BEYOND NEURONAL ANATOMY:

VASCULAR, BLOOD BRAIN BARRIER, AND MICROBIOTA CONTRIBUTIONS TO DEMENTIA AND ALZHEIMER'S DISEASE

EDITOR:
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SERÜVEN YAYINEVİ

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PREFACE

Dementia and Alzheimer's disease are among the most complex disorders of the human brain, extending far beyond a purely neuronal pathology. Traditional models focused on amyloid-β and tau accumulation fail to fully explain disease onset and progression, highlighting the need for a broader anatomical and biological perspective.

Anatomy provides the structural foundation of brain function and dysfunction. Increasing evidence indicates that dementia is a disorder of neuroanatomical interfaces, involving not only neurons but also cerebral vessels, pericytes, endothelial cells, and the blood–brain barrier. Alterations in intracranial hemodynamics, blood–brain barrier integrity, and pericyte function represent early pathological events that reshape brain structure prior to overt neurodegeneration.

In addition, the microbiota–brain axis has emerged as a key modulator of neuroinflammation, vascular stability, and barrier function, further expanding the anatomical boundaries of dementia research. These systemic influences interact with cerebral microanatomy, contributing to cognitive decline through complex, interconnected pathways.

This book integrates neuroanatomy, neurovascular biology, and microbiota-related mechanisms within a unified anatomical framework. By emphasizing structural and functional interdependence, it aims to bridge classical anatomy with contemporary neuroscience and provide a comprehensive perspective on dementia and Alzheimer's disease.

Chapter 1

Neuroanatomy in Dementia and Alzheimer's Disease

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Introduction

Dementia is a progressive neurological syndrome characterized by a decline in cognitive, behavioral, and functional abilities severe enough to interfere with independent daily living. Rather than representing a single disease entity, dementia encompasses a spectrum of disorders arising from distinct neurodegenerative and vascular pathologies, each associated with characteristic patterns of brain involvement. Understanding these patterns is essential for accurate diagnosis, staging, and therapeutic development.

Neuroanatomically, dementia reflects selective vulnerability of specific cortical regions, subcortical nuclei, and large-scale brain networks. Advances in neuroimaging and biomarker research have demonstrated that neurodegeneration follows reproducible trajectories constrained by connectivity architecture and neurotransmitter systems, supporting a network-based conceptualization of cognitive decline. Accordingly, different dementia subtypes—such as dementia with Lewy bodies, frontotemporal dementia, and vascular dementia—exhibit distinct anatomical signatures that underlie their clinical heterogeneity.

Alzheimer's disease, the most common cause of dementia, is now defined as a biologically driven neurodegenerative continuum rather than solely a clinical syndrome. The disease is characterized by progressive involvement of medial temporal lobe structures followed by widespread neocortical and subcortical degeneration. This chapter aims to outline the neuroanatomical basis of dementia and Alzheimer's disease, emphasizing subtype-specific patterns of neurodegeneration and the systems-level mechanisms that link molecular pathology to cognitive dysfunction.

1. Definition of Dementia and Neuroanatomical Framework

Dementia is a clinical syndrome characterized by progressive decline in multiple cognitive domains severe enough to impair independent functioning in daily life, with deficits spanning episodic memory, executive functions, attention, language, visuospatial processing, and socio-emotional regulation (Jack et al., 2024; Dubois et al., 2021; O'Brien & Thomas, 2015). Modern nosology emphasizes that dementia is not a single disease but a convergence phenotype produced by heterogeneous neurodegenerative and vascular pathologies, each with distinct temporal dynamics and neuroanatomical signatures (Jack et al., 2018; Wardlaw et al., 2021; Zetterberg & Blennow, 2021) (Figure 1).

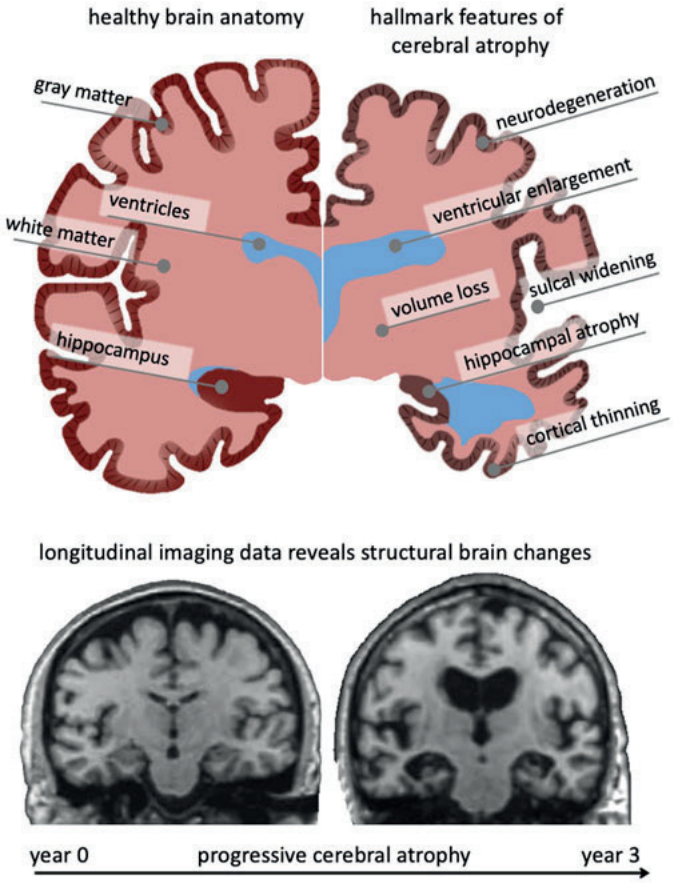

Figure 1. *Structural changes in Alzheimer's disease (Blinkouskaya & Weickenmeier, 2021)*

From a neuroanatomical standpoint, dementia reflects the cumulative impact of selective neuronal vulnerability, synaptic dysfunction, and large-scale network disintegration rather than focal lesions. The concept of selective vulnerability explains why specific cortical hubs, laminar compartments, and subcortical nuclei are consistently targeted across syndromic variants (Seeley, 2017; Antonioni et al., 2023; Braak & Braak, 1991). Network-level framing is reinforced by the observation that clinical severity often correlates better with connectome disruption than with regional atrophy alone (Jones et al., 2016; Raj et al., 2012; Cope & Rittman, 2020).

A major organizing principle is the vulnerability of highly connected association cortices and "hub" regions embedded in the default mode and frontoparietal control networks. Disruption of the default mode network (DMN)—including posterior cingulate, precuneus, and medial prefrontal cortex—has been linked to memory and self-referential processing deficits

and interacts with amyloid and tau biology in Alzheimer's disease (Buckner et al., 2005; Buckner, Andrews-Hanna, & Schacter, 2008; Sepulcre et al., 2018). In this framework, neurodegeneration is conceptualized as a process that unfolds along connectivity gradients and anatomical pathways rather than isolated "hotspots" (Jones et al., 2016; Raj et al., 2012; Iturria-Medina et al., 2017) (Figure 2).

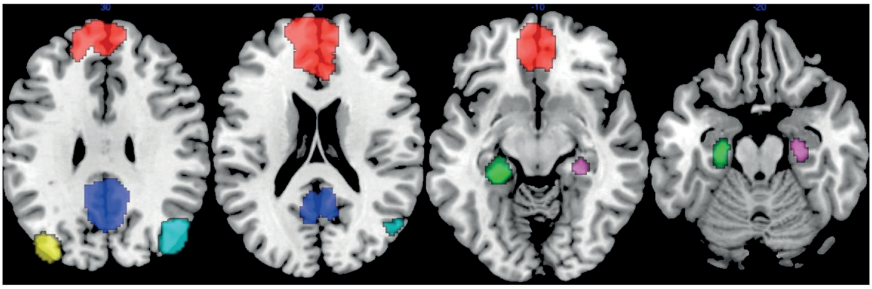

Figure 2. *The highlighted regions include the medial prefrontal cortex (red), posterior cingulate cortex (blue), left inferior parietal lobule (yellow), right inferior parietal lobule (cyan), left hippocampus (green), and right hippocampus (purple), each serving as a node contributing to the default mode network's (DMN) functional integration (Ghaffari, 2025; Grieder, 2018).*

Multimodal biomarker science further supports a systems-neuroanatomy approach: CSF/plasma markers, structural MRI, tau/amyloid PET, and diffusion imaging collectively describe molecular burden, neuronal injury, and tract-level disconnection. Such convergence improves prediction of clinical trajectories and helps distinguish neurodegenerative from vascular drivers of decline (Zetterberg & Blennow, 2021; Hansson, 2021; Ewers et al., 2021). Importantly, biomarker-informed staging models formalize how neuroanatomical changes precede symptoms and how combinations of biomarker abnormalities forecast conversion risk (Frisoni et al., 2022; Jack et al., 2019; Bischof et al., 2019).

2. Dementia Subtypes and Anatomical Patterns of Neurodegeneration

2.1. Dementia with Lewy Bodies

Dementia with Lewy bodies (DLB) is defined by widespread α-synuclein pathology with characteristic clinical features including cognitive fluctuations, visual hallucinations, REM sleep behavior disorder, and parkinsonism (Figure 3). Contemporary consensus criteria emphasize the multisystem nature of DLB and its overlap with Alzheimer's pathobiology in many individuals (McKeith et al., 2017; McKeith et al., 2020; Taylor et al., 2020). Neuroanatomically, DLB often shows relative early sparing of medial temporal structures compared with Alzheimer's disease, alongside prominent posterior cortical and subcortical involvement (McKeith et al., 2020; Mak et al., 2025; Devenyi & Hamedani, 2024).

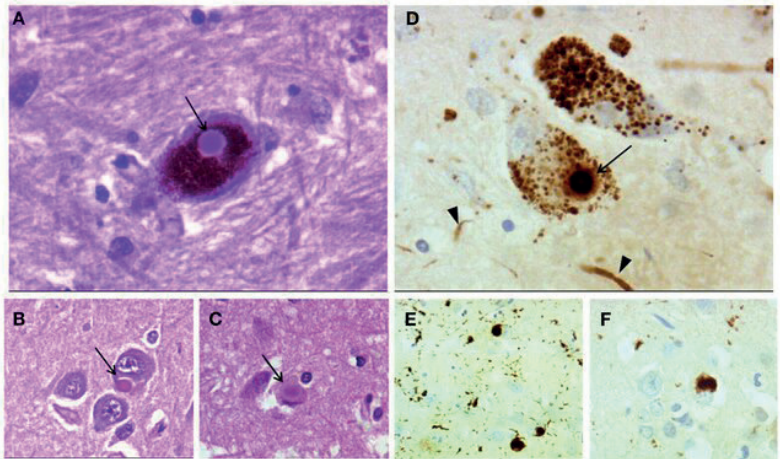

Figure 3. *Dementia with Lewy bodies neuropathology. Lewy body in a neuron of the substantia nigra (A), in a pyramidal cell of CA1 area of the hippocampus (B), and in cingulated cortex (C) (arrows). Lewy body (arrow) and Lewy neurites (arrowheads) in the substantia nigra (D). Cortical Lewy bodies (E,F). (Taipa, 2012).*

Subcortical neuromodulatory nuclei are central to the DLB phenotype. Degeneration of the substantia nigra contributes to parkinsonism, while involvement of the locus coeruleus and basal forebrain cholinergic system is linked to attentional instability, arousal dysregulation, and cognitive fluctuations (Taylor et al., 2020; Galgani et al., 2023; Berry & Harrison, 2023). This multi-transmitter disruption helps explain why DLB often presents with prominent attentional and perceptual disturbances even when global atrophy is modest (McKeith et al., 2017; Devenyi & Hamedani, 2024; Cope & Rittman, 2020).

At the cortical level, DLB preferentially impacts occipital and posterior parietal association cortices—regions critical for visuoperceptual integration. Structural and microstructural imaging demonstrates posterior cortical vulnerability and cortical microstructural abnormalities that plausibly underlie hallucinations and visuospatial dysfunction (Devenyi & Hamedani, 2024; Mak et al., 2025; McKeith et al., 2020). From a network perspective, posterior attentional and visual networks may become unstable, producing fluctuating perceptual inference and cognitive variability (Jones et al., 2016; Cope & Rittman, 2020; Raj et al., 2012).

Clinically, DLB also illustrates the importance of mixed pathologies and biomarker-informed stratification. Many patients exhibit concomitant amyloid and/or tau abnormalities, which can influence neuroanatomical progression and cognitive profiles, complicating clinicopathologic mapping (Hansson, 2021; Zetterberg & Blennow, 2021; Jack et al., 2018). Multimodal assessment—combining clinical criteria with imaging/biomarkers—therefore strengthens differential diagnosis and supports individualized prognostication (Bischof et al., 2019; Ewers et al., 2021; McKeith et al., 2017).

2.2. Frontotemporal Dementia

Frontotemporal dementia (FTD) comprises a group of disorders marked by selective degeneration of frontal and anterior temporal cortices with relative preservation of posterior cortices in many cases. This anatomical selectivity aligns with early behavioral, socio-emotional, and language impairments rather than predominant episodic memory loss (Antonioni et al., 2023; Whitwell et al., 2012; Peet et al., 2021). Neuroimaging signatures underscore substantial heterogeneity across FTD syndromes and reflect differing underlying proteinopathies and network targets (Whitwell et al., 2012; Bocchetta et al., 2020; Seeley, 2017).

In behavioral variant FTD (bvFTD), orbitofrontal, ventromedial prefrontal, and anterior cingulate cortices—key nodes of the salience and social cognition networks—are preferentially affected. Degeneration within these circuits manifests clinically as disinhibition, apathy, loss of empathy, compulsive behaviors, and impaired moral reasoning (Rascovsky et al., 2011; Seeley, 2017; Antonioni et al., 2023). Prodromal criteria and longitudinal work highlight that network and regional changes can precede full syndrome expression, supporting earlier recognition and trial enrollment (Barker et al., 2022; Rohrer et al., 2015; Peet et al., 2021) (Figure 4).

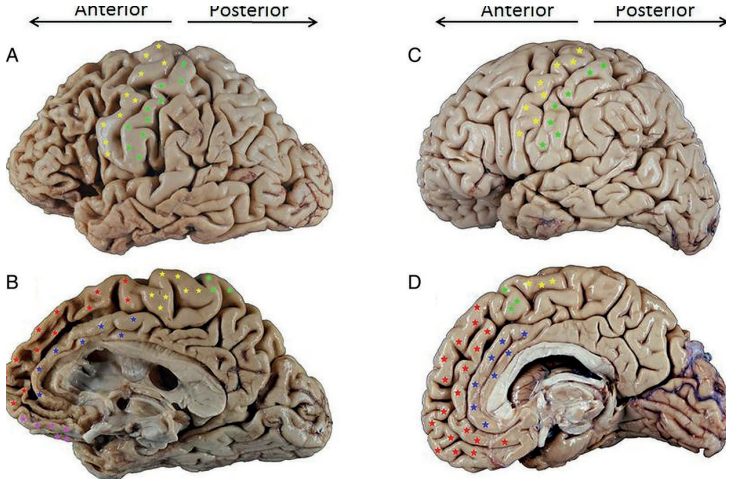

Figure 4. *In a male patient with behavioral variant frontotemporal dementia due to τ-Pick disease, marked frontal lobe–predominant atrophy is observed on the lateral and medial surfaces of the right hemisphere. Compared with an age-matched normal brain, the lateral surface shows pronounced atrophy of the dorsolateral prefrontal cortex , located anterior to the primary motor and premotor cortices (yellow stars), with significant reduction in gyral volume and secondary widening of the sulci. On the medial surface, the affected brain demonstrates prominent atrophy of the anterior cingulate gyrus (blue stars), superior frontal gyrus (red stars), and orbitofrontal cortex (pink stars). This pattern highlights a selective and striking frontal lobe atrophy compared with the normal age-matched brain. (Lanata & Miller, 2016)*

Language-led FTD syndromes demonstrate anatomically distinct vulnerability patterns consistent with the neuroanatomy of speech and semantic processing. The semantic variant is typically associated with anterior temporal lobe degeneration, whereas the nonfluent/agrammatic variant involves inferior frontal gyrus, insula, and premotor regions, producing effortful speech and agrammatism (Gorno-Tempini et al., 2011; Bocchetta et al., 2020; Whitwell et al., 2012). These phenotypes further illustrate how focal network collapse yields domain-specific cognitive and behavioral deficits (Seeley, 2017; Jones et al., 2016; Raj et al., 2012).

Methodologically, FTD exemplifies the value of syndrome-informed imaging pipelines and multimodal approaches. Patterns of regional atrophy across FTD variants can be quantified and related to clinical measures, while diffusion and connectivity analyses illuminate tract-level contributions to symptom emergence (Peet et al., 2021; Bocchetta et al., 2020; Cope & Rittman, 2020). Moreover, biomarker-based stratification and longitudinal modeling improve prediction of progression and clarify heterogeneity within and across syndromes (Ewers et al., 2021; Young et al., 2024; Bischof et al., 2019).

2.3. Vascular Dementia and Vascular Cognitive Impairment

Vascular dementia arises from cumulative cerebrovascular injury and is frequently driven by cerebral small vessel disease (SVD). Neuroanatomically, the disorder is characterized by lesions affecting subcortical white matter, basal ganglia, and thalamus, often resulting in executive dysfunction, slowed processing speed, and attentional deficits (O'Brien & Thomas, 2015; Wardlaw et al., 2021; Elahi et al., 2023). The contemporary view emphasizes vascular cognitive impairment (VCI) as a spectrum, with diagnostic criteria and standards increasingly harmonized for clinical and research use (Sachdev et al., 2025; Wardlaw et al., 2013; Duering et al., 2023).

White matter hyperintensities, lacunes, and microbleeds disrupt cortico-cortical and cortico-subcortical connectivity, producing a "disconnection syndrome." This accounts for the typical phenotype in which executive dysfunction and psychomotor slowing may predominate over amnestic presentation (Prins & Scheltens, 2015; Guo & Shi, 2022; O'Brien & Thomas, 2015). Imaging standards such as STRIVE and STRIVE-2 provide structured reporting for SVD markers, supporting consistent anatomical characterization across cohorts and trials (Wardlaw et al., 2013; Duering et al., 2023; Wardlaw et al., 2021).

VCI also intersects biologically with neurodegeneration: vascular dysfunction can amplify amyloid/tau accumulation and reduce resilience of vulnerable networks. Neurovascular pathway models propose that blood–brain barrier dysfunction, impaired clearance, and chronic hypoperfusion contribute to neurodegenerative cascades (Zlokovic, 2011; Sweeney et al., 2019; Wardlaw et al., 2021). Clinically, this implies mixed etiologies are common, motivating integrated diagnostic frameworks that incorporate vascular imaging, neurodegenerative biomarkers, and symptom profiles (Hansson, 2021; Zetterberg & Blennow, 2021; Jack et al., 2024).

Network diffusion and connectivity frameworks provide an additional lens: structural disconnection may facilitate downstream network instability, interacting with neurodegenerative propagation mechanisms. Modeling approaches and connectome-informed analyses support the notion that lesion topology and tract disruption shape cognitive outcomes beyond lesion volume metrics alone (Raj et al., 2012; Iturria-Medina et al., 2017; Young et al., 2024). Accordingly, modern VCI criteria emphasize both vascular lesion characterization and functional consequences at the circuit/network level (Sachdev et al., 2025; Duering et al., 2023; Dichgans & Leys, 2017).

3. Definition of Alzheimer's Disease

Alzheimer's disease (AD) is defined neuropathologically by amyloid-β plaques, neurofibrillary tangles composed of hyperphosphorylated tau, and progressive synaptic and neuronal loss. The classical Braak framework captures the stereotyped anatomical progression of tau pathology, while modern in vivo imaging enables biological staging across the AD continuum (Braak & Braak, 1991; Therriault et al., 2022; Villemagne et al., 2015). Contemporary diagnostic thinking increasingly treats AD as a biological construct measurable with biomarkers rather than a purely clinical syndrome (Jack et al., 2018; Jack et al., 2024; Jack et al., 2021).

Clinical-biological integration has been strengthened by proposals from international working groups and by revised staging frameworks that explicitly connect biomarkers to disease definition, timing, and prognosis. This shift recognizes that molecular pathology precedes dementia by many years and that neuroanatomical changes unfold gradually from prodromal to symptomatic stages (Dubois et al., 2021; Frisoni et al., 2022; Jack et al., 2019). Fluid biomarkers and imaging markers contribute complementary information: amyloid and tau quantify hallmark pathologies, whereas neurodegeneration markers reflect neuronal injury and synaptic loss (Zetterberg & Blennow, 2021; Hansson, 2021; Ewers et al., 2021).

AD heterogeneity is increasingly framed through phenotypic variants (e.g., typical amnestic vs posterior cortical phenotypes) and through differential network involvement. In this view, anatomical progression reflects both pathology burden and connectivity-mediated vulnerability of large-scale networks (Jones et al., 2016; Buckner et al., 2005; Young et al., 2024). Such reconceptualization directly motivates network-informed treatment targets and personalized staging strategies (Frisoni et al., 2022; Jack et al., 2024; Bischof et al., 2019).

4. Neuroanatomical Progression of Neurodegeneration in Alzheimer's Disease

4.1. Medial Temporal Lobe and Limbic System

Early AD pathology concentrates in medial temporal lobe structures, especially entorhinal cortex and hippocampal subfields, disrupting episodic memory encoding and consolidation. This anatomical epicenter aligns with early clinical memory impairment and has strong support from both neuropathologic staging and biomarker-based imaging (Braak & Braak, 1991; Therriault et al., 2022; Frisoni et al., 2022). Longitudinal biomarker trajectories further indicate that neurodegenerative changes and clinical conversion risk are quantifiable well before overt dementia (Jack et al., 2019; Ewers et al., 2021; Zetterberg & Blennow, 2021).

Neuroanatomically, hippocampal–neocortical communication is embedded within DMN-related memory systems; early disruption may therefore reflect network-level dysconnectivity rather than gross atrophy alone. Seminal work linking default network properties to AD vulnerability supports this systems view of medial temporal dysfunction (Buckner et al., 2005; Buckner et al., 2008; Sepulcre et al., 2018). In parallel, multimodal imaging demonstrates that medial temporal atrophy and connectivity alterations can be integrated with molecular markers to improve staging and prognosis (Teipel et al., 2018; Bischof et al., 2019; Frisoni et al., 2022).

Amyloid and tau biomarkers are not simply parallel signals; their interaction shapes neuroanatomical degeneration. Evidence suggests synergistic relationships between amyloid and tau that amplify neurodegeneration and cognitive decline, particularly as pathology spreads beyond the medial temporal lobe (Pascoal et al., 2021; Pereira et al., 2019; Hansson, 2021). This synergy offers a mechanistic explanation for why some individuals with amyloid positivity remain stable until tau pathology engages vulnerable circuits (Jack et al., 2018; Dubois et al., 2021; Ewers et al., 2021).

4.2. Tau Propagation and Neocortical Involvement

Tau pathology follows a stereotyped anatomical progression (Braak staging), extending from entorhinal cortex to limbic structures and then to associative neocortex. In vivo tau PET has validated and refined these staging concepts by enabling spatial mapping of tau burden in living individuals across clinical stages (Braak & Braak, 1991; Therriault et al., 2022; Schöll et al., 2016). Tau PET tracer work and methodological syntheses further clarify quantification challenges and interpretative caveats across tauopathies (Villemagne et al., 2015; Beyer et al., 2021; Gogola et al., 2025).

Neocortical tau accumulation preferentially affects hubs of the DMN and other association networks, including posterior cingulate and precuneus, providing an anatomical substrate for expanding cognitive deficits beyond memory. This is consistent with network-based neurodegeneration models in which pathology spreads and impacts cognition along connectivity-defined architecture (Buckner et al., 2005; Jones et al., 2016; St-Onge et al., 2024). Functional network evidence links tau distribution to network vulnerability and cognitive symptom patterns, supporting the relevance of connectome-informed frameworks (Sepulcre et al., 2018; Cope & Rittman, 2020; Young et al., 2024).

Importantly, tau PET reveals heterogeneity in spatial tau patterns that relate to cognition and clinical phenotype, suggesting multiple "tau topographies" even within biomarker-defined AD. Pattern studies and region-specific relationships between tau burden and neurodegeneration strengthen the link between tau distribution and clinical course (Ossenkoppele et al., 2020; La Joie et al., 2020; Vogel et al., 2020). This heterogeneity has direct implications for staging, prognostication, and trial stratification in AD (Frisoni et al., 2022; Jack et al., 2024; Ewers et al., 2021). (Figure 5)

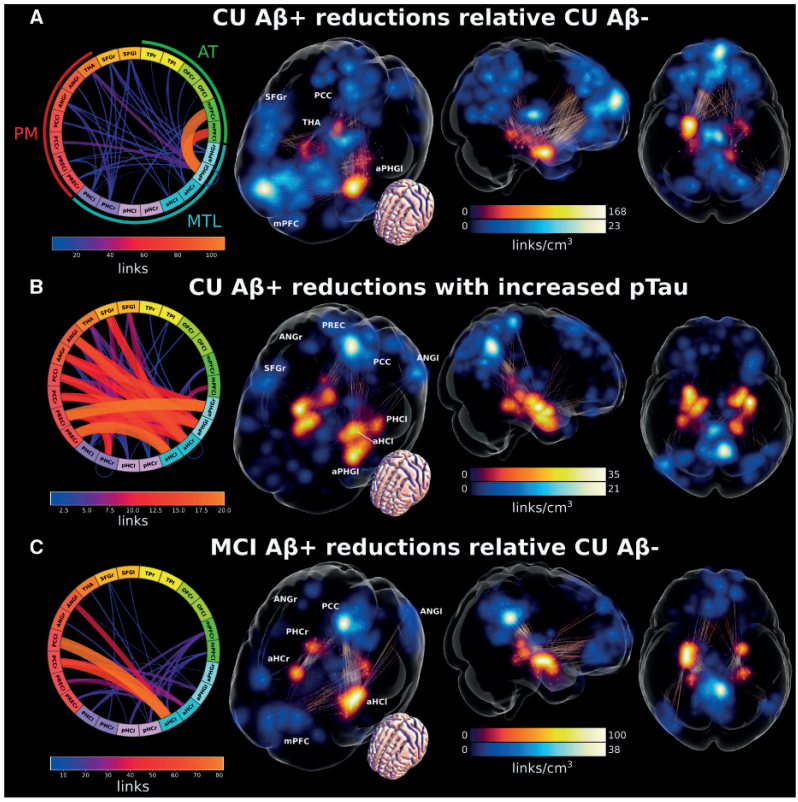

Figure 5. *Changes in medial temporal lobe (MTL) functional connectivity (FC) with other cortical areas in preclinical Alzheimer's disease (AD) and mild cognitive impairment (MCI). Brain glass images illustrate the density of FCs connected to the MTL (red) and to other regions of interest (blue), and the edges between blue and red regions in the glass brains show the FCs with significant changes. Connectograms (the circular diagrams) show the number of links (FCs) between each pair of regions that are significantly different across the conditions compared within each panel. Each panel shows which FCs were significantly different across the two conditions or populations compared. (A) Illustration of FCs with significantly reduced values for Aβ+ in cognitively unimpaired (CU) subjects compared to Aβ− CU controls. (B) FCs that show reduced strength in Aβ+ CU individuals when tau pathology (p-tau) increases. (C) Illustration of FCs with reduced values for Aβ+ MCI subjects compared to Aβ− CU controls. aHC = anterior hippocampus; ANG = angular gyrus; aPHG = anterior parahippocampal gyrus including entorhinal and perirhinal cortices; l = left; mPFC = medial prefrontal cortex; OFC = orbitofrontal cortex; PCC = posterior cingulate cortex; PHC = parahippocampal cortex; pHC = posterior hippocampus; PREC = precuneus; r = right; SFG = superior frontal gyrus; TP = temporal pole.; PM = posterior-medial system; AT = anterior-temporal system; MTL = medial temporal lobe. (Berron, 2020; Ghaffari, 2025)*

At the mechanism level, connectivity-driven models propose that tau may propagate trans-synaptically along anatomical pathways, consistent with observed spreading patterns and network diffusion frameworks. Computational and empirical work supports that connectome architecture shapes spread dynamics, bridging molecular pathology and macroscale neuroanatomy (Raj et al., 2012; Iturria-Medina et al., 2017; Vogel et al., 2020). This integration provides a principled explanation for why network hubs exhibit heightened vulnerability and why clinical phenotypes reflect the networks engaged by propagation pathways (Seeley, 2017; Jones et al., 2016; Young et al., 2024).

4.3. Subcortical Neuromodulatory Systems

AD is not solely a cortical disease: subcortical neuromodulatory nuclei such as the basal forebrain cholinergic system and locus coeruleus show early vulnerability and contribute to attentional and arousal-related symptomatology. Contemporary syntheses highlight how cholinergic degeneration impacts cortical plasticity, attention, and learning, complementing cortical pathology-driven deficits (Berry & Harrison, 2023; Chen et al., 2022; Zetterberg & Blennow, 2021). Noradrenergic involvement further shapes network-level resilience and may influence inflammatory and vascular interfaces relevant to neurodegeneration (Galgani et al., 2023; Sweeney et al., 2019; Zlokovic, 2011).

Empirical evidence links locus coeruleus integrity to tau burden and cognitive decline, supporting the view that brainstem nuclei may be early sites of pathological involvement with downstream cortical consequences. Such findings align with staging frameworks that consider subcortical contributions to symptom variability and progression (Dahl et al., 2022; Therriault et al., 2022; Jack et al., 2019). Integrating neuromodulatory degeneration into network models provides a plausible pathway by which modest cortical pathology can yield substantial cognitive effects via reduced neuromodulatory support (Seeley, 2017; Cope & Rittman, 2020; Young et al., 2024).

This systems view converges with biomarker science: fluid and imaging markers capture molecular pathology, while neuromodulatory system integrity may represent a mechanistic modifier of clinical expression and therapeutic responsiveness. Multimodal approaches thus strengthen explanatory models by linking molecular burden to circuit function and symptom domains (Hansson, 2021; Ewers et al., 2021; Bischof et al., 2019). This perspective is particularly relevant for mixed pathology states where vascular dysfunction, amyloid/tau burden, and neuromodulatory decline jointly shape neuroanatomical outcomes (Zlokovic, 2011; Wardlaw et al., 2021; Sweeney et al., 2019).

Conclusion

Dementia is best understood as a spectrum of disorders unified by progressive disruption of large-scale brain networks, with each subtype exhibiting characteristic neuroanatomical signatures shaped by selective vulnerability and connectivity architecture. DLB highlights posterior cortical and neuromodulatory system vulnerability; FTD demonstrates syndrome-specific collapse of frontal/anterior temporal networks; and vascular dementia emphasizes white matter disconnection and neurovascular contributions to cognitive impairment (McKeith et al., 2020; Seeley, 2017; Wardlaw et al., 2021). In AD, the trajectory from medial temporal structures to associative neocortex is clarified by biomarker frameworks and in vivo tau imaging, with network diffusion and amyloid–tau synergy providing mechanistic bridges between molecular pathology and macroscale neuroanatomy (Jack et al., 2024; Therriault et al., 2022; Pascoal et al., 2021).

A connectome-informed framework—integrating multimodal biomarkers, imaging standards, and data-driven progression models—offers a robust foundation for diagnosis, staging, and therapeutic targeting across dementia syndromes (Frisoni et al., 2022; Duering et al., 2023; Young et al., 2024). This approach also accommodates mixed etiologies by explicitly modeling vascular–neurodegenerative intersections, thereby reflecting real-world clinical complexity (Zlokovic, 2011; Sweeney et al., 2019; Sachdev et al., 2025).

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Chapter 2

Intracranial Hemodynamics, the Blood–Brain Barrier, and Pericytes: Relevance to Dementia and Alzheimer's Disease

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1. Introduction: Why the "hemodynamics–BBB–pericyte" axis?

The human brain operates under exceptionally high metabolic demands while possessing minimal intrinsic energy reserves. For this reason, even subtle disturbances in cerebral blood delivery can rapidly compromise neuronal function. Cerebral perfusion is therefore not governed solely by systemic arterial pressure, but rather by a finely coordinated interaction among intracranial volume compartments (brain tissue, blood, and cerebrospinal fluid), venous outflow pathways, cerebrospinal fluid circulation, and microvascular dynamics within the neurovascular unit (NVU) (Benson, 2023; Brasil, 2025; Wilson et al., 2016).

Within this integrated system, the NVU fulfills two critical functions: preservation of blood–brain barrier (BBB) integrity and activity-dependent regulation of regional cerebral blood flow through neurovascular coupling. These processes ensure that metabolic supply is dynamically matched to neuronal demand while maintaining a tightly controlled cerebral microenvironment (Iadecola, 2017; Kisler et al., 2017). Central to both functions are pericytes—cells that were historically regarded as passive structural elements, but are now recognized as active regulators of capillary stability, microcirculatory flow, and endothelial signaling (Armulik et al., 2011; Benarroch, 2023; Uemura et al., 2020).

In the context of dementia, and particularly Alzheimer's disease (AD), classical neuron-centered models emphasizing amyloid-β and tau pathology remain fundamental but incomplete. Accumulating evidence indicates that vascular dysfunction, increased BBB permeability, chronic cerebral hypoperfusion, and progressive pericyte injury occur early in the disease course and may actively shape downstream neurodegenerative processes (Montagne et al., 2015; Nation et al., 2019; Sweeney et al., 2018; Zlokovic, 2011). These alterations are not merely secondary consequences of neuronal loss, but instead contribute to a state of neurovascular vulnerability that lowers the brain's tolerance to metabolic and hemodynamic stress.

Accordingly, this chapter adopts an integrative perspective that follows the pathological continuum from intracranial hemodynamic alterations to BBB dysfunction and pericyte pathology, ultimately linking these mechanisms to the clinical manifestations of dementia and Alzheimer's disease. Framing neurodegeneration within this vascular–barrier–cellular axis highlights the NVU as a critical convergence point where hemodynamic regulation, microvascular integrity, and neuronal viability intersect.

2. Intracranial Hemodynamics and Vascular Anatomy

2.1. Intracranial arterial system and regional perfusion

Intracranial arterial circulation is primarily supplied by the internal carotid artery (anterior circulation) and the vertebral artery (posterior circulation) systems. The internal carotid artery supports a large portion of the frontal–parietal cortex and deep structures via the anterior cerebral artery (ACA) and middle cerebral artery (MCA), including perforating branches that supply subcortical territories. The vertebral arteries merge to form the basilar artery, from which the posterior cerebral artery (PCA) arises; the PCA plays a critical role in perfusion of the occipital lobe, inferior temporal cortex, and thalamus (Iadecola, 2017; Kisler et al., 2017) (Figure 1).

These arterial systems anastomose at the base of the brain via the circulus arteriosus cerebri (Circle of Willis), which theoretically enables collateral circulation. However, the "completeness" and functional efficiency of the Circle of Willis vary among individuals. Anatomical variations such as posterior communicating artery hypoplasia or A1 segment asymmetry may render certain regions more susceptible to hypoperfusion (Mut et al., 2015; Hartkamp et al., 2019). Such anatomical variability is increasingly viewed as a predisposing factor that may contribute to chronic small vessel injury and diminished cognitive reserve (Rundek et al., 2022) (Figure 1).

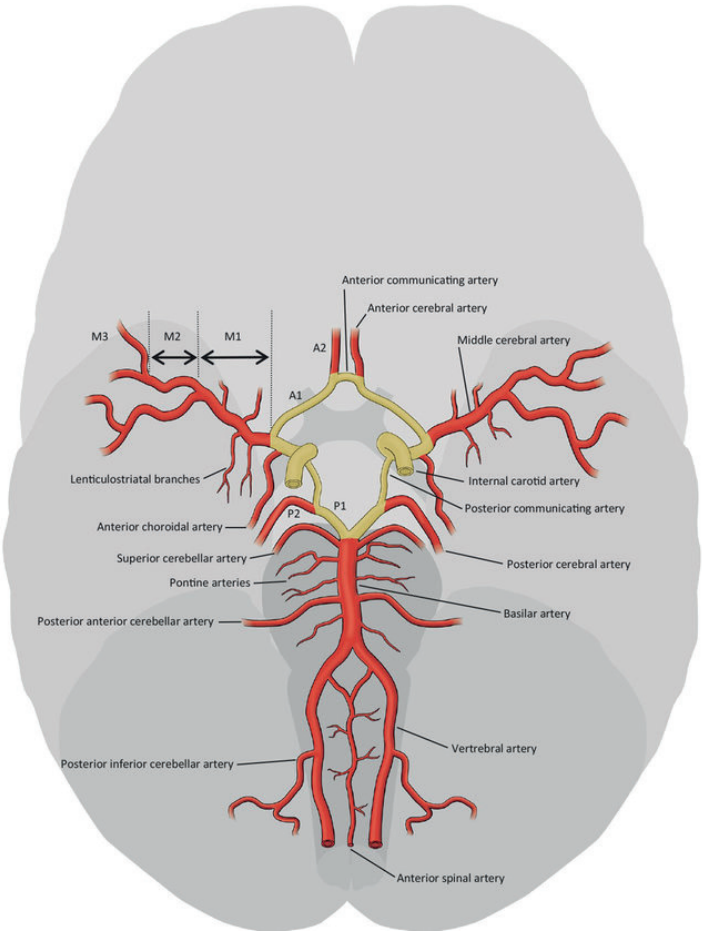

Figure 1. *The circulus arteriosus cerebri (Circle of Willis) on the base of the brain and the distribution of perforating branches (Jung et al., 2017).*

The continuity of regional perfusion depends not only on anatomical connectivity but also on cerebral autoregulation and neurovascular coupling. For example, increased cortical activity within the MCA territory is met by local vasodilation and increased flow, mediated through resistance changes at the arteriolar–capillary level (Iadecola, 2017). Therefore, intracranial arterial anatomy is not a passive template determining hemodynamics, but rather the functional infrastructure upon which physiological control systems operate (Sweeney et al., 2018).

2.2. Penetrating arteries, capillary network, and microcirculation

Penetrating (perforating) arteries descend perpendicularly from the cortical surface into the parenchyma and are particularly critical in regions such as the basal ganglia, internal capsule, and deep white matter. Because

these vessels exhibit limited collateralization and approximate "end-artery" behavior, even minor narrowing or occlusion can be associated with lacunar infarcts, white matter lesions, and cognitive impairment on the basis of chronic hypoperfusion (Rundek et al., 2022; Østergaard et al., 2016). (Figure 2).

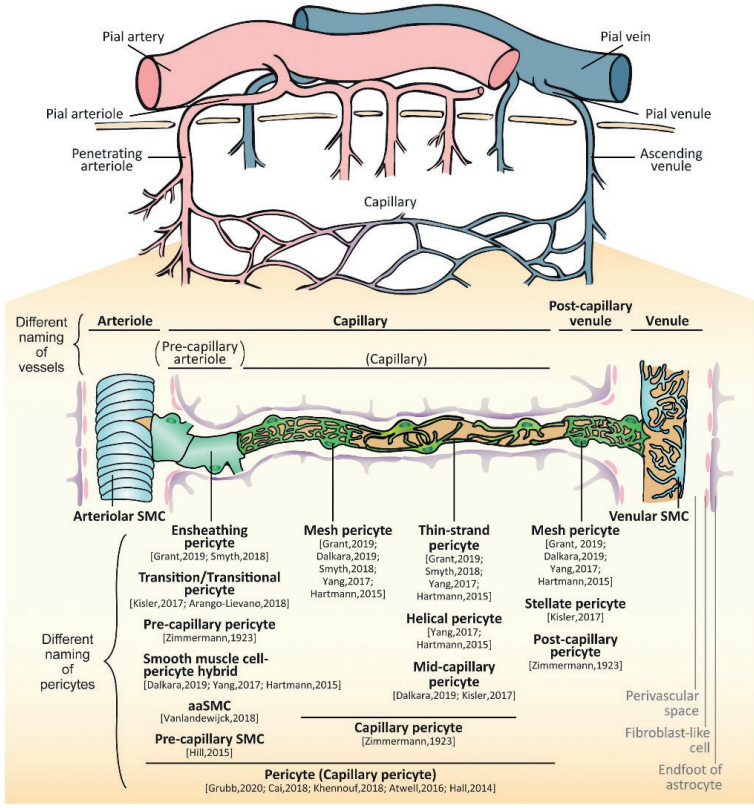

Figure 2. *Brain vessels and mural cells (Uemura, Maki, Ihara, Lee, & Trojanowski, 2020).*

Distal to the perforating arteries, the vascular tree continues through precapillary arterioles and ultimately the capillary network, where oxygen and glucose exchange primarily occurs. In recent years, the concept of microcirculatory heterogeneity has become prominent: within the same region, some capillaries may carry reduced flow, generating focal microhypoxic zones. This heterogeneity is sufficiently important to influence neuronal network function and long-term synaptic integrity (Østergaard et al., 2016; Kisler et al., 2017).

At the capillary level, the role of pericytes in regulating flow is emphasized. Experimental evidence suggests that pericytes can modify local perfusion by altering capillary diameter; under ischemic conditions, persistent pericyte contraction may contribute to sustained narrowing and exacerbate the

no-reflow phenomenon (Hall et al., 2014; Korte et al., 2022). Accordingly, microcirculation should be considered an active system regulated not only by arteriolar smooth muscle but also by the behavior of mural cells—particularly pericytes—within the capillary wall (Uemura et al., 2020).

2.3. Venous drainage, CSF dynamics, and intracranial pressure

Intracranial hemodynamics is determined not only by arterial inflow but also by venous outflow. Superficial cortical veins and the deep venous system drain blood into the dural venous sinuses, which in turn empty through the internal jugular veins. Even relatively small increases in venous pressure can raise capillary hydrostatic pressure, thereby affecting tissue fluid balance and potentially influencing barrier function (Wilson et al., 2016).

Within the rigid cranial vault, the brain maintains a balance among blood, cerebrospinal fluid (CSF), and parenchymal volume. CSF production (by the choroid plexus), circulation, and absorption are closely related to venous and sinus pressures. Thus, impaired venous return or elevated sinus pressure may be expected to alter CSF dynamics, reduce intracranial compliance, and change pulsatile flow components (Wagshul et al., 2011; Wilson et al., 2016).

In recent years, "brain clearance" through glymphatic and meningeal lymphatic pathways—particularly the removal of proteins such as amyloid-β (Aβ)—has gained attention. Flow dynamics related to sleep, arterial pulsatility, and venous drainage can influence interstitial fluid movement and waste clearance (Da Mesquita et al., 2018; Rasmussen et al., 2018). In this context, venous anatomy and CSF dynamics are considered not merely consequences but potential determinants of protein accumulation associated with aging and Alzheimer's disease (Sweeney et al., 2018).

2.4. Intracranial Hemodynamic Alterations in Neurodegenerative Disorders

Intracranial hemodynamics reflects the integrated performance of multiple physiological components that collectively ensure adequate cerebral energy supply. Rather than being determined by a single parameter, cerebral blood flow (CBF) emerges from the interaction among cerebral perfusion pressure (CPP), cerebrovascular resistance (CVR), autoregulatory capacity, cerebrovascular reactivity (CVR), neurovascular coupling (NVC), microcirculatory transit dynamics, venous outflow efficiency, and intracranial compliance. Disruption of more than one of these elements frequently converges on a shared pathophysiological outcome characterized by chronic hypoperfusion and impaired vascular adaptability (Iadecola, 2004; Kisler et al., 2017).

In neurodegenerative conditions—including Alzheimer's disease, vascular cognitive impairment related to small vessel pathology (VCID), and selected phenotypes of frontotemporal dementia and Parkinson's disease—these disturbances rarely occur in isolation. Instead, cumulative deficits across the hemodynamic spectrum progressively limit the brain's capacity to respond to metabolic and systemic challenges, producing a state of neurovascular insufficiency that precedes or accompanies neuronal degeneration (Soto-Rojas et al., 2021; Liu et al., 2024).

2.4.1. Compartment Physiology and Fundamental Hemodynamic Relationships

The Monro–Kellie doctrine provides a conceptual framework for understanding intracranial pressure (ICP) regulation by assuming a fixed total intracranial volume composed of brain parenchyma, blood, and cerebrospinal fluid. When compensatory reserve is reduced, even minor volume shifts can generate disproportionate increases in ICP, thereby narrowing the effective perfusion gradient and altering pulsatile flow characteristics (Benson et al., 2023; Ocamoto et al., 2021).

Clinically, CPP is commonly approximated as the difference between mean arterial pressure (MAP) and ICP. Any factor that lowers MAP, elevates ICP, or increases venous back-pressure can compromise this gradient. Under healthy conditions, autoregulatory mechanisms adjust vascular resistance to stabilize CBF; however, in neurodegenerative disease states, this compensatory flexibility is often diminished, rendering cerebral perfusion increasingly pressure-dependent (Mount & Das, 2023; Kisler et al., 2017).

2.4.2. Autoregulatory Failure and the Shift Toward Pressure-Dependent Flow

Cerebral autoregulation normally buffers fluctuations in systemic blood pressure by dynamically adjusting arteriolar tone. In the setting of neurodegeneration, this buffering capacity may become narrowed or displaced, such that stable CBF is maintained only within a reduced pressure range. Outside this window, cerebral perfusion becomes more directly coupled to systemic pressure variations (Silverman & Restrepo, 2023; Vu et al., 2024).

Dynamic assessments of autoregulation further demonstrate altered transmission of blood pressure oscillations into cerebral flow signals, indicating reduced damping of hemodynamic stress. In clinical contexts such as Parkinson's disease with autonomic dysfunction, these abnormalities may be unmasked or exacerbated during orthostatic challenges, increasing vulnerability to episodic hypoperfusion (Panerai, 2022; Xing et al., 2022). Over time, repeated exposure to such stress may contribute to cumulative microvascular injury within a fragile neurovascular unit.

2.4.3. Diminished Cerebrovascular Reactivity and Loss of Reserve Capacity

Cerebrovascular reactivity represents the ability of cerebral vessels to dilate in response to vasomodulatory stimuli, including hypercapnia or pharmacological agents. In aging and neurodegenerative disease, this adaptive reserve is frequently attenuated, resulting in blunted flow augmentation even when metabolic demand increases (Fisher & Mikulis, 2021).

Advanced imaging studies reveal not only reduced magnitude of vasodilatory responses but also delayed temporal dynamics and regional heterogeneity. Some cortical territories may retain partial responsiveness, whereas others exhibit pronounced impairment, reflecting uneven microvascular health (Keeling et al., 2025; Liu et al., 2024). Clinically, loss of cerebrovascular reserve reduces tolerance to everyday physiological fluctuations—such as sleep-related CO_2 changes or medication effects—and increases susceptibility to chronic low-grade hypoperfusion.

2.4.4. Neurovascular Coupling Dysfunction and Metabolic Mismatch

Neurovascular coupling ensures that local increases in neuronal activity are matched by proportional increases in blood flow. This process relies on coordinated signaling among neurons, astrocytes, endothelial cells, pericytes, and smooth muscle cells within the neurovascular unit (Iadecola, 2017).

In neurodegenerative disorders, this coupling may become inefficient, such that neural activation no longer elicits an adequate vascular response. Functional imaging studies demonstrate attenuated activity-related increases in cerebral blood volume and flow, particularly in metabolically demanding regions such as the hippocampus and association cortices (Kisler et al., 2017). The resulting mismatch between energy demand and substrate delivery promotes neuronal stress and may accelerate synaptic dysfunction.

2.4.5. Microcirculatory Transit Heterogeneity and Inefficient Oxygen Utilization

Beyond global reductions in CBF, alterations in capillary-level flow distribution exert a critical influence on tissue oxygenation. Even when mean flow appears preserved, increased heterogeneity in capillary transit times can limit effective oxygen extraction, producing a state in which perfusion is quantitatively adequate but functionally inefficient (Østergaard, 2020).

Clinical studies link elevated transit-time heterogeneity with impaired cerebral oxygen metabolism in patients with reduced vascular reserve, underscoring that microcirculatory organization—not merely bulk flow—determines metabolic sufficiency (Vestergaard et al., 2023). In neurodegeneration, abnormal flow distribution may therefore represent a hidden contributor to neuronal energy failure.

2.4.6. BBB Disruption and Pericyte-Related Microvascular Instability

Pericytes occupy a strategic position at the capillary wall, where they regulate vascular tone, support BBB integrity, and coordinate signaling within the neurovascular unit. Loss or dysfunction of pericytes destabilizes these processes, facilitating barrier leakage and impairing microcirculatory control (Soto-Rojas et al., 2021).

Human postmortem studies document pericyte loss in association with BBB breakdown, particularly in white matter regions vulnerable to chronic hypoperfusion. As barrier integrity deteriorates, inflammatory signaling, reduced vascular responsiveness, and impaired clearance mechanisms may reinforce one another, establishing a self-perpetuating cycle of neurovascular dysfunction (Ding et al., 2020; Kisler et al., 2017).

2.4.7. Arterial Pulsatility, Stiffness, and Glymphatic Clearance

Cerebral waste clearance depends in part on pulsatile vascular dynamics that drive perivascular fluid movement. Age-related increases in arterial stiffness and pulsatility index reflect heightened distal resistance and impose mechanical stress on the microvasculature (Lim et al., 2017).

Experimental and human data suggest that altered pulsatility can disrupt glymphatic transport, reducing clearance of interstitial solutes such as amyloid-β (Jessen et al., 2015; Mestre et al., 2018). Consequently, vascular stiffening may simultaneously compromise microcirculatory integrity and protein clearance, linking hemodynamic aging to neurodegenerative pathology.

2.4.8. Venous Outflow Disturbance and Hemodynamic Back-Pressure

Cerebral perfusion is ultimately governed by the pressure gradient between arterial inflow and venous outflow. Elevation of venous pressure—whether due to congestion, sinus pathology, or impaired drainage—can reduce effective capillary perfusion and alter intracranial compliance (Fargen et al., 2025).

Although venous contributions to intracranial dynamics have traditionally been emphasized in conditions such as idiopathic intracranial hypertension, growing evidence suggests that venous outflow inefficiency may also influence neurovascular physiology in neurodegenerative disease. By increasing back-pressure and disrupting clearance pathways, venous dysfunction may further amplify the consequences of arterial and microvascular impairment.

3. Blood–Brain Barrier: Structure and Function

3.1. Cellular components of the BBB

The blood–brain barrier (BBB) is a selective interface that protects the brain parenchyma from systemic circulatory fluctuations. Its primary structural component is the brain microvascular endothelial cell, which differs from peripheral endothelium by exhibiting high electrical resistance tight junctions and low basal transcytotic activity (Kadry et al., 2020).

The BBB is not composed solely of endothelial cells; it functions within the neurovascular unit, incorporating pericytes, the basement membrane, astrocytic end-feet, microglia, and neuronal elements. The physical proximity of pericytes to endothelial cells and their shared basement membrane organization are critical for both the structural and signaling continuity of the barrier (Armulik et al., 2011; Sweeney et al., 2018) (Figure 3).

Astrocytic end-feet contribute to water/ion homeostasis and metabolic support via channels such as AQP4, while endothelial–pericyte interactions play key roles in maintaining the barrier phenotype and restricting inflammatory cell trafficking. Thus, the BBB should be viewed not as a static "wall," but as a dynamic regulatory system responsive to environmental cues (Uemura et al., 2020; Iadecola, 2017).

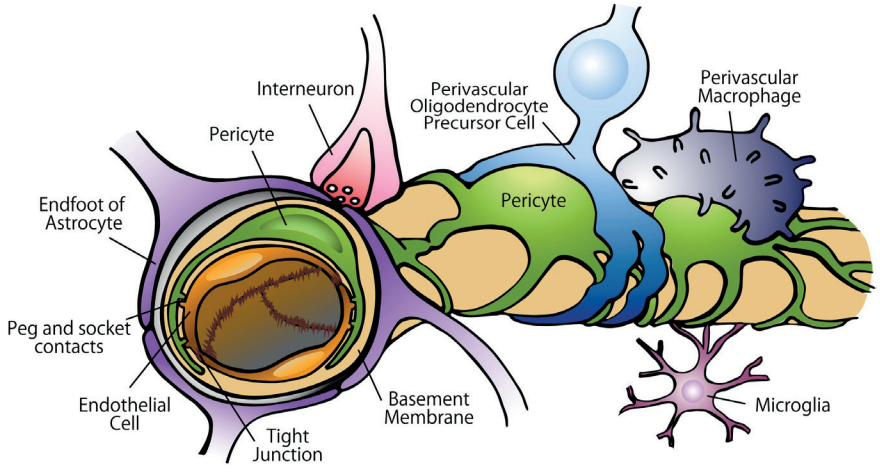

Figure 3. *BBB components (Uemura, Maki, Ihara, Lee, & Trojanowski, 2020).*

3.2. Physiological regulation of BBB permeability

BBB permeability can be considered through two major routes: the paracellular pathway (tight-junction clefts) and the transcellular pathway (vesicular transport/transcytosis and carrier-mediated systems). Under physiological conditions, paracellular passage is minimal, and key transport occurs via tightly regulated carriers for molecules such as glucose (GLUT1) and amino acids (Kadry et al., 2020) (Figure 4).

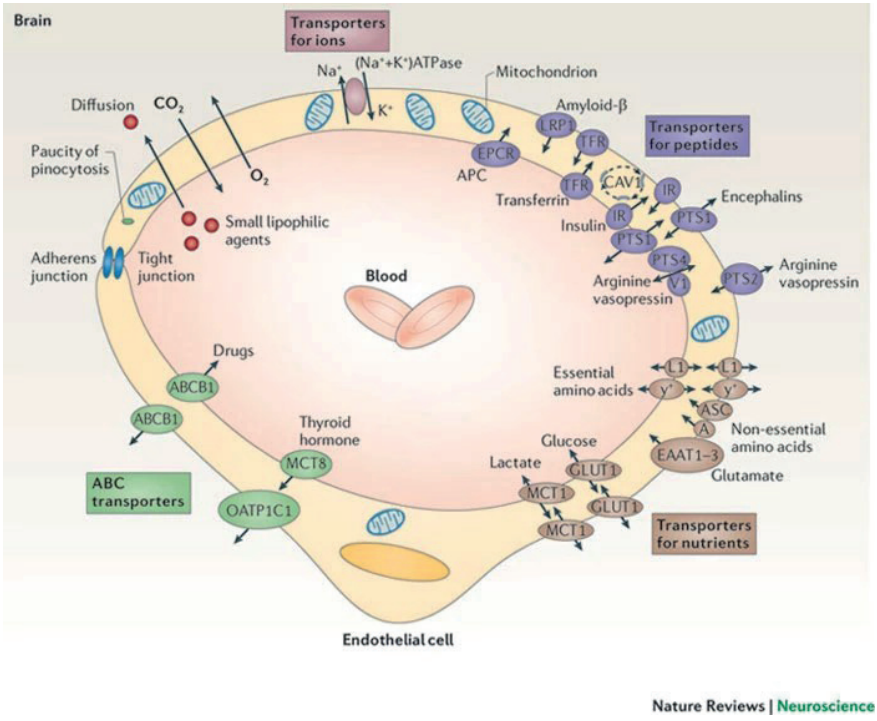

Figure 4. *Blood–brain barrier transport mechanisms (Zlokovic, 2011).*

The effect of pericytes on the BBB becomes particularly apparent at the level of transcytosis. In models of pericyte loss or disrupted PDGFRβ signaling, increased endothelial transcytosis and reduced barrier selectivity have been reported (Armulik et al., 2010; Sweeney et al., 2018). This suggests that even if tight junction proteins appear morphologically intact, the BBB may still be functionally compromised.

BBB regulation is dynamic and can be altered by inflammation, hypoxia, oxidative stress, and vascular aging. Chronic low-grade inflammation may increase adhesion molecules, facilitate leukocyte trafficking, remodel the basement membrane, and raise microvascular permeability (Uemura et al., 2020). Accordingly, BBB homeostasis depends on a multilayered control network requiring coordinated responses across vascular cell types (Iadecola, 2017).

3.3. Neurodegenerative consequences of BBB disruption

BBB disruption can permit plasma proteins (e.g., fibrinogen, albumin) to leak into the parenchyma, resulting in a neurotoxic microenvironment through glial activation. This process may impair synaptic plasticity and promote cognitive decline (Sweeney et al., 2018). Increased barrier permeability can also facilitate the entry of peripheral inflammatory mediators into the CNS, thereby sustaining chronic neuroinflammation (Uemura et al., 2020).

In human studies, techniques such as dynamic contrast-enhanced MRI have reported that hippocampal BBB permeability is associated with aging and early cognitive impairment, and that this disruption may be detectable before overt clinical dementia in certain cohorts (Montagne et al., 2015; Nation et al., 2019). These findings support the idea that BBB breakdown may represent an early event rather than merely a downstream consequence of neurodegeneration.

BBB dysfunction may also indirectly influence amyloid-β clearance. Reduced neurovascular function can impair Aβ removal through perivascular spaces and transport systems, which may increase Aβ accumulation and accelerate disease progression (Zlokovic, 2011; Kisler et al., 2017). Therefore, barrier dysfunction should be considered in a bidirectional relationship with Alzheimer pathology (Sweeney et al., 2018).

4. Pericytes: Definition, Subtypes, Functions, and Clinical Relevance

4.1. Definition and morphological diversity

Pericytes are mural cells embedded within the basement membrane of capillaries and postcapillary venules, located adjacent to endothelial cells. Pericyte density is higher in the brain than in peripheral tissues, consistent with the BBB's stringent selectivity requirements (Armulik et al., 2011). Their cell bodies are distributed along capillaries and extend long cytoplasmic processes that partially envelop the vessel wall (Figure 5).

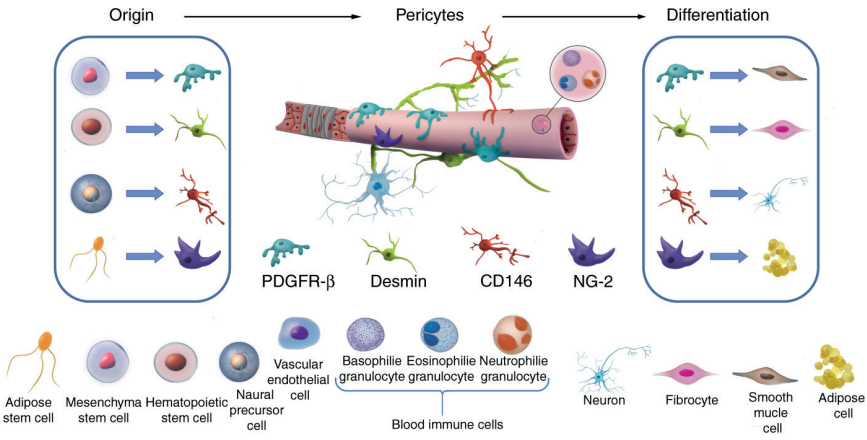

Figure 5. *Model demonstrating the pericytes by the expression of pericyte markers of PDGFRβ, CD146, desmin, and NG2 as examples, and their potential differentiation lineages (Zhu et al., 2022).*

A widely used morphological framework classifies pericytes by vascular segment and coverage pattern into ensheathing, mesh, and thin-strand pericytes. Ensheathing pericytes, located more proximally near precapillary

regions, exhibit greater coverage and potential contractile properties; thin-strand pericytes extend slender processes along distal capillaries (Grant et al., 2017; Uemura et al., 2020). This diversity suggests segment-specific functional "modules" rather than a single uniform pericyte function.

Clinically, this heterogeneity is important: in small vessel disease, loss of distal capillary pericytes may contribute to BBB fragility and microhypoxia, whereas impairment of more proximal mural cells may disrupt hemodynamic reactivity (Kisler et al., 2017; Østergaard et al., 2016). Thus, pericytes should be conceptualized not as a single cell type but as a family of cells distributed throughout the microcirculation (Uemura et al., 2020).

4.2. Molecular markers and heterogeneity

Pericyte identification commonly relies on markers such as PDGFR-β, NG2 (CSPG4), CD13 (ANPEP), RGS5, and desmin. However, none of these markers is fully specific: expression can overlap with vascular smooth muscle cells and show regional variability (Uemura et al., 2020). Therefore, current best practice is to integrate morphology, anatomical localization, and multi-marker combinations rather than relying on a single marker.

Single-cell transcriptomic studies have refined classification of brain vascular cell types and demonstrated pericyte heterogeneity with distinct transcriptional signatures. These studies suggest that pericytes are not merely supportive but include subpopulations with gene programs related to extracellular matrix regulation, immune response, transport processes, and contractility (Vanlandewijck et al., 2018; Wälchli et al., 2024).

Pericyte phenotypes may change with aging and disease. Chronic inflammation or metabolic stress can alter ECM production, inflammatory responsiveness, and endothelial communication, thereby contributing to BBB dysfunction and microcirculatory impairment (Sweeney et al., 2018; Uemura et al., 2020). Such dynamic phenotype shifts directly influence biomarker development and the feasibility of targeted therapeutic approaches.

4.3. Capillary blood flow and neurovascular coupling

Although cerebral blood flow regulation has classically been explained through arteriolar smooth muscle, capillary-level flow distribution is now recognized as comparably important. Neurovascular coupling matches increased synaptic activity with enhanced oxygen/glucose delivery through regional vasodilation and increased CBF (Iadecola, 2017) (Figure 6). The microcirculatory components of this response include capillary resistance elements and flow heterogeneity (Østergaard et al., 2016).

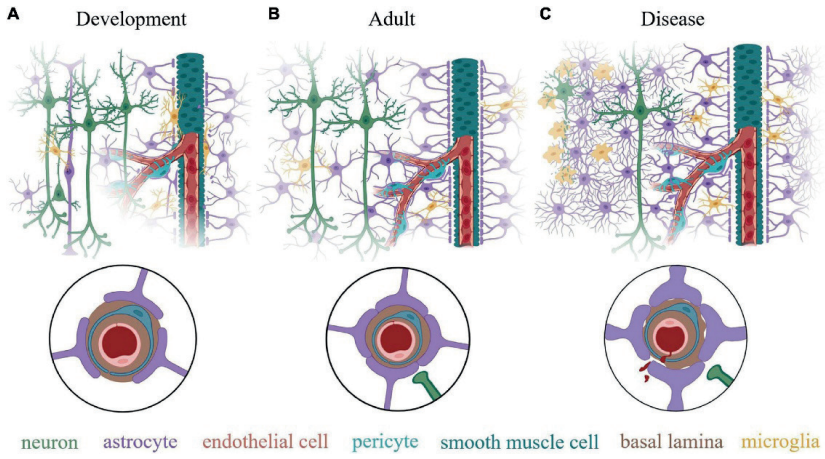

Figure 6. *Neurovascular unit at different life stages (Stackhouse and Mishra, 2021).*

Pericyte contractility and its potential influence on capillary diameter are central in this context. Experimental data indicate that pericytes can modulate red blood cell transit and tissue oxygenation by altering capillary caliber (Hall et al., 2014). This fine control may be especially important in metabolically vulnerable regions such as the hippocampus, where subtle microcirculatory disturbances can have functional consequences (Kisler et al., 2017).

In ischemic conditions, pericyte involvement may become even more critical. Some evidence suggests that ischemia can trigger persistent pericyte contraction, resulting in sustained capillary narrowing and the emergence of no-reflow regions even after reperfusion (Hall et al., 2014; Korte et al., 2022). This implies that microperfusion-targeted strategies must address not only clot resolution but also capillary wall biology (Uemura et al., 2020) (Figure 7).

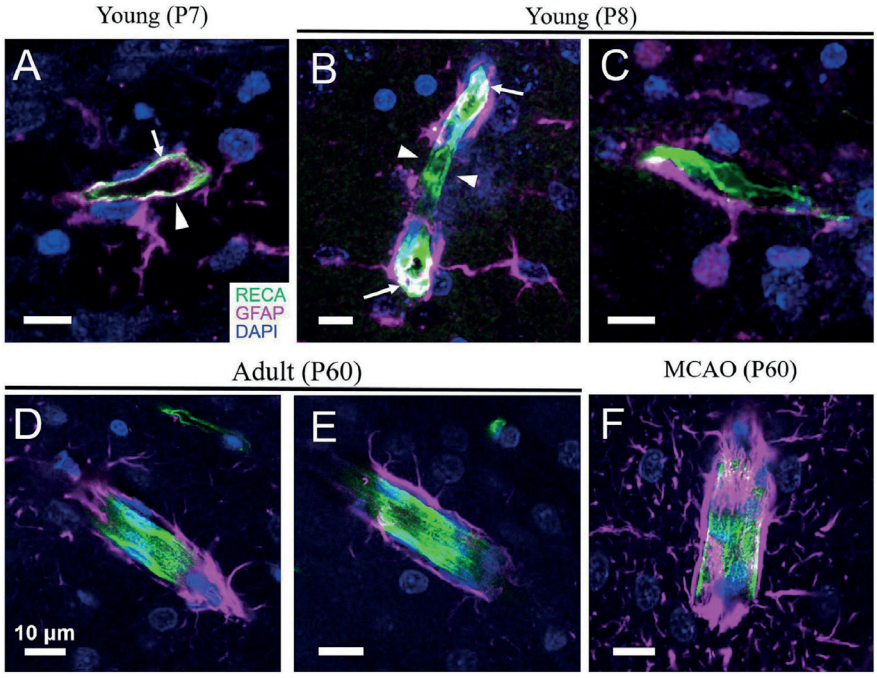

Figure 7. *Astrocyte coverage of arterioles during development, adulthood and after stroke. (A,B) In the cortex of developing rats, angiogenesis and astrogliogenesis is occurring concurrently. Although astrocytes begin enwrapping the vasculature immediately, this coverage is incomplete (arrowheads). GFAP expression can sometimes also be detected in the endothelium of very young rats (arrows). (C) An astrocyte with immature morphology lacking many processes is shown with a primary process extending to form an endfoot on a nearby capillary. (D,E) By mature adulthood (P60), astrocyte endfeet coverage of the blood vessels is complete. (F) Following middle cerebral artery occlusion (MCAO, a model of ischemic stroke), increased expression of GFAP and thickening of astrocyte endfeet on vessels is evident. Green = rat endothelial cell antigen-1 (RECA-1), magenta = glial fibrillary acidic protein (GFAP), blue = 4',6-diamidino-2-phenylindole (DAPI). Scale bars = 10 µm. (McConnell et al. 2019; Stackhouse and Mishra, 2021).*

4.4. BBB integrity, ECM, and inflammation control

Pericytes play a key role in maintaining BBB integrity, preserving the endothelial phenotype, and organizing the basement membrane. Pericyte–endothelial communication regulates tight junction stability, transcytosis levels, and vessel wall permeability (Armulik et al., 2010; Sweeney et al., 2018). Therefore, pericyte loss can disrupt the "fine tuning" of the barrier and create a leak-prone microenvironment.

Pericytes also contribute to extracellular matrix (ECM) production and remodeling. Basement membrane thickening, altered perivascular spaces, and perivascular fibrosis can increase diffusion distances, thereby impairing tissue

oxygenation (Østergaard et al., 2016). Such ECM alterations may constitute a microstructural substrate linking aging and chronic vascular disease to cognitive decline (Rundek et al., 2022).

Immunologically, pericytes can shape the perivascular niche governing leukocyte transmigration. Through adhesion molecules and cytokine responses, pericytes modulate inflammatory cell trafficking (Uemura et al., 2020). When combined with chronic inflammation, this can enhance microglial activation and synaptic loss, accelerating neurodegenerative processes (Sweeney et al., 2018). Thus, pericytes function as a multidimensional regulatory hub at the intersection of hemodynamic, barrier, and immune pathways.

5. Clinical Perspective: Pericytes in Dementia and Alzheimer's Disease

5.1. Neurovascular hypothesis and the "two-hit" model

Alongside the classical amyloid–tau axis, the neurovascular hypothesis has gained increasing support in Alzheimer's disease. According to this view, NVU disruption, increased BBB permeability, and microcirculatory dysfunction may emerge early and accelerate cognitive decline (Sweeney et al., 2018; Kisler et al., 2017). Even small hemodynamic deficits may have meaningful functional consequences in metabolically sensitive regions such as the hippocampus (Iadecola, 2017).

Zlokovic's "two-hit" model makes this framework clinically intuitive: the first hit involves vascular/barrier dysfunction and hypoperfusion, while the second hit comprises Aβ accumulation, tau pathology, and progressive neuronal injury (Zlokovic, 2011). Hit 1 (Vascular / Neurovascular Damage): In the first stage of the two-hit model, primary dysfunction of the vascular and neurovascular systems emerges as the initiating event of the neurodegenerative process. During this phase, increased permeability of the blood–brain barrier (BBB) and reduced cerebral blood flow occur, accompanied by pericyte degeneration and endothelial inflammation, which collectively disrupt the structural and functional integrity of the neurovascular unit. As a consequence of these alterations, toxic molecules that are normally excluded from the brain parenchyma gain access, oxidative stress is amplified, and neuronal metabolic demands can no longer be adequately met, resulting in neuronal energy insufficiency. Importantly, this stage may develop in the absence of amyloid-β (Aβ) accumulation, representing an early pathological phase that creates a vulnerable biological milieu for subsequent neurodegeneration. Hit 2 (Neuronal and Amyloid Pathology): The second stage unfolds on the fragile substrate established by the vascular and neurovascular impairments of the first hit. Ongoing BBB dysfunction and cerebral hypoperfusion lead to impaired Aβ clearance, promoting amyloid plaque accumulation, tau

hyperphosphorylation, and progressive synaptic loss. These molecular and cellular events culminate in irreversible neurodegeneration. Thus, the second hit builds upon the vulnerability created by the first hit, linking vascular pathology to classical neurodegenerative changes that underlie the clinical manifestation of dementia. This approach argues that vascular dysfunction is not merely a comorbidity but an active component of pathogenesis (Figure 8).

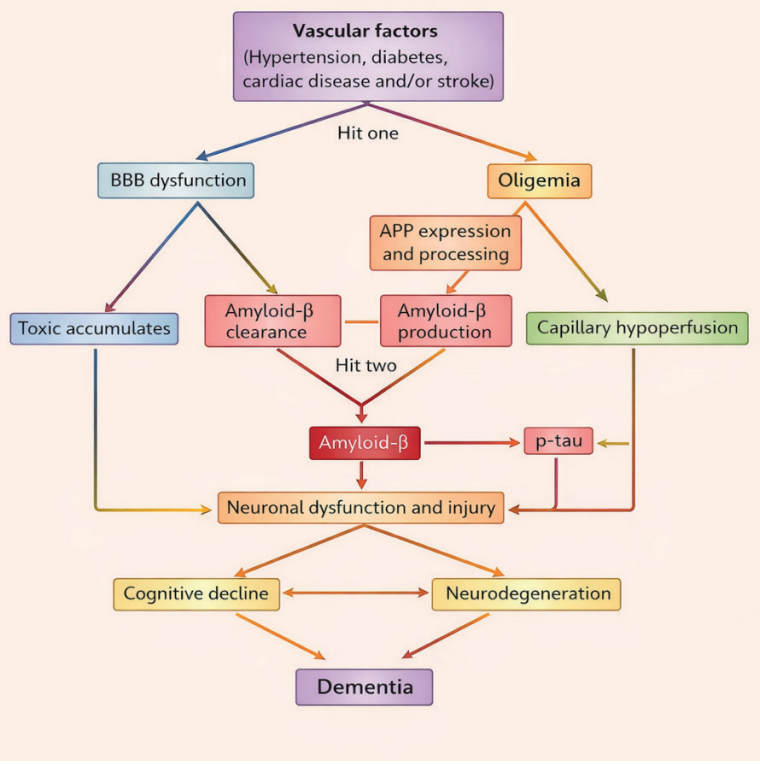

Figure 8. *Two hit model in Alzheimer's disease ((Zlokovic, 2011).*

Within this model, pericytes become strategic targets: a proposed cascade involves pericyte loss leading to BBB leakage and microcirculatory heterogeneity, followed by inflammation and microhypoxia, thereby facilitating Aβ/tau pathology (Sweeney et al., 2018; Uemura et al., 2020). Consequently, pericyte injury is increasingly viewed as an early accelerating mechanism on the trajectory toward Alzheimer's disease (Figure 9).

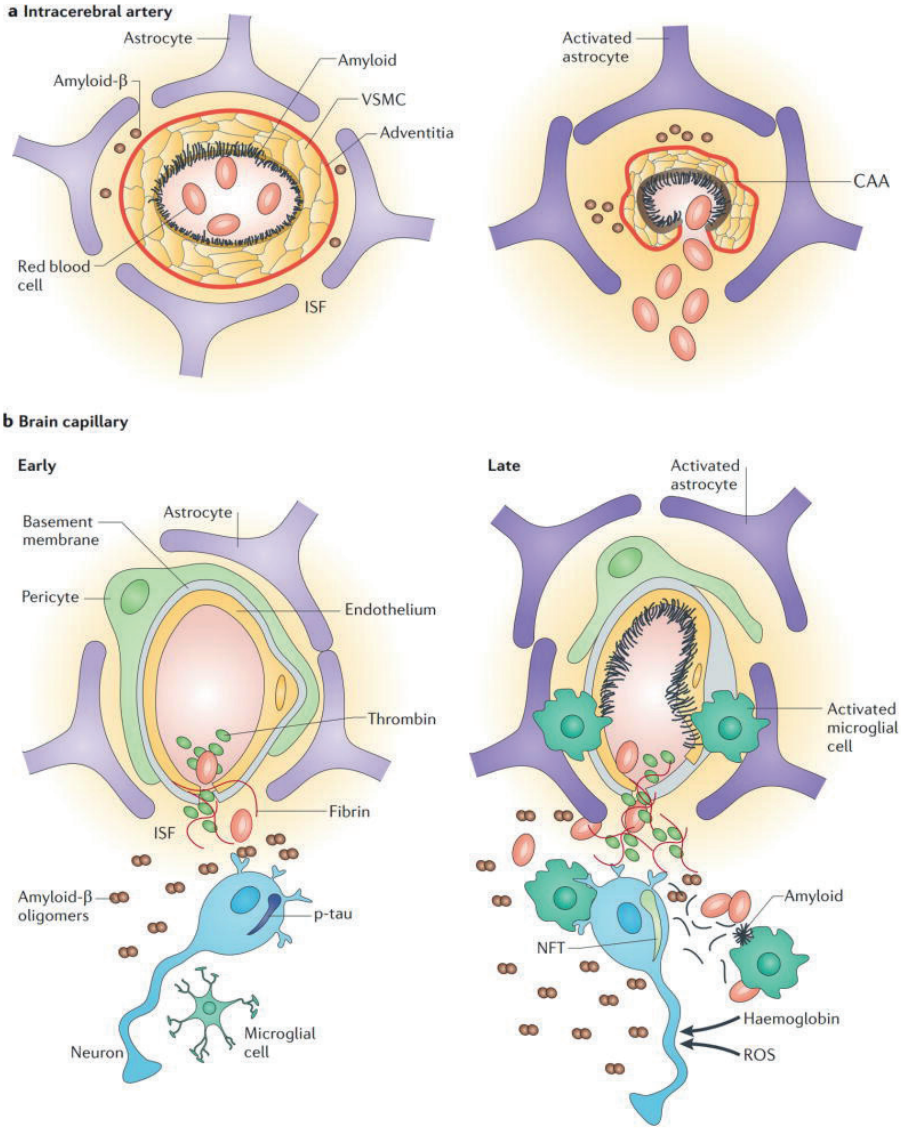

Figure 9. *Neurovascular degeneration in Alzheimer's disease (Zlokovic, 2011).*

5.2. Human studies: imaging, biomarkers, and pathology

In human studies, measuring BBB permeability with techniques such as dynamic contrast-enhanced MRI has yielded evidence linking early cognitive impairment to hippocampal barrier vulnerability (Montagne et al., 2015; Nation et al., 2019). These findings suggest that NVU-level changes may be trackable even before overt clinical symptoms develop, highlighting potential value for early diagnosis.

CSF biomarker studies indicate that molecules reflecting pericyte injury (e.g., soluble PDGFRβ) may correlate with cognitive performance and BBB measures (Nation et al., 2019). This supports the idea that pericyte dysfunction is not merely a histopathological observation but may represent a clinically traceable process. However, biomarker specificity remains a methodological challenge, particularly in distinguishing pericyte-related signals from broader vascular or inflammatory processes (Sweeney et al., 2018).

Postmortem studies further support microvascular alterations in Alzheimer's disease, including basement membrane thickening, reduced pericyte coverage, and inflammatory changes in vessel walls. These findings may coexist with cerebral amyloid angiopathy and small vessel disease, emphasizing that mixed pathologies can be decisive for cognitive outcomes (Rundek et al., 2022; Uemura et al., 2020). Thus, the clinical spectrum of Alzheimer's disease may be more effectively explained by a multifactorial model incorporating NVU dysfunction.

5.3. Therapeutic and translational implications

Pericyte-targeted approaches are emerging as promising translational strategies in Alzheimer's disease and vascular cognitive impairment. Mechanisms that preserve or strengthen pericyte–endothelial communication (e.g., the PDGF-B/PDGFRβ axis) are theoretically attractive for reducing BBB leakage and stabilizing the microcirculation (Armulik et al., 2011; Uemura et al., 2020). However, because excessive activation of this axis may promote fibrosis and ECM accumulation, balanced modulation is essential.

Another clinical target is reducing microcirculatory heterogeneity. The relationship among capillary no-reflow, pericyte contraction, and oxidative stress suggests that reperfusion therapies should focus not only on large-vessel patency but also on capillary-level reflow (Korte et al., 2022). This has clear relevance to mitigating post-stroke cognitive decline and reducing dementia risk (Rundek et al., 2022).

Finally, BBB permeability metrics and pericyte injury biomarkers may be used to stratify patient subgroups and monitor therapeutic response. Rather than targeting "amyloid only," Alzheimer clinical trials may benefit from combination strategies that also address concurrent NVU dysfunction (vascular stabilization + anti-inflammatory modulation + proteostasis support) (Sweeney et al., 2018; Kisler et al., 2017). In this context, pericyte biology sits at the center of next-generation neurovascular paradigms for both diagnosis and therapy.

6. Conclusion

6.1. Clinical Implications

The findings presented in this chapter clearly show that a neuron-centered framework alone is insufficient to explain the pathophysiology of dementia and Alzheimer's disease. The interplay among intracranial hemodynamics, microvascular anatomy, and BBB integrity plays a decisive role in maintaining cognitive function. In particular, pericyte dysfunction triggers processes such as capillary flow heterogeneity, increased barrier permeability, and chronic neuroinflammation, thereby constituting a critical intermediate step on the path to clinical dementia. Pericytes should therefore be regarded as a "silent but powerful" pathological component in vascular cognitive impairment and Alzheimer's disease.

From a clinical standpoint, early detection of pericyte and NVU injury is important for predicting disease progression and identifying patient subgroups. Dynamic contrast-enhanced MRI for BBB permeability assessment, CSF biomarkers reflecting pericyte injury (e.g., sPDGFR-β), and advanced perfusion analyses stand out as candidate tools that could be integrated into diagnostic algorithms. These approaches may enable identification of neurovascular vulnerability before overt clinical symptoms appear (Figure 8).

Therapeutically, the limited clinical benefit of monotherapies targeting amyloid or tau pathology highlights the need for more integrative strategies. Stabilizing the NVU, preserving pericyte function, and improving microcirculatory dynamics may serve as complementary targets capable of slowing cognitive decline. In this regard, pericytes are increasingly emerging as a cellular target of both diagnostic and therapeutic relevance across Alzheimer's disease and other dementia subtypes.

6.2. Future Directions

One of the most critical needs in future research is a more detailed definition of pericyte heterogeneity. Single-cell transcriptomic and proteomic approaches have the potential to distinguish regional, functional, and disease-specific pericyte subtypes in the human brain. Such studies may identify which pericyte populations are particularly vulnerable in Alzheimer's disease and vascular dementia, thereby enabling targeted interventions.

Another major line of investigation is clarifying the timing of pericyte dysfunction. Determining whether pericyte injury precedes amyloid accumulation or develops in parallel will strengthen the clinical relevance of the neurovascular hypothesis. Longitudinal cohort studies integrating

advanced imaging and CSF biomarkers will be essential to delineate these causal relationships. In addition, careful assessment is needed to determine how well findings from animal models translate to human biology.

Finally, translational research should focus increasingly on pericyte-targeted therapeutic strategies. Modulating pathways governing pericyte–endothelial communication, developing agents that improve microcirculatory flow, and interventions that regulate the inflammatory microenvironment may become integral components of future combination regimens. Given the complex nature of neurodegenerative diseases, a pericyte-centered neurovascular paradigm has the potential to usher in a new era in Alzheimer's disease and dementia research.

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Chapter 3

Microbiota and Alzheimer's Disease: Current Knowledge and Future Perspectives

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Introduction

Alzheimer's disease (AD) constitutes the leading cause of dementia on a global scale, accounting for more than four-fifths of all dementia cases. The disorder is defined by a gradual and irreversible deterioration of cognitive abilities, behavioral regulation, and functional independence. Despite extensive research efforts, AD remains a heterogeneous and multifactorial neurodegenerative condition, and its underlying pathophysiological mechanisms have not yet been fully elucidated (Kapoor et al., 2024). Among the various pathogenic frameworks proposed, the amyloid cascade hypothesis and the tau hyperphosphorylation hypothesis continue to dominate the field; however, neither model sufficiently explains the full clinical variability, temporal progression, or therapeutic resistance observed in AD (Kaur et al., 2020).

In parallel with advances in human microbiome research, increasing emphasis has been placed on the contribution of host-associated microbial ecosystems to health and disease. Disruptions in the structure, diversity, and metabolic activity of these microbial communities—commonly referred to as dysbiosis—have been implicated in a broad spectrum of pathological conditions. Initially linked primarily to metabolic disorders such as obesity and type 2 diabetes mellitus, dysbiosis is now increasingly recognized as a systemic phenomenon with potential relevance to neurological disease processes (Liu et al., 2023).

Emerging evidence suggests that alterations in gut microbiota composition are not confined to peripheral metabolic effects but may also influence central nervous system (CNS) function and vulnerability to neurodegeneration. Communication between the gastrointestinal tract and the CNS occurs through an integrated network of neural, endocrine, and immune signaling pathways collectively described as the gut–brain axis. This bidirectional system plays a critical role in maintaining CNS homeostasis under physiological conditions. Perturbations within this axis, particularly those driven by microbial imbalance, have been associated with a range of neurological and neuropsychiatric disorders, including Parkinson's disease, Huntington's disease, depression, multiple sclerosis, and Alzheimer's disease (Cammann et al., 2023; Kandpal et al., 2022).

The Microbiome: Development, Influences, and Functions

Marked interindividual heterogeneity characterizes the human gut microbiota, with particularly pronounced variation observed at the bacterial strain level. Although members of the phyla *Firmicutes* and *Bacteroidetes* generally dominate the adult intestinal ecosystem, individuals may be further stratified into distinct microbial configurations, commonly referred to as

enterotypes, according to the relative predominance of *Prevotella*, *Bacteroides*, or *Ruminococcus*. Accumulating evidence indicates that the distribution of these enterotypes is strongly influenced by long-term dietary habits rather than transient environmental exposures (Arumugam et al., 2011).

Despite emerging reports suggesting that microbial exposure may commence during intrauterine life, current consensus supports the notion that colonization of the gut microbiota predominantly occurs at birth and is subsequently shaped by postnatal environmental conditions (Neu, 2016). Following initial colonization, the microbial community undergoes a progressive maturation process, acquiring an adult-like configuration within the first two to three years of life. This developmental trajectory is modulated by multiple factors, including mode of delivery, infant feeding strategies, geographic and cultural context, and exposure to antimicrobial agents. Importantly, this early-life window is regarded as a critical period due to its potential long-term implications for immune maturation and neurodevelopmental outcomes (Zeissig & Blumberg, 2014).

Although the gut microbiota remains dynamic throughout the lifespan, age-related compositional shifts become particularly evident in older individuals, a demographic in which neurodegenerative disorders are disproportionately represented (Kumar et al., 2016). In advanced age, a decline in microbial diversity is frequently observed and is often associated with inadequate nutritional intake. Such alterations have been linked to the emergence of chronic low-grade systemic inflammation, a process widely described as "inflammaging" (Odamaki et al., 2016). Nevertheless, the relative contribution of biological aging itself, as opposed to age-associated lifestyle and health factors, to microbiota remodeling has yet to be definitively established.

Among environmental determinants, diet has been identified as one of the most potent modulators of gut microbiota composition across all stages of life and therefore constitutes a central variable in studies exploring microbiota-related disease mechanisms (Shanahan et al., 2017). Beyond the intake of specific macronutrients and micronutrients, broader dietary patterns such as predominantly plant-based regimens or diets enriched in ultra-processed foods have been shown to exert substantial effects on microbial diversity and metabolic capacity. While dietary influences on the microbiota are generally cumulative and long-term, evidence also suggests that short-term dietary modifications may induce rapid yet reversible shifts in microbial community structure (Claesson et al., 2012).

In individuals affected by neurodegenerative diseases, additional factors may further disrupt gut microbial balance. Nutritional disturbances

arising from dysphagia, cognitive decline, or gastrointestinal dysfunction are common in this population and may exacerbate microbiota alterations. Moreover, pharmacological agents frequently prescribed to older patients including antibiotics, proton pump inhibitors, and metformin have been demonstrated to exert significant and sometimes profound effects on gut microbial composition, thereby acting as important confounders in microbiota–disease associations (Forslund et al., 2015; Jackson et al., 2016).

Taken together, the gut microbiota contributes fundamentally to a wide range of physiological processes, including maturation of the mucosal immune system, preservation of intestinal barrier integrity, regulation of enteric neuromuscular activity, and biosynthesis of neuroactive and immunomodulatory metabolites. In light of these multifaceted functions, the gut microbiota should be regarded as an integral biological component underpinning systemic homeostasis rather than a passive bystander.

Microbiome-Gut-Brain Axis

The brain–gut axis refers to a complex bidirectional signaling system linking the central nervous system and the enteric nervous system through integrated neural circuits, including sympathetic and parasympathetic pathways, in conjunction with endocrine and circulating neuromodulatory signals. This communication network has traditionally been implicated in the development of stress-associated gastrointestinal disturbances. However, recent advances have substantially expanded this view, demonstrating that disturbances in gut microbiota composition represent a critical contributor to neurodegenerative disease pathogenesis, primarily through sustained neuroinflammatory signaling along the microbiota–gut–brain axis (Carter, 2011).

Alterations in gut microbial ecology driven by aging, prolonged psychological stress, obesity, and dietary imbalance have been shown to activate a range of molecular and cellular pathways that disrupt gut–brain communication. These microbiota-driven perturbations are increasingly regarded as key modulators in both the onset and progression of Alzheimer's disease. Mechanistic pathways most consistently implicated include compromised intestinal barrier function, amplification of inflammatory signaling cascades, and acceleration of amyloid-β (Aβ) peptide accumulation within the central nervous system (Janeiro et al., 2022).

Importantly, the functional relevance of the gut–brain axis is not confined to gastrointestinal symptoms associated with affective disorders such as stress, anxiety, or depression. Rather, this axis encompasses a broader spectrum of pathological conditions characterized by concurrent involvement of the central nervous system, gastrointestinal tract, and autonomic nervous system. These include neurodegenerative disorders such as Parkinson's

disease and dementia, as well as clinical scenarios in which neurological manifestations arise secondary to primary gastrointestinal dysfunctions, including malabsorption syndromes. Functional gastrointestinal disorders, most notably irritable bowel syndrome (IBS), are widely considered canonical examples of dysregulation along this axis (Mayer, 2011).

The conceptual framework underpinning the gut–brain axis was initially established nearly six decades ago following observations linking intestinal bacterial metabolites to the development of hepatic encephalopathy and demonstrating clinical improvement after antibiotic intervention (Phear et al., 1956). These early investigations highlighted the pathological relevance of small intestinal bacterial overgrowth (SIBO), particularly involving coliform species, and revealed that microbially driven inflammatory responses contribute to the pathogenesis of complications such as spontaneous bacterial peritonitis, sepsis, and coagulation abnormalities in the setting of portal hypertension and chronic liver disease.

Within this integrated model, the gut microbiota has emerged as a central mediator of shared pathophysiological pathways connecting the gastrointestinal tract, liver, and central nervous system. Key processes—including SIBO, microbial dysbiosis, disruption of intestinal epithelial barrier integrity, systemic inflammatory activation, and the translocation of neuroactive microbial metabolites into the circulation—are now recognized as pivotal drivers of both liver-related and neurocognitive disorders (Quigley et al., 2016; Stärkel & Schnabl, 2016).

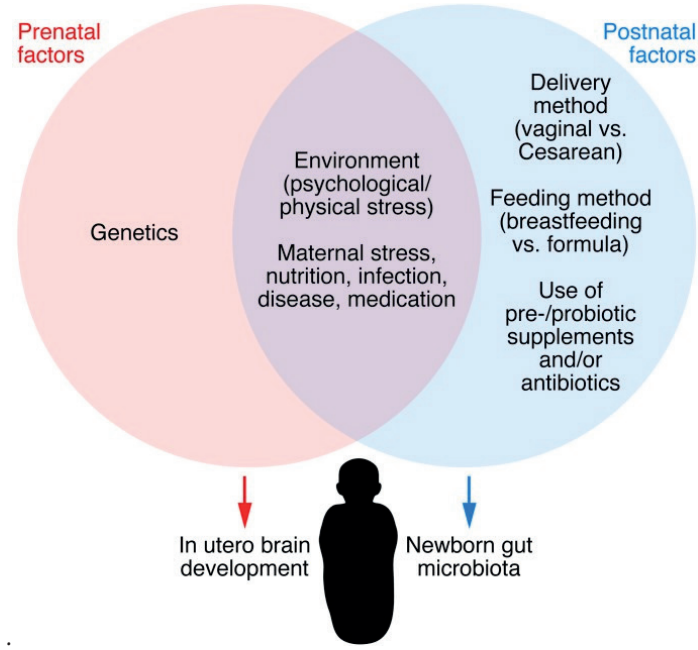
Dysbiosis-associated increases in intestinal permeability have been mechanistically linked to downregulation of tight junction protein expression in colonic epithelial cells. This loss of barrier integrity initiates immune system activation, facilitates disruption of the blood–brain barrier, and promotes sustained neuroinflammatory signaling, ultimately leading to neuronal damage and progressive neurodegeneration. As a result of intestinal barrier failure, microbial-derived metabolites—including lipopolysaccharides (LPS), trimethylamine-N-oxide (TMAO), and short-chain fatty acids (SCFAs)—enter the systemic circulation. These bioactive molecules have been shown to induce proinflammatory cytokine production, access the central nervous system, and amplify neuroinflammatory responses through activation of astrocytes and microglial cells (Itzhaki et al., 2016).

The Role of Gut Microbiota in Brain Development

Environmental exposures occurring during the perinatal window have been conclusively shown to exert a decisive impact on nervous system maturation. Accumulating evidence indicates that unfavorable conditions encountered during early developmental stages profoundly alter signaling

along the gut–brain axis. These observations have shifted current perspectives, positioning the gut microbiota not as a passive bystander, but as a dynamic biological determinant actively shaping neurodevelopmental trajectories (Figure 1) (Mayer, Tillisch, & Gupta, 2015).

Figure 1. *Fetal brain development may be influenced by a range of factors that modulate the maternal gut microbiota, including microbially derived metabolites, pharmacologically generated chemical by-products, and inflammation-associated alterations occurring during pregnancy. Following birth, the establishment of the neonatal microbiota is strongly determined by maternal microbial exposure at delivery derived predominantly from vaginal or skin-associated sources according to the mode of birth as well as by postnatal nutritional inputs such as breastfeeding or formula feeding*



Reference: Mayer et al., 2015

To delineate the modulatory contribution of the gut microbiota to gut–brain signaling, a range of experimental paradigms has been implemented, including antibiotic-mediated disruption of microbial communities, fecal microbiota transplantation, and germ-free (GF) animal models. Despite inherent experimental limitations associated with each approach, seminal investigations led by Sudo et al. established that the complete absence of commensal intestinal microorganisms profoundly reshapes stress-related physiological responses in adult organisms. Notably, reintroduction of microbial colonization was shown to partially normalize these altered stress phenotypes, underscoring the functional plasticity of microbiota-dependent neuroendocrine regulation (Sudo et al., 2004).

Beyond stress reactivity, alterations in gut microbial composition have been linked to a broad array of behavioral and physiological outcomes. These include changes in anxiety- and depression-associated behaviors, nociceptive processing, hypothalamic–pituitary–adrenal (HPA) axis responsiveness, feeding behavior, gustatory preferences, and metabolic regulation, collectively highlighting the extensive systemic influence of the gut microbiota (Tanida et al., 2005).

1. Perinatal stress models

A substantial body of preclinical evidence indicates that stress exposure during the perinatal period induces long-lasting modifications in neurobiological systems governing HPA axis activity, emotional regulation, pain modulation, and central circuits involved in gastrointestinal control. Findings derived predominantly from rodent models suggest translational relevance for functional gastrointestinal disorders and selected psychiatric conditions in humans. Experimental paradigms have demonstrated that both prenatal maternal stress and postnatal maternal separation lead to discernible shifts in gut microbial composition. For instance, transient depletion of *Lactobacillus* species has been observed in maternally separated non-human primates, whereas early-life stress in rodents has been associated with sustained alterations in fecal microbiota profiles persisting into adulthood. Although it remains unresolved whether these microbial perturbations arise as a direct consequence of stress exposure or as secondary effects of stress-induced physiological alterations, disruption of microbiota–brain signaling during sensitive developmental windows is increasingly regarded as a determinant of enduring behavioral and neurobiological outcomes (O'Mahony et al., 2009).

2. Adult stress models

Compelling experimental data further indicate that stress experienced during adulthood is accompanied by dynamic remodeling of gut microbial communities. In murine models, psychosocial stress paradigms have been associated with reductions in *Bacteroides* abundance alongside enrichment of *Clostridium* taxa, changes that coincide with elevated systemic inflammatory markers, including interleukin-6 (IL-6) and monocyte chemoattractant protein-1 (MCP-1). Evidence from animal studies, supported by limited human observations, suggests that these microbial shifts may arise either indirectly through stress-induced alterations in intestinal motility and secretory function or through direct stress-mediated effects on microbial ecology. The relative contribution of these mechanisms remains to be fully clarified. Nevertheless, cumulative findings support a regulatory role for the gut microbiota in shaping emotional behavior, pain sensitivity, and feeding-related processes in adult organisms, thereby providing a robust conceptual foundation for future translational research (Benton et al., 2007; Tillisch et al., 2013).

Collectively, environmental exposures during critical developmental periods, in concert with gut microbiota composition, exert a profound influence on nervous system maturation and long-term neurobehavioral outcomes. Continued investigation in this rapidly evolving field is expected to refine current models of gut–brain axis biology and to inform the development of mechanistically driven and translationally relevant therapeutic strategies

Clinical Evidence Linking Gut Dysbiosis to Alzheimer's Disease

Accumulating clinical and experimental evidence has increasingly supported the notion that microbial factors may participate in the multifactorial pathogenesis of AD. Rather than implicating a single infectious agent, a diverse spectrum of microorganisms has been associated with AD-related neuropathology, including *Chlamydophila pneumoniae*, *Borrelia burgdorferi* and other spirochetal species, as well as herpes simplex virus type 1 (HSV-1). The detection of these pathogens in conjunction with characteristic AD lesions has reinforced hypotheses proposing that chronic microbial exposure may contribute to long-term neurodegenerative vulnerability.

Among bacterial pathogens, *Helicobacter pylori* has emerged as a microorganism of particular interest. Clinical and epidemiological observations have suggested that AD patients with serological evidence of *H. pylori* infection exhibit significantly poorer cognitive performance, as reflected by reduced Mini-Mental State Examination (MMSE) scores. Complementary findings derived from amyloid precursor protein (APP) transgenic mouse models have demonstrated an increased relative abundance of *Helicobacter* species accompanied by a depletion of *Prevotella*, indicating that pathogen-associated microbial shifts may modulate disease-relevant pathways.

Parallel associations have been reported in Parkinson's disease (PD), where *H. pylori* infection has been linked to accelerated disease progression and increased clinical severity. In the context of AD, elevated titers of *H. pylori*-specific immunoglobulin G (IgG) antibodies detected in both cerebrospinal fluid and peripheral circulation have been interpreted as markers of heightened infectious burden. However, these associations remain controversial, as at least one large-scale population-based cohort study failed to confirm a significant relationship, underscoring the heterogeneity of clinical findings and the complexity of host–microbe interactions in neurodegenerative disorders.

Multiple biological mechanisms have been proposed to explain how microbial agents or their components may gain access to the central nervous system. These include immune cell-mediated trafficking across a compromised blood–brain barrier, particularly via infected monocytes and T lymphocytes, as well as direct neural transmission through olfactory pathways. In parallel, chronic oral inflammation and periodontal disease have been increasingly

implicated, supporting the hypothesis that sustained peripheral infections may act as persistent drivers of neuroinflammatory cascades relevant to AD pathogenesis.

Beyond the contribution of individual pathogens, increasing emphasis has been placed on the broader role of gut microbiota composition in shaping brain function and disease susceptibility. Extensive research efforts have begun to delineate the molecular, immunological, and metabolic pathways through which the gut–brain–microbiota axis modulates stress responses and neurological disease risk. Emerging clinical evidence suggests that microbial alterations observed in functional gastrointestinal disorders, such as irritable bowel syndrome (IBS), may predispose individuals to cognitive decline and dementia, including AD.

Consistent with this framework, gut microbiota dysregulation has also been reported across a range of neuropsychiatric and neuroinflammatory conditions, including autism spectrum disorders, schizophrenia, and multiple sclerosis. Recent clinical investigations have identified distinct microbial signatures in patients with cognitive impairment and cerebral amyloidosis, characterized by an increased relative abundance of *Escherichia/Shigella* and a concomitant reduction in the anti-inflammatory taxon *Eubacterium rectale*. These alterations have been proposed as peripheral indicators of systemic inflammation associated with AD.

Comparative analyses of fecal microbiota profiles from individuals with and without AD have further revealed a consistent reduction in microbial diversity in affected patients, accompanied by decreased representation of *Firmicutes* and *Bifidobacterium* and an increased proportion of *Bacteroidetes*. Notably, these microbial shifts have been shown to correlate with elevated levels of AD-specific biomarkers in cerebrospinal fluid, suggesting a functional link between intestinal dysbiosis and central pathological processes.

Neurodegenerative diseases predominantly manifest in advanced age, a life stage during which gut microbiota composition is profoundly influenced by age-related factors such as nutritional insufficiency, chronic low-grade inflammation commonly referred to as "inflammaging" and the accumulation of multiple comorbidities. Furthermore, pharmacological agents frequently prescribed in elderly populations, including antibiotics, metformin, and proton pump inhibitors, have been demonstrated to exert substantial and direct effects on microbial community structure. These medication-related influences represent critical confounding variables that must be carefully considered when interpreting disease-associated microbiota profiles in AD.

Microbiota Modulation as a Therapeutic Target in Alzheimer's Disease

Advances in understanding the relationship between intestinal dysbiosis, increased gut permeability, and neurological dysfunction in AD have enabled the identification of novel therapeutic strategies aimed at modulating the gut microbiota. A growing body of evidence indicates that targeted manipulation of microbial communities may contribute to the preservation of intestinal barrier integrity, attenuation of systemic and neuroinflammatory signaling, and modulation of disease-related neuropathological processes.

Probiotic-based interventions have received considerable attention due to their capacity to enhance epithelial tight junction function and counteract inflammation-associated barrier disruption. Experimental studies have demonstrated that specific probiotic strains, including *Enterococcus faecium* and *Lactobacillus rhamnosus*, suppress tumor necrosis factor-α (TNF-α) production in vitro. In vivo investigations further suggest that administration of these microorganisms is associated with reduced oxidative stress and regulation of endogenous antioxidant defense mechanisms. Similarly, members of the *Lactobacillus* and *Bifidobacterium* genera have been shown to mitigate lipopolysaccharide-induced neuroinflammatory responses and cognitive deficits in animal models, potentially through acetylcholinesterase inhibition and enhancement of antioxidant capacity. Clinical studies have reported modest yet significant improvements in cognitive performance, as assessed by Mini-Mental State Examination scores, following probiotic supplementation in patients with AD.

Antibiotic-based strategies represent an alternative approach to microbial modulation. Rifaximin, a non-absorbable antibiotic commonly used in the management of small intestinal bacterial overgrowth, has been reported to exert beneficial effects extending beyond gastrointestinal symptom control. Improvements in motor function and disease fluctuations have been documented in Parkinson's disease patients, suggesting that selective alteration of gut microbial populations may influence neurological outcomes. However, the applicability of such interventions to AD remains insufficiently characterized.

Fecal microbiota transplantation (FMT) has emerged as a promising modality for restoring microbial diversity and functional stability in various neurological disorders, including Parkinson's disease, multiple sclerosis, and autism spectrum disorders. Despite encouraging preliminary findings, robust clinical evidence supporting the safety and efficacy of FMT in AD is currently lacking. It has been hypothesized that transplantation of microbiota from young, healthy donors may counteract age-associated dysbiosis; however, this concept remains largely speculative in the context of AD.

Dietary modification constitutes one of the most accessible and sustainable means of influencing gut microbiota composition. Diets enriched in plant-derived foods, probiotics, antioxidants, soy products, nuts, and omega-3 fatty acids—while limiting saturated fats, refined sugars, and excessive animal protein intake—have been associated with reduced systemic inflammation, improved metabolic homeostasis, and a lower risk of cognitive decline. In addition to microbiota-mediated effects, dietary components may exert direct modulatory influences on both enteric and central nervous system function.

Recent progress in human microbiome research has reinforced the notion that gut microbial alterations play a contributory role in AD pathogenesis. Dysbiosis characterized by reduced microbial diversity, shifts in taxonomic composition, and enrichment of potentially pathogenic taxa has been associated not only with gastrointestinal disorders but also with neurodegenerative diseases. Mechanistic studies suggest that dysbiosis may promote AD progression through increased intestinal and blood–brain barrier permeability, enhanced production of amyloid-like bacterial proteins, and elevated levels of lipopolysaccharides, ultimately driving proinflammatory cytokine release and neuroinflammation.

Despite these advances, translation of microbiota-targeted interventions into clinical practice remains challenging due to the high interindividual specificity of host–microbiota interactions. Future progress in AD research will depend on large-scale, longitudinal studies integrating host genetics, dietary habits, microbiota composition, and aging-related factors. Comprehensive multi-omics approaches, including metabolomics and systems-level analyses, will be essential for elucidating functional microbiota-host interactions. Moreover, beyond the intestinal microbiota, other microbial niches such as the oral, nasal, cutaneous, and viral microbiomes warrant systematic investigation to achieve a holistic understanding of neurodegenerative disease pathophysiology.

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AN INTEGRATED VIEW

Understanding dementia and Alzheimer's disease requires moving beyond isolated pathological hallmarks toward an integrated anatomical perspective. As emphasized throughout this volume, cognitive decline emerges from the dynamic interplay between neuroanatomy, vascular structure, cellular interfaces, and systemic influences rather than from neuronal pathology alone.

By bringing together intracranial hemodynamics, blood–brain barrier integrity, pericyte biology, classical neuroanatomy, and the microbiota–brain axis, this book underscores the importance of structural relationships in both disease vulnerability and progression. Such an approach not only enriches our conceptual understanding of dementia but also opens new avenues for early diagnosis, prevention, and therapeutic strategies grounded in anatomy.

We hope that this volume encourages anatomists, clinicians, and neuroscientists to reconsider dementia through a broader anatomical lens—one that recognizes the brain as an integrated organ shaped by vascular, cellular, and systemic networks. Advancing this perspective may be essential for addressing the unresolved challenges of dementia and Alzheimer's disease in the years to come.