The Neurovascular-Neuroinflammatory Continuum: A Multi-Modal Diagnostic Framework for Distinguishing Pure Vascular Cognitive Impairment from Mixed-Pathology Dementia in the Absence of Specific Proteinopathies

Abstract

The differential diagnosis of dementia in the elderly remains one of the most complex challenges in clinical neurology. While the dominance of the amyloid cascade hypothesis has provided robust biomarkers for Alzheimer's Disease (AD), a significant diagnostic gap persists for patients presenting with cognitive decline who lack definitive amyloid or tau pathology, or in whom vascular injury co-exists with neurodegeneration. This doctoral thesis addresses the urgent clinical need to distinguish Pure Vascular Cognitive Impairment (VCI) from Mixed Dementia and non-amyloid mimics, specifically Limbic-predominant Age-related TDP-43 Encephalopathy (LATE). Grounded in the "Vascular-Immune Hypothesis," this research posits that VCI is characterized by a distinct inflammatory and microstructural signature driven by endothelial dysfunction and blood-brain barrier (BBB) breakdown, separable from the astrocytic and cortical neurodegeneration of AD and LATE. By synthesizing data on advanced neuroimaging metrics—specifically Peak Width of Skeletonized Mean Diffusivity (PSMD), Free-Water (FW) imaging, and Diffusion Tensor Imaging Analysis Along the Perivascular Space (DTI-ALPS)—with fluid biomarkers of neuroinflammation (Matrix Metalloproteinase-9 [MMP-9], Placental Growth Factor [PlGF], and Glial Fibrillary Acidic Protein [GFAP]), this thesis constructs a comprehensive diagnostic framework. The analysis demonstrates that Pure VCI is defined by a "High MMP-9/High PSMD/Low GFAP" profile, reflecting active vascular remodeling and diffuse white matter disintegration. In contrast, Mixed Dementia exhibits a synergistic "High MMP-9/High GFAP" profile, while LATE presents a distinct "Low Vascular/High Atrophy" signature. This work provides a theoretical and practical basis for precision phenotyping in dementia, facilitating targeted therapeutic interventions for vascular contributions to cognitive impairment.

Chapter 1: Introduction

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1.1 The Evolving Nosology of Cognitive Impairment

Historically, the classification of cognitive impairment has operated under a binary paradigm, separating "neurodegenerative" diseases, typified by Alzheimer's Disease (AD), from "vascular" cognitive impairment (VCI) resulting from cerebrovascular disease (CVD).[1] This dichotomy was codified in early diagnostic criteria such as the NINDS-AIREN, which demanded a clear temporal relationship between clinical stroke and the onset of dementia to diagnose Vascular Dementia (VaD).[1] However, the advent of advanced neuroimaging and large-scale autopsy studies has dismantled this binary, revealing that "pure" pathologies are the exception rather than the rule in the aging brain.

Current epidemiological data indicate that while pure VaD accounts for approximately 5-10% of dementia cases, cerebrovascular pathology contributes to cognitive decline in 30-40% of all dementia diagnoses, frequently co-occurring with AD pathology.[1] This overlap creates a spectrum of "Mixed Dementia," where vascular injury and proteinopathy act additively or synergistically to accelerate cognitive decline.[2] The complexity is further compounded by the recent characterization of Limbic-predominant Age-related TDP-43 Encephalopathy (LATE), a non-amyloid neurodegenerative condition that mimics AD clinically but lacks specific in vivo biomarkers, often leading to misdiagnosis in elderly populations.[4]

1.2 The Diagnostic Gap: Absence of Specific Proteinopathies

The central problem addressed by this thesis is the diagnostic ambiguity that arises in the absence of specific proteinopathies. The "A/T/N" framework (Amyloid/Tau/Neurodegeneration) has revolutionized AD research by providing biological definitions for the disease.[6] However, this framework creates a diagnostic orphan category: patients who are amyloid-negative (A-) and tau-negative (T-) but exhibit significant neurodegeneration (N+) and cognitive impairment. These patients, often labeled as "Suspected Non-Alzheimer's Pathophysiology" (SNAP), may suffer from pure VCI, LATE, or other rare etiologies.

Standard structural imaging, such as T2-weighted MRI, identifies White Matter Hyperintensities (WMH), but these lesions are non-specific and correlate imperfectly with cognition.[7] A patient with extensive WMH may be cognitively normal, while another with mild burden suffers severe executive dysfunction. This "clinico-radiological paradox" suggests that conventional imaging fails to capture the true extent of tissue injury and the underlying biological drivers.[8] Furthermore, the mere presence of WMH does not confirm VCI as the *sole* driver of dementia, as WMH are also observed in AD and LATE.[9]

1.3 The Vascular-Immune Hypothesis

To resolve this diagnostic dilemma, this thesis adopts the "Vascular-Immune Hypothesis" as its theoretical lens. This hypothesis postulates that vascular contributions to cognitive impairment are not merely structural (e.g., infarcts) but active biological processes driven by

neuroimmune dysregulation.[10] According to this model, cardiovascular risk factors trigger endothelial dysfunction and blood-brain barrier (BBB) breakdown. This leads to the extravasation of serum proteins (e.g., fibrinogen) and the activation of perivascular immune cells, releasing pro-inflammatory cytokines (IL-6) and matrix-degrading enzymes (MMP-9).[12]

This inflammatory cascade results in diffuse microstructural disintegration of the white matter—changes that are subtle on standard MRI but detectable via advanced diffusion metrics like PSMD and Free-Water imaging.[14] Simultaneously, the shedding of inflammatory mediators into the cerebrospinal fluid (CSF) and plasma provides a distinct "fluid signature" of vascular injury.[16] By integrating these domains, it becomes possible to fingerprint the vascular etiology of cognitive impairment even when specific proteinopathies are absent or ambiguous.

1.4 Research Objectives

This doctoral thesis aims to rigorously answer the question: *How can the integration of advanced neuroimaging and fluid biomarkers for neuroinflammation effectively distinguish pure VCI from mixed-pathology dementia?*

The specific research objectives are:

1. **To Define the Microstructural Phenotype of VCI:** To evaluate the diagnostic utility of Peak Width of Skeletonized Mean Diffusivity (PSMD) and Free-Water (FW) imaging in detecting diffuse vascular injury beyond visible WMH.
2. **To Characterize the Vascular-Inflammatory Biomarker Profile:** To assess the specificity of MMP-9, TIMP-1, and PlGF in distinguishing vascular-driven inflammation from the astrocytic reactivity (GFAP) associated with AD.
3. **To Disentangle Co-Pathologies:** To construct a diagnostic algorithm that differentiates Pure VCI from LATE-NC and Mixed Dementia, providing a roadmap for precision diagnosis in amyloid-negative cohorts.

Chapter 2: Literature Review and Theoretical Framework

2.1 The Evolution of Vascular Cognitive Impairment Concepts

The conceptualization of vascular contributions to dementia has undergone significant revision over the past century. Early 20th-century definitions focused on "hardening of the arteries" (arteriosclerosis) as the primary cause of senility. This was replaced in the 1970s and 80s by the "multi-infarct" paradigm, which posited that dementia resulted from the cumulative volume of necrotic tissue caused by large-vessel strokes.[1]

However, the "multi-infarct" model proved inadequate for explaining the cognitive decline seen in patients with diffuse small vessel disease (SVD) but no history of acute stroke. This led to the introduction of the term "Vascular Cognitive Impairment" (VCI) by Hachinski and Bowler, a broad category encompassing everything from mild cognitive impairment (MCI) to frank vascular dementia.[2] More recently, the focus has shifted to "Vascular Contributions to Cognitive Impairment and Dementia" (VCID), acknowledging that vascular pathology is a ubiquitous co-conspirator in neurodegeneration.[2]

Current diagnostic criteria, such as the VICCCS guidelines, emphasize the heterogeneity of VCI, categorizing it into post-stroke dementia, subcortical ischemic vascular dementia (SIVD), multi-infarct dementia, and mixed dementia.[18] SIVD, characterized by extensive small vessel pathology, is the most common form and the most difficult to distinguish from AD in its early stages due to its insidious, progressive course.[18]

2.2 The Biology of Cerebral Small Vessel Disease (SVD)

Cerebral Small Vessel Disease (SVD) affects the small perforating arteries, arterioles, capillaries, and venules that supply the brain's deep structures.[3] These vessels are uniquely vulnerable to hypertension and metabolic dysregulation. The hallmark pathologies are arteriolosclerosis (lipohyalinosis) and cerebral amyloid angiopathy (CAA).[3]

2.2.1 The Neurovascular Unit (NVU)

The central pathophysiological structure in VCI is the Neurovascular Unit (NVU), comprising the endothelial cell, pericyte, astrocytic end-feet, and the adjacent neuron.[12] In health, the NVU maintains the Blood-Brain Barrier (BBB), regulating the transport of nutrients and clearing metabolic waste via the glymphatic system.[21]

In SVD, endothelial dysfunction disrupts NVU coupling. Chronic hypoperfusion creates a hypoxic environment, upregulating Hypoxia-Inducible Factor 1-alpha (HIF-1α).[20] This triggers the release of Vascular Endothelial Growth Factor (VEGF) and Matrix Metalloproteinases (MMPs). While intended to promote angiogenesis, in the chronic phase, these factors increase BBB permeability, leading to fluid extravasation and "vasogenic edema".[8]

2.3 The Vascular-Immune Hypothesis of Alzheimer's and VCI

The "Vascular-Immune Hypothesis" represents a paradigm shift, proposing that vascular injury and immune activation are not merely downstream consequences of amyloid deposition but are primary drivers of synaptic failure.[10]

Recent reviews from 2024 and 2025 highlight that vascular risk factors (hypertension, diabetes) induce a state of "inflammaging"—chronic, low-grade systemic inflammation that degrades the BBB.[23] Once the barrier is breached, serum proteins like fibrinogen enter the

parenchyma, activating microglia and converting them to a pro-inflammatory phenotype.[12] This creates a toxic cycle:

1. **Vascular Injury:** Arteriolosclerosis reduces compliance and blood flow.
2. **BBB Leakage:** MMPs degrade tight junctions.
3. **Inflammation:** Infiltrating leukocytes and activated microglia release ROS and cytokines.
4. **White Matter Damage:** Oligodendrocytes, highly sensitive to oxidative stress and inflammation, undergo apoptosis, leading to demyelination (WMH).[24]

Crucially, this hypothesis provides a mechanism for distinguishing VCI from AD. While AD also involves inflammation, it is primarily driven by plaque-associated microglia and often involves *impaired* clearance of amyloid rather than the gross BBB disruption and mechanical pulsatility failure seen in VCI.[11]

2.4 The Challenge of LATE-NC

Limbic-predominant Age-related TDP-43 Encephalopathy (LATE) has recently been defined as a distinct neurodegenerative entity affecting adults over 80.[4] LATE is characterized by TDP-43 proteinopathy in the amygdala and hippocampus, causing an amnestic syndrome that mimics AD. Crucially, LATE patients are often amyloid-negative.[28]

Because LATE is highly prevalent in the oldest-old, the same demographic most affected by SVD, co-occurrence is common. Identifying pure VCI requires excluding LATE, yet there are no FDA-approved fluid biomarkers for TDP-43.[5] This thesis proposes that distinguishing VCI from LATE requires examining the *discrepancy* between vascular burden (high in VCI, variable in LATE) and specific patterns of atrophy (medial temporal lobe atrophy is severe in LATE, often mild in pure VCI).[29]

Chapter 3: Methodology and Approach

3.1 Research Design

This thesis employs a theoretical synthesis approach, integrating data from a wide array of recent clinical studies, meta-analyses, and neuropathological reviews (2020-2025) to construct a diagnostic framework. The methodology mimics a "virtual multi-modal cohort study," synthesizing findings from distinct domains—radiomics (imaging) and fluidomics (biomarkers)—to propose a unified diagnostic model.

3.2 Criteria for Biomarker Selection

The selection of biomarkers for this framework was based on the following criteria:

1. **Specificity:** The marker must show differential expression in VCI vs. AD/LATE.
2. **Mechanistic Relevance:** The marker must reflect a core pathological process of the

Vascular-Immune Hypothesis (e.g., BBB breakdown, demyelination).
3. **Clinical Feasibility:** The marker should be measurable in plasma or MRI, maximizing accessibility (though CSF data is also considered).

Selected biomarkers include:

- **Imaging:** PSMD (SVD burden), Free-Water (Microstructure/Inflammation), DTI-ALPS (Glymphatics).
- **Fluid:** MMP-9 (Vascular Inflammation), GFAP (Astrocytosis), NfL (Neuroaxonal injury), PlGF (Angiogenesis).

3.3 Data Integration Strategy

The analysis integrates these markers by mapping them onto the two primary axes of pathology:

1. **The Vascular Axis:** Driven by SVD, ischemia, and BBB leakage.
2. **The Neurodegenerative Axis:** Driven by protein aggregation (Amyloid/Tau/TDP-43) and subsequent gliosis.

By evaluating where a patient falls on these two axes, distinct phenotypes (Pure VCI, Pure AD/LATE, Mixed) can be resolved.

Chapter 4: Advanced Neuroimaging of White Matter and Glymphatics

Standard T2-weighted/FLAIR MRI is the workhorse of VCI diagnosis, visualizing White Matter Hyperintensities (WMH) of presumed vascular origin. However, WMH volume is a crude metric. It fails to distinguish between etiology (ischemic vs. inflammatory vs. degenerative) and lacks sensitivity to changes in the "Normal Appearing White Matter" (NAWM).[7] This chapter explores advanced diffusion metrics that surpass these limitations.

4.1 Peak Width of Skeletonized Mean Diffusivity (PSMD)

Peak Width of Skeletonized Mean Diffusivity (PSMD) has emerged as one of the most robust and biologically valid biomarkers for Cerebral Small Vessel Disease (SVD).[14]

4.1.1 Technical Principles

PSMD is derived from Diffusion Tensor Imaging (DTI). Unlike standard Mean Diffusivity (MD) which averages diffusion across a region, PSMD assesses the *heterogeneity* of diffusion. The process involves:

1. **Skeletonization:** FSL-TBSS software projects the subject's MD map onto a standard

white matter skeleton, eliminating contamination from CSF and gray matter partial volume effects.[14]
2. **Histogram Analysis:** A histogram of MD values within the skeleton is generated.
3. **Calculation:** PSMD is the difference between the 95th and 5th percentiles of this histogram.[32]

4.1.2 Diagnostic Utility in VCI

A wider peak (High PSMD) indicates greater variance in water diffusivity, reflecting a brain riddled with micro-lesions, demyelination, and lacunes. Studies consistently show that PSMD correlates more strongly with processing speed—the cognitive hallmark of VCI—than total WMH volume.[31]

Crucially, PSMD acts as a specific marker for the *vascular* contribution to cognitive decline. In comparisons between AD and SVD cohorts, PSMD is significantly higher in SVD.[14] In mixed cohorts, PSMD mediates the relationship between vascular risk factors and cognitive impairment, acting as the structural correlate of "vascular burden".[33]

Table 4.1: PSMD as a Discriminator

Condition	PSMD Value	Biological Correlate
Healthy Control	Low	Intact Myelin, Homogeneous Diffusion
Pure VCI (SVD)	**Very High**	Diffuse Demyelination, Micro-infarcts, Edema
Pure AD	Low/Moderate	Tract-specific degeneration (e.g., Cingulum), less diffuse
Mixed Dementia	High	Additive effect of vascular injury

4.2 Free-Water (FW) Imaging: Mapping Neuroinflammation

Free-Water (FW) imaging is a bi-tensor DTI model that separates the diffusion signal into two compartments:

1. **Tissue Compartment:** Water molecules restricted by axons and myelin (providing FA/MD metrics corrected for edema).

2. **Free-Water Compartment:** Extracellular water that is free to diffuse (representing edema, atrophy, or inflammation).[15]

4.2.1 Deep vs. Juxtacortical Signatures

The spatial distribution of Free Water offers a powerful tool for differentiation.

- **VCI Pattern:** In VCI, BBB leakage and venous hypertension lead to interstitial fluid accumulation primarily in the **deep white matter** and periventricular regions. This "vasogenic edema" results in a widespread elevation of FW in the deep tracts.[34]
- **AD/Mixed Pattern:** In AD, FW elevation is prominently observed in the **juxtacortical white matter** (U-fibers adjacent to the cortex). This reflects the underlying cortical neurodegeneration, atrophy, and microscopic tau pathology spreading from the gray matter into the white matter.[36]

Therefore, a ratio of Deep-to-Juxtacortical FW could serve as a phenotypic marker. High deep FW suggests VCI; high juxtacortical FW suggests neurodegeneration.

4.3 DTI-ALPS: Assessing Glymphatic Clearance

The Diffusion Tensor Imaging Analysis Along the Perivascular Space (DTI-ALPS) measures the diffusivity of water along the perivascular spaces (PVS) of the medullary veins, serving as a proxy for glymphatic function.[21]

4.3.1 Glymphatics in VCI vs. AD

While both VCI and AD involve glymphatic failure, the mechanisms differ.

- **VCI:** Arteriolosclerosis leads to vessel stiffening. Since glymphatic flow is driven by arterial pulsatility, vascular stiffness directly halts clearance. Low DTI-ALPS scores are strongly predictive of VCI severity and future dementia risk in stroke patients.[21]
- **AD:** Glymphatic failure is often related to Aβ deposition blocking the PVS (CAA) or aquaporin-4 dysregulation.

However, the combination of PSMD and DTI-ALPS is potent. VCI is characterized by the specific combination of **High PSMD** (tissue damage) and **Low DTI-ALPS** (clearance failure).[37] This "Vascular Failure" profile contrasts with early AD, where tissue heterogeneity (PSMD) might be lower despite localized clearance issues.

Chapter 5: Fluid Biomarkers: The Inflammatory Fingerprint

While neuroimaging visualizes the structural consequences of disease, fluid biomarkers

provide a real-time readout of the molecular pathophysiology. To distinguish VCI from mixed pathologies in the absence of amyloid/tau, we must rely on biomarkers that reflect the specific inflammatory cascades of the neurovascular unit.

5.1 Matrix Metalloproteinase-9 (MMP-9): The Vascular Remodeler

Matrix Metalloproteinase-9 (MMP-9) is arguably the most specific circulating biomarker for vascular brain injury available today. It is an inducible zinc-metalloproteinase responsible for degrading the extracellular matrix, particularly the basal lamina components (Type IV collagen, laminin) that support the BBB.[13]

5.1.1 MMP-9 in VCI vs. AD

Multiple studies have established that MMP-9 levels are significantly elevated in the CSF and plasma of patients with VCI compared to AD and healthy controls.[16]

- **Mechanism:** In VCI, chronic hypoxia and endothelial activation trigger the release of MMP-9 from endothelial cells and neutrophils. This leads to BBB opening and white matter degradation.
- **Differentiation:** In pure AD (without significant vascular pathology), MMP-9 levels are often normal or only mildly elevated. The "Vascular-Immune" signature of VCI is defined by a massive upregulation of proteolytic activity.[16]

5.1.2 The MMP-9/TIMP-1 Ratio

MMP-9 is regulated by Tissue Inhibitor of Metalloproteinase-1 (TIMP-1). In VCI, this balance is disrupted. A high **MMP-9/TIMP-1 ratio** indicates unchecked proteolysis and active BBB breakdown.[38] This ratio correlates with white matter lesion volume and poor cognitive outcomes in stroke patients.[39]

5.2 Glial Fibrillary Acidic Protein (GFAP): The Astrocytic Discriminator

Glial Fibrillary Acidic Protein (GFAP) is a marker of reactive astrogliosis. While traditionally viewed as a general injury marker, recent ultrasensitive plasma assays have revealed a distinct specificity for amyloid pathology.

5.2.1 GFAP in AD vs. VCI

Plasma GFAP is markedly elevated in amyloid-positive individuals (AD and Mixed Dementia) due to the intense astrocytic reaction to amyloid plaques.[40] Crucially, in patients with Pure VCI (amyloid-negative), GFAP levels are significantly lower, even in the presence of extensive WMH.[41]

- **The Discrimination:** This creates a powerful dichotomy. VCI drives **NfL** (axonal injury) and **MMP-9** (vascular injury) but induces only a moderate GFAP response. AD drives **GFAP** aggressively.

- **Study Data:** The Mayo Clinic study on plasma biomarkers in VCI found that GFAP separated VCI from AD better in amyloid-negative groups, establishing it as a negative predictor for Pure VCI.[41]

5.3 Placental Growth Factor (PlGF) and Angiogenesis

Placental Growth Factor (PlGF), a member of the VEGF family, is another biomarker gaining traction for VCI.

- **Vascular Specificity:** PlGF is upregulated in response to cerebral hypoperfusion/ischemia. Higher levels correlate with greater WMH volume and cognitive decline.[8]
- **Mechanism:** It represents the brain's attempt at angiogenesis in the face of capillary rarefaction. Elevated PlGF, particularly when combined with high MMP-9, signals an active "angiogenic-inflammatory" state characteristic of VCI.[42]

5.4 Neurofilament Light (NfL): The Non-Specific Intensity Marker

Neurofilament Light (NfL) is elevated in almost all neurodegenerative conditions, reflecting axonal destruction. While not specific for etiology, it serves as a "severity" marker.

- In VCI, NfL correlates strongly with PSMD and WMH burden.[40]
- **Diagnostic Utility:** NfL confirms the *presence* of neurodegeneration. Its utility lies in combination: High NfL + High GFAP suggests AD/Mixed. High NfL + Low GFAP suggests VCI or LATE.

Chapter 6: The Confounder of LATE-NC and Differential Diagnosis

The "absence of specific proteinopathies" often implies a patient who is amyloid-negative. In the oldest-old, this clinical picture is frequently caused by Limbic-predominant Age-related TDP-43 Encephalopathy (LATE). Because LATE lacks a specific fluid biomarker, it is the primary mimic of VCI in amyloid-negative cohorts. Distinguishing Pure VCI from LATE (or VCI + LATE) is essential for prognosis, as LATE progresses more slowly but is resistant to vascular interventions.[4]

6.1 Clinical and Radiological Profiles of LATE

LATE neuropathological change (LATE-NC) affects the medial temporal lobe (MTL), causing an amnestic syndrome.

- **Atrophy Pattern:** LATE is associated with severe, disproportionate atrophy of the hippocampus and amygdala.[5]
- **Cognitive Profile:** Predominantly episodic memory loss, contrasting with the

dysexecutive profile of VCI.[4]

6.2 Distinguishing VCI from LATE

Since we cannot yet measure TDP-43 directly in plasma (though NULISA assays are in development [30]), we must use a "Process of Elimination" based on the biomarkers established in previous chapters.

The "Vascular-Atrophy Mismatch":

- **Pure VCI:** High Vascular Burden (High PSMD, High MMP-9) + Mild/Moderate Hippocampal Atrophy (often proportional to global atrophy).
- **Pure LATE:** Low Vascular Burden (Low PSMD, Normal MMP-9) + Severe Hippocampal Atrophy (Hippocampal Sclerosis).
- **Mixed VCI + LATE:** High Vascular Burden + Severe Hippocampal Atrophy.

This distinction is vital. A patient with severe memory loss and WMH might be diagnosed as Mixed Dementia. However, if their MMP-9 is normal and PSMD is low, the WMH may be incidental, and the primary driver is likely LATE. Conversely, high MMP-9 confirms the vascular lesions are active and contributing to the pathology.[29]

Chapter 7: Integrated Diagnostic Framework and Conclusions

7.1 The Integrated Algorithm

Synthesizing the neuroimaging and fluid biomarker data, this thesis proposes a multi-modal diagnostic algorithm for stratifying cognitively impaired patients in the absence of amyloid/tau biomarkers.

Figure 7.1: The VCI vs. Mixed Diagnostic Matrix

Phenotype	Pure VCI	Mixed (VCI + AD)	Pure LATE	Mixed (VCI + LATE)
Pathophysiology	Endothelial Dysfunction, Ischemia	Ischemia + Amyloid/Tau	TDP-43 Proteinopathy	Ischemia + TDP-43
PSMD (DTI)	**High** (>95th %ile)	High	Normal/Mild	High

Free Water	**Deep WM Dominant**	**Juxtacortical** + Deep	Medial Temporal	Deep + Medial Temporal
MMP-9	**Elevated**	Elevated	Normal	Elevated
Plasma GFAP	**Low/Normal**	**Very High**	Low/Normal	Low/Normal
PlGF	**High**	Variable	Normal	High
Atrophy	Subcortical/Diffuse	Hippocampal + Cortical	**Severe Hippocampal**	Severe Hippocampal

7.2 Interpretation of the "Absence of Proteinopathies"

In a patient who is Amyloid-Negative (A-):

1. **High PSMD + High MMP-9 + Low GFAP:** Confirms **Pure VCI**. The cognitive decline is driven by white matter disintegration and vascular inflammation.
2. **Low PSMD + Normal MMP-9 + Severe Atrophy:** Suggests **Pure LATE**. The vascular markers rule out VCI as the primary driver; the atrophy points to TDP-43.
3. **High PSMD + High MMP-9 + Severe Atrophy:** Suggests **VCI + LATE**. Both pathologies are active.

7.3 Conclusion and Future Directions

The "Vascular-Immune Hypothesis" provides the missing link in the differential diagnosis of non-amyloid dementia. By moving beyond simple structural MRI and adopting advanced microstructural metrics (PSMD, Free-Water) alongside specific inflammatory biomarkers (MMP-9, PlGF), clinicians can effectively phenotype patients who fall into the diagnostic "gray zone."

This framework has profound implications for clinical trials. Currently, "vascular dementia" trials likely recruit significant numbers of LATE patients (diluting efficacy), while AD trials exclude patients with WMH who might benefit from vascular optimization. The precision phenotyping proposed here allows for the separation of "Angiogenic-Inflammatory" dementias (VCI) from "Neurodegenerative-Astrocytic" dementias (AD), paving the way for targeted therapies that address the specific biological drivers of cognitive decline—whether they be the vessel wall, the blood-brain barrier, or the neuron itself.

Future research must focus on the standardization of PSMD acquisition protocols across scanners [43] and the validation of plasma TDP-43 assays [30] to eventually replace the inferential diagnosis of LATE. Until then, the multi-modal integration of white matter imaging and

inflammatory fluid markers remains our most powerful tool for dissecting the vascular contribution to the dementia continuum.

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