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UNIVERSITY OF CALIFORNIA,
IRVINE

Beyond amyloid: contributions of cerebrovascular injury to Alzheimer's disease

DISSERTATION

submitted in partial satisfaction of the requirements
for the degree of

DOCTOR OF PHILOSOPHY

in Biological Sciences

by

Batool Rizvi

Dissertation Committee:
Professor Michael A. Yassa, Chair
Associate Professor Elizabeth Chrastil
Professor Elizabeth Head

2024

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DEDICATION

To my parents (Ammi and Abu),

for their unwavering support in my pursuit of higher education and a career in science.

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LIST OF KEY ABBREVIATIONS

Aβ	amyloid-beta
AD	Alzheimer's disease
ADDS	Alzheimer's Disease in Adults with Down Syndrome study
ANTs	Advanced Normalization Tools software
APP	amyloid precursor protein
ARIA	amyloid-related imaging abnormalities
ASHS	Automatic Segmentation of Hippocampal Subfields
ASL	arterial spin labeling
ATN	amyloid-tau-neurodegeneration
BEACoN	Biomarker Exploration in Aging, Cognition, and Neurodegeneration
CAA	cerebral amyloid angiopathy
CI	cognitively impaired
CS	cognitively stable
CU	cognitively unimpaired
CVID	cerebrovascular injury and dysfunction
CBF	cerebral blood flow
DBP	diastolic blood pressure
DMTs	disease modifying therapies
DS	Down syndrome
ERC	entorhinal cortex
FLAIR	fluid attenuated inversion recovery
MRI	magnetic resonance imaging
GFAP	glial fibrillary acidic protein
MCI	mild cognitive impairment
MTL	medial temporal lobe
NIA-AA	National Institute on Aging and Alzheimer's Association
PCA	posterior cerebral artery
PHC	parahippocampal cortex
PP	pulse pressure
PRC	perirhinal cortex
PVS	perivascular spaces
RAVLT	Rey Auditory Verbal Learning Test
SBP	systolic blood pressure
SSDOH	structural and social determinants of health

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MANUSCRIPTS IN PROGRESS

Rizvi, B., Yassa, M. A. (In Progress). Shifting the Paradigm: Overcoming the Hyperfocus on Amyloid Mechanisms and Therapeutics in Alzheimer's Disease

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ORAL PRESENTATIONS

Rizvi, B., Adams, J. N., Kim, S., Sathishkumar, M., Taylor, L., McMillan, L., Brickman, A. M., Yassa, M. A. Education moderates the associations of white matter hyperintensities with memory and Alzheimer's disease biomarkers. Oral Presentation: International Neuropsychological Society Meeting; 2024 Feb, New York, NY.

Rizvi, B., Adams, J. N., Granger, S., Kim, S., Sathishkumar, M., Larson, M. S., Tustison, N. J., McMillan, L., Brickman, A. M., Greenia, D., Corrada, M. M., Kawas, C. H., Yassa, M. A. Posterior cerebral artery-defined white matter hyperintensities are associated with memory and transentorhinal volume. Oral presentation: Learning and Memory Conference; 2023 April, Huntington Beach, CA.

Rizvi, B., Adams, J. N., Sathishkumar, M., Kim, S., Larson, M. S., Tustison, N. J., McMillan, L., Brickman, A. M., Greenia, D., Corrada, M. M., Kawas, C. H., Yassa, M. A. Vascular territory-defined WMH, amyloid, and medial temporal subregional integrity. Oral Presentation: International Neuropsychological Society Meeting; 2023 Feb, San Diego, CA.

Rizvi, B., Lao, P. J., Igwe, K. C., Abrams, C. Laing K. K., Chesebro A. G., Banerjee, A., Manly, J. J., Brickman, A.M. Feeling older than you are: The relationship between subjective age and cortical thickness. Selected for Oral Presentation: International Neuropsychological Society Meeting, 2020 Feb, Denver, CO.

Rizvi, B., Narkhede, A., Budge, M., Colon, J., Hale, C., Igwe, K.C., Manly, J. J., Schupf, N., Mayeux, R., Brickman, A. M. Fiber Tract-defined regional white matter hyperintensities and Memory. Oral Presentation: International Neuropsychological Society Meeting; 2018 Feb, Washington, D.C.

ABSTRACTS / POSTER PRESENTATIONS

Rizvi, B., Adams, J. N., Bamford, A., Sathishkumar, M., Kim, S., McMillan, L., Brickman, A. M., Mapstone, M., Thomas, E. A., Yassa, M. A. (2024) Interplay of inflammatory, vascular, and Alzheimer's disease biomarkers in cognitively unimpaired older adults. Alzheimer's Association International Conference; 2024 July, Philadelphia, PA.

Rizvi, B., Adams, J. N., Sathishkumar, M., Kim, S., Larson, M. S., Tustison, N. J., McMillan, L., Brickman A. M., Mapstone, M., Thomas, E. A., Greenia, D., Corrada, M. M., Kawas, C. H., Yassa, M. A. The Interplay of vascular disease, peripheral interleukin-6, beta-amyloid, and memory in older adults. Human Amyloid Imaging Conference; 2023 Jan, Miami, Florida.

Rizvi, B., Lao, P. J., Sathishkumar, M., Laing K. K., Igwe, K. C., McMillan, L., … Brickman, A. M., Yassa., M. A., Associations of Pulse Pressure with Alzheimer's Disease-Related Structural Imaging Markers and Memory in Adults with Down Syndrome. International Neuropsychological Society 50th Annual Meeting; 2022 Feb 2-4, Virtual/Online.

Rizvi, B., Sathishkumar, M., Marquez, F., Granger, S. J., McMillan, L. , Brickman, A. M., Tustison N. J., Yassa M. A., Associations between regional white matter hyperintensities, medial temporal lobe subregional volumes, and memory in older adults. Poster presented at: Society for Neuroscience 50th Annual Meeting; 2021 Nov 8 - 11, Virtual/Online.

Rizvi, B., Lao, P. J., Brickman, A. M. Blood pressure is associated with tau pathology independent of beta-amyloid. Poster presented at: Alzheimer's Association International Conference (AAIC), 2020, Virtual/Online.

Rizvi, B., Lao, P. J., Chesebro, A.G., Igwe, K.C., Amarante, E., Beato, J.M., Rivera, A., Gutierrez, J., Schupf, N., Zahodne, L. B., Manly, J. J., Mayeux, R., Brickman, A. M. Regional white matter hyperintensities predict Alzheimer's-like neurodegeneration. Poster presented at: Alzheimer's Association International Conference (AAIC), 2020, Virtual/Online.

Rizvi, B., Narkhede, A., Last, B.S., Guzman, V., Manly, J. J., Mayeux, R., Brickman, A.M. The relationship between white matter hyperintensities and cognition and the mediating role of cortical thickness. Poster presented at: International Neuropsychological Society 45th Annual Conference; 2017 Feb 1-4, New Orleans, LA.

Rizvi, B., Kamal, T., Leung J.M. Perioperative sleep disruption in older surgical patients. Poster presented at: UCSF Anesthesia Research Day; 2015 Dec, San Francisco, CA.

Kamal, T., **Rizvi, B.**, Leung, J.M. Correlation of end tidal anesthetic concentration with anesthetic depth as measured by patient state index, a processed EEG. Poster presented at: Stanford-UCSF Poster Retreat; 2015 Mar, Millbrae, CA

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ABSTRACT OF THE DISSERTATION

Beyond amyloid: contributions of cerebrovascular injury to Alzheimer's disease

by

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Doctor of Philosophy in Biological Sciences
University of California, Irvine, 2024
Professor Michael A. Yassa, Chair

While the current criteria for defining Alzheimer's disease (AD) primarily consider amyloid pathology, increasing evidence suggests that other key factors, such as cerebrovascular injury and neuroinflammation, also contribute to memory decline among older adults. We asked how white matter hyperintensities (WMH), vascular risk factors, and neuroinflammatory markers impact neurodegeneration and memory dysfunction in the context of aging and AD. Our goal is to enhance our understanding of these non-amyloid pathologies so that they can be integrated into mechanistic models of AD and influence future therapeutic interventions.

My first study (Chapter 1) investigated whether WMH and medial temporal lobe (MTL) subregional volumes are linked to memory performance in older adults at risk for AD. I found that posterior WMH, in particular, were associated with hippocampal and rhinal cortical volumes, which in turn predicted memory performance. Importantly, the relationship between WMH and memory was fully mediated by perirhinal cortical volume, indicating that cerebrovascular injury may drive memory decline by exacerbating neurodegeneration in specific MTL subregions. These results were published in Rizvi et al. (2022).

In my second study (Chapter 2), I extended my investigation of cerebrovascular risk and pathology to a sample of older adults with Down syndrome (DS), a genetic condition that predisposes adults to AD. Interestingly, individuals with DS are less prone to hypertension but remain vulnerable to cerebrovascular injury. In this sample, I found that higher pulse pressure

was associated with increased posterior WMH. Higher pulse pressure was also associated with dementia diagnosis, which was mediated by WMH and neurodegenerative changes. This work highlights the critical role of vascular health in cognitive outcomes for individuals with DS, even in the absence of classic hypertension. These results were published in Rizvi et al. (2024b).

In my third study (Chapter 3), I focused on upstream pathologies that may lead to cerebrovascular injury and dysfunction. In particular, I studied the role of neuroinflammation in AD, revealing two distinct pathways involving plasma markers YKL-40 and GFAP. YKL-40 was related to cerebrovascular injury, while GFAP was linked to amyloid-beta (Aβ) deposition. Both pathways converged on tau pathology, leading to MTL atrophy and memory deficits. These findings point to neuroinflammation as a key component of AD, and to the parallel and convergent pathways by which it impacts tau-mediated neurodegeneration and cognitive decline. These results have been submitted for publication and posted to bioRxiv (Rizvi et al., 2024a).

Collectively, these findings emphasize the critical contributions of vascular injury, vascular health, and neuroinflammation to neurodegeneration and memory loss in older adults. They suggest that both WMH and inflammatory markers are important predictors of AD-related cognitive decline, with implications for interventions to preserve brain health and mitigate memory impairment in at-risk populations.

CHAPTER 1: BACKGROUND AND SIGNIFICANCE

1.1. Public health and societal relevance of Alzheimer's disease

In 2024, approximately 6.9 million Americans aged 65 years and older are living with Alzheimer's disease (AD), and globally, over 55 million are affected with AD and other dementias ("2024 Alzheimer's disease facts and figures," 2024). The profound impact on the affected individuals, families, caregivers, healthcare systems, and society, along with the significant economic burden, calls for an urgent and innovative response from the field. As both the U.S. and global populations continue to age and life expectancy rises, the number of individuals affected by AD and the associated psychosocial and economic burdens are expected to increase exponentially ("2024 Alzheimer's disease facts and figures," 2024).

1.2. Amyloid hypothesis and current definition of Alzheimer's disease

AD is typically recognized as a progressive neurodegenerative disorder characterized by the accumulation of amyloid-beta (Aβ) plaques, neurofibrillary tau tangles, neurodegenerative changes, and cognitive decline. In 1991, Hardy, Allsop, and Selkoe introduced the Amyloid Cascade Hypothesis (Hardy & Allsop, 1991; Selkoe, 1991), which was later reinforced in 1992 by Hardy and Higgins (Hardy & Higgins, 1992). This hypothesis redefined how Alzheimer's disease would be understood, diagnosed, and treated. They proposed that accumulation of Aβ triggers a cascade of events including the aggregation and spread of neurofibrillary tau tangles, neuroinflammation, and neuronal loss, ultimately leading to dementia. Their work highlighted that Aβ is derived from the proteolytic cleavage of amyloid precursor protein (APP). In a more recent review (Selkoe & Hardy), Selkoe and Hardy reaffirmed that in both genetic and sporadic forms of AD, Aβ accumulates, the genetic forms due to mutations in genes such as APP, PSEN1, or PSEN2, and the sporadic forms due to failures in Aβ clearance. However, despite prevalent support for the amyloid hypothesis, many researchers have also questioned or

outright rejected the hypothesis (Herrup, 2015; Kepp et al., 2023a; Pimplikar, 2009; Reitz, 2012). For example, Herrup (2015) argues that the linear pathway of disease progression proposed from the amyloid cascade hypothesis, from Aβ to AD dementia, is inadequate as a disease model, and should be rejected. He presents compelling evidence against the hypothesis, such as the finding that overexpression of the human APP in mouse models does not result in tau tangles, neurodegeneration, or AD-like dementia. The failure to observe human-like AD progression in these models suggests there is insufficient evidence for the amyloid hypothesis. Critics of the hypothesis note this lack of additional AD-associated pathology may explain the translational gap between preclinical findings and clinical trial outcomes (Wu et al., 2022).

Furthermore, in human studies, Aβ burden has not been consistently linked to cortical neurodegeneration in patients with mild cognitive impairment (MCI) or AD (Chételat et al., 2010; La Joie et al., 2012). More than a quarter of individuals with Aβ accumulation do not develop dementia-like symptoms (Haroutunian et al., 1998; Jansen et al., 2022). Compared to other biomarkers, Aβ shows a weaker association with cognitive decline and clinical outcomes (Khosravi et al., 2019; Terry et al., 1991). Additionally, another reported that up to 40% of cognitively normal older adults exhibited neurodegeneration without elevated Aβ levels, with neurodegeneration being more strongly associated with worse memory and executive function than Aβ deposition (Wirth et al., 2013).

The single-pathway cascade, where Aβ accumulates early in the disease process, followed by tau deposition, neurodegeneration and eventual cognitive decline (Figure 1.1), has been widely adopted in research frameworks.

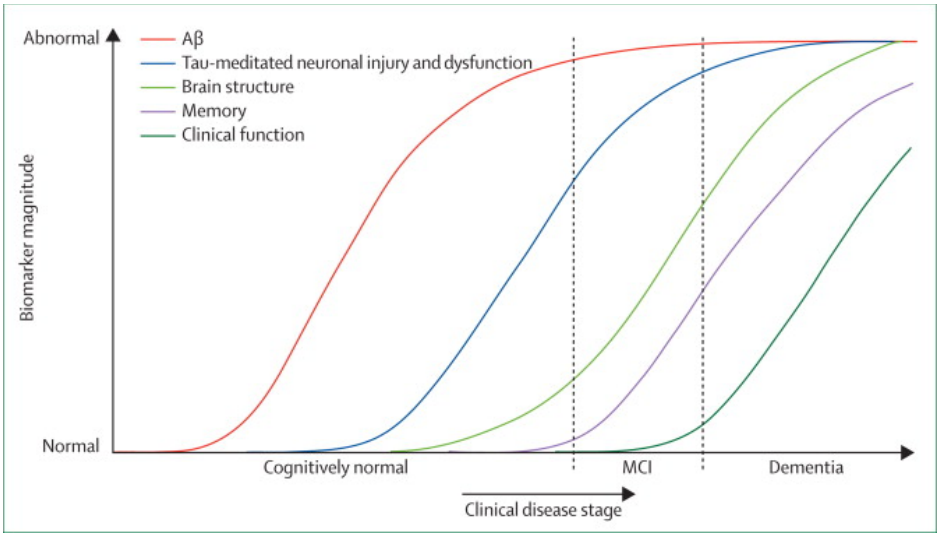

Figure 1.1. Model demonstrating temporal ordering of AD-related biomarkers and subsequent cognitive and clinical impairment (Jack et al., 2010).

In 2018, the National Institute on Aging and Alzheimer's Association (NIA-AA) committee led and introduced a research and theoretical approach that incorporated a contemporary view of the amyloid hypothesis. This approach, known as the AT(N) framework – characterized Alzheimer's disease based on the presence of amyloid-beta Aβ (A), tau tangles (T). With this framework, the definition of AD shifted from a clinical syndrome characterized by symptoms to a biologically driven definition. In 2023, a working group, now solely led by AA, introduced a new diagnostic definition of AD, in which Aβ alone is sufficient to diagnosis. Notably, neurodegeneration was removed as a core biomarker in this updated diagnostic framework (Jack Jr et al., 2024).

1.3. Influence of the Alzheimer's disease framework on clinical trials and current treatments

As a result of changes in the theoretical framework of AD, which now primarily focuses on Aβ and tau as the core defining features of the disease, numerous "disease modifying therapies" (DMTs) have been pursued in clinical trials to limited success (Cummings et al., 2018). These

DMTs were designed to alter the progression of AD, following models similar to those portrayed in Figure 1.1 (Huang et al., 2023; Jack et al., 2010) (see Figure 1.1). However, the lack of clinically meaningful benefits has raised doubts about the amyloid hypothesis. Notable examples of unsuccessful anti-amyloid antibody therapies include Solanezumab and Gantenerumab, both of which failed to meet their primary endpoints (Fedele, 2023; Lozupone et al., 2024).

At present, the only FDA-approved AD treatment is Lecanemab, which selectively binds to soluble Aβ aggregates (Cummings et al., 2023; Hoy, 2023). In the CLARITY AD trial, Lecanemab was reported to slow cognitive decline, as measured by the Clinical Dementia Rating - Sum of Boxes (CDR-SB) by 27% compared with placebo, or an absolute difference of 0.45 points (Kepp et al., 2023b). However, a 0.45-point difference on the 18 point CDR-SB scale is considered to not be clinically meaningful. The minimal clinically important difference (MCID), which assesses whether the magnitude of the drug's effect compared to placebo is clinically relevant, has been suggested to be 0.98 points for those with mild cognitive impairment (MCI) and 1.63 for those with mild AD (Andrews et al., 2019).

Significant safety concerns are associated with these anti-amyloid antibody therapies, which may have long-term consequences for patients. In the phase 3 of the Lecanemab trial, amyloid-related imaging abnormalities (ARIA) were observed, either with edema or effusion (ARIA-E) or with microhemorrhages or hemosiderosis (ARIA-H) (Van Dyck et al., 2023). ARIA-E was reported in 12.6% of the Lecanemab group compared to 1.7% in the placebo group, while ARIA-H occurred in 17.3% of the Lecanemab group versus 9.0% in the placebo group (Van Dyck et al., 2023).

With targeting Aβ remaining at the forefront of AD therapies, other promising targets have been largely neglected. The original amyloid hypothesis and the more recent research and diagnostic framework proposed by Jack et al. heavily influenced therapeutic targets considered in AD

clinical trials. Despite over a hundred ongoing clinical trials (Cummings et al., 2018), the majority of which are focused on Aβ, there is a pressing need for alternative approaches, possibly including multi-targeted ones.

1.4. Alternative neurobiological causes and targets of Alzheimer's disease

As Korczyn and Grinberg (Korczyn & Grinberg) noted, while specific subpopulations – such as individuals with autosomal dominant Alzheimer's disease or with Down syndrome – may exhibit Aβ and tau tangles as the initial pathogenic triggers as described by the amyloid hypothesis, it is likely unreasonable to generalize this hypothesis to the entire AD population.

Rather than a singular explanation, evidence supports a multifactorial perspective of AD, where multiple systems might fail and interact at various stages of the disease. Among the diverse alternative pathways contributing to AD, four key categories are briefly highlighted: excitation/inhibition imbalance, neuroinflammation, cerebrovascular injury, and oxidative stress.

1. Excitation/inhibition imbalance

Research shows there is cortical and hippocampal hyperexcitability in the earlier stages of AD, followed by hypoactivation in later stages, which coincides with neurodegeneration (Bassett et al., 2006; Targa Dias Anastacio et al., 2022). Hyperactivity in individual neurons, brain regions, and networks, as observed in both rodent models and humans, has emerged as an early biomarker of AD (Busche & Konnerth, 2015). Previous work used high-resolution fMRI to study activity profiles of the dentate gyrus and CA3 in young and older adults and found evidence for functional rigidity in these areas leading to age-related memory decline (Yassa et al., 2011). A recent review covers evidence supporting the close relationship between hyperactivation and in vivo markers of AD pathology (Corriveau-Lecavalier et al., 2024). Neuronal hyperexcitability and functional hyperactivation are now considered potential therapeutic targets, offering the possibility of cognitive improvement and disease modification (Mohs et al., 2024; Toniolo et al., 2020).

2. Neuroinflammation

Microglia and astrocytes play central roles in the neuroinflammatory response. When microglia are activated, they undergo morphological changes to reach injury sites and release cytokines and neurotoxic agents (Calsolaro & Edison, 2016). It is believed that microglial activation occurs early in the disease process, then subsides, before steadily increasing again as Aβ and tau accumulate (Ismail et al., 2020). Understanding the stages of inflammation in relation to each phase of AD could guide the timing, location, and pathways for new immunomodulatory strategies (Onyango et al., 2021).

3. Cerebrovascular injury

Cerebrovascular disease is present in most cases of dementia, with growing evidence strongly it is a key feature of AD. Vascular risk factors, increased inflammation, and genetic predispositions contribute significantly to cerebrovascular disease. One of the earliest markers of vascular dysregulation in AD is reduced blood flow, or hypoperfusion (Eisenmenger et al., 2023). Magnetic resonance imaging (MRI) allows for the detection of small vessel cerebrovascular disease markers, including white matter hyperintensities, microbleeds, perivascular spaces, and microinfarcts. These markers are potentially modifiable, correlate with cognitive decline in aging, and serve as strong predictors of AD onset.

4. Oxidative stress

Oxidative stress results from an imbalance between pro-oxidants and antioxidants. Antioxidants protect against reactive oxygen species, which damage cellular macromolecules and induce neuronal apoptosis (Bai et al., 2022; Schieber & Chandel, 2014). Increasing evidence links free radicals to the aging process and AD. Neurons, being post-mitotic, are particularly vulnerable to mitochondrial dysfunction and calcium dysregulation, which leads to synaptic oxidative damage (Ionescu-Tucker & Cotman, 2021). Potential therapies aimed at reducing oxidative stress,

including antioxidants supplements, calorie restriction, and physical activity, are being explored as ways to mitigate AD-related decline (Ionescu-Tucker & Cotman, 2021).

1.5. Underrecognized risk factors of Alzheimer's disease

There is an underrecognized importance of risk factors that increase the likelihood for AD dementia, potentially exacerbating one or more of the previously mentioned neurobiological pathways contributing to disease burden. Among these risk factors, we will highlight and briefly discuss vascular risk factors, sex and hormonal differences, health equity, and structural and social determinants of health. How these factors interact or act independently to influence AD pathology remains largely unknown.

1. Vascular risk factors

An updated 2024 Lancet Commission report highlighted that addressing 14 modifiable risk factors could potentially prevent or delay 45% of dementia cases. These risk factors include less education, hypertension, hearing impairment, high LDL cholesterol, smoking, obesity, depression, physical inactivity, diabetes, low social contact, excessive alcohol consumption, traumatic brain injury, air pollution, and vision loss (Livingston et al., 2024). The report underscores the need for lifelong strategies to reduce risk, while combining public health approaches to personalized interventions. Other reviews similarly suggest the need for multimodal approaches to reduce dementia risk by addressing these modifiable risk factors (Takeda et al., 2020).

2. Sex/Gender differences and hormonal risk factors

Nearly two-thirds of individuals diagnosed with AD are women ("2024 Alzheimer's disease facts and figures," 2024). While this disparity is often attributed to women's longer lifespans, research remains inconclusive as to whether longevity is the only factor. Sex-specific biological factors and gender-related sociocultural factors also play critical roles (Beam et al., 2018). Despite

having similar AD biomarker burden, women demonstrate greater brain reserve and resilience to tau pathology compared to men. Research by Buckley et al. (2022) found that menopause status moderated sex differences in tau burden, where post-menopausal women showed higher tau-PET signal than age-matched men. Additionally, there is a growing need to investigate whether women respond differently than men to AD-related therapies (Lynch, 2024). For example, recent monoclonal anti-amyloid therapies like Lecanemab have shown reduced efficacy in women (Kurkinen, 2023).

3. Structural and social determinants of health

The prevalence of AD is approximately twice as high among Black older adults compared to White older adults ("2024 Alzheimer's disease facts and figures," 2024). Despite clear evidence of disparities, a clear understanding of upstream factors driving such differences is limited (Adkins-Jackson et al., 2023). Social determinants of health include factors such as economic stability, social and community context, access to and quality of health care, educational and occupational settings, and neighborhood environments (Adkins-Jackson et al., 2023). These factors are inequitably distributed across populations, due to social, economic, political, and historical power structures. These structural and social determinants of health (SSDOH) contribute to negative outcomes of brain health and exacerbate disparities in AD risk and incidence (Adkins-Jackson et al., 2023).

1.6 Increased risk of Alzheimer’s disease in Down syndrome

While AD is prevalent in the neurotypical or the general population, it poses a unique set of challenges and questions in populations with genetic predispositions, including individuals with Down syndrome (DS). People with DS have an extra copy of chromosome 21, which also carries the APP gene. The triplication and overexpression of the APP gene leads to the accumulation of Aβ. Nearly all individuals with DS develop Aβ plaques and tau tangles by the age of 40, and over 90% face risk of AD clinical dementia by the age of 65 (Fortea et al., 2021;

McCarron et al., 2017). With improvements in healthcare and treatment, adults with DS are living longer (de Graaf et al., 2017), making them more susceptible to age-dependent processes of AD. Due to the high prevalence of AD in this population, the long-term consequences of AD on individuals with DS, families, caregivers and society makes it a public health issue. The progression of AD in adults with DS mirrors the pattern in the neurotypical or general population, including the hallmark features of AD such as Aβ and tau tangles. Understanding the pathophysiology and mechanisms involved in AD in adults with DS will inform us about the neurobiological pathways and clinical course of AD that takes place in the neurotypical population.

1.7. Markers of cerebrovascular injury and dysfunction

Cerebrovascular injury is a significant contributor to both the risk and progression of clinical AD (Barnes et al., 2009; Schneider & Bennett, 2010), yet it is often thought to be a comorbidity rather than a core feature of the disease (Jack et al., 2010; Jack et al., 2024). Cerebrovascular disease is typically thought to be largely driven by vascular risk factors, such as hypertension, diabetes, obesity, and hyperlipidemia. It can be broadly organized into large and small vessel disease. The most common, chronic, and progressive form of cerebrovascular disease is cerebral small vessel disease, also known as cerebrovascular injury and dysfunction (CVID). CVID affects the smallest cerebral blood vessels, including arterioles, capillaries, and venules (Li et al., 2018b; Pantoni, 2010). Key MRI findings of CVID include white matter hyperintensities (WMH), enlarged perivascular spaces, microbleeds, infarcts, and impaired cerebral blood flow (CBF).

WMH are areas of increased signal intensity (see Figure 1.2) that appear on T2-weighted fluid attenuated inversion recovery (FLAIR) scans. They reflect demyelination and axonal degeneration, often resulting from arteriosclerotic changes and gliosis. Of interest, WMH are also associated with reduced cerebral blood flow (CBF), as measured by arterial spin labeling

(ASL), compared to normal-appearing white matter (Brickman et al., 2009b). While considerable evidence suggests WMH have a vascular origin, an alternative hypothesis is that they may partially be secondary to AD-related processes, such as tau pathology. It is hypothesized that tau pathology leads to WMH formation through Wallerian degeneration (Garnier-Crussard et al., 2023; McAleese et al., 2017).

Cerebral microbleeds are small hypointense lesions, or hemorrhages, seen on susceptibility-weighted and gradient-recalled echo T2* MR sequences. When distributed in posterior brain regions, cerebral microbleeds can also be associated with cerebral amyloid angiopathy (CAA). Enlarged perivascular spaces appear hyperintense on T2-weighted MRIs and are fluid-filled cavities surrounding small penetrating vessels. Enlarged perivascular spaces tend to expand with age (Wardlaw et al., 2013). Lastly, cerebral blood flow (CBF), the volume of arterial blood reaching brain tissue per unit of time (Ferre et al., 2013), is a sensitive marker for detecting perfusion abnormalities (Lacalle-Aurioles et al., 2014).

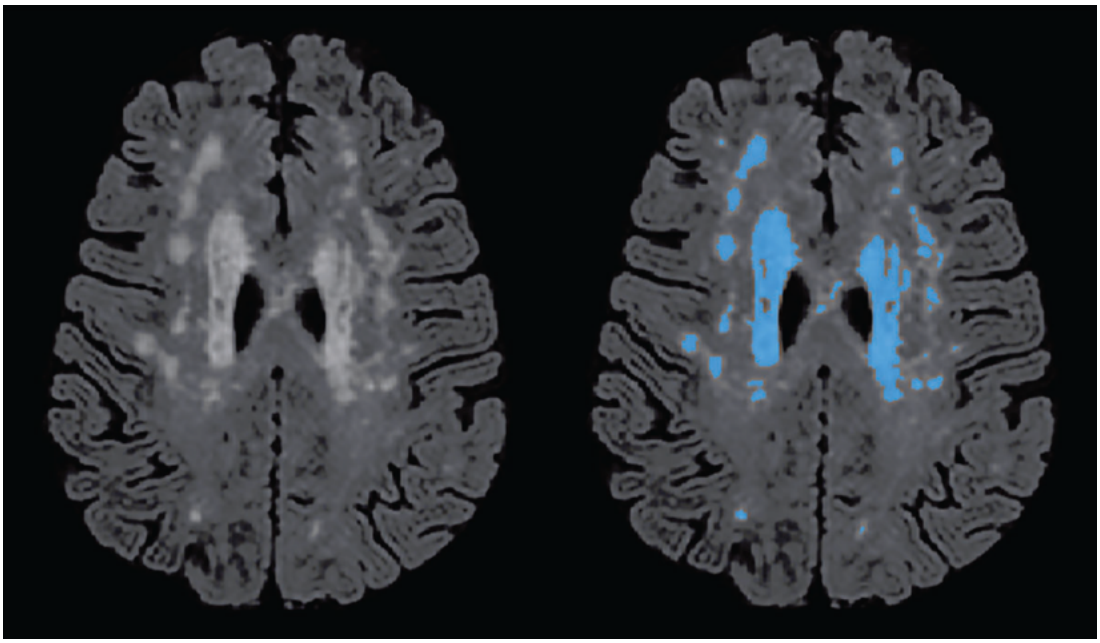

Figure 1.2. Axial views of FLAIR images with unlabeled WMH on the left, and labeled WMH on the right (Rizvi et al., 2021).

1.8. The role of white matter hyperintensities in memory decline

WMH burden increases with aging due to microvascular changes in cerebral small arteries, small veins, and capillaries. WMH are strong predictors of cognitive functioning (Debette & Markus, 2010; Gunning-Dixon & Raz, 2000), and both the severity and distribution of WMH can affect the risk and progression of Alzheimer's disease (Alosco et al., 2013; Brickman). These lesions have been linked to impairment and decline across cognitive domains including processing speed, executive function, attention, and memory (Gunning-Dixon & Raz, 2000; Kaskikallio et al., 2019; Rizvi et al., 2018).

While earlier research primarily focused on the link between WMH and executive function, a growing body of evidence now suggests that WMH are a sensitive marker for memory impairment. Understanding the regional or spatial specificity of WMH has become increasingly important in determining whether they would be a strong predictor of memory decline. For example, regional specificity of WMH can be further explored by examining WMH within white matter tracts. In a community-based sample of older adults, we found that WMH in association and projection tracts were related to memory (Rizvi et al., 2018; see Figure 1.3).

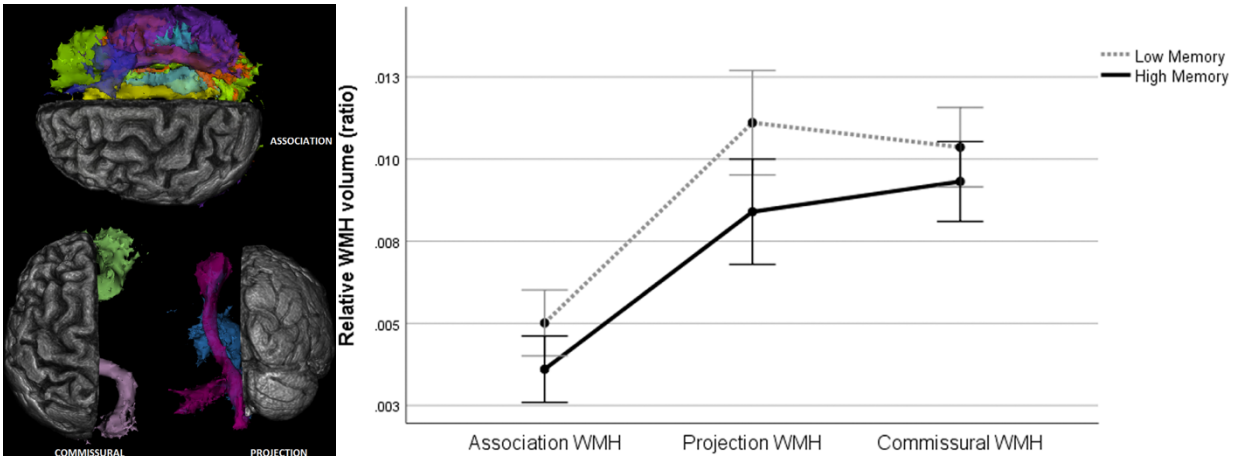

Figure 1.3. 3D rendering of cortex and association, projection, and commissural tracts are shown on the left. Line graph, depicting that those with worse memory performance had higher association and projection tract-defined WMH, is shown on the right (Adapted from Rizvi et al., 2019).

1.9. The association of white matter hyperintensities with amyloid-beta and tau

A systematic review of the associations between Aβ and WMH burden demonstrated that amyloid accumulation and WMH are independent yet additive processes (Roseborough et al., 2017). However, posterior WMH was found to be an independent predictor of CAA, even in the absence of lobar microbleeds (Thanprasertsuk et al., 2014). Additionally, a longitudinal study revealed that that baseline WMH predicted the progression of amyloid burden, especially in parieto-occipital regions (Grimmer et al., 2012).

A more recent study showed that increased WMH was associated with higher plasma tau concentration, particularly in those diagnosed with Alzheimer's disease (Laing et al., 2020). The same study, using a mouse model, revealed that mice subjected to transient middle cerebral artery occlusion showed elevated plasma and cerebrospinal fluid tau concentrations, along with induced myelin loss and hyperphosphorylated tau pathology. However, alternative hypotheses suggest that tau pathology and other neurodegenerative processes may partially lead to WMH progression. For example, McAleese et al. (2015) found that cortical tau pathology correlated with white matter abnormalities in postmortem tissue, pointing to a neurodegenerative rather than a vascular origin.

1.10. The effect of white matter hyperintensities on cortical thinning

While vascular risk factors have been linked to increased rates of cortical thinning (Gonzalez et al., 2015; Seo et al., 2012), fewer studies have examined whether WMH promote cortical atrophy over time (Kim et al., 2020; Raz et al., 2007). In a previous study involving a community sample of older adults, we found that CVID, as measured by WMH, was associated with a pattern of cortical thinning similar to that observed in the early stages of AD (Rizvi et al., 2021) (see Figure 1.4.).

Increased parietal WMH were associated with left entorhinal cortical thinning over four years, while both total and parietal WMH were associated with frontal and parietal cortical thinning. These changes in cortical thinning were linked to worse memory. We further found that the association between WMH and cortical thinning was strongest among Black participants (Rizvi et al., 2021).

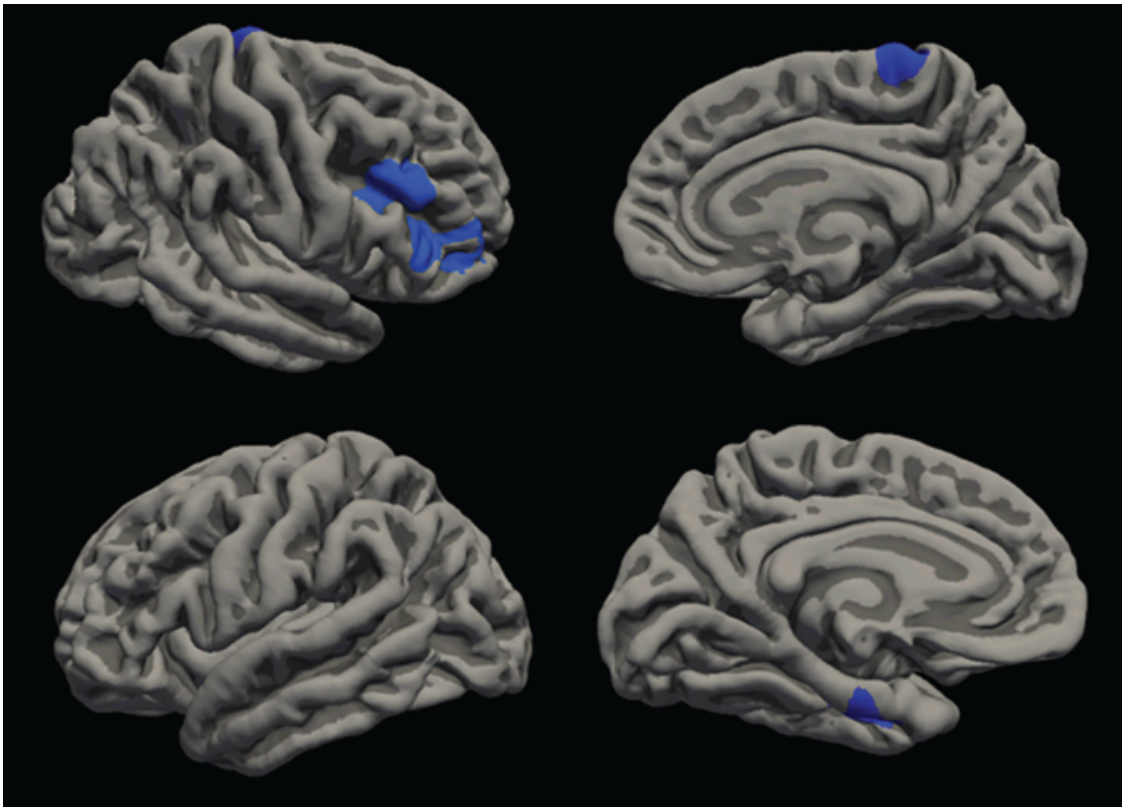

Figure 1.4. Areas of cortical thinning that are associated with regional WMH are depicted in blue (Rizvi et al., 2021).

1.11. Roles of vascular risk factors and cerebrovascular injury in Down syndrome

As individuals with Down syndrome (DS) reach 50 years of age, most exhibit sufficient Aβ and tau pathology to meet the clinical criteria for AD (Fortea et al., 2020; Fortea et al., 2021; McCarron et al., 2017). However, there is significant variability in the age of onset, severity, and

the progression of dementia among this population (Fortea et al., 2021; Mann & Esiri, 1989). While some studies show lower levels of classical vascular risk factors in individuals with DS (Wilcock et al., 2016), others reveal higher risk for other health comorbidities. For instance, rates of hypertension and atherosclerosis are reduced, while rates of obesity and sleep apnea are higher in individuals with DS. Despite the lowered prevalence of atherosclerosis, findings of cerebrovascular abnormalities on magnetic resonance imaging (MRI) are frequently observed, including WMH, enlarged perivascular spaces (PVS), microbleeds, and infarcts (Lao et al., 2020).

MRI studies and postmortem findings indicate high rates of cerebral microbleeds that are likely associated with CAA (Vinters, 1987). In a recent study conducted by Lao et al. (2020), it was observed that the severity of white matter hyperintensities (WMH) increases across Alzheimer's disease-related diagnostic groups, with more pronounced distribution in the posterior brain regions.

1.12. The role of neuroinflammation on Alzheimer’s disease pathology

Neuroinflammation is an inflammatory response in the central nervous system, secondary to neuronal insult. Microglia and astrocytes are two types of cells that play central roles in the neuroinflammatory response. Microglia are important for neurogenesis, regeneration, as well as in phagocytosis (Calsolaro & Edison, 2016). When activated, they undergo morphological changes and reach the site of injury, releasing neurotoxic agents and cytokines. Astrocytes are macroglial cells that have important roles in neurogenesis, synaptogenesis, formation, and maintenance of the blood-brain barrier (BBB) (Calsolaro & Edison, 2016). While acute neuroinflammation can be protective, chronic neuroinflammation leads to long-term microglial activation, worsening neuronal injury and stimulating further microglial activation in a cyclic manner (Cherry et al., 2014). Furthermore, when amyloid plaques form in the brain, microglia surround these plaques and become reactive, which has been linked to plaque growth (d’Errico

et al., 2022). One study found that as tau tangles develop in Aβ positive MCI cases, the increase in tau is associated with higher levels of inflammation (Ismail et al., 2020).

1.13. Neuroinflammation and cerebrovascular injury

Neuroinflammation, similar to how it responds to AD pathology, can cyclically exacerbate cerebrovascular injury. Activated glial cells can impact BBB integrity, and BBB dysfunction can amplify the neuroinflammatory response (Takata et al., 2021). Although traditional vascular risk factors are recognized to significantly contribute to WMH development, there is growing evidence of neuroinflammation as an additional critical factor. Several candidate neuroinflammatory markers have been identified to predict an increase in WMH burden, including YKL-40, C-reactive protein (CRP), GFAP, and IL-6 (Satizabal et al., 2012; Shir et al., 2022; Van Dijk et al., 2005; Zhang et al., 2023).

1.14. Unanswered questions and basis for dissertation research

Given that AD is a multifactorial disease and rarely exists in its pure form with the sole presence of Aβ and tau, it is essential to investigate other underlying mechanisms and contributors. Past and current AD treatments, which are mostly amyloid antibodies, have not been clinically effective in delaying or improving cognitive symptoms in older adults (Panza et al., 2019). It is therefore critical to broaden our consideration of other therapeutic targets and interventions. One significant contributor to AD onset and progression is cerebrovascular injury, measured as WMH, which are associated with potentially modifiable factors and neuroinflammation (Lin et al., 2024; Walsh et al., 2021). Our understanding of the link between WMH and episodic and long-term memory is less evident, and the mediating roles of neurodegeneration of specific MTL subregions have not been investigated. Moreover, while both neuroinflammation and vascular health are upstream factors contributing to WMH burden, it is unclear which specific measures of the two umbrella categories are strongly associated with cerebrovascular injury. Furthermore,

the mechanistic cascade of cerebrovascular pathology and their parallel and convergent roles with amyloidosis to downstream markers is yet to be explored.

My dissertation addresses these novel areas of investigation. In Chapter 2, we test whether regionally specific WMH are linked to memory impairment in older adults without dementia, and whether this is mediated by MTL subregional atrophy. The findings of this chapter were published in Rizvi et al. (2023). In Chapter 3, we investigate how pulse pressure affects cerebrovascular pathology in adults with DS, and whether it is related to dementia diagnosis through the structural markers of WMH and neurodegeneration. These findings were published in Rizvi et al. (2024b). In Chapter 4, we study if two upstream neuroinflammatory markers are distinguishably associated with WMH and Aβ, and whether this converges to downstream markers of tau, neurodegeneration, and subsequent memory deficits in older adults without dementia. These findings were recently submitted as a preprint to bioRxiv (Rizvi et al., 2024a).

CHAPTER 2: POSTERIOR WHITE MATTER HYPERINTENSITIES ARE ASSOCIATED WITH REDUCED MEDIAL TEMPORAL LOBE SUBREGIONAL INTEGRITY AND LONG-TERM MEMORY IN OLDER ADULTS

2.1. Introduction

White matter hyperintensities (WMH) are regions of increased brightness that are best visualized on T2-weighted fluid-attenuated inversion recovery (FLAIR) magnetic resonance imaging (MRI) and are a radiological marker of small vessel cerebrovascular disease (Moran et al., 2012). WMH are associated with reduced cognitive function in older adults without dementia (Brugulat-Serrat et al., 2020; Gunning-Dixon & Raz, 2000). Much of the work involving the contributions of WMH on cognitive functions in healthy older adults has thus far focused on the decline of processing speed and executive functioning (Geerlings et al., 2009; Gunning-Dixon &

Raz, 2000; Prins et al., 2005), while the impact of WMH on memory specifically is less well characterized and studied (Rizvi et al., 2020; Swardfager et al., 2018). Importantly, WMH also contribute to both the onset and progression of Alzheimer's disease (AD) and related pathophysiology (Brickman, 2013; Laing et al., 2020; Mortamais et al., 2014; Prasad et al., 2011). Supporting this line of work, WMH are implicated specifically in age- and AD-related neurodegeneration, providing some evidence of atrophy of medial temporal lobe (MTL) structures (Rizvi et al., 2021; Rizvi et al., 2018; Swardfager et al., 2018; Tosto et al., 2015). However, the relationship between WMH and MTL subregional atrophy has been understudied.

The MTL plays a crucial role in episodic memory. In particular, the hippocampus and rhinal cortices are necessary for the encoding and consolidation of new episodic and semantic memories (Eichenbaum, 2000; Squire et al., 2004). Neurodegeneration of MTL subregions is linked to memory loss, both in aging and in AD. Hippocampal subfields including CA1 and the dentate gyrus (DG) undergo selective atrophy in aging and AD, changes that are, in turn, associated with substantial memory decline (Apostolova et al., 2010; De Flores et al., 2015; Wisse et al., 2014). Additionally, extra-hippocampal MTL cortical regions such as the perirhinal cortex and the entorhinal cortex are especially sensitive to effects of AD pathophysiology, including regional accumulation of tau pathology (Holbrook et al., 2020; Olsen et al., 2017; Sone et al., 2017; Xie et al., 2020).

Despite evidence of both cerebrovascular related structural changes and MTL subregional atrophy in aging and AD, these two lines of work have been investigated mostly separately, and how these two features might be linked to memory decline has remained unclear. Additionally, while most of the work on WMH and cognition applies measures of global WMH burden, other studies point to the utility of investigating the effects of regionally specific WMH on cognition (Birdsill et al., 2014; Garnier-Crussard et al., 2022; Rizvi et al., 2021; Rizvi et al., 2020). Likewise, the study of MTL atrophy subregionally, including hippocampal subfields and extra-

hippocampal subregions, allows us to further understand these regionally specific associations (Chauveau et al., 2021; Xie et al., 2020)

In the current study, we first determined whether regional WMH accumulation is associated with memory outcomes. We focused on word list delayed recall performance as assessed by the Rey Auditory Verbal Learning Test (RAVLT). We tested the hypothesis that regional patterns of WMH accumulation will be associated with MTL subregional volumes in older adults without dementia, and subsequently tested whether these MTL subregional volumes are related to delayed recall performance. Finally, using a mediation model, we tested the hypothesis that the association of WMH with memory performance is through their impact on MTL subregional volume.

2.2. Methods

Participants

One-hundred thirty-nine participants were included in the study. Eighty-seven community-dwelling adults were part of the Biomarker Exploration in Aging, Cognition, and Neurodegeneration (BEACoN) study, 23 were recruited from the UCI Alzheimer's Disease Research Center (ADRC) longitudinal cohort, and 29 were recruited from the 90+ Study of the Oldest Old. All participants gave written informed consent and were compensated for their participation; study procedures are in agreement with the Institutional Review Board of the University of California, Irvine. The study was carried out in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki). The study only included participants who underwent both MR imaging (T2- and T1-weighted MRI) and neuropsychological testing. Participants were included if they had performed RAVLT and had structural images analyzed. A total of N=139 participants with RAVLT measures had WMH (including n=130, missing n=9) and/or MTL volume data (included n=134, missing n=5). None of the participants were

diagnosed with dementia at the time of testing. However, a subset of them (n=18) received a diagnosis of cognitive impairment (either mild cognitive impairment – MCI (n=4), cognitive impairment/no dementia – CIND (n=6), or questionable cognitive impairment – QCI (n=8)). This subset of participants is color coded in all association plots. Demographic characteristics of the participants based on the whole sample and separately by cohorts are included in Table 1.

Magnetic Resonance Imaging

For the BEACoN and 90+ cohorts, magnetic resonance imaging (MRI) data were acquired on a 3.0 Tesla Siemens Prisma scanner at the Facility for Imaging and Brain Research (FIBRE) at the University of California, Irvine. The following scans were acquired: Structural T1-weighted MPRAGE (resolution = 0.8 x 0.8 x 0.8 mm, repetition time = 2300 ms, echo time = 2.38 ms, FOV read = 256 mm, slices = 240, slice orientation = sagittal), T2-weighted fluid-attenuated inversion recovery (FLAIR; resolution = 1.0 x 1.0 x 1.2 mm, repetition time = 4800 ms, echo time = 441 ms, FOV read = 256 mm, slices = 160, inversion time = 1550 ms, slice orientation = sagittal) and T2-Turbo Spin Echo (resolution = 0.4 mm x 0.4 mm x 2.0, repetition time = 5000 ms, echo time = 84 ms, FOV read = 190 mm). For the ADRC cohort, MRIs were acquired on a 3 Tesla Philips scanner. The following scans were acquired: Structural T1-weighted MPRAGE (resolution = 0.54 x 0.54 x 0.65 mm, repetition time = 11 ms, echo time = 18 ms, FOV = 240 mm x 231 mm x 150 mm, slices = 231, slice orientation = sagittal), T2-weighted FLAIR (FLAIR; resolution = 0.65 x 0.87 x 4 mm, repetition time = 11000 ms, echo time = 125 ms, FOV = 230 mm x 103 mm x 119, slices = 24, inversion time = 2800 ms, slice orientation = transverse) and T2-Turbo Spin Echo (resolution = 0.47 mm x 0.47 mm x 2 mm, repetition time = 3000 ms, echo time = 80 ms, FOV = 180 mm x 180 mm x 109 mm).

MRI analyses

White matter hyperintensities segmentation

Image processing leveraged the open-source ANTsX software ecosystem (Tustison et al., 2021) with a particular focus on specific deep learning applications developed for neuroimaging made available for both Python and R via the ANTsXNet (ANTsPyNet/ANTsRNet) libraries. Specifically, for the work described here, WMH segmentation and lobar parcellation (see Figure 2.1B) based on the Desikan-Killiany-Tourville (DKT) cortical labels (Klein & Tourville) employed the two ANTsPyNet functions respectively: sysu_white_matter_hypterintensity_segmentation and desikan_killiany_tourville_labeling.

In conjunction with the International Conference on Medical Image Computing and Computer Assisted Intervention (MICCAI) held in 2017, a challenge was held for the automatic segmentation of WMH using T1-weighted and FLAIR images (Kuijf et al., 2019). The winning entry used a simplified preprocessing scheme (e.g., simple thresholding for brain extraction) and an ensemble (n=3) of randomly initialized 2-D U-nets to produce the probabilistic output (Li et al., 2018). Importantly, they made both the architecture and weights available to the public. This permitted a direct porting to the ANTsXNet libraries with the only difference being the substitution of the threshold-based brain extraction with a deep-learning approach (Tustison et al., 2021). All WMH masks resulting from the above automated segmentation procedure were manually edited by an expert rater (B.R.) for improved accuracy.

The segmentation above was followed by lobar parcellation. The process involved an automated, deep learning-based DKT labeling protocol for T1-weighted images, which was described in Tustison (2014) in the context of cortical thickness. Briefly, data from several neuroimaging studies described in Tustison (2021) were used to train two deep learning networks—one for the “inner” (e.g., subcortical, cerebellar) labels and one for the “outer” cortical labels.

After an individual T1-weighted scan was labeled with the cortical DKT regions, the six-tissue (i.e., CSF, gray matter, white matter, deep gray matter, cerebellum, and brain stem) segmentation network was applied to the skull stripped image. Cortical labels corresponding to the same hemispheric lobes were combined and then propagated through the non-CSF brain tissue to produce left/right parcellations of the frontal, temporal, parietal, and occipital lobes, as well as left/right divisions of the brainstem and cerebellum. Left and right lobar WMH volumes were derived and summed across hemispheres. Due to a positively skewed distribution and values of zero within our WMH data, we square root transformed all regional and total WMH data. WMH volumes were not corrected for TIV, as the expected WMH burden for any head size is still zero (Gunning-Dixon & Raz, 2003) and prior work demonstrating a relationship between WMH volumes and cortical thickness used non-adjusted WMH volumes (Rizvi et al., 2021; Rizvi et al., 2018).

MTL subregional volumes

Medial temporal lobe subregions including hippocampal subfields were automatically segmented with the Automatic Segmentation of Hippocampal Subfields (ASHS) (Yushkevich et al., 2015) software using T1 and T2-weighted images. The ASHS pipeline implements joint label fusion and corrective learning to accurately segment hippocampal subfield volumes and cortical medial temporal lobe subregions. The resulting output included volumes of the following subregions in native T2 space: CA1, CA2, CA3, dentate gyrus (DG), subiculum, entorhinal cortex (ERC), perirhinal cortex subdivided into Brodmann Areas 35 and 36 (PRC; BA35, BA36), and parahippocampal cortex (PHC) volumes (see Figure 2.1C). Left and right subregional volumes were summed to provide total subregional volumes. The resulting total subregional volumes were then adjusted for total intracranial volume (TIV), by dividing the total subregional volume by the individual's TIV. The ratios were then multiplied by 1000: (MTL subregional

volume / TIV) x 1000. TIV was obtained by implementing ANTs brain extraction and creating a binary brain mask and calculating total volume of the brain mask.

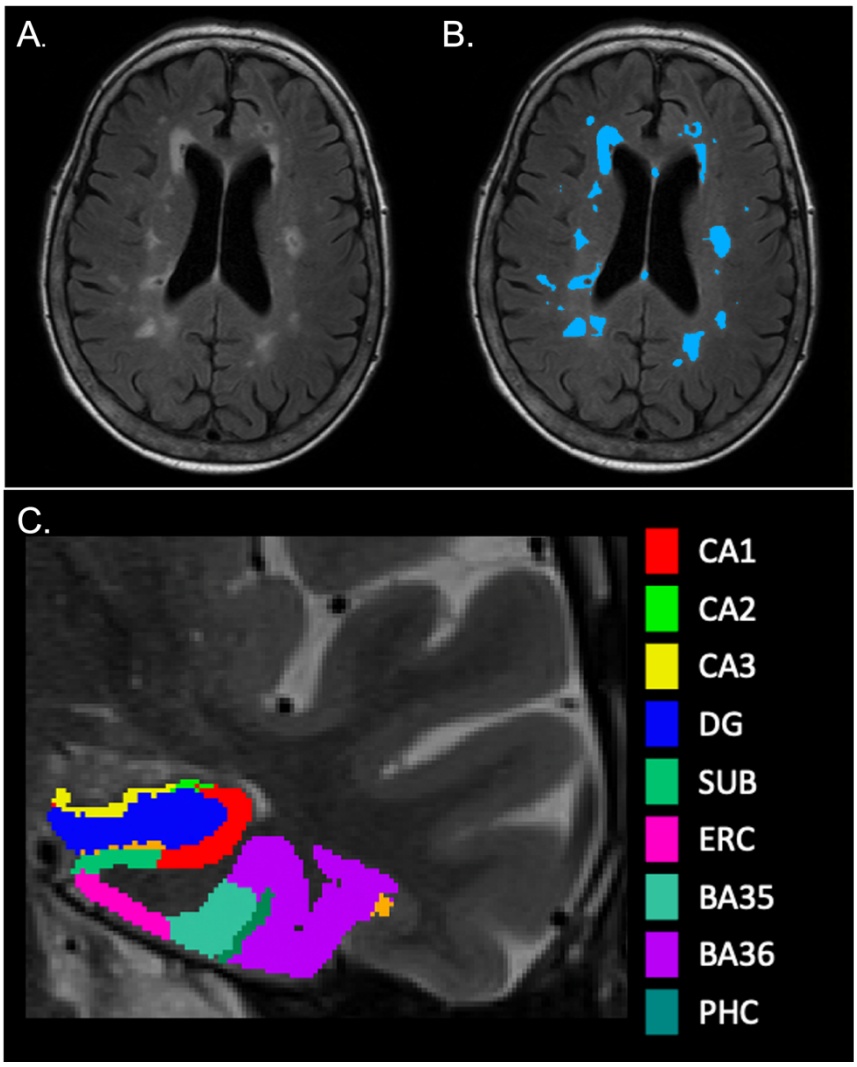

Figure 2.1. (A). Axial view of a FLAIR image with unlabeled WMH. **(B)**. Axial view of a FLAIR image with labeled WMH. **(C)**. Coronal view of a T2-weighted image with MTL segmentation from ASHS. PHC is not captured in this image slice.

Neuropsychological Testing

Participants were administered the Rey Auditory Verbal Learning Test (RAVLT), which assesses word list learning and memory, including rate of learning, retention, and recognition memory. RAVLT delayed recall has is sensitive to age-related memory decline (Andersson et al., 2006; Vakil & Blachstein, 1997), and thus was used as the outcome measure of primary

interest. Other outcome measures of RAVLT, including learning slope, percent forgetting, retroactive interference and recognition, are reported in supplemental tables.

Statistical Analysis

Statistical analyses were performed using SPSS Statistics v. 28. The first three sets of analyses below were performed using linear regressions. In the first set of analyses, we tested the separate associations between regional and total WMH and RAVLT delayed recall scores. We report associations between regional and total WMH and other RAVLT outcome measures in Appendix A Supplemental Table A1. In the second set of analyses, we tested associations between regional WMH and total MTL subregional volumes in separate models. For associations found to be significant between regional WMH and MTL total MTL subregional volumes, we report associations with the regional WMH and lateralized (left and right) MTL subregional volumes in Appendix A Supplemental Table A2. MTL subregions that were significantly associated with regional WMH were subsequently included in the third set of analyses to separately test the association between the specific MTL subregions and RAVLT delayed recall. We report associations with between specific MTL subregions and other RAVLT outcomes measures in Appendix A, Supplemental Table A3. The associations between the lateralized (left and right) MTL subregional volumes and RAVLT delayed recall are reported in Appendix A, Supplemental Table A4. All regression models adjusted for age, sex, and education. For analyses testing associations between regional WMH and MTL subregions, multiple comparisons were corrected for using the Holm-Bonferroni method. We then conducted mediation models that tested the effect of regional WMH on delayed recall, with MTL subregional volume(s) mediating this relationship, while adjusting for age, sex, and education. Regional WMH that were associated with MTL subregional volumes were included as the independent variable; MTL subregional volumes that were associated with delayed recall were included as the mediator(s). We used SPSS PROCESS macro v.3.5 (processmacro.org),

written by Andrew F. Hayes (Hayes, 2017) to perform the mediation models. A standard mediation model (model 4) was used with the previously defined independent, mediating, and dependent variables. We applied a 95% confidence interval (CI) with 5000 bootstrap samples to examine indirect effects. As post-hoc analyses, we tested whether findings would remain when we included cognitive or diagnostic status as an additional covariate in the above models, and separately tested whether effect sizes of findings were similar when study cohort was added as an additional covariate in the above models.

2.3. Results

One-hundred thirty-nine participants (88 F, mean age = 76.95 $\pm$ 10.61) were included in the study. Table 2.1 displays their demographic and other summary characteristics.

Table 2.1. Demographics and Summary Variables

Characteristics	Whole Sample	BEACoN	ADRC	90+
N	139	87	23	29
Age, mean (SD) years	76.95 (10.61)	71.54 (6.28)	76.46 (7.99)	93.60 (2.21)
Sex, n (%) Women	88 (63.3%)	58 (66.7%)	12 (52.2%)	18 (62.1%)
Education, mean (SD) years	16.11 (2.62)	16.46 (2.26)	16.17 (2.62)	15.03 (3.36)
Diagnostic Category, n (%)				
Cognitively normal	121 (87.1%)	87 (100%)	13 (56.5%)	21 (72.4%)
Cognitively impaired*	18 (12.9%)	0	10 (43.5%)	8 (27.6%)
Race and Ethnicity, n (%)				
White	115 (81.6%)	68 (78.2%)	19 (82.6%)	28 (96.6%)
Asian	18 (13.6%)	14 (16.1%)	4 (17.4%)	0
Black	1 (<1%)	1 (1.1%)	0	0
More than 1 race or Other	3 (2.2%)	4 (4.5%)	0	1 (3.4%)
Hispanic	5 (3.6%)	3 (3.4%)	0	1 (3.4%)
Vascular Risk History†, n (%)				
Heart disease	6 (4.3%)	1 (1.1%)	2 (8.7%)	3 (10.3%)
Stroke	0	0	0	0
Diabetes	10 (7.2%)	7 (8%)	1 (4.3%)	2 (6.9%)
Sleep apnea	24 (17.3%)	19 (21.8%)	3 (13%)	2 (6.9%)
High blood pressure	34 (25.7%)	16 (19.5%)	18 (17.3%)	13 (44.8%)

Square-root WMH volume, mean (SD)				
Total WMH	1.90 (1.49)	1.54 (1.21)	2.55 (1.86)	2.60 (1.62)
Frontal WMH	1.19 (0.96)	0.97 (0.86)	1.6 (1.33)	1.58 (1.11)
Temporal WMH	0.24 (0.13)	0.20 (0.25)	0.40 (0.47)	0.24 (0.15)
Parietal WMH	0.93 (0.96)	0.69 (0.74)	1.28 (1.22)	1.50 (1.10)
Occipital WMH	0.50 (0.39)	0.37 (0.26)	0.84 (0.41)	0.63 (0.30)
Neuropsychological Tests				
RAVLT delayed recall (Raw)	9.45 (4.11)	11.05 (3.26)	7.91 (4.57)	5.86 (3.32)
RAVLT delayed recall (Adj. T)$^{\lambda}$	50 (9.89)	51.52 (9.49)	46.23 (12.54)	48.31 (7.76)
MTL Subregional volumes (TIV adj.)				
CA1	1.62 (0.32)	1.75 (0.25)	1.19 (0.20)	1.50 (0.27)
CA2	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)	0.03 (0.01)
CA3	0.09 (0.03)	0.10 (0.02)	0.05 (0.02)	0.11 (0.03)
Dendate gyrus	1.02 (0.19)	1.10 (0.15)	0.76 (0.13)	0.94 (0.17)
Subiculum	0.61 (0.10)	0.64 (0.09)	0.52 (0.10)	0.59 (0.08)
Entorhinal cortex	0.72 (0.15)	0.78 (0.11)	0.50 (0.10)	0.68 (0.13)
BA 35 (Transentorhinal cortex)	0.69 (0.12)	0.73 (0.11)	0.58 (0.07)	0.64 (0.71)
BA 36 (Perirhinal cortex)	2.53 (0.47)	2.70 (0.36)	1.78 (0.24)	2.47 (0.41)
Parahippocampal cortex	1.27 (0.29)	1.38 (0.26)	0.91 (0.16)	1.16 (0.21)

* Cognitively Impaired category consists of those with QCI (n=4), MCI (n=6), and CIND (n=8) under the whole sample.† Vascular Risk History: self-reported as current or past diagnoses, with n=7 missing data. $^{\lambda}$ T-score adjusted with age, sex, and education.

Associations between regional WMH and memory

We tested whether total and regional (lobar) WMH were associated with RAVLT delayed recall, while adjusting for age, sex, and education. We found that only increased occipital WMH were related to lower RAVLT delayed recall scores (b = -2.009, 95 CIs [-3.929, -0.089], p = 0.040; Figure 2.2A). Though trending in the same direction, there was no longer a statistically significant association between occipital WMH and RAVLT delayed recall once additionally controlling for cognitive status (b = -1.343, 95 CIs [-3.135, 0.448], p = 0.140). When adding cohort as an additional covariate to the original model, the effect size remained similar (*b* = -1.730).

Associations between regional WMH and MTL subregional volumes

We examined associations between total and regional WMH and MTL subregional volumes, while adjusting for age, sex, and education. After applying Holm-Bonferroni multiple comparison correction, increased occipital WMH was associated with reduced CA1 (*b* = -0.254, 95% CIs [-0.408, -0.109], p = 0.001), DG (b = -0.163, 95% CIs [-0.256, -0.069], p < 0.001), BA36 volumes (b = -0.426, 95% CIs [-0.686, -0.167], p = 0.001; Figure 2.2B), and PHC volumes (b = -0.212, 95% CIs [-0.366, -0.059], p = 0.007). No other regional or total WMH associations with MTL volume survived Holm-Bonferroni correction. When additionally controlling for cognitive status, findings remained statistically significant (CA1: *b* = -0.245, 95% CIs [-0.393, -0.096], p = 0.001; DG: *b* = -0.155, 95% CIs [-0.242, -0.068], p < 0.001; BA36: *b* = -0.409, 95% CIs [-0.658, -0.161], p = 0.001; PHC: *b* = -0.203, 95% CIs [-0.352, -0.055], p = 0.008) Effect sizes of our findings remained similar once cohort was added as an additional covariate to the original models (CA1: *b* = -0.247, DG: *b* = -0.156, BA36: *b* = -0.410, PHC: *b* = -0.202)

Associations between MTL subregional volumes and delayed recall memory

MTL subregions that were significantly associated with WMH after applying Holm-Bonferroni correction were included in the second analysis, in which we tested associations between MTL subregional volumes and RAVLT delayed recall. All four MTL subregional volumes, including CA1, DG, BA36, and PHC, were also significantly associated with RAVLT delayed recall performance (CA1: b = 2.114, 95% CIs [0.115, 4.113], p = 0.038; DG: b = 3.956, 95% CIs [0.737, 7.176], p = 0.016; BA36: b = 2.445, 95% CIs [1.263, 3.628], p < 0.001; PHC: b = 2.381, 95% CIs [0.222, 4.541], p = 0.031; Figure 2.2C). In additionally controlling for cognitive status, only the association between BA36 volume and RAVLT delayed recall remained statistically significant (*b* = 1.727, 95% CIs [0.515, 2.938], p = 0.006). Effect sizes of our findings remained similar once cohort was added as an additional covariate to the original models (CA1: *b* = 1.775; DG: *b* = 3.216; BA36: *b* = 2.201; PHC: *b* = 1.851)

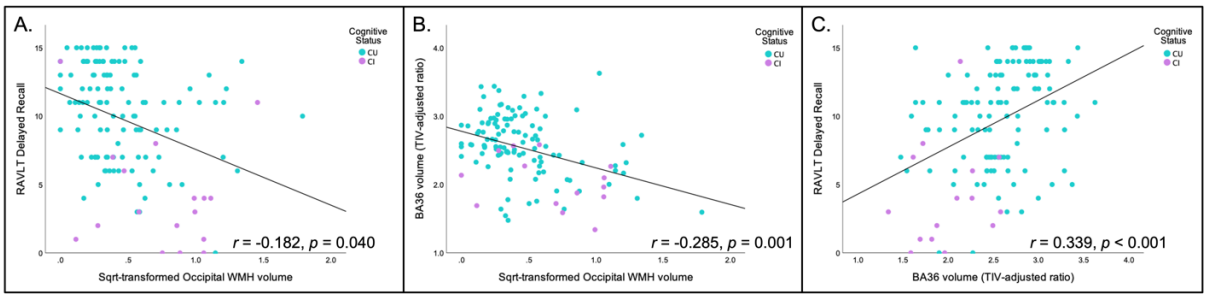

Figure 2.2. In all three scatterplots, cognitive status is color-coded, with cognitively unimpaired (CU) in blue and cognitively impaired (CI) in purple. **(A)** A scatterplot of the negative association between square root transformed occipital WMH and delayed recall. **(B).** A scatterplot of the negative association between square root transformed occipital WMH and BA36 volume (TIV adjusted ratio). **(C).** A scatterplot of the positive association between BA36 volume (TIV adjusted ratio) and delayed recall. Other significant associations found that were not involved in the mediation model (as seen in Figure 2.3.) can be found in Supplemental materials.

MTL subregional volumes mediate the effect of WMH on delayed recall memory

Four separate mediation models were run, informed by the previous analyses. As only occipital WMH were associated with memory and with MTL subregional volumes, it was included in the mediation model as the primary independent variable. CA1, DG, BA36, and PHC volumes were associated with both occipital WMH and with delayed recall, and thus were included as mediators separately in the four models. We found there was no direct effect of occipital WMH on delayed recall in any mediation model (M=CA1: b = -1.513, p = 0.150, 95% CIs [-3.580, 0.554]; M=DG: b =-1.399, p = 0.183, 95% CIs [-3.467, 0.668]; M=BA36: b = -0.895, p = 0.386, 95% CIs [-2.837, 1.106]; M=PHC: b = -1.528, p = 0.140, 95% CIs [-3.565, 0.506]). However, there was an indirect effect of occipital WMH on delayed recall and that only BA36 volume mediated this association (M=BA36: b = -1.052, 95% CIs [-2.184, -0.233]; Figure 2.3). In additionally controlling for cognitive status, the finding of the indirect effect remained statistically significant (M=BA36: b = -0.7100, 95% CIs [-1.570, -0.1108]). The effect size of the indirect effect was similar when cohort was included as an additional covariate to the original model (M=BA36: b = -0.8905).

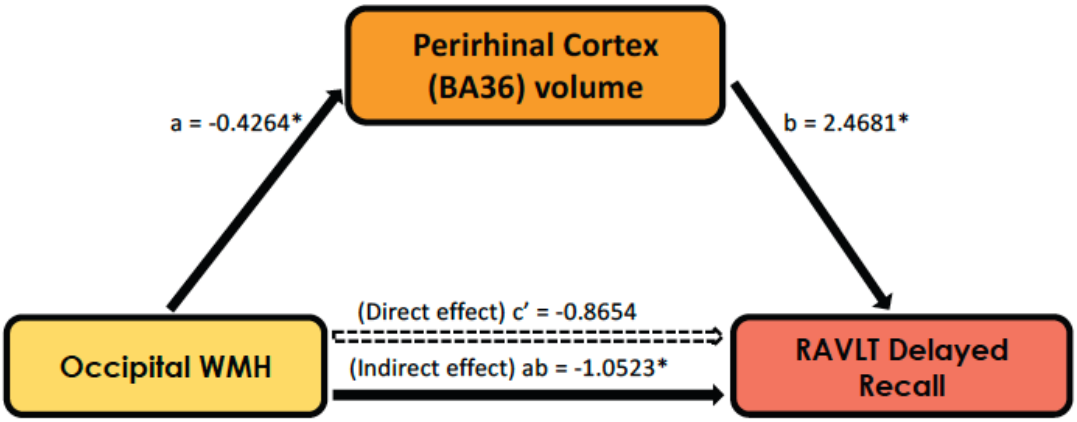

Figure 2.3. In this mediation model, there is an indirect effect where perirhinal cortex (BA36) volume mediates the relationship between occipital WMH and RAVLT delayed recall. Path a: *b*=-0.426, p=0.0015; Path b: *b*=2.4681, p=0.0003; Path c' (Direct effect): *b*=-0.8654, 95% CIs [-2.8366, 1.1058]; Path ab (Indirect effect): *b*=-1.0523, 95% CIs [-2.1835, -0.2328].

2.4. Discussion

We interrogated the relationships among regional WMH, MTL subregional volumes, and delayed memory in older adults. We found that only occipital WMH burden was associated with lower RAVLT delayed recall performance. Increased occipital WMH was also associated with reduced CA1, DG, perirhinal cortical (BA36), and parahippocampal cortical (PHC) volumes. CA1, DG, perirhinal cortical (BA36) and parahippocampal volumes were related to worse RAVLT delayed recall in these older adults. Furthermore, in a mediation test, we found that occipital WMH had an indirect effect on delayed recall with perirhinal cortex (BA36) volume fully mediating this association.

Our results provide new evidence that regional patterns of small vessel cerebrovascular disease, here measured as lobar WMH volume, exhibits associations with medial temporal and hippocampal subregional volumes in older adults without dementia. Increased occipital WMH volume was related to lower volumes of CA1, DG, perirhinal cortex (BA36), and parahippocampal cortex (PHC) – all of which are structures that have been found to be critical to episodic memory formation and retrieval in older adults (Bennett et al., 2019; Burke et al.,

2018). Our results are somewhat in contrast to a recent study (Pin et al., 2021) suggesting that WMH were related to longitudinal atrophy of the subiculum in aging participants, although they did not relate this association to neuropsychological outcome measures. Another study in older adults with depression showed that depressed older individuals had smaller perirhinal (BA36) volumes and that higher temporal WMH volume was related to lower BA36 volume (Taylor et al. 2017).

The DG is known to be important for pattern separation – the ability to store similar experiences using non-overlapping neural codes (Yassa & Stark, 2011), which is known to be compromised with aging and AD. The CA1 is the hippocampus' major output pathway and is also known to be impacted by aging and AD (Small et al., 2004). Similarly, the parahippocampal and perirhinal cortices undergo early age-related structural changes and have important implications for episodic memory decline (Echávarri et al., 2011; Schmidt-Wilcke et al., 2009). Importantly, the perirhinal cortex and the transentorhinal regions are among the first to deposit tau pathology in AD (Braak & Braak, 1991), and regional accumulation of tau in the temporal lobes as measured by tau PET is correlated with atrophy of the perirhinal cortex (Sone et al., 2017). Mechanistically, it is possible that WMH may increase susceptibility to neurodegeneration in areas typically affected in AD such as the MTL via their role in promoting tau hyperphosphorylation (Laing et al., 2020).

A potentially surprising aspect of our findings was that only occipital WMH of the regionally subdivided WMH volumes was related to lower MTL and hippocampal subregional volumes. While we may have not expected this pattern to be restricted to occipital WMH, previous work has indeed demonstrated that posterior WMH, including parietal and occipital WMH, are more linked to earlier AD onset in older adults (Lee et al., 2016). Additionally, posterior WMH has been associated with greater entorhinal cortical thinning, along with an increase in longitudinal CSF tau (Rizvi et al., 2021; Tosto et al., 2015). The neurobiological mechanism by which

posterior WMH contribute more to cognitive decline is yet to be elucidated. One possible mechanism could be related to the vascular supply to these regions. As the posterior cerebral artery (PCA) supplies blood to posterior areas, hippocampus, and areas of the MTL (Brandt et al. 2000), a possible explanation may be that lower perfusion leads to increased posterior WMH, which has also been linked to tau accumulation (Laing et al., 2020; Tosto et al., 2015) and subsequent MTL neurodegeneration (Liu et al., 2018a).

There were some limitations of this study that are important to note. First, this study was conducted in a convenience sample that is comprised of predominantly affluent, highly educated, non-Hispanic white participants, which is not representative of an ethnically and socioeconomically diverse population. Second, due to a cross-sectional study design, this study cannot infer longitudinal relationships. Lastly, we did not have the ability to examine how clinical diagnosis would interact with these associations, due to a very limited number of individuals with mild cognitive impairment and the absence of patients with dementia. We felt it was important to not exclude those who classified as cognitively impaired as to maintain sufficient parametric range with respect to neuropsychological test performance. Future work should attempt to incorporate data from more diverse samples, increase the representation across the clinical impairment spectrum, as well as follow participants longitudinally to monitor the onset of these biomarker features over time. Additional inclusion of markers of AD neurodegenerative pathology such as tau PET will also help understand whether spatial colocalization of tau and MTL atrophy occurs as a result of posterior WMH.

In summary, the current work demonstrates the potential role of WMH in MTL atrophy, specifically increased posterior WMH burden in relation to lower volume of hippocampal subfields and surrounding cortex. The study specifically identified an association between occipital WMH and word list delayed recall, whereby perirhinal cortex (BA36) volume fully mediated this association. This work highlights the relevance of cerebrovascular pathology to

neurodegenerative changes and cognitive decline even in older adults without dementia. It also suggests that examining modifiable vascular risk factors that can lower cerebrovascular burden could potentially reduce or slow down neurodegenerative cascades and thereby stem memory loss in older adults, particularly those at increased risk for AD. In Chapter 3, I consider one such vascular risk factor that promotes WMH in a population of adults with DS, who are not prone to traditional vascular risk factors such as hypertension. We will investigate whether pulse pressure, an indicator of arterial stiffness, predicts brain health outcomes and the presence of dementia in adults with DS.

CHAPTER 3: A PATHWAY LINKING PULSE PRESSURE TO DEMENTIA IN ADULTS WITH DOWN SYNDROME

3.1. Introduction

Despite the inevitable accumulation of Aβ and tau pathology in adults with Down syndrome (DS), there is some variability in the age of onset of clinical symptoms of dementia and in the severity and the course of decline of clinical symptoms (Fortea et al., 2021b; Lott & Head, 2019; Sinai et al., 2018). The factors that account for the variability in clinical AD onset and course among adults with DS are poorly understood. Although AD pathogenesis in the context of DS is typically attributed to a single pathway model (i.e., the amyloid cascade hypothesis) (Glenner & Wong, 1984; Hardy & Higgins, 1992b; Head et al., 2018a), and the clinical course is typically framed according to the amyloid-tau-neurodegeneration (ATN) biomarker classification scheme (Jack et al., 2018; Rafii et al., 2020), there is increasing evidence of the contribution of cerebrovascular disease to both clinical and pathogenic progression (Head et al., 2017; Kalaria, 2012; Laing et al., 2020; Vemuri & Knopman, 2016). Despite relatively low prevalence of classical vascular risk factors (Rizvi et al., 2022; Wilcock et al., 2016), individuals with DS have

cerebrovascular abnormalities on magnetic resonance imaging (MRI), including white matter hyperintensities (WMH), enlarged perivascular spaces (PVS), microbleeds, and infarcts, which increase across AD-related clinical diagnoses (Lao et al., 2020).

In the neurotypical population the presence and severity of vascular risk factors, particularly high blood pressure or hypertension, lead to cerebrovascular disease, which in turn, is associated with neurodegeneration, cognitive decline, and risk and progression of clinical AD (Qiu et al., 2005; Sierra, 2020; Sierra et al., 2011). These relationships have not been examined systematically among adults with DS, likely due to the low prevalence of vascular risk factors (Wilcock et al., 2016). Individuals with DS have lower blood pressure than individuals from the neurotypical population (Morrison et al., 1996; Richards & Enver; Rodrigues et al., 2011), as well as lower prevalence and incidence of hypertension (Alexander et al., 2016). The physiological mechanisms of these observations are not well understood. Nonetheless, it is possible that increases in blood pressure measurements may be associated with poorer brain outcomes among older adults with DS even if those measurements are within the normal range for the neurotypical population. In support of this hypothesis, studies in the neurotypical population found that elevated blood pressure even in non-hypertensive adults is associated with worse cognition (Jennings et al., 2017; Knecht et al., 2008).

In the current study, we examined the association of common clinical blood pressure-related measurements of vascular health with MRI markers of small vessel disease or dysfunction and factors that might link pulse pressure with diagnosis of dementia in older adults with DS. Systolic blood pressure (SBP) measures the force of the heart exerting on artery walls at each beat, while diastolic blood pressure (DBP) measures the force of the heart exerting on the artery walls in between beats, reflecting peripheral resistance. Pulse pressure (PP), or the difference between systolic and diastolic blood pressure, is an indicator of arterial stiffness. Mean arterial pressure (MAP) is the average arterial pressure during one cardiac cycle (DeMers & Wachs,

2023). In the neurotypical population, hypertension is related to increased risk for stroke, WMH, infarcts, and AD related pathology (Skoog & Gustafson, 2006). Increased pulse pressure can lead to atherosclerosis even in normotensive individuals (Zakopoulos et al., 2001), which is associated with WMH (Safar, 1989; Zang et al., 2021). Higher pulse pressure is also associated with medial temporal lobe atrophy in AD (Korf et al., 2005). Compared with other measures of blood pressure, pulse pressure is more tightly linked to AD pathology (Nation et al., 2012; Weigand et al., 2022). Higher pulse pressure can affect cerebral blood flow, gray matter and white matter integrity, increasing the risk for dementia (Badji et al., 2019; Waldstein et al., 2008).

Given the documented stronger associations of clinical outcomes with pulse pressure than other blood pressure indicators (Nation et al., 2012; Safar et al., 2012), we focused primarily on this measure in the current analyses. We assessed the associations of these blood pressure measures with MRI markers of cerebrovascular disease. Previously, we showed that regional WMH burden is associated with medial temporal lobe atrophy in community-dwelling older adults (Rizvi et al., 2018, Rizvi et al., 2021; Rizvi et al., 2023). Prior work also demonstrated that greater posterior WMH burden is associated with a diagnosis of dementia in adults with DS and in autosomal dominant AD (Lao et al., 2020; Lee et al., 2016). Based on these observations, we hypothesized that increased pulse pressure is related to greater WMH, which in turn is related to lower cortical thickness, and subsequently to dementia.

3.2. Materials and Methods

Participants

This study included participants from the Biomarkers of Alzheimer's Disease in Adults with Down Syndrome (ADDS; U01 AG051412) study, which characterizes the factors that contribute to the development of AD dementia among older adults with DS. Participants were enrolled at multiple sites, including Columbia University/New York State Institute for Basic Research in Developmental Disabilities (n=54), Massachusetts General Hospital/Harvard Medical School

(n=75), and University of California, Irvine (n=66). Participants whose blood pressure was measured during their baseline visit were included in the analyses (N=195).

The study was approved by the institutional review boards of the participating institutions, and written informed consent was obtained from the participants and/or their legal guardian or legally authorized representative. We received assent from every participant before every procedure.

Blood Pressure Measures

Blood pressure, including systolic and diastolic blood pressure was assessed within three months of the MRI visit. Blood pressure was assessed within a single measurement while the participant was seated. The blood pressure measurement device was not specified; sites used a standardized automatic blood pressure cuff used in their center or a sphygmomanometer when the automatic cuff was not available. Pulse pressure was derived by taking the difference between systolic blood pressure and diastolic blood pressure: PP = SBP - DBP. Mean arterial pressure was calculated using the following equation: MAP = (SBP + 2(DBP)) / 3. We used a structured interview, the Health History Review of Systems, to determine whether participants had a clinical history of hypertension or hypotension. If these diagnoses were endorsed, we asked whether the participant was receiving treatment, which was coded dichotomously (yes/no).

Clinical Diagnosis

As part of the diagnostic procedure, participants underwent neuropsychological testing to assess cognition in domains typically affected by AD. Study personnel reviewed clinical charts, conducted interviews with knowledgeable informants, and conducted a standardized clinical and neurological examination. A consensus panel of clinicians, expert in the diagnosis of dementia in individuals with DS, assigned a final diagnosis based on the information collected, which did not include any biomarker data (Krinsky-McHale et al., 2020). One of four AD-related diagnoses

was assigned to each participant: cognitively stable (CS), mild cognitive impairment-DS (MCI-DS), possible AD dementia, and definite AD-dementia. For our analyses, we categorized individuals into two groups: with AD dementia (including possible and definite AD dementia) or without dementia (including CS or MCI-DS). A diagnosis of CS indicated absence of clinically significant cognitive decline; MCI-DS indicated subtle cognitive decline over time beyond what was expected with age but not severe enough to indicate dementia; possible AD dementia indicated some symptoms of dementia present but with inconsistent evidence of progression; and definite AD dementia indicated substantial evidence of cognitive and associated functional decline with high degree of confidence.

MRI

MRI scans (n=145) were acquired on a Siemens Prisma 3T at Columbia University (n=30) and MGH (n=58) or a Philips Achieva 3T at UC Irvine (n=57). The Alzheimer's Disease Neuroimaging Initiative MRI protocol was used at all sites (T1-weighted scan: repetition time (TR)/echo time (TE)/inversion time (TI): 2300/2.96/900ms; voxel size: 1x1x1mm3; T2-weighted fluid attenuated inversion recovery (FLAIR) scan (TR/TE/TI: 5000/386/1800ms; voxel size: 0.4x0.4x0.9mm3); and a T2-*-weighted gradient echo (GRE) scan (TR/TE: 650/20ms; voxel size: 0.8x0.8x4mm3) or susceptibility weighted image (SWI: TRE/TE: 27/30ms; voxel size: 0.9x0.9x1.5 mm3)). Total and regional (by cerebral lobe) WMH volumes were quantified from T2-weighted FLAIR scans, using a previously described method (see Figure 3.1A, 1B) (Igwe et al., 2022; Lao et al., 2020). Microbleeds were counted by visual inspection, as hypointense round or ovoid lesions in deep and/or lobar regions on GRE or SWI, and were globally scored as present or not (See Figure 3.1C). Enlarged perivascular spaces (PVS) were visually rated as hypointensities on T1 scans across 13 brain regions and rated from 0 to 2 based on FLAIR characteristics (see Figure 3.1D). These ratings were then summed for a global score ranging from 0 (no enlarged PVS in any region) to 26 (severe enlarged PVS in all regions) (Gutierrez et

al., 2017). Infarcts were visually counted on FLAIR scans as discrete hypointense lesions (> 5 mm) with partial or complete hyperintense ring and confirmed on T1 scans (hypointense areas) and were globally scored as present or not (see Figure 3.1E, 1F).

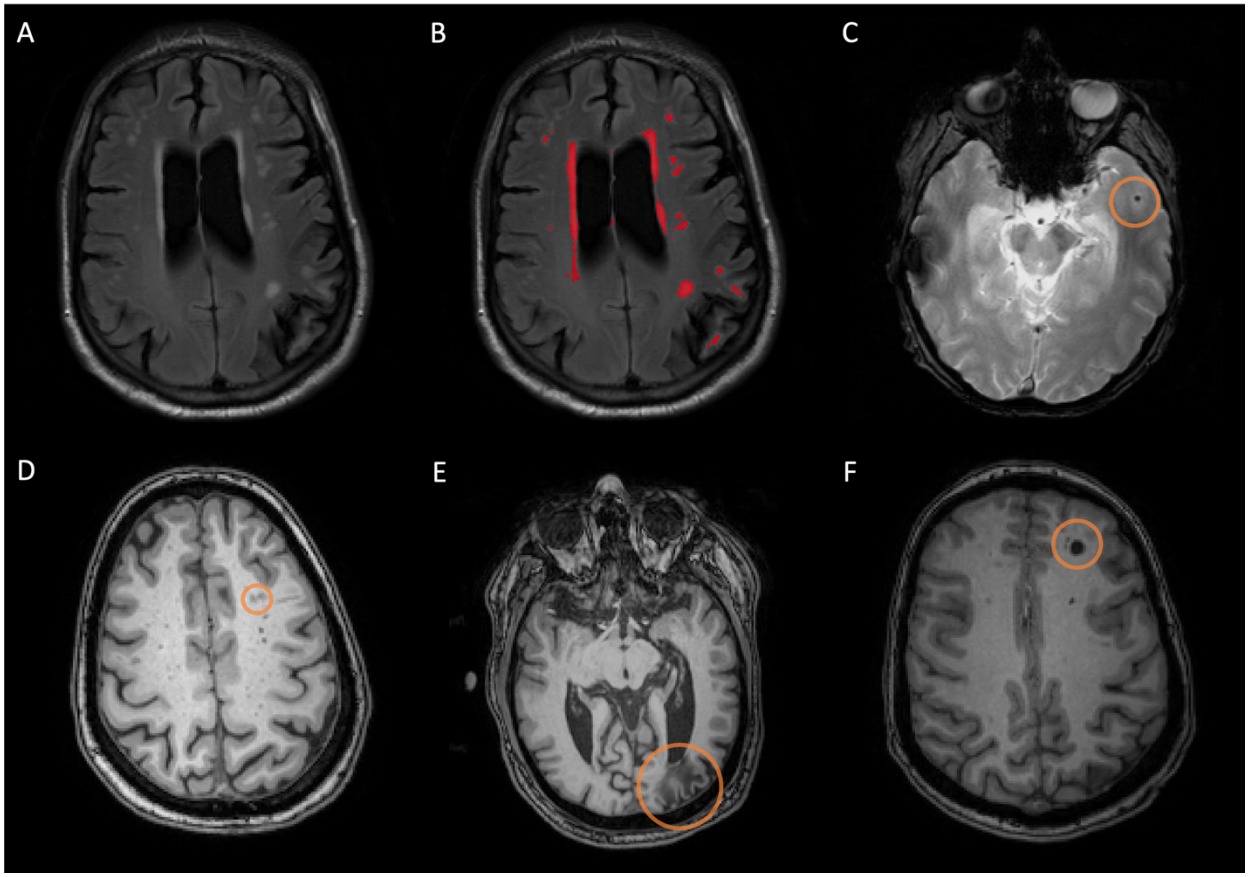

Figure 3.1. MRI markers of cerebrovascular disease included in the study.
A. Unlabeled WMH on an axial FLAIR image. **B.** Labeled WMH in red on an axial FLAIR image **C.** Microbleed circled on an axial T2*-GRE. **D.** Perivascular spaces circled on an axial T1-weighed image. **E.** Distal cortical infarct circled on an axial T1-weighted image. **F.** Deep infarct circled on an axial T1-weighted image.

Volume and Cortical Thickness

Each participant's T1-weighted image was processed with FreeSurfer v.6.0 (*http://surfer.nmr.mgh.harvard.edu/*). We calculated hippocampal volume by averaging left and right hippocampal volume, dividing by estimated total intracranial volume, and multiplying the value by 1000. We calculated the AD cortical signature by averaging left and right entorhinal cortical thickness, parahippocampal cortex, inferior parietal lobe, pars opercularis, pars orbitalis,

pars triangularis, inferior temporal lobe, temporal pole, precuneus, supramarginal gyrus, superior parietal lobe, and superior frontal lobe.

Statistical Analysis

Separate general linear models were used to test the association of pulse pressure with regional WMH and enlarged PVS score. We used separate logistic regression models to test the association between pulse pressure and the presence of microbleeds, and infarcts. All regression analyses were adjusted for age, sex/gender, and scanner type. In a sensitivity analysis, we tested whether associations remained after removing participants who were treated for either hypertension or hypotension. Associations with SBP, DBP and MAP were reported in supplementary results.

Structural equation model (Bassett et al., 2006) analyses were conducted in R (version 4.3.0) through RStudio, using lavaan. We tested whether pulse pressure is associated with greater WMH, and whether WMH is related to increased neurodegeneration, and subsequently to dementia. We also tested whether pulse pressure is directly related to dementia. The latent variable of WMH was estimated by the four regional distributions of WMH (i.e. frontal WMH, temporal WMH, parietal WMH, occipital WMH), and the latent variable of neurodegeneration was estimated by hippocampal volume and AD cortical signature thickness. Pulse pressure and dementia were included as single indicator variables. We included those who were assigned the diagnosis of possible dementia or definite dementia in the category of dementia. Prior to performing the SEM analysis, all neuroimaging variables were log transformed with an added constant of 0.01. We used full information maximum likelihood estimation and allowed the loadings of the first manifest variables of each factor to be estimated freely. We assessed the overall model fit to be “acceptable” if: $X2$ $p > 0.05$, Comparative Fit Index (CFI ≥ 0.90), Tucker-Lewis Index (TLI ≥ 0.90), Root Mean Square Error of Approximation (RMSEA < 0.08), and Standardized Root Mean Square Residual (SRMR < 0.08) (Schumacker & Lomax). Because

the chi-square test is sensitive to sample size, we considered other measures of model fit more heavily. We conducted this SEM analysis without age as a covariate, and report results when including age in the supplementary results.

3.3. Results

One-hundred ninety-five participants were included. Table 3.1. displays summary characteristics, including demographic, clinical, and imaging variables, and the sample size associated with each variable. About 17% of the participants with DS were characterized as having a high blood pressure reading (SBP > 130 and/or DBP > 80 mmHg), while around 28% demonstrated a low blood pressure reading (SBP < 90 and/or DBP < 60 mmHg).

Table 3.1. Sample demographic characteristics and summary variables.

Characteristic	Values
N	195
Age, mean (SD) years	50.58 (7.19)
Sex, n (%) Women	85 (43.6%)
Diagnostic Category (n=187)	
Cognitively Stable, n (%)	110 (56.4%)
MCI-DS, n (%)	42 (21.5%)
Dementia, n (%)	35 (17.9%)
Blood Pressure Measure, mmHg (n=195)	
Pulse pressure, mean (SD)	44.01 (12.57)
Systolic blood pressure, mean (SD)	110.16 (14.57)
Diastolic blood pressure, mean (SD)	66.15 (10.36)
Mean Arterial Pressure, mean (SD)	80.81 (10.36)
High blood pressure reading*, n (%)	33 (16.9%)
Low blood pressure reading*, n (%)	55 (28.2%)
High pulse pressure reading‡, n (%)	19 (9%)
Treated for hypertension, n (%)	2 (1%)
Treated for hypotension, n (%)	9 (4.6%)
WMH volume, cm^3 (n=123)	
Total WMH, mean (SD)	3.93 (1.93)
Frontal WMH, mean (SD)	1.43 (1.98)
Temporal WMH, mean (SD)	0.51 (0.71)
Parietal WMH, mean (SD)	0.54 (0.16)
Occipital WMH, mean (SD)	0.94 (1.31)
Enlarged PVS score, mean (n=110)	9.19 (5.57)
Presence of microbleeds, n (%) (n=92)	13 (6.7%)
Presence of infarcts, n (%) (n=113)	20 (10.3%)
Regional volume/thickness (n=125)	
Average hippocampal volume (TIV adj.), mean (SD)	2.35 (0.38)
Average AD cortical signature thickness, mean (SD)	2.75 (0.16)

*Based on baseline SBP and DBP and the general guidelines for hypertension (SBP $\geq$130 and/or DBP $\geq$ 80 mmHg) and hypotension (SBP < 90 and/or DBP < 60 mmHg).

‡Included when pulse pressure reading was ≥ 60 mmHg.

Association of Pulse Pressure with Cerebrovascular Imaging Markers

Higher pulse pressure was associated with greater global WMH, parietal WMH, and occipital WMH (see Table 3.2 and Figure 3.2). Of the covariates, age was associated with higher frontal, parietal, and occipital WMH. Sex/gender was not associated with any of the WMH measures. Scanner type was associated with all of the WMH measures. In a sensitivity analysis, after removing participants who were treated for either hypotension or hypertension, higher pulse pressure remained associated with greater global, parietal, and occipital WMH volumes (see Appendix B, Supplemental Table B1). Systolic blood pressure, diastolic blood pressure, and MAP were not associated with global or regional WMH volumes (see Appendix B, Supplemental Table B2). Pulse pressure was not associated with enlarged perivascular spaces, microbleeds, or infarcts (see Table 3.2). Similarly, systolic blood pressure, diastolic blood pressure, and MAP were also not associated with enlarged perivascular spaces, microbleeds, or infarcts (See Appendix B, Supplemental Table B2).

Table 3.2. Associations of pulse pressure and covariates with cerebrovascular imaging markers.

Predictor	Outcome Measure	*B*	95% CI	β	t / Wald‡	p-value
Pulse pressure	Global WMH	0.057	(0.001, 0.114)	0.154	2.002	0.048
	Frontal WMH	0.012	(-0.015, 0.039)	0.073	0.871	0.385
	Temporal WMH	0.008	(-0.001, 0.018)	0.140	1.697	0.092
	Parietal WMH	0.012	(0.001, 0.024)	0.172	2.139	0.035
	Occipital WMH	0.018	(0.003, 0.034)	0.172	0.023	0.023
	Microbleeds[λ]	-0.012	(0.942, 1.037)	0.998	0.234	0.629
	Perivascular spaces	0.073	(-0.008, 0.155)	0.164	1.781	0.078
	Infarcts[λ]	0.019	(0.979, 1.062)	1.019	0.874	0.350
Age	Global WMH	0.124	(0.012, 0.227)	0.186	2.376	0.019
	Frontal WMH	0.066	(0.017, 0.115)	0.227	2.672	0.009
	Temporal WMH	0.004	(-0.013, 0.022)	0.040	0.485	0.629

	Parietal WMH	0.022	(0.002, 0.043)	0.174	2.132	0.035
	Occipital WMH	0.043	(0.014, 0.072)	0.224	2.953	0.004
	Microbleeds[λ]	0.089	(0.994, 1.203)	1.093	3.354	0.067
	Enlarged perivascular spaces	0.265	(0.110, 0.420)	0.325	3.396	<0.001
	Infarcts[λ]	0.083	(1.003, 1.176)	1.086	4.148	0.042
Sex/Gender	Global WMH	-0.542	(-1.970, 0.887)	-0.058	-0.751	0.454
	Frontal WMH	-0.038	(-0.716, 0.641)	-0.009	-0.110	0.912
	Temporal WMH	-0.056	(-0.297, 0.184)	-0.038	-0.464	0.644
	Parietal WMH	-0.019	(-0.306, 0.267)	-0.011	-0.135	0.893
	Occipital WMH	-0.343	(-0.745, 0.059)	-0.127	-1.690	0.094
	Microbleeds[λ]	0.272	(0.364, 4.735)	1.313	0.173	0.678
	Enlarged perivascular spaces	0.082	(-1.982, 2.146)	0.007	0.079	0.937
	Infarcts[λ]	0.688	(0.652, 6.075)	1.990	1.461	0.227
Scanner Type	Global WMH	4.286	(2.900, 5.671)	0.469	6.126	<0.001
	Frontal WMH	1.370	(0.712, 2.028)	0.343	4.124	<0.001
	Temporal WMH	0.620	(0.387, 0.853)	0.430	5.265	<0.001
	Parietal WMH	0.717	(0.440, 0.995)	0.409	5.119	<0.001
	Occipital WMH	1.213	(0.823, 1.603)	0.458	6.160	<0.001
	Microbleeds[λ]	0.436	(0.448, 5.337)	1.546	0.476	0.490
	Enlarged perivascular spaces	1.140	(-0.887, 3.168)	0.099	1.115	0.267
	Infarcts[λ]	0.517	(0.979, 1.062)	1.677	0.957	0.227

Separate primary regression models: Outcome measure ~ pulse pressure + age + sex/gender + scanner type + intercept.

[‡] A t-value is shown for linear regressions, and a Wald statistic is shown for logistic regressions.

[λ] Logistic regression was applied for dichotomous outcomes. β = Exponential (β) and 95%CI = 95% CI for Exponential (β).

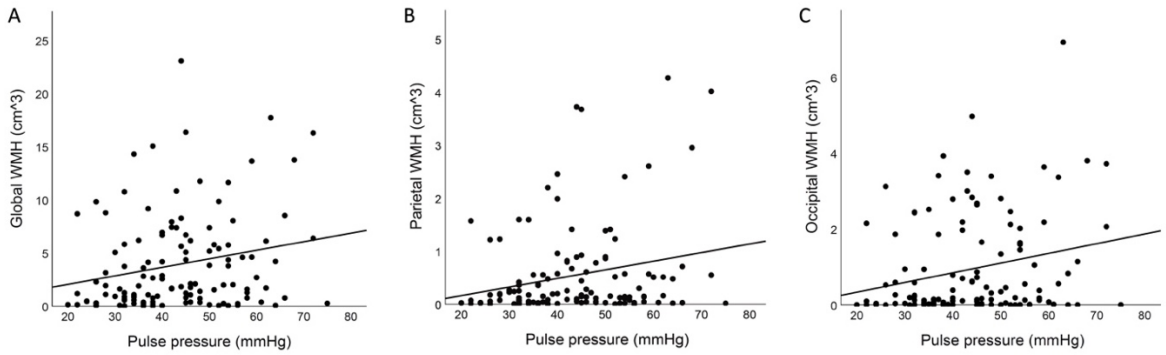

Figure 3.2. Scatterplots of associations between pulse pressure with WMH volumes. Scatterplots displaying bivariate associations between: A) pulse pressure and global WMH; B) pulse pressure and parietal WMH; C) pulse pressure and occipital WMH. Results of these associations with covariate adjustment are displayed in Table 2.

Pathway from Pulse Pressure to Dementia

There was acceptable overall model fit: $X2$ (17, N=195) = 43.622, $p < 0.001$, CFI = 0.947, TLI = 0.912, RMSEA = 0.090, and SRMR = 0.058. However, model fit was weaker when age was included as a covariate, though some indices were still considered acceptable (see Appendix B, Supplemental Figure 1). Higher pulse pressure was related to greater WMH burden (see Figure 3.3). In turn, greater WMH volume was associated with increased neurodegeneration. Increased neurodegeneration was subsequently related to dementia. Pulse pressure was not directly associated with dementia. Findings remained when age was added as a covariate to the structural equation model (see Appendix B, Supplemental Figure B1).

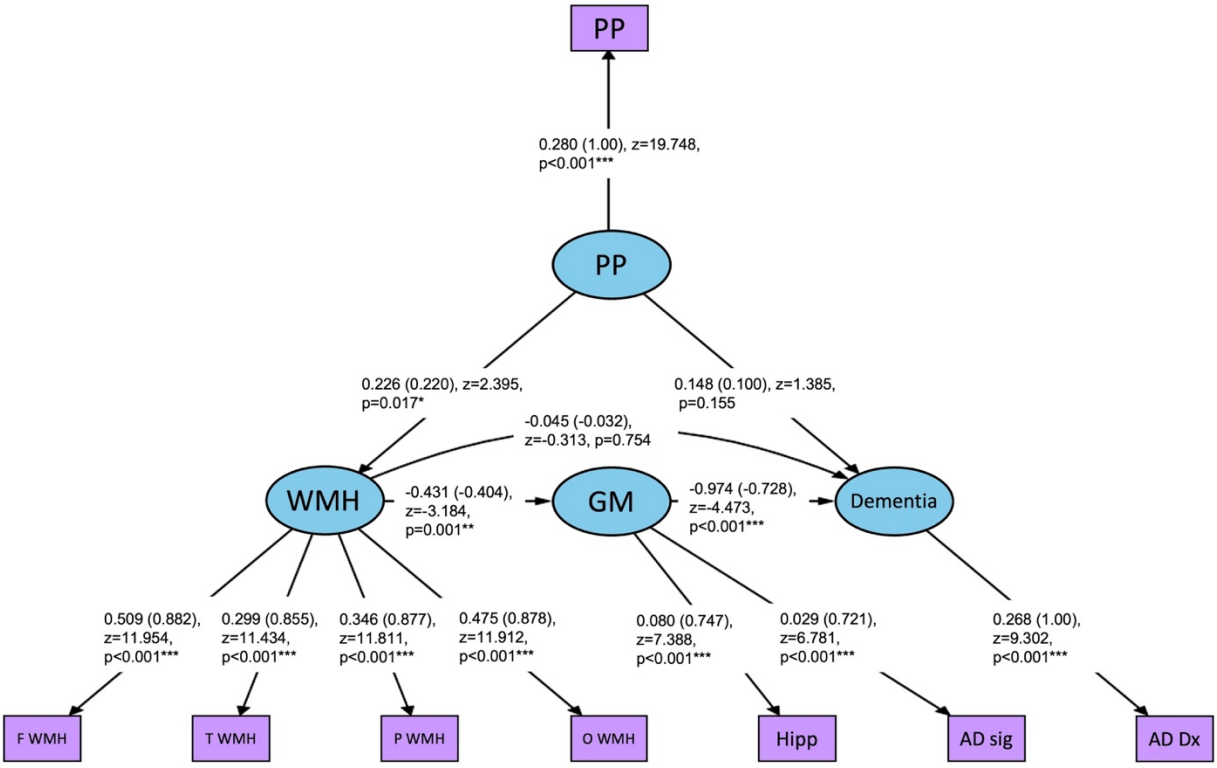

Figure 3.2. Structural equation model demonstrating pathway from pulse pressure to dementia and intermediate markers.
Standardized beta coefficients are included in parentheses.
Paths indicated as significant (*) for p-values $\leq$ 0.05, (**) for p $\leq$ 0.01, and (***) for p $\leq$ 0.001.
PP: pulse pressure, WMH: white matter hyperintensities, GM: gray matter, F WMH: frontal WMH, T WMH: temporal WMH, P WMH: parietal WMH, O WMH: occipital WMH, Hipp: hippocampal volume (TIV adjusted), AD sig: Alzheimer's disease cortical signature thickness, AD Dx: Alzheimer's disease dementia diagnosis.

3.4. Discussion

Higher pulse pressure was associated with greater global, parietal, and occipital WMH in older adults with DS, but not with other markers of cerebrovascular disease. Pulse pressure was not directly associated with dementia status. However, higher pulse pressure was indirectly associated with diagnosis of dementia, through WMH and subsequent neurodegeneration.

Blood pressure has not been studied comprehensively in relation to brain or any clinical marker associated with AD in adults with DS. To our knowledge, only one previous study examined blood pressure in DS, and found that blood pressure did not increase with age in people with

DS despite observed age-associated increases in neurotypical participants (Morrison et al., 1996). The relationship of pulse pressure with cerebrovascular disease was specific to WMH. We did not find any association of pulse pressure with enlarged perivascular spaces, microbleeds, or infarcts, suggesting that WMH, a marker of chronic and subtle small vessel disease (Wardlaw et al., 2015), is more sensitive to the impact of relatively higher pulse pressure. The other cerebrovascular imaging markers may indicate other mechanistic processes, including impaired glymphatic clearance resulting in enlarged perivascular spaces (Gouveia-Freitas & Bastos-Leite, 2021), cerebral amyloid angiopathy that is more frequent in the brains of people with DS and associated with microbleeds (Head et al., 2017; Helman et al., 2019; Nakata-Kudo et al., 2006), and large artery disease leading to infarcts (Xu, 2014).

The lack of direct association of pulse pressure with dementia may be explained by the mechanistic chain of events occurring prior to the onset of dementia. For example, higher pulse pressure may directly induce cerebrovascular changes rather than act on neurodegenerative processes directly. This possibility is highlighted in the structural equation model, in which regional WMH burden and neurodegeneration mediated the association between higher pulse pressure and dementia diagnosis. The association between WMH and lower cortical thickness and hippocampal volume is supported by our previous work (Rizvi et al., 2018; Rizvi et al., 2021).

This study has some limitations. Blood pressure was assessed with a single measurement, which can lower the likelihood of finding robust associations due to measurement reliability. There may have been additional sources of error in the blood pressure measurement that we did not control, including patient and procedure-related factors (e.g., movement or time of day during measurement). However, these limitations would likely bias our findings towards the null. Despite these concerns, we observed reliable associations of pulse pressure with hypothesized outcomes, suggesting that our findings are reliable but may even underestimate the overall

effect. Additionally, due to the cross-sectional design, we could not investigate the temporality or causality of the observed relationships. Based on a number of studies highlighting the role of blood pressure as a risk factor for age- and AD-related changes in the neurotypical population (see reviews; Breteler, 2000; Kennelly et al., 2009; Skoog & Gustafson, 2006), it is more likely that higher blood pressure and pulse pressure emerge gradually in adulthood and precede associated structural brain changes and subsequent clinical status. The adults with DS included in the study were predominantly non-Hispanic White. In the neurotypical aging population, higher blood pressure is more prevalent among racially and ethnically minoritized populations (Carson et al., 2011), potentially contributing to health disparities among groups. Another future direction is to examine markers other than pulse pressure that can more accurately capture arterial stiffness in adults with DS, such as with intracranial pulse wave velocity (Avolio et al., 2018).

To summarize, we demonstrated that higher pulse pressure is associated with both global and posterior WMH burden. In examining a pathway from pulse pressure to dementia, we found that pulse pressure was related to WMH, which was associated with neurodegeneration, and subsequently to dementia. This work highlights the potential impact of elevated pulse pressure in individuals with DS. Monitoring and targeting blood pressure through nonpharmacological or pharmacological approaches may be helpful for people with DS. In the next chapter, we will explore a different upstream pathway, neuroinflammation, which also promotes cerebrovascular injury. While we know that in DS, amyloid is heavily involved in the aggregation and spread of tau, we will next also investigate whether WMH and Aβ are parallel processes that converge to promote tau. We study how two neuroinflammatory pathways distinctly lead to WMH and Aβ, which impact downstream neurodegeneration and memory performance in older adults without cognitive impairment.

CHAPTER 4: PARALLEL NEUROINFLAMMATORY PATHWAYS TO CEREBROVASCULAR INJURY AND AMYLOID-BETA IN ALZHEIMER'S DISEASE

4.1. Introduction

Alzheimer's disease (AD) is defined by two pathologies – amyloid-beta (Aβ) plaques and neurofibrillary tangles (Jack Jr et al., 2024). However, less emphasis is placed on the heterogeneity of processes in AD, which impedes us from determining novel potential mechanistic pathways preceding clinical symptoms and identifying effective markers for treatment. While Aβ is hypothesized to initiate a biological cascade that leads to accelerated deposition and spread of tau pathology and neurodegeneration (Hampel et al., 2021; Hardy & Higgins, 1992; Jack et al., 2010), there are likely multiple pathways that converge to promote neurodegeneration and cognitive impairment. One such pathway involves the interplay between neuroinflammation and cerebrovascular injury, which may parallel the cascading impact of Aβ pathology (Hardy & Higgins, 1992; Selkoe & Hardy, 2016).

Reactive astrocytes and microglia are important to both Aβ and tau pathogenesis (Kumar et al., 2023; St-Pierre et al., 2022) and the possible bidirectional roles of neuroinflammation with AD proteinopathy have been examined (Ahmad et al., 2019; Kaur et al., 2019). For example, initial glial activation is thought to be an early mechanism to eliminate Aβ, yet this process often leads to a vicious cycle of development of further chronic neuroinflammatory and neurotoxic damage (Zhu et al., 2017). Specific reactive astrocytic and microglial markers, such as glial fibrillary acidic protein (GFAP) and chitinase-3-like protein 1 (YKL-40), contribute to higher risk of AD (Chatterjee et al., 2021; Craig-Schapiro et al., 2010; Mavroudis et al., 2021; Oeckl et al., 2019). YKL-40 has emerged as an important candidate biomarker for examining the clinical progression of AD (Lista et al., 2024), and can be detected at the earliest stage of pathogenesis (Connolly et al., 2023; Hampel et al., 2018; Janelidze et al., 2018). Similarly, GFAP is a valuable

marker in the early detection and prediction of the course of AD (Hansen et al., 2022). One study comparing several candidate AD plasma biomarkers found that plasma GFAP combined with AD risk factors had the highest accuracy in differentiating between cognitively unimpaired older adults with amyloidosis and without amyloidosis, demonstrating its potential as a diagnostic marker in AD (Chatterjee et al., 2021). Comparing whether GFAP and YKL-40 are differentially linked to Aβ and cerebrovascular injury has not yet been investigated. One marker reflecting cerebrovascular injury and small vessel cerebrovascular disease, broadly studied in aging and dementia (Brickman et al., 2009a; Desmond, 2002; Gunning-Dixon & Raz, 2000), are white matter hyperintensities (WMH), which are visualized as areas with increased brightness on T2-weighted magnetic resonance imaging (MRI).

One study found that CSF GFAP was related to Aβ while CSF YKL-40 was related to higher tau-PET (Ferrari-Souza et al., 2022). Ferrari-Souza et al. (2022) further found that CSF GFAP and YKL-40 mediated the effects of Aβ and tau respectively on hippocampal atrophy, which was subsequently related to worse cognition. Similarly, Pelkmans et al. (2024) reported CSF Aβ is linked to GFAP. However, Pelkmans et al. (2024) determined that CSF YKL-40 mediated the effect of Aβ on tau-phosphorylation and its association to neurodegeneration. Furthermore, another study suggested that GFAP mediated the association between Aβ and tau (Pereira et al., 2021). Increases in plasma GFAP levels have also been associated with WMH in early-onset AD, late-onset AD, and in adults with Down syndrome (DS) (Edwards et al., 2024; Elahi et al., 2019). Similarly, there is growing evidence of the association between YKL-40 and WMH (Zhang et al., 2023). A longitudinal study demonstrated a strong association between plasma and CSF YKL-40 levels (Craig-Schapiro et al., 2010). Another study indicated that plasma GFAP was a sensitive biomarker that outperformed CSF GFAP in detecting amyloid pathology in early AD (Benedet et al., 2021). Given the inconsistency of the reported links of GFAP and

YKL-40 with Aβ, tau, and WMH, we tested these associations in the context of an AD pathogenic pathway.

A novel feature of the current study is the examination of cerebrovascular injury and its interface with neuroinflammation, Aβ, and tau burden. Past work indicates an association of WMH with structural imaging markers of medial temporal lobe (MTL) neurodegeneration and memory deficits in older adults (Rizvi et al., 2021; Rizvi et al., 2023). Furthermore, related work shows that WMH precede and promote tau (Laing et al., 2020; Tosto et al., 2015). We hypothesize that one mechanism by which WMH lead to MTL and hippocampal neurodegeneration is through tau burden. Overall, we propose that cerebrovascular injury and dysfunction is a distinguishable pathology from amyloidosis. We further suggest that these two types of pathologies may be associated with different neuroinflammatory cascades. This is in contrast with the single pathogenic pathway proposed by the A/T/N framework (Jack et al., 2018; Sweeney et al., 2019).

4.3. Materials and Methods

Participants

One-hundred twenty-six community-dwelling adults were included in the study, as part of the Biomarker Exploration in Aging, Cognition, and Neurodegeneration (BEACoN) study. Inclusion criteria for BEACoN consists of age ≥ 60 years and performance on cognitive assessments within age-adjusted normal range (within 1.5 standard deviations). Exclusion criteria include diagnosis of dementia or mild cognitive impairment, major health problems (e.g. uncontrolled diabetes mellitus, uncontrolled hypertension, history of stroke), comorbid neurological disease, significant psychiatric disorders, use of medication for anxiety or depression or illicit drugs, and MRI or PET contraindications. All participants gave written informed consent and were compensated for their participation. Study procedures were approved by the Institutional Review Board of the University of California, Irvine. The study is in accordance with *The Code of Ethics of the World Medical Association (Declaration of Helsinki).* Participants were included in the

study if MRI, Aβ PET, plasma, or neuropsychological data of interest in our primary analyses were available. Demographic characteristics of the participants, including the sample size of each marker, are included in Table 1.

Table 4.1. Demographic Characteristics and Summary Variables

Characteristic	Values	
N	126	
Age, mean (SD)	70.60 (6.29)	
Education, mean (SD)	16.57 (2.32)	
Sex/Gender, n (%) women	78 (61.90%)	
Race and Ethnicity, n (%)		
White	102 (80.95%)	
Asian	18 (14.29%)	
Black	1 (0.79%)	
More than 1 race or Other	5 (3.97%)	
Hispanic	6 (4.76%)	
Markers (Plasma, Imaging, Neuropsychological)	Raw values	Log-transformed values
YKL-40 pg/mL (n=69), mean (SD)	51.41 (41.23)	3.73 (0.64)
GFAP pg/mL (n=69), mean (SD)	353.90 (331.89)	5.65 (0.63)
Total WMH, cm^3 (n=112), mean (SD)	3.60 (8.14)	1.02 (0.83)
Global FBP SUVR (n=108), mean (SD)	1.11 (0.17)	0.74 (0.08)
pTau-217 pg/mL (n=64), mean (SD)	0.12 (0.10)	0.11 (0.08)
MTL Cortical Thickness, mm (n=122), mean (SD)	1.20 (0.06)	0.79 (0.27)
Hippocampal Volume, TIV adjusted (n=122), mean (SD)	1.96 (0.26)	1.08 (0.09)
Retroactive Interference (n=111), mean (SD)	0.84 (0.18)	0.60 (0.10)
Delayed Recall (n=111), mean (SD)	10.72 (3.52)	2.39 (0.47)

Magnetic Resonance Imaging

Magnetic resonance imaging (MRI) data were acquired on a 3.0 Tesla Siemens Prisma scanner at the Facility for Imaging and Brain Research (FIBRE) at the University of California, Irvine. The following scans were acquired: Structural T1-weighted MPRAGE (resolution = 0.8 x 0.8 x 0.8 mm, repetition time = 2300 ms, echo time = 2.38 ms, FOV read = 256 mm, slices = 240, slice orientation = sagittal), T2-weighted fluid-attenuated inversion recovery (FLAIR; resolution = 1.0 x 1.0 x 1.2 mm, repetition time = 4800 ms, echo time = 441 ms, FOV read = 256 mm, slices = 160, inversion time = 1550 ms, slice orientation = sagittal) and T2-Turbo Spin Echo (resolution =

0.4 mm x 0.4 mm x 2.0, repetition time = 5000 ms, echo time = 84 ms, FOV read = 190 mm, acquired perpendicular to the long axis of the hippocampus).

MRI analyses

White Matter Hyperintensities Segmentation

Image processing leveraged the open-source ANTsX software ecosystem with a particular focus on specific deep-learning applications developed for neuroimaging made available for both Python and R via the ANTsXNet (ANTsPyNet/ANTsRNet) libraries. Specifically, for the work described here, WMH segmentation used the ANTsPyNet function: sysu_white_matter_hypterintensity_segmentation.

The methods used in this paper for WMH segmentation (see Figure 4.1A, 4.1B) and quantification are previously described (Rizvi et al., 2023). Briefly, a preprocessing scheme is used that includes thresholding for brain extraction and an ensemble (n=3) of randomly initialized 2-D U-nets to produce the probabilistic output, implemented in ANTsXNET (Tustison et al., 2021). All WMH masks resulting from the above automated segmentation procedure were manually edited by an expert rater (B.R.) for improved accuracy. These edited global WMH volumes were used in our analyses.

Medial Temporal Lobe Subregion Segmentation

Medial temporal lobe (MTL) subregions were automatically segmented (see Figure 4.1D) with the Automatic Segmentation of Hippocampal Subfields (ASHS) (Yushkevich et al., 2015) software using T1- and T2-weighted images. The ASHS pipeline implements joint label fusion and corrective learning to segment hippocampal subfields and medial temporal lobe cortical subregions. The left and right MTL segmentation images from ASHS were then loaded using Advanced Normalization Tools software (ANTs). Label geometry measures, including volume

and surface area, were extracted from the segmented subregions. For each labeled subregion, the thickness was computed by dividing the volume by the surface area.

The resulting output included thickness of the following MTL cortical subregions in native T2 space: entorhinal cortex (ERC), perirhinal cortex subdivided into Brodmann Areas 35 and 36 (PRC; BA35, BA36), and parahippocampal cortex (PHC). Total MTL cortical thickness was derived from averaging the thickness of these four subregions. Separately, the output included volumes of the following hippocampal subfields: dentate gyrus (DG), CA1, CA2, CA3, and subiculum. All hippocampal subfield volumes were adjusted for intracranial volume (ICV) by dividing the subfield volume by the individual's ICV. Total hippocampal volume was derived by taking the sum of the ICV-adjusted bilateral hippocampal subfield volumes. Total hippocampal volume was then multiplied by 1000.

Plasma Markers

Plasma Collection

Blood was collected without regard to prandial state, time of day or medication timing. Blood was drawn via venipuncture from each participant into 7 mL lavender top EDTA tubes (BD 366450). Immediately after collection, each tube was gently mixed by inverting 8 to 10 times to ensure proper mixing of blood and anticoagulant, and then placed on wet ice. Blood samples were centrifuged in a swinging rotor bucket within 1 hour of collection at 2600 x RPM at 20°C for 10 minutes. The isolated plasma was transferred and pooled into a sterile 50 mL polypropylene conical tube and mixed by inversion a few times. The plasma samples were aliquoted by 0.750 mL increments into 2 mL polypropylene cryovials. The plasma aliquots were transferred into a −80 °C freezer for storage until required for analysis.

Plasma Biomarker Quantification

Levels of YKL-40 were quantified in plasma samples from BEACoN participants using the U-PLEX Human YKL-40 ECL immunoassay MesoScale Discovery (MSD; Cat #K151VLK Gaithersburg, MD). Levels of GFAP were quantified using the R-PLEX Neurology Panel 1 (Thiebaut de Schotten et al., K15639). Assays were run according to MSD manufacturers protocol using plasma samples diluted 1:2 in Diluent 3 or 64 (MSD) for YKL-40 and GFAP, respectively. Samples were assayed after a single thaw to room temperature. Measurements were performed in duplicate, and sample measurements accepted if signal coefficients of variation (CVs) across duplicates were less than 15%. The human YKL-40 and GFAP calibrators provided with the kit were used for generating the standard curve, and sample concentrations (pg/ml) were determined with MSD Discovery Workbench Software using curve fit models. Lower limits of detection (LLoD) were as follows: YKL-40 (0.858 pg/mL) and GFAP (29.1 pg/mL). Plasma p-Tau 217 levels were quantified using an immunoassay developed by ALZpath, using a previously described method (Ashton et al., 2024).

Amyloid PET

PET Acquisition

18F-Florbetapir (FBP) positron emission tomography (PET) was used to measure Aβ plaque pathology. PET was acquired on an ECAT High Resolution Research Tomograph (HRRT, CTI/Siemens, Knoxville, TN, USA). Ten mCi of tracer was injected, and then four 5-minute frames were collected from 50-70 minutes post-injection. FBP-PET data was reconstructed with attenuation correction, scatter correction, and 2mm3 Gaussian smoothing.

PET Processing

FBP frame data were realigned, averaged, and then co-registered to the T1-weighted MPRAGE image. T1 MPRAGE images were processed with FreeSurfer v.6.0 to generate native-space regions of interest for PET reference regions and quantification. FBP images were then

normalized by a whole cerebellum reference region to produce standardized uptake value ratio (SUVR) images (see Figure 4.1C). Additional 6mm3 smoothing was then applied to achieve an effective resolution of 8mm3. The mean SUVR of a validated cortical composite region (Landau et al., 2013; Landau et al., 2012) was then quantified to obtain a global measure of FBP uptake for analysis.

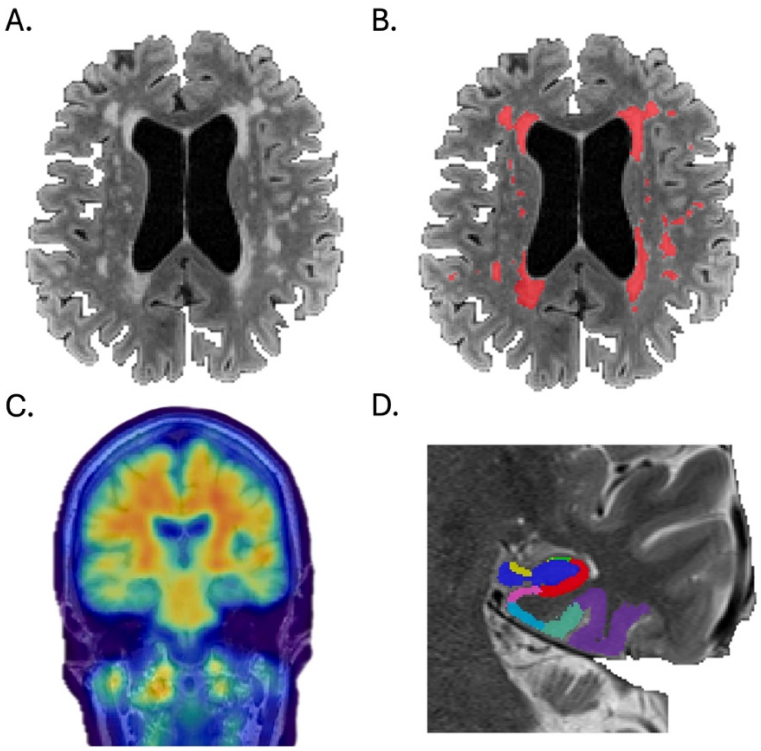

Figure 4.1. Visualizing imaging analyses. A) Unlabeled WMH on an axial T2-FLAIR image. B) Labeled WMH in red on an axial T2-FLAIR image. C) Global FBP SUVR image D) T2 image with hippocampal and MTL cortical subregions labeled using ASHS.

Neuropsychological Testing

Participants were administered the Rey Auditory Verbal Learning Test (RAVLT), which assesses word list learning, immediate and delayed memory (Savage & Gouvier, 1992). Our primary outcome measure of memory in this study was retroactive interference (RI) from RAVLT, which reflects resistance to interference during consolidation. RI compares memory for the target list of words before (A5) and after (A6) a distractor list is presented (A6/A5; with lower

scores indicating increased interference). Previous work suggests that RI is a more sensitive behavioral biomarker of subtle memory deficits than delayed recall, reflecting AD pathology and MTL subregional integrity (Adams et al., 2023; Lillywhite et al., 2007). In a supplementary analysis, we used delayed recall from RAVLT (A7), which tests free recall for the target word list after a 20-minute delay from the last learning trial (Appendix C, Table C1).

Statistical Analysis

Statistical analyses were conducted in R (version 4.3.0) through RStudio. All imaging, plasma, and neuropsychological markers of interest were log-transformed to reduce the skewness of the data prior to running path analysis, with a constant of 1 added before transforming to handle any zeros and to preserve non-negative values.

We conducted path analysis, which is a subset of structural equation modeling, using the *lavaan* package in R in a series of linear regressions simultaneously. We used full information maximum likelihood to handle missing data. Independent variables were considered as random. In our path analysis, we tested whether neuroinflammatory markers, including plasma GFAP and YKL-40, are associated with global WMH volume and global FBP SUVR. WMH volume and global FBP SUVR (Aβ) were then tested as two dissociable markers associated with plasma pTau-217. We also tested whether plasma pTau-217 is associated with MTL cortical thickness and hippocampal volume, and subsequently to lower performance on retroactive interference from RAVLT. In the supplementary results, (Appendix C, Table C1), we additionally report results using RAVLT delayed recall as an alternative outcome measure. We assessed goodness of model fit as "acceptable" if: $X2$ $p > 0.05$, Comparative Fit Index (CFI ≥ 0.90), Tucker-Lewis Index (TLI ≥ 0.90), Root Mean Square Error of Approximation (RMSEA < 0.08), and Standardized Root Mean Square Residual (SRMR < 0.08). Age was not controlled for in the path analysis, as the biomarkers and their relationships being studied are largely age dependent. Furthermore, as this sample does not include participants with frank clinical

impairment or dementia, adjusting for age would limit our ability to capture important associations among biomarkers and between biomarkers and cognitive function.

4.4. Results

Path Analysis

In our path analysis model, we tested associations among markers and hypothesized a theoretically driven mechanistic cascade. The overall model fit was considered acceptable: X*2* (9, N=126) = 21.049, p = 0.10, CFI = 0.90, TLI = 0.81, RMSEA = 0.063, and SRMR = 0.068. Plasma YKL-40 levels were not correlated with plasma GFAP levels (see Table 2, Figure 4.2). Higher plasma YKL-40 levels were associated with greater global WMH, but not with global FBP SUVR. Meanwhile, higher plasma GFAP levels were associated with higher global FBP SUVR, but not with global WMH. Higher plasma GFAP levels were also related to higher plasma pTau-217 levels. Both greater global WMH and increased global FBP SUVR were independently associated with higher plasma pTau-217 levels. Higher plasma pTau-217 levels were in turn associated with both reduced MTL cortical thickness and lower hippocampal volume. Subsequently, only hippocampal volume was related to lower performance on retroactive interference (RAVLT). In a supplemental analysis, we found similar patterns of associations among biomarkers, and determined that lower hippocampal volume was related to lower scores on delayed recall (RAVLT; see Appendix C, Table C1). Simple associations among markers included in the path model can be visualized in the scatterplots shown (see Figure 4.3).

Table 4.2. Results of path analysis.

Dependent variable	Independent variable	*B*	Standardized Estimate	p-value	95% CI
Total WMH (log) ~	YKL-40 (log)	0.393	0.299	0.005	(0.12, 0.666)
	GFAP (log)	0.098	0.076	0.465	(-0.166, 0.362)
Global FBP SUVR (log) ~	YKL-40 (log)	-0.02	-0.161	0.176	(-0.05, 0.009)

	GFAP (log)	0.054	0.435	<0.001	(0.027, 0.08)
pTau-217 (log) ~	Total WMH (log)	0.023	0.226	0.014	(0.004, 0.041)
	Global FBP SUVR (log)	0.371	0.357	0.002	(0.139, 0.602)
	YKL-40 (log)	-0.004	-0.029	0.789	(-0.032, 0.024)
	GFAP (log)	0.036	0.279	0.013	(0.008, 0.064)
MTL Cortical Thickness (log) ~	pTau-217 (log)	-0.112	-0.345	0.001	(-0.177,-0.047)
Hippocampal Volume (log) ~	pTau-217 (log)	-0.278	-0.254	0.013	(-0.498, -0.058)
Retroactive Interference (log) ~	MTL Cortical Thickness (log)	0.471	0.121	0.217	(-0.277, 1.218)
	Hippocampal Volume (log)	0.387	0.333	0.001	(0.163, 0.611)
	pTau-217 (log)	0.182	0.143	0.202	(-0.097, 0.46)
Covariances		***B***	**Standardized Estimate**	**p-value**	**95% CI**
YKL-40 (log) ~~ GFAP (log)		0.073	0.183	0.137	(-0.023, 0.169)

Path analysis model with the following regression and covariance equations:
Total WMH ~ YKL-40 + GFAP
Global GFP SUVR ~ YKL-40 + GFAP
pTau-217 ~ Total WMH + Global FBP SUVR + YKL-40 + GFAP
MTL Cortical Thickness ~ pTau-217
Hippocampal Volume ~ pTau-217
Retroactive Interference ~ MTL Cortical Thickness + Hippocampal Volume + pTau-217
YKL-40 ~~ GFAP

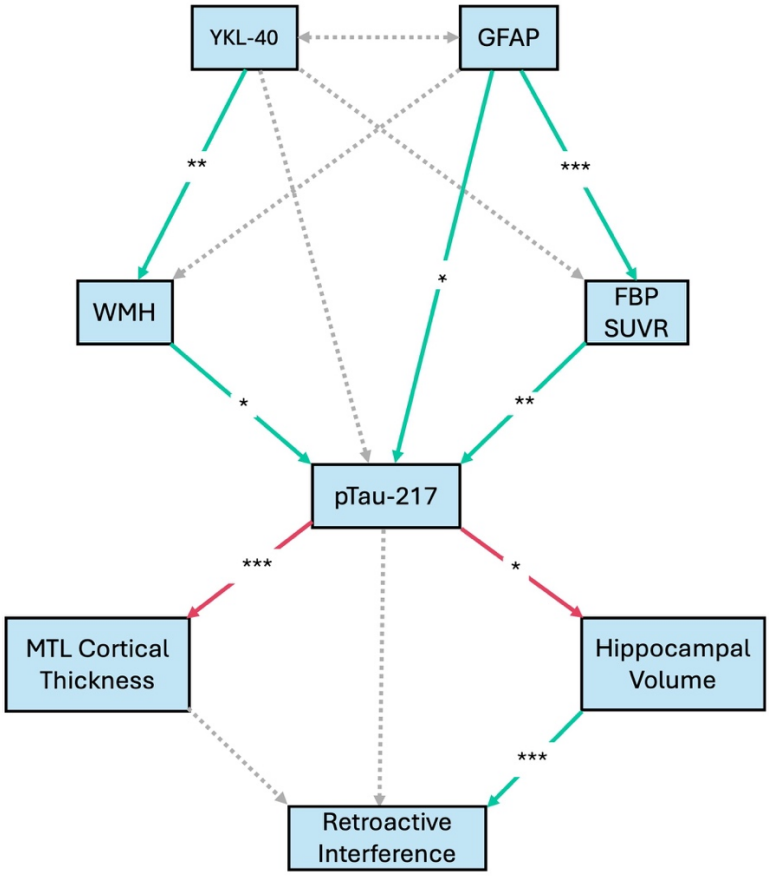

Figure 4.2. Path diagram indicating pathway from neuroinflammatory markers (YKL-40 and GFAP) to downstream biomarkers and subsequent memory deficits. Solid lines demonstrate significant paths, and dotted lines represent non-significant paths. Green arrows represent positive associations, and red arrows represent negative associations. Paths indicated as significant (*) for p-values $\leq$ 0.05, (**) for p $\leq$ 0.01, and (***) for p $\leq$ 0.001. Results of path analyses are shown in Table 2.

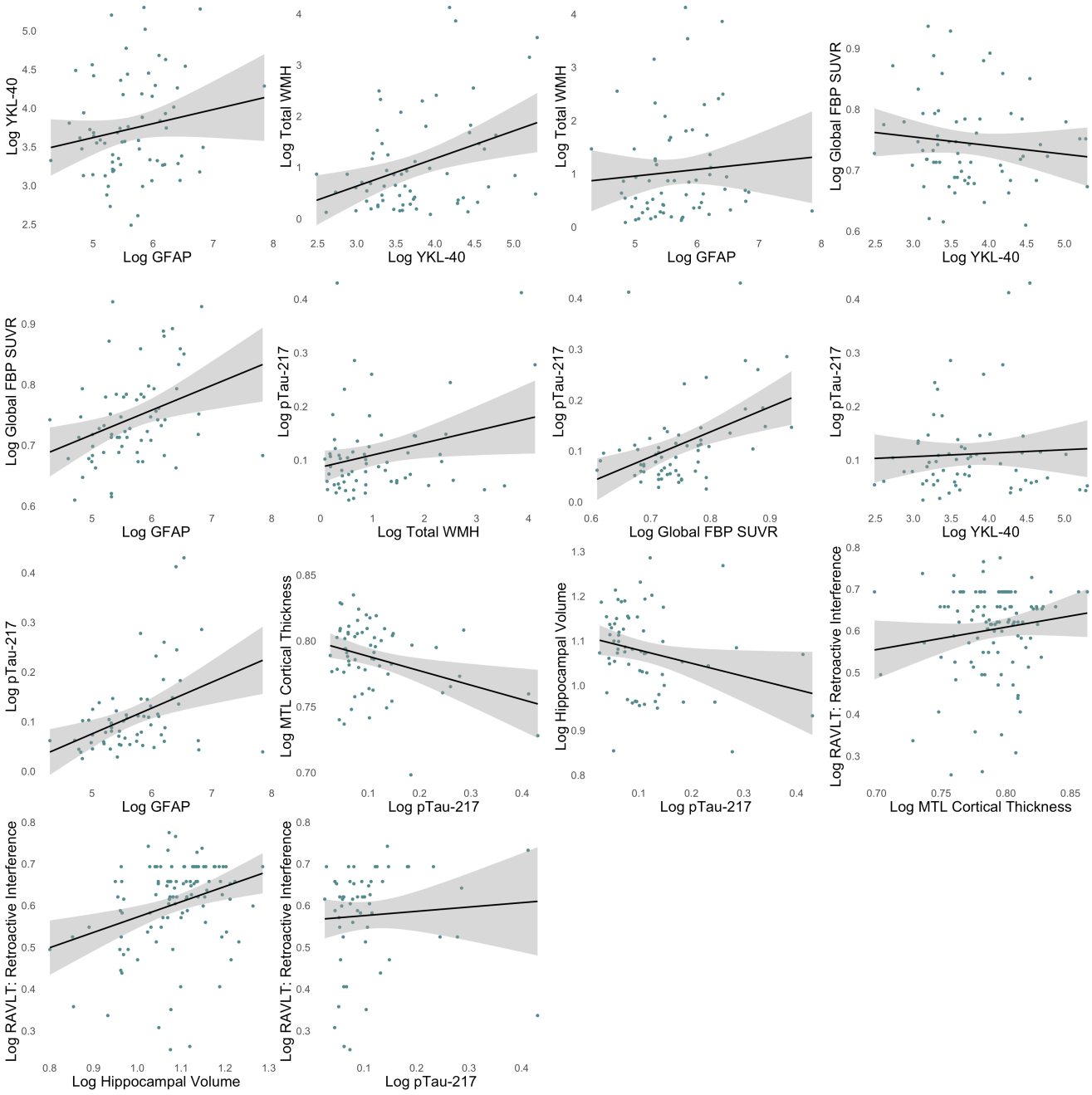

Figure 4.3. Scatterplots of associations among markers that were included in linear regressions, as part of the path analysis.

4.5. Discussion

Our results support a model in which two glial cell activation and neuroinflammatory markers, YKL-40 and GFAP, are differentially related to small vessel cerebrovascular disease and

amyloid, respectively, suggesting at least two pathways converging to phosphorylated tau. Phosphorylated tau was subsequently associated with neurodegeneration and lower memory performance in older adults. This pathophysiological cascade is depicted in Appendix C, Supplemental Figure C1.

While many studies showed a temporal ordering among amyloid, tau, and neurodegeneration (Ebenau et al., 2022; Luo et al., 2020; Milà-Alomà et al., 2020; Tan et al., 2020), a similar temporal pathway has not been described with respect to cerebrovascular disease, tau, and neurodegeneration. However, previous work demonstrated associations between cerebrovascular disease and tau in both humans and mice (Kapasi et al., 2022; Laing et al., 2020; Tosto et al., 2015). Similarly, prior work showed WMH are associated with MTL atrophy in both longitudinal and cross-sectional analyses (Rizvi et al., 2021; Rizvi et al., 2023; Swardfager et al., 2018). We did not explicitly model a relationship between amyloid and WMH, given that we did not expect a relationship between amyloid and WMH. Many previous studies reported no association between the two markers among clinically unimpaired individuals (Liu et al., 2018b; Roseborough et al., 2017). Of interest, we expected to observe a direct effect of phosphorylated tau on memory given past studies suggesting alternative pathways toward memory loss (Berron et al., 2021; Tracy & Gan, 2018), but we did not find a direct association between p-Tau217 and memory. It is possible that hippocampal volume fully mediates the association between phosphorylated tau and memory deficits.

We found that plasma YKL-40, a glycoprotein secreted and synthesized by astrocytes, microglia, and peripheral macrophages (Lautner et al., 2011; Zhang et al., 2023), was associated with WMH but not with Aβ. Previous work on serum YKL-40 demonstrated its association with WMH volume, and, further, that macroscopic and microscopic white matter damage mediated the correlation between serum YKL-40 and cognitive impairment in patients with small vessel disease (Zhang et al., 2023).

In contrast to our findings with YKL-40, we found that plasma GFAP was associated with Aβ, but not with WMH. Prior work demonstrated that GFAP is associated with Aβ burden in unimpaired older adults and in those who are at risk for AD (Chatterjee et al., 2021; Pereira et al., 2021; Shir et al., 2022). Studies have also reported a link between GFAP and WMH (Edwards et al., 2024; Shir et al., 2022); Shir et al. (2022) demonstrated that the relationship between GFAP and WMH is only found in individuals with elevated levels of Aβ. Consistent with this understanding, the link between GFAP and WMH shown by Edwards et al. (2024) was found in adults with Down syndrome, who also demonstrate elevated levels of amyloid (Head et al., 2018b; Schupf et al., 2001).

Two previous studies did not show a link between GFAP and tau when Aβ is accounted for (Pereira et al., 2021; Shir et al., 2022), but we found an association between GFAP and tau even when amyloid was included in the model. However, an important difference between their studies and ours is their use of tau-PET, which is more likely than plasma pTau-217 to reflect tau aggregation (Therriault et al., 2023).

There are some limitations with the current study. One limitation is that path analysis cannot examine bidirectional relationships that might be recursive in nature, for example between WMH and YKL-40, or between Aβ and GFAP. Due to the cross-sectional nature of the study design, we are unable to address the temporality or causality of the correlational associations found through the path analysis. With the limited parametric range of cognitive performance among clinically unimpaired older adults within our sample, we did not adjust for age in our path analysis model, as these associations are substantially driven by aging. Future work should include a more diverse sample of participants, as our study had predominantly non-Hispanic White participants. Another future direction is to include a broader array of markers of inflammatory disease and small vessel disease while applying a latent factor SEM approach. Given that plasma pTau-217 is associated with both amyloid and tau pathology (Therriault et al.,

2023), another future step would include using a more specific measure of tau aggregation, such as tau-PET. Regional distributions of amyloid and tau can also be considered with the use of PET, allowing for understanding more specific mechanistic roles of these two markers in this pathway.

In summary, we found that cerebrovascular injury and Aβ form two parallel and distinct pathways by which neuroinflammatory changes may alter Alzheimer's pathological features, converging on the neurodegenerative cascade leading to cognitive decline. Identifying these pathways enables the early detection of biomarkers and the targeting of therapeutic interventions to the appropriate windows of disease. This understanding can also provide traction for addressing individual differences in AD vulnerability and resilience, potentially paving the way for personalized therapeutic strategies.

CHAPTER 5: SYNTHESIS AND FUTURE DIRECTIONS

5.1. General Summary

The main objective of this dissertation was to assess the roles of cerebrovascular injury in its impact on neurodegeneration and memory decline in Alzheimer’s disease. We further elucidated upstream factors leading to cerebrovascular injury, such as higher pulse pressure and neuroinflammation and identified the secondary processes associated with CVID, including tau and neurodegeneration. While we did not expect a link between cerebrovascular injury and Aβ, we found that these separable pathways converged to downstream pathology including tau and neurodegeneration. These studies discussed in Chapters 2-4 highlight the importance of examining relationships between WMH and markers of AD pathology, emphasizing the need to explore pathways beyond those defined by the single pathway as proposed by the A/T/N framework. In the subsequent sections, I will discuss the key findings and concepts of Chapters

2, 3, and 4. Lastly, I will close with future directions and highlight potential approaches to accelerate the development of interventions for AD, informed by our findings.

5.2. WMH, MTL subregional integrity, and memory

In Chapter 2, we assessed the associations of WMH with MTL subregional volumes and delayed memory performance in older adults without dementia. Prior work had established the strong link between WMH and generalized cognitive functions in older adults, such as speed of processing and executive function. However, the relationship between WMH and long-term and episodic memory is less clear. Another novel aim of this work was to investigate the relationships of regional WMH with hippocampal and extra-hippocampal subregions. Using a mediation model, we tested the hypothesis that the association of WMH with memory performance is through their impact on regional MTL subregional volume.

We found that increased occipital WMH were related to worse performance on delayed recall. Occipital WMH were also associated with reduced MTL subregional volumes, including the CA1, DG, BA36, and PHC, which in turn were related to delayed recall. Of interest, we found that the association between occipital WMH and delayed recall was only mediated by perirhinal cortex (BA36) volume.

These findings point to the relevance of WMH to neurodegeneration and cognitive decline even in older adults without dementia. It also suggests that targeting modifiable risk factors that are known to increase WMH burden, such as hypertension, can potentially reduce or slow down neurodegenerative changes, thereby slowing memory decline in those at risk for AD.

5.2. Pulse pressure to dementia in adults with Down syndrome

Chapter 3 focused on the link between vascular risk and brain health measures in Down syndrome (DS), a population that is less likely to develop classical vascular risk factors. While nearly all individuals with DS who reach the age of 50 develop amyloid plaques, there is some

variability in the age of onset and severity of clinical decline. Additionally, despite that individuals with DS show low risk of classic hypertension, they demonstrate cerebrovascular abnormalities including WMH, enlarged PVS, microbleeds, and infarcts (Lao et al., 2020). Here, we assessed whether pulse pressure, obtained by blood pressure readings (systolic minus diastolic blood pressure), is associated with measures of cerebrovascular injury and with a diagnosis of dementia in adults with DS, mediated by structural markers. We found that higher pulse pressure was associated with greater global, parietal, and occipital WMH, but not to enlarged PVS, microbleeds, or infarcts. Pulse pressure was associated with WMH, which in turn was related to GM atrophy and subsequent diagnosis of dementia. This study, published in Rizvi et al. (2024b), highlights the potential value of monitoring and targeting blood pressure through interventions in people with DS. Since the pathophysiological features and clinical course of AD are similar in the neurotypical population to those with DS, it is relevant to study how vascular risk factors such as pulse pressure affect cerebrovascular markers even when the risk of hypertension remains low. It suggests that cerebrovascular markers such as WMH are not completely secondary to AD pathology and that vascular risk factors make one prone to AD dementia even when these risk factors are not classified as severe. These findings also can inform us about the neurotypical population, who exhibit higher rates of hypertension, suggesting pulse pressure may be a targetable and modifiable risk factor of cerebrovascular burden and AD dementia.

5.3. Parallel neuroinflammatory pathways to Alzheimer's disease

In Chapter 4, I tested whether two distinct neuroinflammatory markers are associated with cerebrovascular injury and Aβ, which subsequently converge to tau, MTL atrophy, and memory decline. While Aβ is thought to initiate the biological cascade leading to tau pathology and neurodegeneration, it is likely other pathways converge to promote neurodegeneration. We focus on two upstream neuroinflammatory pathways, contributing to both Aβ and

cerebrovascular injury, which in parallel, converge to tauopathy and neurodegeneration. We found that higher YKL-40 was related to increased cerebrovascular injury, while higher GFAP was associated with greater Aβ deposition. Both factors, Aβ and WMH, were in turn associated with increased tau, which mediated MTL atrophy and subsequent memory deficits. These findings potentially enable clinicians and researchers to detect biomarkers earlier and to intervene therapeutically during optimal windows of the disease course. This study was recently submitted and is available as a preprint in biorXiv (Rizvi et al., 2024a).

5.4. Future Directions

Longitudinal analyses

The importance of validating and extending findings from cross-sectional studies in longitudinal analyses cannot be understated. Cross-sectional studies do not alone establish or infer causality or sufficiently allow one to determine disease development or progression. However, cross-sectional studies offer researchers the added value of lower-cost studies, faster data collection, and lower participant attrition (Wang & Cheng, 2020). For example, the findings presented in Chapter 1, including the associations of posterior WMH to MTL subregional volumes in older adults, would benefit from the longitudinal analyses of associations of WMH and the progression of MTL subregional atrophy. Extending this work would allow us to determine the directionality of these associations.

Using a diversified sample inclusive of minoritized individuals

The prevalence of AD among Black and Hispanic older adults is considerably higher than non-Hispanic Whites (Mayeda et al., 2016). While ethnically and racially minoritized groups are at increased risk of AD, they are heavily underrepresented in research studies and clinical trials for AD (Lim et al., 2023). Cerebrovascular disease is more commonly found among Black and Hispanic populations ("2024 Alzheimer's disease facts and figures," 2024), potentially explaining

their increased risk of AD. Given the disproportionate impact of negative social determinants of health (SDOH), stress, and discrimination on these populations, understanding these factors is essential for developing effective interventions to protect brain health. Unfortunately, most community-based studies have not included well-represented minoritized individuals in their samples (Lim et al., 2023; Raman et al., 2021). This applies to the studies described in Chapters 2, 3, and 4, which are composed of predominantly non-Hispanic White participants. This underrepresentation precludes understanding important factors such as health disparities, SDOH, and resilience in these populations in relation to brain health outcomes. For example, Chapter 2 reveals the associations of increased pulse pressure with greater posterior WMH burden in individuals with DS. However, hardly any participant data exists on non-White individuals with DS within the ADDS dataset, making it difficult to assume that these associations would be identical in Black or Hispanic/Latino individuals with DS. Minoritized individuals may experience higher rates of pulse pressure, increasing their risk of developing WMH and dementia.

Use of tau-PET

When assessing true aggregation of tau pathology, tau-PET is a more specific measure than plasma measures of tau, such as pTau-217 (Therriault et al., 2023). It has been shown that plasma pTau-217 can be used as a marker of Aβ pathology in preclinical AD (Milà-Alomà et al., 2022). This is a large limitation of our study in Chapter 4, where we demonstrated that both cerebrovascular injury and Aβ were related to increased plasma pTau-217 levels. Without a specific and robust marker of tau aggregation, it is difficult to conclude that these upstream markers are related to tau, and amyloid burden may be a confounder in these associations. Future work will establish these links using tau-PET, enabling researchers to identify regional specificity in the associations between WMH and tau, or tau and MTL atrophy.

Parcellation by arterial vascular territories

The link between WMH and dementia risk and MTL atrophy is most pronounced with posterior WMH burden. WMH have typically been parcellated by lobes (Brickman, 2013), periventricular or deep territories (DeCarli et al., 2005), or even within tracts (Garnier-Crussard et al., 2022; Rizvi et al., 2020). However, it is unexplored how assessing cerebrovascular injury within vascular territories may be an important marker for AD diagnosis and related pathology. This novel method would provide insight into the neurobiological mechanisms involved in the cerebrovascular contributions to AD pathogenesis. For example, the posterior cerebral artery (PCA) infuses both posterior regions of the brain and MTL regions vulnerable to AD pathology (Brandt et al., 2000). Previously, we have found that posterior WMH, most likely supplied by the PCA, are particularly more sensitive to predicting memory decline and neurodegeneration (Rizvi et al., 2023). Similar to the study described in Chapter 2, it would be relevant to study whether WMH within specific arterial territories, in particular within the PCA, are linked to MTL subregional atrophy and memory decline. Future work should also investigate whether changes in blood flow as measured by CBF in these vascular territories precede the expected regional changes in WMH volumes within the arterial territories.

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APPENDIX A

Supplemental Table A1. Associations between WMH and RAVLT measures

WMH Distribution	RAVLT Measure	*b*-coefficient	Standardized β-coefficient	p-value	95% CI
Frontal WMH	Delayed Recall	0.273	0.069	0.407	(-0.377, 0.924)
	Learning Slope	0.087	0.149	0.116	(-0.022, 0.195)
	Percent Forgetting	-0.016	-0.065	0.475	(-0.062, 0.029)
	Retroactive Interference	0.003	0.013	0.897	(-0.041, 0.047)
	Recognition	0.054	0.035	0.355	(-0.248, 0.356)
Temporal WMH	Delayed Recall	0.605	0.044	0.574	(-1.518, 2.728)
	Learning Slope	0.127	0.063	0.484	(-0.230, 0.483)
	Percent Forgetting	-0.011	0.013	0.883	(-0.160, 0.137)
	Retroactive Interference	0.008	0.010	0.912	(-0.135, 0.151)
	Recognition	-0.087	-0.016	0.862	(-1.070. 0.897)
Parietal WMH	Delayed Recall	0.104	0.024	0.777	(-0.624, 0.832)
	Learning Slope	0.070	0.111	0.255	(-0.051, 0.192)
	Percent Forgetting	0.004	0.013	0.890	(-0.047, 0.054)
	Retroactive Interference	-0.011	-0.043	0.669	(-0.059, 0.038)
	Recognition	-0.049	-0.029	0.776	(-0.386, 0.289)
Occipital WMH	Delayed Recall	-2.009	-0.171	0.040*	(-0.348, -0.182)
	Learning Slope	-0.312	-0.180	0.059	(-0.636, 0.011)
	Percent Forgetting	0.097	0.129	0.158	(-0.038, 0.232)
	Retroactive Interference	-0.038	-0.056	0.568	(-0.169, 0.093)
	Recognition	-0.878	-0.190	0.055	(-1.774, 0.019)
Total WMH	Delayed Recall	0.070	0.025	0.768	(-0.396, 0.535)
	Learning Slope	0.039	0.096	0.324	(-0.039, 0.117)
	Percent Forgetting	-0.002	-0.012	0.897	(-0.035, 0.030)
	Retroactive Interference	-0.003	0.016	0.825	(-0.035, 0.028)
	Recognition	-0.007	-0.007	0.946	(-0.223, 0.209)

Significant values indicated by *.
Regression model: RAVLT measure ~ Regional WMH + age + sex + education + intercept.

Supplemental Table A2. Associations between occipital WMH and left/right MTL subregional volumes.

WMH Distribution	MTL Subregion	*b*-coefficient	Standardized β-coefficient	p-value	95% CI
Occipital WMH	Left CA1	-0.138	-0.281	<0.001*	(-0.219, -0.058)

	Right CA1	-0.116	-0.248	0.005*	(-0.196, -0.036)
	Left CA2	0.001	0.057	0.560	(-0.002, 0.004)
	Right CA2	-0.002	-0.174	0.072	(-0.005, 0.000)
	Left CA3	-0.010	-0.217	0.028*	(-0.019, -0.001)
	Right CA3	$9.8x10^{-5}$	0.002	0.985	(-0.010, 0.010)
	Left DG	-0.088	-0.301	<0.001*	(-0.137, -0.039)
	Right DG	-0.075	-0.263	0.003*	(-0.124, -0.025)
	Left ERC	-0.041	-0.199	0.032*	(-0.079, -0.004)
	Right ERC	-0.055	-0.222	0.021*	(-0.102, -0.009)
	Left BA35	-0.043	-0.190	0.042	(-0.084, -0.002)
	Right BA35	0.000	-0.011	0.992	(-0.39, 0.038)
	Left BA36	-0.250	-0.338	<0.001*	(-0.388, -0.112)
	Right BA36	-0.176	-0.235	0.015*	(-0.318, -0.034)
	Left SUB	-0.009	-0.060	0.526	(-0.036, 0.018)
	Right SUB	-0.037	-0.212	0.027*	(-0.069, -0.004)
	Left PHC	-0.152	-0.285	0.002*	(-0.244, -0.059)
	Right PHC	-0.061	-0.153	0.105	(-0.134, 0.013)

Significant values indicated by *.
Regression model: Left/Right MTL subregional volume ~ Regional WMH + age + sex + education + intercept.

Supplemental Table A3. Associations between MTL subregional volumes and RAVLT measures

MTL Subregion	RAVLT Measure	*b*-coefficient	Standardized β-coefficient	p-value	95% CI
Total CA1	Delayed Recall	2.114	0.166	0.038*	(0.115, 4.113)
	Learning Slope	-0.142	-0.077	0.418	(-0.488, 0.204)
	Percent Forgetting	-0.181	-0.222	0.013*	(-0.322, -0.039)
	Retroactive Interference	0.135	0.185	0.052	(-0.001, 0.271)
	Recognition	0.690	0.151	0.126	(-0.198, 1.578)
Total Dentate Gyrus	Delayed Recall	3.956	0.187	0.016*	(0.737, 7.176)
	Learning Slope	0.006	0.002	0.983	(-0.556, 0.568)
	Percent Forgetting	-0.368	-0.272	0.002*	(-0.593, -0.142)
	Retroactive Interference	0.248	0.205	0.027*	(0.028, 0.468)
	Recognition	1.293	0.168	0.083	(-0.170, 2.755)
Total Perirhinal Cortex (BA36)	Delayed Recall	2.445	0.285	<0.001*	(1.263, 3.628)
	Learning Slope	0.011	0.009	0.918	(0.203, 0.226)
	Percent Forgetting	-0.179	-0.327	<0.001*	(-0.263, -0.095)

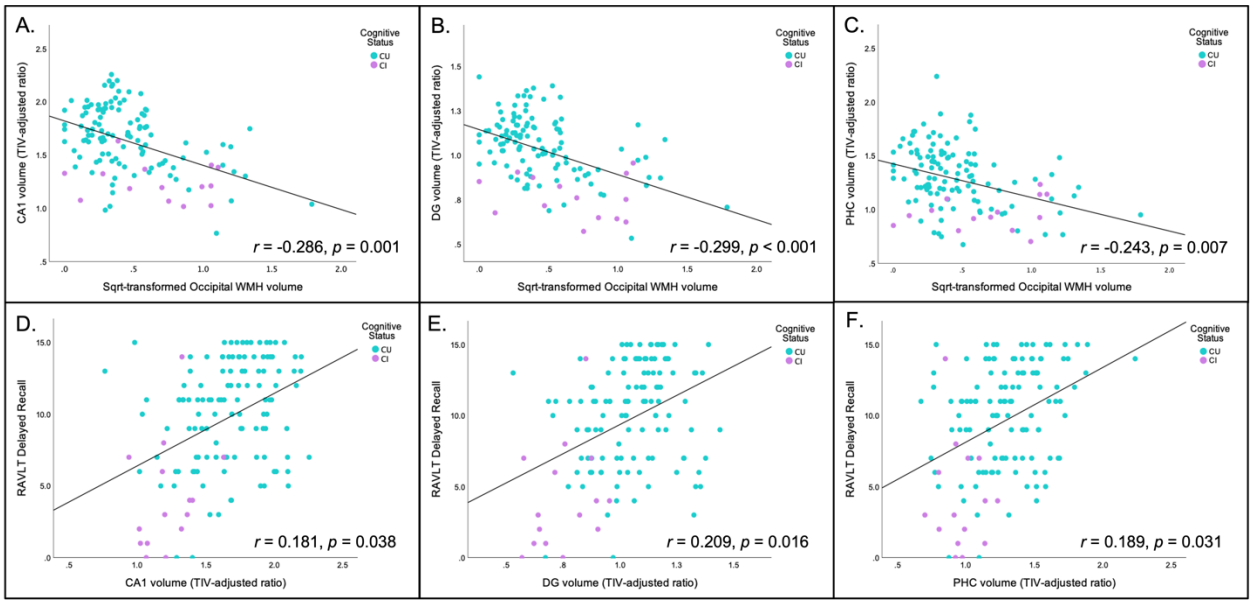
	Retroactive Interference	0.143	0.291	<0.001 *	(0.062, 0.225)
	Recognition	0.653	0.214	0.018*	(0.115, 1.190)
Total Parahippocampal Cortex	Delayed Recall	2.381	0.170	0.031*	(0.222, 4.541)
	Learning Slope	-0.165	-0.081	0.383	(-0.540, 0.209)
	Percent Forgetting	-0.237	-0.265	0.002*	(-0.387, -0.087)
	Retroactive Interference	0.069	0.086	0.359	(-0.080, 0.218)
	Recognition	0.159	0.030	0.756	(-0.849, 1.166)

Significant values indicated by *.
Regression model: RAVLT measure ~ Total MTL subregional volume + age + sex + education + intercept.

Supplemental Table A4. Associations between left/right MTL subregional volumes and delayed recall

MTL Subregion	RAVLT Measure	*b*-coefficient	Standardized β-coefficient	p-value	95% CI
Left CA1	Delayed Recall	4.112	0.170	0.036*	(0.270, 7.954)
Right CA1		3.808	0.151	0.056	(-0.100, 7.717)
Left DG		7.806	0.192	0.014*	(1.611, 14.00)
Right DG		6.750	0.166	0.032*	(0.575, 12.925)
Left BA36		4.048	0.253	<0.001*	(1.837, 6.258)
Right BA36		4.496	0.279	<0.001*	(2.252, 6.741)
Left PHC		4.450	0.195	0.013*	(0.948, 7.953)
Right PHC		3.301	0.106	0.168	(-1.407, 8.008)

Significant values indicated by *.
Regression model: Delayed Recall ~ Left/Right MTL subregional volume + age + sex + education + intercept.



Supplemental Figure A1. A. A scatterplot of the negative association between square root transformed occipital WMH and CA1 volume (TIV adjusted ratio). **B.** A scatterplot of the negative association between square root transformed occipital WMH and DG volume (TIV adjusted ratio). **C.** A scatterplot of the negative association between square root transformed occipital WMH and PHC volume (TIV adjusted ratio). **D.** A scatterplot of the positive association between CA1 volume (TIV adjusted ratio) and delayed recall. **E.** A scatterplot of the positive association between DG volume (TIV adjusted ratio) and delayed recall. **F.** A scatterplot of the positive association between PHC volume (TIV adjusted ratio) and delayed recall.

APPENDIX B

Supplemental Table B1. Sensitivity analyses examining pulse pressure and cerebrovascular imaging markers, excluding participants treated with anti-hypertensive or anti-hypotensive medication.

BP Measure	Outcome Measure	*B*	95% CI	β	t / Wald‡	p-value
Pulse pressure	Global WMH	0.061	(0.004, 0.119)	0.167	2.106	0.037
	Frontal WMH	0.012	(-0.015, 0.039)	0.076	0.878	0.382
	Temporal WMH	0.009	(-0.001, 0.019)	0.157	1.845	0.068
	Parietal WMH	0.014	(0.002, 0.026)	0.193	2.314	0.023
	Occipital WMH	0.021	(0.005, 0.038)	0.200	2.583	0.011
	Microbleeds$^{\lambda}$	-0.010	(0.941, 1.042)	0.990	0.150	0.698
	Enlarged perivascular spaces	0.072	(-0.012, 0.155)	0.166	1.708	0.091
	Infarcts$^{\lambda}$	0.019	(0.977, 1.063)	1.019	0.769	0.381

Sensitivity analysis: excluding participants treated with anti-hypertensive or anti-hypotensive medication. Separate regression models: Outcome measure ~ pulse pressure + age + sex/gender + scanner type + intercept.

‡ A t-value is shown for linear regressions, and a Wald statistic is shown for logistic regressions.

$^{\lambda}$ Logistic regression was applied for dichotomous outcomes. B = Exponential (β) and 95%CI = 95% CI for Exponential (β).

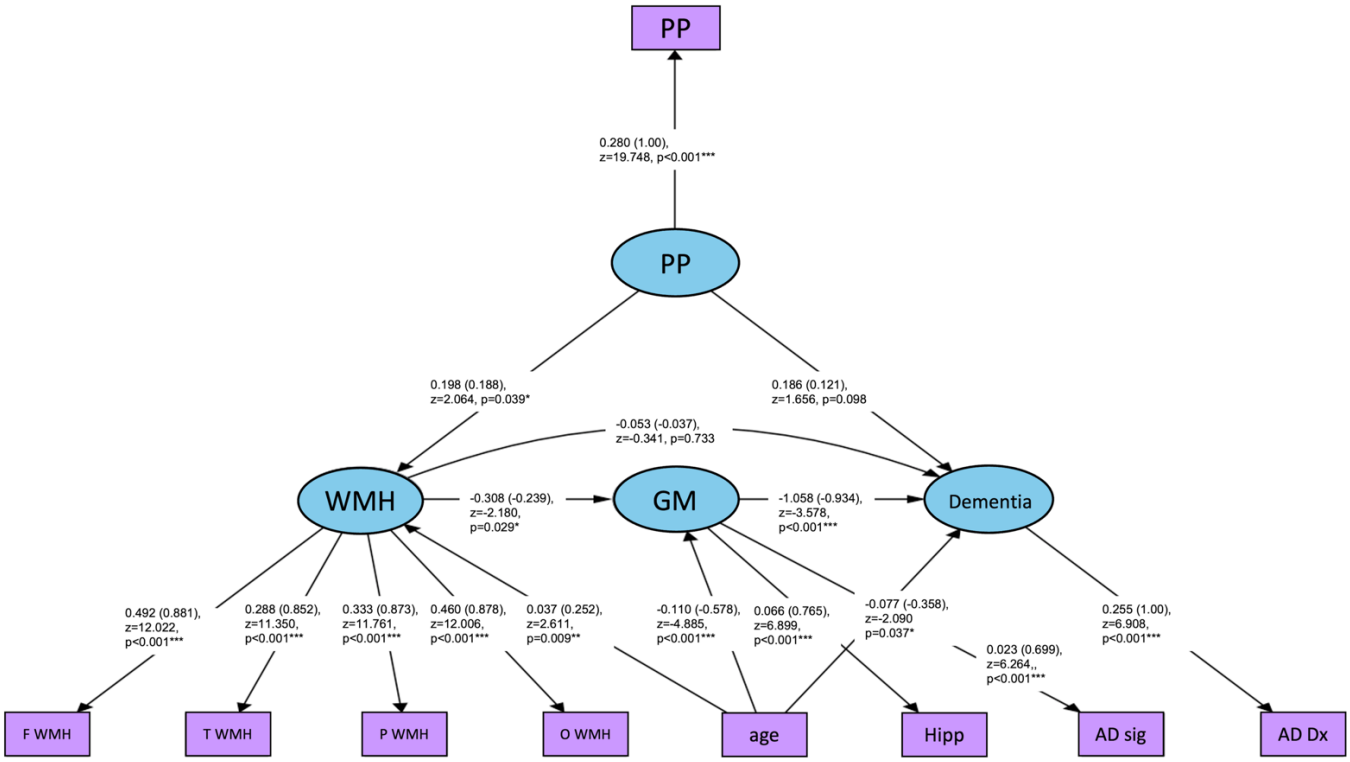
Supplemental Table B2. Associations of systolic BP, diastolic BP, and MAP with cerebrovascular imaging markers.

BP Variable	Outcome Marker	*B*	95% CI	β	t / Wald‡	p-value
Systolic BP	Global WMH	0.036	(-0.013, 0.084)	0.113	1.456	0.148
	Frontal WMH	0.004	(-0.019, 0.027)	0.027	0.318	0.751
	Temporal WMH	0.007	(-0.001, 0.015)	0.143	1.743	0.084
	Parietal WMH	0.008	(-0.002, 0.018)	0.132	1.630	0.106
	Occipital WMH	0.013	(-0.001, 0.026)	0.138	1.825	0.071
	Microbleeds[λ]	-0.022	(0.936, 1.023)	0.978	0.938	0.333
	Enlarged Perivascular spaces	0.049	(-0.023, 0.121)	0.126	1.359	0.177
	Infarcts[λ]	0.012	(0.975, 1.050)	1.012	0.529	0.529
Diastolic BP	Global WMH	-0.014	(-0.090, 0.062)	-0.029	-0.361	0.719
	Frontal WMH	-0.012	(-0.048, 0.024)	-0.056	-0.658	0.512
	Temporal WMH	0.003	(-0.010, 0.016)	0.039	0.463	0.644
	Parietal WMH	-0.002	(-0.017, 0.013)	-0.022	-0.268	0.789
	Occipital WMH	-0.002	(-0.024, 0.020)	-0.013	-0.174	0.863
	Microbleeds[λ]	-0.030	(0.905, 1.040)	0.970	0.732	0.229
	Enlarged perivascular spaces	-0.015	(-0.123, 0.092)	-0.027	-0.283	0.777
	Infarcts[λ]	-0.009	(0.938, 1.047)	0.991	0.109	0.741
Mean Arterial Pressure	Global WMH	0.018	(-0.055, 0.091)	0.039	0.490	0.625
	Frontal WMH	-0.005	(-0.039, 0.030)	-0.022	-0.261	0.795
	Temporal WMH	0.007	(-0.005, 0.019)	0.097	1.161	0.248
	Parietal WMH	0.005	(-0.010, 0.019)	0.052	0.635	0.527
	Occipital WMH	0.008	(-0.012, 0.029)	0.061	0.789	0.431
	Microbleeds[λ]	-0.037	(0.901, 1.032)	0.964	1.119	0.290
	Enlarged perivascular spaces	0.025	(-0.081, 0.131)	0.044	0.471	0.638
	Infarcts[λ]	0.003	(0.949, 1.059)	1.0039	0.009	0.925

Separate regression model: Outcome measure ~ BP measure + age + sex/gender + scanner type + intercept.

‡ A t-value is shown for linear regressions, and a Wald statistic is shown for logistic regressions.

[λ] Logistic regression was applied for dichotomous outcomes. β = Exponential (β) and 95%CI = 95% CI for Exponential (β).



Supplemental Figure B1. Structural equation model demonstrating pathway from pulse pressure to dementia and intermediate markers when age is included as a covariate.
Standardized beta coefficients are included in parentheses.
Paths indicated as significant (*) for p-values $\leq$ 0.05, (**) for p $\leq$ 0.01, and (***) for p $\leq$ 0.001.
PP: pulse pressure, WMH: white matter hyperintensities, GM: gray matter, F WMH: frontal WMH, T WMH: temporal WMH, P WMH: parietal WMH, O WMH: occipital WMH, Hipp: hippocampal volume (TIV adjusted), AD sig: Alzheimer's disease cortical signature thickness, AD Dx: Alzheimer's disease dementia diagnosis. Model fit indices: X^2 (22, N=195) = 63.834, p < 0.001, CFI = 0.925, TLI = 0.877, RMSEA = 0.099, and SRMR = 0.059.

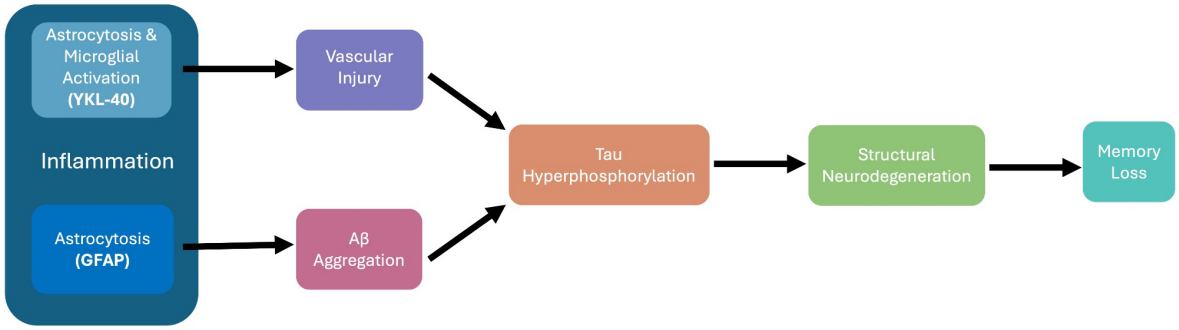
APPENDIX C

Supplemental Table C1.

Dependent variable	Independent variable	*B*	Standardized Estimate	p-value	95% CI
Total WMH (log) ~	YKL-40 (log)	0.393	0.299	0.005	(0.12, 0.666)
	GFAP (log)	0.098	0.076	0.466	(-0.166, 0.362)
Global FBP SUVR (log) ~	YKL-40 (log)	-0.02	-0.161	0.176	(-0.05, 0.009)
	GFAP (log)	0.054	0.435	0	(0.027, 0.08)
pTau-217 (log) ~	Total WMH (log)	0.022	0.225	0.015	(0.004, 0.04)
	Global FBP SUVR (log)	0.369	0.355	0.002	(0.137, 0.6)
	YKL-40 (log)	-0.004	-0.029	0.792	(-0.032, 0.024)
	GFAP (log)	0.036	0.278	0.013	(0.007, 0.064)
MTL Cortical Thickness (log) ~	pTau-217 (log)	-0.111	-0.341	0.001	(-0.177, -0.046)
Hippocampal Volume (log) ~	pTau-217 (log)	-0.282	-0.256	0.014	(-0.505, -0.058)
Delayed Recall (log) ~	MTL Cortical Thickness (log)	1.211	0.069	0.535	(-2.618, 5.041)
	Hippocampal Volume (log)	1.426	0.273	0.015	(0.275, 2.577)
	pTau-217 (log)	0.915	0.159	0.202	(-0.491, 2.321)
Covariances		***B***	**Standardized Estimate**	**p-value**	**95% CI**
YKL-40 (log) ~~ GFAP (log)		0.073	0.183	0.137	(-0.023, 0.169)

Path analysis model with the following regression and covariance equations:
Total WMH ~ YKL-40 + GFAP
Global GFP SUVR ~ YKL-40 + GFAP
pTau-217 ~ Total WMH + Global FBP SUVR + YKL-40 + GFAP
MTL Cortical Thickness ~ pTau-217
Hippocampal Volume ~ pTau-217
Delayed Recall ~ MTL Cortical Thickness + Hippocampal Volume + pTau-217
YKL-40 ~~ GFAP

Supplemental Figure C1. Conceptual mechanistic diagram



Supplemental Figure C1. Conceptual diagram of the mechanistic cascade leading to memory deficits in older adults. Two parallel neuroinflammatory (plasma YKL-40 and GFAP) pathways highlight distinct mechanisms by which cerebrovascular injury (WMH) and Aβ (FBP SUVR) converge to tau pathology (plasma pTau-217), and subsequently to neurodegeneration (hippocampal and MTL cortical atrophy) and memory decline (RAVLT RI performance).