging (poster number 284). Presented at the 13th annual CCTS conference, Lexington, KY.

Omar M. Al-Janabi, Christ Brown, Richard Murphy, Brian Gold, Larry Goldstein, Charles Smith, Donna Wilcock, Gregory Jicha. (March 2018). White Matter Alterations Due to Alzheimer's Disease and Hypertension Are Spatially Distinct. 10th Annual Postdoc Poster Session. Lexington, KY.

Omar M. Al-Janabi, Ahmed A. Bahrani, Ronan R. Murphy, Peter T. Nelson, Charles D. Smith, Donna Wilcock and Gregory A. Jicha. Parietal Lobe Cerebral Microbleeds Are Associated with Lower Cerebrospinal Fluid Beta Amyloid $_{1\text{-}42}$ in Patients with Sporadic AD. Presented at the Alzheimer's Association International Conference (AAIC) (poster number 25512). Chicago, Illinois.

Omar M. Al-Janabi, Pradeep Panuganti, Ronan R. Murphy, Peter T. Nelson, Charles D. Smith, Donna Wilcock and Gregory A. Jicha. Moderate-Severe Left Medial Temporal Lobe Atrophy Is Associated with Worse Cognitive Testing Scores in a Community Based Elderly Cohort. Presented at the Alzheimer's Association International Conference (AAIC) (poster number 25479). Chicago, Illinois.

Omar M. Al-Janabi, Ahmed A. Bahrani, Donna Wilcock, Charles D. Smith and Gregory A. Jicha. Eliminating the Sources of Variability in a Semi-Automated WMH Quantification Method. Presented at the Alzheimer's Imaging Conference (AIC) Preconference (poster number 25472). Chicago, Illinois.

Ahmed A. Bahrani, ***Omar M. Al-Janabi***, Donna Wilcock, Charles D. Smith, and Gregory A. Jicha. WMH Longitudinal Study Analysis Using Different Protocols. Presented (poster number 25536) at the Alzheimer's Imaging Conference (AIC) Preconference. Chicago, Illinois.

Omar M. Al-Janabi, Ahmed A. Bahrani, Peter T. Nelson, Charles D. Smith Donna Wilcock and Gregory A. Jicha. Exploring the Validity of Disease-Specific Masks as a Novel Non-Invasive Imaging Biomarker for Alzheimer's or Vascular

Associated White Matter Hyperintensities. Presented (poster number 27) at the Appalachian Translational Research Network. Lexington, KY.

Omar M. Al-Janabi, Christopher E. Bauer, Larry B Goldstein, Richard R Murphy, Ahmed A. Bahrani, Charles D. Smith, Donna M. Wilcock, Brian T Gold and Gregory A. Jicha. White Matter Hyperintensity Regression is Associated with Better Executive Function. Presented at the 3rd Annual Kentucky Neuroscience Institute Clinical-Translational Research Symposium. Lexington, KY.

Ahmed A. Bahrani, ***Omar M. Al-Janabi***, Donna Wilcock, Charles D. Smith, and Gregory A. Jicha. Semi-Automated Volumetric Quantifying Method of Cerebral Microhemorrhage Using T2-Weighted MRI Images. Presented (poster number M165) at American Neurological Association's (ANA) 2018 Annual Meeting. Atlanta, GA.

Omar M. Al-Janabi, Ahmed A. Bahrani, Peter T. Nelson, Charles D. Smith, Donna Wilcock and Gregory A. Jicha. Exploring the Validity of Disease-Specific Masks as a Novel Non-Invasive Imaging Biomarker for Alzheimer's or Vascular Associated White Matter Hyperintensities. Presented (poster number 2018-LB-810-ANA) at American Neurological Association's (ANA) 2018 Annual Meeting. Atlanta, GA.

Omar M. Al-Janabi, Christopher E. Bauer, Larry B Goldstein, Richard R Murphy, Ahmed A. Bahrani, Charles D. Smith, Donna M. Wilcock, Brian T Gold, and Gregory A. Jicha. White Matter Hyperintensities Regression Association with Less Brain Atrophy Measures in ADNI2. Department of Neurology's Trainee Research Day 2018. Lexington, KY.

Omar M. Al-Janabi, Christopher E. Bauer, Chintan Rupareliya, Larry B Goldstein, Richard R Murphy, Ahmed A. Bahrani, Charles D. Smith, Donna M. Wilcock, Brian T Gold, and Gregory A. Jicha. WMH Progression but not Regression is Associated with a Higher CSF tau/Aβ and Temporal Amyloid Concentration in The Amyloid PET Scan. Department of Neurology's Trainee Research Day 2018. Lexington, KY.

Presentations and Speaking Engagements:

2015 The 2015 Clinical and Translational Neuroscience Exposition. Al-Janabi, O. M., Clinical Features of Mild Cognitive Impairment of the Cerebrovascular Type (MCI-CVD). Lexington, KY.

2016 The 7th annual Midwest Graduate Research Symposium (MGRS). Al-Janabi, O. M., Arteriolar Sclerosis and Cognitive Decline in the Kentucky Appalachian "Stroke-belt." Toledo, OH.

2016 The 11th annual CCTS conference. Al-Janabi, O.M., Cerebrovascular Disease Risk Factors and Arteriolar Sclerosis in the Kentucky Appalachian "Stroke- belt." Lexington, KY.

2016 Department of Neurology Grand Rounds: "Vascular Cognitive Impairment – The Second Most Common Dementia?" Co-Presented with Dr. Ronan Murphy, University of Kentucky College of Medicine, Lexington, KY.

2017 Department of Neurology's Trainee Research Day: Cerebrovascular disease and Cerebrovascular disease and Alzheimer's disease, but not aging, are associated with moderate to severe global cerebral atrophy seen on clinical brain imaging studies. University of Kentucky College of Medicine, Lexington, KY.

2017 Markesbery symposium on aging and dementia. Amyloid pathology and hypertension are associated with white matter injury through different mechanisms as assessed by FLAIR and DTI MRI. Lexington, KY.

2017 Sanders-Brown Center on Aging. Visual rating of white matter hyperintensities and medial temporal lobe atrophy. Neuropathology consensus meeting. Lexington, KY.

2017 Department of Neurology's Trainee Research Day. Distinct spatial distribution of white matter hyperintensities associated with Alzheimer's disease pathology and hypertension. Lexington, KY.

2018 The 13th annual CCTS conference. Remember Alzheimer's Disease When Evaluating White Matter Hyperintensities as a Marker for Cerebral Small Vessels Disease. Lexington, KY.

2018 The 143rd Annual Meeting of the American Neurological Association. Plenary Session: Vascular Contribution to Neurodegeneration/Data Blitz Speaker. Atlanta, GA.

Invited Presentations:

2018 NIH/NINDS close session Mark VCID. The confound of comorbid Alzheimer's disease in subcortical white matter injury. Los Angeles, CA.

2018 University of Kentucky Impact week. A Non-Invasive Imaging Marker For Alzheimer's Disease. Lexington, KY.

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