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Review

Pathophysiological Divergence Between Vascular and Post-Stroke Dementia: Bridging Human and Experimental Perspectives

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Abstract

Vascular dementia (VaD) and post-stroke dementia (PSD) are two leading subtypes of vascular cognitive impairment (VCI), each arising from distinct cerebrovascular pathologies. VaD typically results from chronic cerebral hypoperfusion and small vessel disease, leading to progressive executive dysfunction and white matter degradation. In contrast, PSD occurs following acute ischemic events and is frequently associated with hippocampal damage and episodic memory deficits. This review delineates the pathophysiological divergence between VaD and PSD by integrating findings from human clinical studies and preclinical animal models. While rodent models of chronic hypoperfusion replicate key features of VaD, such as oligodendrocyte injury and myelin loss, transient ischemia models—particularly middle cerebral artery occlusion—capture hallmark PSD features, including excitotoxic neuronal death, blood–brain barrier disruption, and glial activation. Emerging research also highlights the involvement of neurovascular unit dysfunction, inflammation-driven neurodegeneration, and region-specific synaptic alterations. Recognizing these mechanistic differences is critical for advancing diagnostic precision, identifying therapeutic windows, and improving translational relevance. Furthermore, the review underscores the need for aged and comorbid animal models, integration of human biomarker studies, and implementation of novel therapies targeting endothelial function, glial reactivity, and cognitive plasticity. Through this comparative approach, we propose a unified framework to guide future investigations and interventions across the spectrum of VCI.

Keywords: vascular dementia; post-stroke dementia; cognitive impairment; chronic hypoperfusion; ischemia-reperfusion; neurovascular unit; neuroinflammation; translational models

1. Introduction

Vascular cognitive impairment (VCI) encompasses a spectrum of cognitive disorders arising from cerebrovascular pathology, with vascular dementia (VaD) and post-stroke dementia (PSD) constituting two principal clinical endpoints. Although both share a common vascular origin, they diverge in clinical presentation, temporal onset, and underlying pathophysiological mechanisms. VaD typically results from chronic cerebral hypoperfusion and small vessel disease, leading to progressive or stepwise cognitive decline, especially in executive function [1,2]. Conversely, PSD is defined as a decline in cognitive performance following a clinically apparent ischemic stroke, with onset commonly occurring within three to six months post-event [3,4].

The global burden of both VaD and PSD is considerable, particularly in aging populations where cerebrovascular diseases are prevalent. Epidemiological studies estimate that approximately 25–30% of ischemic stroke survivors experience cognitive decline, with around 10% progressing to dementia within the first year post-stroke [5], a burden further confirmed by recent surveys reporting post-stroke dementia rates of 20–30% within 1 year [6]. More recent data show that up to 70% of stroke survivors exhibit some degree of post-stroke cognitive impairment [7], and that the prevalence of vascular dementia continues to rise globally in parallel with aging populations and accumulated vascular risk factors [8]. Despite overlapping clinical symptoms and shared risk factors, the divergent pathophysiological substrates of VaD and PSD warrant direct comparative evaluation.

From a mechanistic standpoint, VaD is often associated with chronic ischemia, white matter rarefaction, arteriolosclerosis, and microinfarcts. In contrast, PSD

more commonly reflects acute neuronal loss, glutamate-mediated excitotoxicity, and ischemia-reperfusion (I/R)–induced neuroinflammation [9,10]. Recent neuroimaging and neuropathological studies have demonstrated that these conditions affect distinct neural substrates—VaD predominantly involves subcortical white matter tracts, while PSD more frequently impacts the hippocampus and associated cortical networks [11,12]. Furthermore, advances in animal modeling have enabled simulation of both chronic hypoperfusion (e.g., bilateral carotid artery stenosis in rodents) and acute ischemic events (e.g., middle cerebral artery occlusion), offering mechanistic insights under controlled experimental conditions [13–15].

This review provides a side-by-side comparison of VaD and PSD, emphasizing their distinct pathophysiological features as revealed by human studies and experimental models. Previous reviews have tended to discuss VCI in general terms—highlighting clinical criteria [2], small vessel disease mechanisms [16], or post-stroke cognitive decline [3]—without clearly distinguishing VaD and PSD as separate mechanistic entities. In contrast, our approach is to integrate findings across disciplines, including neuroimaging, neuropathology, and molecular biology, to elucidate parallel and divergent disease trajectories. By exploring these differences at cellular, molecular, and systems levels, we aim to refine diagnostic frameworks and support the development of targeted therapeutic strategies for each subtype of vascular cognitive disorder.

Methodology of Literature Selection

To construct this comparative review, we conducted a comprehensive literature search using PubMed (https://pubmed.ncbi.nlm.nih.gov/), Scopus (https://www.scopus.com/), and Web of Science (https://webofscience.com/wos/alldb/basic-search/) for studies published from January 2000 to May 2025. Search terms included combinations of “vascular dementia”, “post-stroke dementia”, “vascular cognitive impairment”, “chronic cerebral hypoperfusion”, “middle cerebral artery occlusion”, and “animal models of dementia”. We prioritized peer-reviewed original articles and systematic reviews offering mechanistic insights, neuroimaging correlations, histopathological findings, or translational relevance. Studies focused exclusively on Alzheimer’s disease or non-vascular dementias were excluded unless they provided comparative perspectives. Over 120 references were screened, and the most representative studies were selected to support the thematic structure of this review.

2. Definitions and Diagnostic Criteria

VaD and PSD are subtypes of VCI, yet they differ significantly in their diagnostic frameworks, temporal association with cerebrovascular events, and cognitive domains predominantly affected. Establishing clear operational definitions is essential for consistent clinical diagnosis, research standardization, and interpretation of translational studies.

VaD is characterized as an acquired cognitive disorder attributed to cerebrovascular pathology, particularly small vessel disease and chronic cerebral hypoperfusion [9]. Over the past two decades, multiple diagnostic frameworks have emerged. Among the most widely adopted is the National Institute of Neurological Disorders and Stroke-the Association Internationale pour la Recherche et l'Enseignement en Neurosciences (NINDS-AIREN) criteria, formulated through consensus by the NINDS and AIREN. This research-oriented framework mandates the presence of cognitive decline in at least two domains, functional impairment, and a clear temporal relationship to cerebrovascular events, supported by neuroimaging evidence of infarction or lesions [17]. NINDS-AIREN offers diagnostic rigor and is more relevant to VaD research, but it is less practical for PSD where rapid post-stroke diagnosis is required. In clinical contexts, the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) classifies VaD under “major neurocognitive disorder due to vascular disease”, emphasizing a stepwise or fluctuating course, focal neurological signs, and a vascular etiology [18]. DSM-5 provides broader clinical applicability and captures both conditions, though it lacks specificity in distinguishing acute versus chronic vascular impairment. The international classification of diseases, 11th revision (ICD-11), developed by the World Health Organization, similarly defines VaD as a cognitive disorder secondary to cerebrovascular disease, incorporating both ischemic and hemorrhagic mechanisms [19]. ICD-11 ensures international standardization and inclusivity, but its criteria do not clearly separate progressive small vessel disease in VaD from acute ischemic injury in PSD. A side-by-side comparison of these diagnostic frameworks is presented in Table 1, outlining their scope, imaging requirements, common usage contexts, and comparative differences between VaD and PSD. In contrast, PSD specifically refers to cognitive impairment that arises within a defined interval following a clinically diagnosed stroke, typically within 3 to 6 months [3]. It is conceptualized as a consequence of acute ischemic injury and is commonly characterized by deficits in memory, executive function, language, or visuospatial skills. While VaD may progress insidiously through cumulative microvascular damage, PSD is typically preceded by an overt cerebrovascular event. The Vascular Impairment of Cognition Classification Consensus Study (VASCOG) has proposed that PSD be diagnosed when dementia emerges within 6 months of a stroke, regardless of prior cognitive status, provided that the stroke is the dominant causative factor [20]. This temporal definition has facilitated greater consistency in clinical trial design and patient stratification.

Despite these formal criteria, clinical differentiation between VaD and PSD can be difficult due to overlapping symptoms and frequent coexistence of mixed pathologies,

Table 1. Comparative summary of diagnostic criteria for VaD.

Criteria	Origin/Purpose	Core requirements	Imaging support	Common usage	Comparative differences between VaD and PSD
NINDS-AIREN	Research-oriented; consensus between NINDS and AIREN	Cognitive decline in ≥2 domains; functional impairment; temporal link to stroke; neuroimaging evidence	Required (CT/MRI evidence of infarcts or lesions)	Primarily in research settings	More applicable to VaD due to emphasis on chronic vascular lesions and multiple domains; less suited for PSD, where acute onset after stroke and rapid diagnosis are critical.
DSM-5	Clinical classification by American Psychiatric Association	Evidence of vascular etiology; stepwise/fluctuating course; focal neurological signs	Recommended but not mandatory	Widely used in clinical practice	Captures both VaD (progressive/subcortical decline) and PSD (acute deficits after stroke), but lacks specificity in distinguishing temporal onset.
ICD-11	Global classification system by WHO for clinical use	Cognitive decline due to cerebrovascular disease (ischemic or hemorrhagic); functional impact	Recommended	Used internationally across healthcare systems	Broadly covers both VaD and PSD; recognizes the vascular origin but lacks detail in distinguishing chronic small vessel pathology seen in VaD from the acute post-stroke onset typical of PSD.

Abbreviations: VaD, Vascular Dementia; NINDS, National Institute of Neurological Disorders and Stroke; AIREN, Association Internationale pour la Recherche et l'Enseignement en Neurosciences; DSM-5, Diagnostic and Statistical Manual of Mental Disorders, 5th Edition; ICD-11, International Classification of Diseases, 11th Revision; CT, Computed Tomography; MRI, Magnetic Resonance Imaging; WHO, World Health Organization; PSD, Post-Stroke Dementia.

Table 2. Comparative pathophysiology of VaD and PSD in humans.

Feature	VaD	PSD	Key pathophysiology	Representative references
Primary cause	Chronic cerebral hypoperfusion, small vessel disease (SVD)	Acute ischemic stroke, large artery infarction	Prolonged ischemia due to small vessel pathology vs. acute infarction	[16,28]
Pathology	Microinfarcts, white matter rarefaction, periventricular lacunes	Hippocampal atrophy, cortical infarcts, focal neuronal loss	Diffuse subcortical damage vs. focal cortical necrosis	[11,12]
Inflammation	Chronic microglial activation, elevated CRP	Acute cytokine surge (↑ TNF-α, ↑ IL-6)	Persistent low-grade vs. acute inflammatory burst	[28,29]
Hemodynamics	Persistent low perfusion	Sudden occlusion and reperfusion injury	Gradual vs. abrupt cerebral blood flow disturbance	[23]
Circuitry disruption	Fronto-subcortical circuit dysfunction	Hippocampal–prefrontal and DMN disruption	Disruption of executive vs. memory-related networks	[25,27]

↑ indicates an increase in the corresponding parameter. Abbreviations: CRP, C-reactive protein; TNF-α, Tumor Necrosis Factor-alpha; IL-6, Interleukin-6; DMN, Default Mode Network.

especially among elderly patients. VaD and Alzheimer's Disease (AD) frequently coexist, particularly in older adults, and the overlap of cerebrovascular disease and Alzheimer-type pathologies often accelerate cognitive decline and complicate diagnosis and treatment [21]. These mixed mechanisms also present challenges for VaD and PSD research, underscoring the need to integrate vascular and neurodegenerative biomarkers in future studies [22]. While this review focuses on VaD and PSD, mixed dementia remains an essential context for interpreting clinical and translational findings. From a diagnostic standpoint, neuroimaging serves as a crucial adjunct, with PSD often associated with focal cortical infarcts or atrophy, whereas VaD more commonly presents with white matter hyperintensities, lacunar infarcts, and other small vessel disease markers [2]. In summary, VaD and PSD are both vascular in origin but differ in temporal onset, lesion characteristics, and diagnostic categorization. Standardized and reliable criteria are essential not only for clinical accuracy but also for the translational relevance of animal models used to study these conditions.

3. Pathophysiology in VaD and PSD (Human and Experimental Models)

3.1 Pathophysiology in Humans

Although VaD and PSD both arise from cerebrovascular pathology, they differ substantially in terms of etiology, lesion distribution, inflammatory response, hemodynamic profile, and neural network disruption. VaD is primarily linked to chronic cerebral hypoperfusion, most commonly due to small vessel disease (SVD). Hemodynamically, VaD emerges in the context of prolonged global hypoperfusion without a discrete vascular event [23], leading to gradual and widespread damage to subcortical structures and white matter tracts. Neuropathological hallmarks include periventricular lacunes, white matter rarefaction, and microinfarcts—especially within fronto-subcortical circuits that mediate executive function, motor planning, and attention regulation [2,16]. By contrast, PSD arises from acute ischemic events—such as large vessel infarctions or multiple embolic occlusions—that frequently involve the hippocampus and adjacent cortical structures and typically followed by reperfusion. This sequence provokes oxidative stress, excitotoxicity, and blood–brain barrier (BBB) disruption [23], leading to focal neuronal loss, hippocampal atrophy, and disconnection of memory-associated networks like the default mode network (DMN) [11,12,24]. At the network level, VaD is associated with fronto-subcortical disconnection, contributing to deficits in psychomotor speed, attention, and executive function. In PSD, hippocampal–prefrontal pathways and DMN integrity are acutely disrupted, correlating with profound memory impairment and impaired consolidation processes [25–27]. Disruption of these networks compromises episodic memory encoding and retrieval, as well as the integration of memory with executive control—manifesting clinically as amnesia and disorientation.

Taken together, these comparisons highlight that VaD and PSD, while both arising from vascular insults, diverge in their temporal dynamics, inflammatory profiles, and network vulnerabilities. VaD exemplifies a chronic disconnection syndrome linked to diffuse white matter injury, whereas PSD reflects an acute circuit breakdown driven by reperfusion-induced neurotoxicity. Such distinctions provide critical insight into differential diagnostic markers and potential therapeutic targets. A comparative overview of these human pathophysiological features is presented in Table 2 (Ref. [11,12,16,23,25,27–29]).

3.2 Pathophysiology in Animal Models

Animal models have been pivotal in dissecting the divergent pathophysiological pathways of VaD and PSD. By simulating chronic hypoperfusion and acute I/R injury in a controlled environment, these models provide mechanistic

Table 3. Comparative features of animal models of VaD and PSD.

Feature	VaD models (e.g., BCAS, 2VO)	PSD models (e.g., tMCAO)	Key pathophysiology	Representative references
Vascular insult type	Chronic hypoperfusion	Acute ischemia–reperfusion	Gradual reduction in cerebral blood flow	[35,36]
Affected regions	White matter (corpus callosum), hippocampus, internal capsule	Cortex, hippocampus	Axonal degeneration vs. focal infarction	[14,34]
Inflammatory response	Low-grade, chronic microgliosis	Acute, robust microgliosis and cytokine storm	TNF-α, IL-6 elevation post-ischemia	[37,38]
Functional impairment	Working memory, executive function, spatial navigation	Episodic memory, learning consolidation	Disrupted fronto-subcortical vs. hippocampal–prefrontal pathways	[40,41]
Network connectivity	↓ Prefrontal–thalamic coherence	↓ Hippocampal–prefrontal, DMN-like networks	Distinct regional vulnerability and reorganization	[30,31]

↓ indicates a decrease in the corresponding parameter. Abbreviations: BCAS, Bilateral Common Carotid Artery Stenosis; 2VO, Two-Vessel Occlusion; tMCAO, Transient Middle Cerebral Artery Occlusion.

insight and translational relevance, though none fully replicate the human disease spectrum.

Models of VaD typically involve bilateral common carotid artery stenosis (BCAS) in mice or two-vessel occlusion (2VO) in rats. These paradigms induce sustained cerebral hypoperfusion, resulting in progressive white matter degeneration, demyelination, and axonal injury—especially in the corpus callosum, internal capsule, and hippocampus. These structures support interhemispheric communication, thalamocortical relay, and memory consolidation, respectively [30–32]. The ensuing cognitive impairments—affecting executive function, working memory, and spatial navigation—mirror fronto-subcortical disconnection [33–36]. Histopathological features include gliosis, oligodendrocyte loss, and perivascular fibrosis—paralleling small vessel disease in humans. In contrast, PSD models typically employ transient middle cerebral artery occlusion (tMCAO) in rodents to replicate acute focal ischemia followed by reperfusion. This results in rapid infarction of cortical and hippocampal regions, widespread neuronal loss, and disruption of the BBB. The ensuing inflammatory cascade involves microglial and astrocytic activation, oxidative stress, and robust upregulation of proinflammatory mediators such as tumor necrosis factor alpha (TNF-α) and interleukin (IL)-6 [14,37–39]. These pathophysiological features mirror human PSD and lead to impairments in episodic-like memory, contextual learning, and memory consolidation, as observed in maze-based behavioral tasks. Infarct size, location, and post-ischemic neuroplasticity collectively influence the severity of cognitive impairment.

Importantly, regional vulnerability and network dysfunction vary across models. VaD paradigms predominantly target deep white matter tracts and subcortical relay nuclei, leading to diffuse disconnection syndromes. In contrast, tMCAO results in focal damage to the hippocampus and neocortex, disrupting circuits critical for memory and cognitive flexibility. Functional imaging studies have shown that BCAS diminishes prefrontal–thalamic and subcortical coherence, whereas tMCAO interrupts hippocampal–prefrontal coupling and DMN-like activity [40,41]. These connectivity patterns align with the cognitive phenotypes observed: attentional and executive deficits in VaD, and amnesia with impaired consolidation in PSD. These animal models recapitulate essential aspects of human VCI. Chronic hypoperfusion paradigms (e.g., BCAS, 2VO) parallel white matter injury and small vessel pathology in VaD, whereas transient MCAO reproduces hippocampal and neocortical vulnerability and network disconnection observed in PSD. While no single model fully captures the complexity of human condition, they provide validated platforms for mechanistic exploration. Future research should integrate longitudinal imaging, advanced behavioral assays, and multimodal biomarkers to enhance translational relevance. A comparative summary of these pathophysiological features in experimental models is provided in Table 3 (Ref. [14,30,31,34–38,40,41]).

4. Molecular Mechanisms of VaD and PSD (Human and Models)

The divergent clinical and neuropathological trajectories of VaD and PSD are underpinned by distinct molecular mechanisms, despite several shared pathogenic elements. This section reviews key overlapping and disease-specific pathways observed in both human studies and animal models, focusing on oxidative stress, neuroinflammation, BBB disruption, and unique molecular signatures—such as Wnt/Notch dysregulation in VaD and excitotoxicity and aquaporin/matrix remodeling in PSD (see Fig. 1).

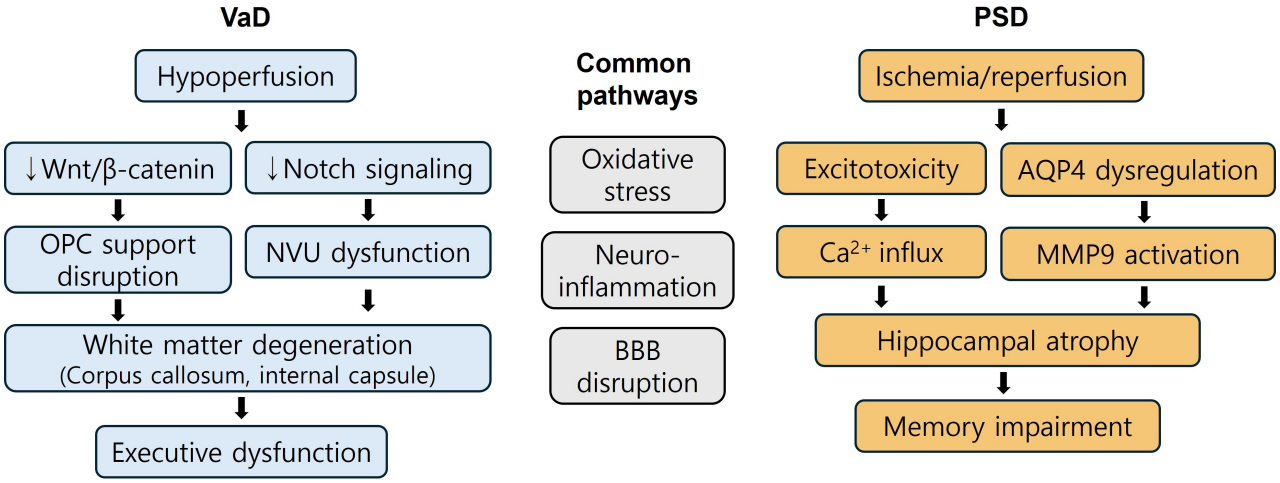

Fig. 1. Molecular mechanisms underlying VaD and PSD. This figure illustrates the shared and distinct molecular pathways contributing to the pathogenesis of VaD and PSD. In the central panel, oxidative stress, neuroinflammation, and blood–brain barrier (BBB) disruption are depicted as common mechanisms found in both conditions. On the left, VaD-specific pathways highlight chronic cerebral hypoperfusion-induced alterations in Wnt/β-catenin and Notch signaling, leading to impaired oligodendrocyte maturation, white matter degeneration, and vascular instability. On the right, PSD-specific processes emphasize acute I/R injury triggering excitotoxicity, AQP4 dysregulation, and MMP-mediated BBB breakdown, resulting in neuronal death, edema, and leukocyte infiltration. ↓ indicates a reduction or downregulation in expression or activity. Abbreviations: I/R, ischemia-reperfusion; AQP4, aquaporin-4; MMP, matrix metalloproteinase; NVU, neurovascular unit; OPC, oligodendrocyte precursor cell.

4.1 Common Molecular Pathways in VaD and PSD

Oxidative stress is a hallmark of both VaD and PSD, primarily resulting from cerebral hypoxia, mitochondrial dysfunction, and excessive production of reactive oxygen species (ROS). These ROS induce lipid peroxidation, DNA damage, and protein nitration, which contribute to injury of neurons and oligodendrocytes in vulnerable areas such as the hippocampus and white matter tracts [1,2]. Neuroinflammation also plays a central role. Activation of microglia and infiltration of peripheral immune cells elevate proinflammatory cytokines including TNF-α, IL-1β, and IL-6 [42]. This proinflammatory milieu promotes synaptic dysfunction and accelerates BBB disruption. VaD-associated inflammation is typically low-grade and sustained, with persistent microglial activation and elevated systemic inflammatory markers such as C-reactive protein [28], whereas the neuroinflammatory response in PSD is more acute and robust, with marked elevations in proinflammatory cytokines such as TNF-α and IL-6 in the early post-stroke phase [29]. In rodent models of global ischemia and chronic hypoperfusion, increased expression of glial fibrillary acidic protein (GFAP), inducible nitric oxide synthase (iNOS), and nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) oxidase subunits underscores the significance of innate immune responses [37,38]. BBB breakdown is observed in both conditions, but the temporal patterns differ. In VaD, BBB disruption progresses gradually due to endothelial degeneration, pericyte loss, and sustained perivascular leakage, as supported by early leakage findings in SVD mouse models and imaging studies demonstrating progressive endothelial dysfunction [43,44]. In PSD, acute reperfusion injury leads to rapid increases in BBB permeability via proinflammatory cytokines and matrix metalloproteinases (MMPs), notably MMP-2 and MMP-9. Elevated MMP-9 levels correlate with hemorrhagic transformation risk in MCAO models [39,45].

Taken together, these molecular differences account for the distinct clinical trajectories of VaD and PSD. In VaD, chronic oxidative stress, sustained neuroinflammation, and progressive BBB disruption—along with impaired Wnt/Notch signaling—contribute to gradual white matter degeneration and fronto-subcortical disconnection, manifesting as deficits in executive function and processing speed. In contrast, PSD is characterized by an acute burst of oxidative stress, robust neuroinflammatory activation, excitotoxicity, and aquaporin/MMP-mediated BBB breakdown, which converge on hippocampal and cortical vulnerability. These mechanisms underlie pronounced impairments in memory consolidation, contextual learning, and spatial orientation. Such contrasts highlight VaD as a chronic disconnection syndrome and PSD as an acute circuit failure, providing critical insight for the development of targeted interventions. These shared pathways, alongside disease-specific mechanisms discussed below, are summarized in Table 4 (Ref. [1,2,34,37,38,41–52]).

4.2 Distinct Mechanisms in VaD

VaD pathogenesis is driven by progressive white matter degeneration and impaired neurovascular repair, notably

Table 4. Comparison of molecular mechanisms in VaD and PSD.

Molecular mechanism	VaD	PSD	References
Oxidative stress	Chronic ROS elevation due to hypoperfusion and mitochondrial dysfunction	Acute ROS burst during reperfusion exacerbates neuronal injury	[1,2]
Neuroinflammation	Microglial activation sustained by vascular injury and white matter degeneration	Rapid microglial and astrocytic response to ischemic insult	[37,38,42]
BBB disruption	Gradual endothelial degeneration, tight-junction loss (claudin-5, occludin), pericyte loss	Abrupt MMP-mediated breakdown of BBB post-reperfusion (e.g., MMP-9 upregulation)	[43–45]
Wnt/Notch signaling	↓ Wnt/β-catenin & Notch signaling → impaired oligodendrocyte maturation, remyelination	Not prominently involved	[46–48]
Excitotoxicity	Not prominent	↑ Glutamate → NMDA/AMPA overactivation → Ca^{2+} influx, mitochondrial failure	[41,49]
Aquaporin/MMP activation	Mild or secondary	↑ AQP4 mislocalization → edema; ↑ MMP-9 → extracellular matrix degradation	[50–52]
White matter integrity	Progressive degeneration (especially in corpus callosum, internal capsule)	Focal secondary degeneration after infarct	[2,34]
Cognitive domains affected	Executive dysfunction, processing speed deficits	Memory consolidation, executive function, spatial orientation deficits	[1,41]

↑ indicates an increase, ↓ indicates a decrease, and → indicates leads to or results in. Abbreviations: ROS, reactive oxygen species; BBB, blood–brain barrier; NMDA, N-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid.

via dysregulation of developmental pathways. Suppression of Wnt/β-catenin and Notch signaling compromises oligodendrocyte precursor cell (OPC) maturation and vascular integrity, hindering remyelination and microvascular stability. In BCAS mouse models, inhibition of canonical Wnt signaling disrupts OPC support and BBB integrity [46,48], while Notch target gene downregulation is associated with microglial activation and impaired neurovascular unit (NVU) coupling [47]. Regionally reduced expression of Wnt-related genes (e.g., *cyclin D1*, *LEF1*) has been reported in the corpus callosum and thalamus, corresponding to areas of early myelin loss in BCAS mice [34]. Notch signaling deficits also diminish astrocytic support and compromise NVU function. Although these alterations have primarily been characterized in animal models, emerging postmortem data suggest that similar Wnt/Notch dysregulation occurs in the human brain, particularly in periventricular white matter and hippocampal zones affected by VaD. Section 5 will further explore the translational relevance of these findings.

4.3 Distinct Mechanisms in PSD

PSD arises from abrupt ischemic insult followed by reperfusion, initiating a cascade of excitotoxic and inflammatory injury. Excessive glutamate release and overactivation of N-methyl-D-aspartate (NMDA) and α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptors cause calcium overload, mitochondrial collapse, caspase activation, and neuronal apoptosis [41,49]. These processes are consistently observed in tMCAO models with subsequent cognitive impairment. Post-ischemic dysregulation of aquaporin-4 (AQP4), predominantly localized in astrocyte endfeet, disrupts water and ion balance, promoting vasogenic edema and synaptic disorganization [53,54]. Concurrently, upregulation of MMP-9 degrades tight junctions and the basement membrane, exacerbating BBB leakage and facilitating leukocyte infiltration [50,51]. These combined mechanisms—excitotoxicity, AQP4 dysfunction, and MMP-driven BBB breakdown—contribute to hippocampal–prefrontal network disruption, underlying the hallmark deficits in memory consolidation and episodic recall seen in PSD.

5. Current Therapy and Translational Insights (Human and Models)

Despite increasing insight into the molecular basis of VaD and PSD, therapeutic strategies remain largely symptomatic, with limited disease-modifying options. This section compares current clinical interventions with experimental strategies from animal models and highlights key translational hurdles. A comparative overview is presented in Table 5 (Ref. [49,55–65]), while Fig. 2 illustrates translational challenges and proposed solutions.

5.1 Clinical Therapies and Lessons From Clinical Trials for VaD and PSD

Cholinesterase inhibitors, such as donepezil and rivastigmine, exert modest cognitive benefits in VaD, particularly in mixed pathologies with concurrent Alzheimer's disease [55,56,66]. Rivastigmine, which inhibits both acetylcholinesterase and butyrylcholinesterase, may be especially beneficial in subcortical VaD. Memantine, an

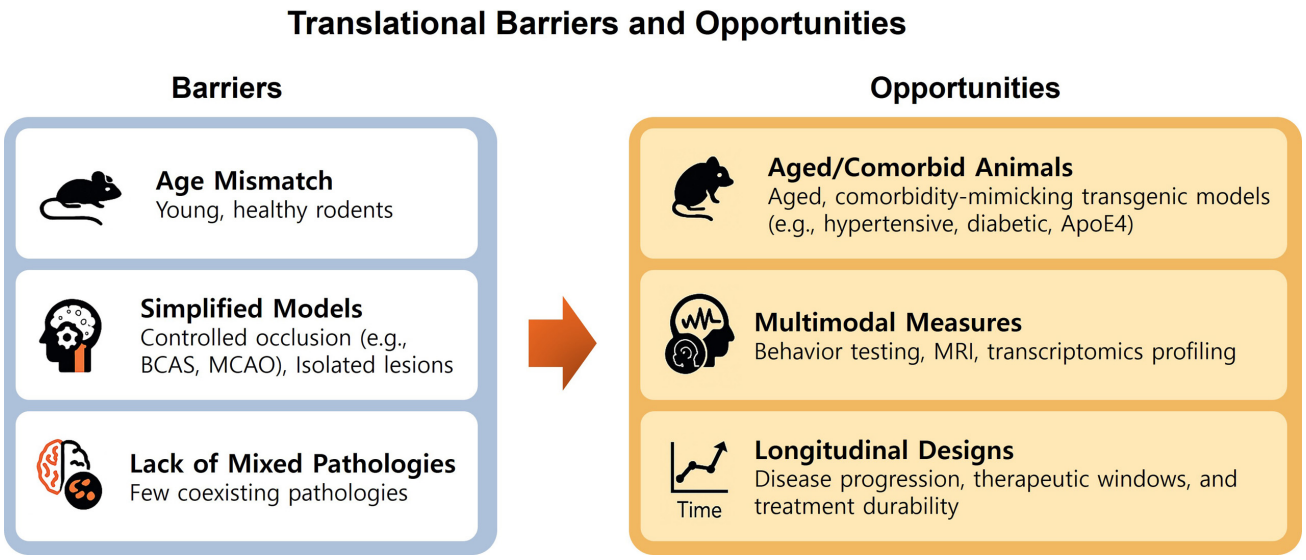

Fig. 2. Translational barriers and opportunities in VaD and PSD research. This infographic summarizes key obstacles and corresponding opportunities for improving translational relevance in preclinical studies of VaD and PSD. On the left, common limitations include the use of young, healthy rodents (age mismatch), reliance on simplified occlusion models (e.g., MCAO, BCAS) that fail to capture human vascular heterogeneity, and the absence of co-pathologies such as amyloid or tau deposition. On the right, corresponding strategies for refinement include use of aged or comorbid transgenic animals, the application of multimodal outcome metrics (e.g., behavior, MRI, transcriptomics), and longitudinal study designs to mimic progressive cognitive decline and therapeutic windows seen in patients. Abbreviations: BCAS, bilateral common carotid artery stenosis.

NMDA receptor antagonist, has shown efficacy in PSD by reducing glutamate-mediated excitotoxicity and promoting synaptic plasticity [57,67]. Citicoline, a cytidine-5′-diphosphocholine derivative, enhances membrane repair and neurogenesis and is used in both VaD and PSD [58,68]. Equally important is rigorous control of vascular risk factors—including hypertension, diabetes, dyslipidemia, and atrial fibrillation—which remains the cornerstone of disease prevention and management [9,69]. Nevertheless, these interventions largely alleviate symptoms without reversing molecular or structural neuropathology. Despite these available options, no pharmacological agent has achieved global approval as a disease-modifying therapy for VaD or PSD. Donepezil is approved for VaD in only a few countries, and memantine provides modest benefits in PSD, while citicoline remains supportive rather than curative. Emerging repurposed drugs, such as metformin, are currently under early-phase clinical investigation for vascular cognitive impairment [66,70]. However, translational failures are frequent, owing to patient heterogeneity, mixed pathologies, underrepresentation of elderly patients with comorbidities, and trial designs that do not fully reflect disease complexity. These challenges highlight why many VaD/PSD drug trials have failed to yield meaningful clinical advances. Looking forward, future therapeutic strategies will require biomarker-guided patient stratification, integration of vascular and neurodegenerative endpoints, and the inclusion of more representative clinical populations. Such approaches will be critical to overcome past limitations and to develop therapies capable of modifying disease trajectories rather than merely alleviating symptoms.

5.2 Experimental Strategies in Animal Models

Rodent models of cerebral hypoperfusion and I/R injury have enabled the discovery of candidate compounds targeting inflammation, oxidative stress, and synaptic damage, as well as biologics such as erythropoietin derivatives for white matter repair and non-pharmacological interventions like high-frequency repetitive transcranial magnetic stimulation (rTMS) for BDNF-mediated plasticity.

Resveratrol, a natural polyphenol, has shown consistent neuroprotection in 2VO models. It suppresses Stimulator of Interferon Genes (STING)/TANK-binding kinase 1 (TBK1)/Interferon Regulatory Factor 3 (IRF3) signaling, attenuates microglial activation and white matter degeneration, and preserves cholinergic neurons. Behavioral improvements include better spatial learning in the Morris water maze and Y-maze [59,60]. Cilostazol, a selective phosphodiesterase-3 (PDE3) inhibitor, enhances nitric oxide availability and activates Cyclic Adenosine Monophosphate (cAMP)/cAMP Response Element–Binding Protein (CREB) signaling. In middle-aged rats subjected to four-vessel occlusion (4VO), it ameliorated working memory deficits and oxidative stress [61,62]. Edaravone–Dexborneol, a novel combination of a free radical scavenger and a BBB-penetrant monoterpene, significantly reduced BBB leakage, microglial pyroptosis (via NLRP3 inhibition), and cognitive decline in stroke and small ves-

Table 5. Clinical and experimental therapeutics for VaD and PSD.

Therapeutic agent	Mechanism of action	Disease context	Model species (if applicable)	Outcomes	References
Donepezil	Cholinesterase inhibitor	VaD (±AD)	Human	Modest cognitive benefit in VaD with hippocampal atrophy	[56]
Rivastigmine	AChE + BuChE inhibition	Subcortical VaD	Human	Mild cognitive improvement	[55]
Memantine	NMDA receptor antagonist	PSD	Human	Improves cognition and reduces excitotoxicity	[57]
Citicoline	Membrane repair, neurogenesis	VaD, PSD	Human	Enhances cognition, delays progression	[58]
Resveratrol	STING/TBK1/IRF3 inhibition, anti-inflammatory, antioxidant	VaD	Rat (2VO)	↓ microglia & white matter damage; ↑ memory, ↑ cholinergic neurons	[59,60]
Cilostazol	PDE3 inhibition, ↑ NO, ↓ oxidative stress, cAMP/CREB activation	Chronic hypoperfusion	Rat (4VO)	Prevents retrograde amnesia, ↑ working memory	[61,62]
Edaravone-dexborneol	Free radical scavenging + BBB-penetrating anti-inflammatory effects	Small vessel disease	Mouse	↓ BBB leakage, ↓ microglial pyroptosis, ↑ M2 polarization, ↑ cognition	[63]
Minocycline/Curcumin	Anti-inflammatory, glial modulation	PSD, VaD	Rodent	↓ TNF-α, IL-6, ↓ microgliosis, ↑ memory performance	[64]
Erythropoietin	White matter repair, neurovascular protection	Chronic ischemia	Rodent	↑ remyelination, ↓ gliosis, ↑ cognition	[65]
rTMS/BDNF mimetics	Synaptic plasticity enhancement	PSD	Rat (MCAO)	↑ BDNF, ↑ LTP, ↓ cognitive deficits	[49]

↑ indicates an increase, whereas ↓ indicates a decrease in the corresponding parameter. Abbreviations: AD, Alzheimer's disease; AChE, acetylcholinesterase; BuChE, butyrylcholinesterase; PDE3, phosphodiesterase-3; NO, Nitric Oxide; 4VO, four-vessel occlusion; cAMP, Cyclic Adenosine Monophosphate; CREB, cAMP Response Element–Binding Protein; rTMS, repetitive transcranial magnetic stimulation; BDNF, brain-derived neurotrophic factor; MCAO, middle cerebral artery occlusion; LTP, long-term potentiation.

sel disease models [63]. Minocycline and curcumin, both broad-spectrum anti-inflammatories, reduced cytokine levels (TNF-α, IL-6), preserved synaptic structure, and improved performance in object recognition and maze-based memory tasks [64]. Erythropoietin and its derivatives promote white matter repair and neurovascular protection in chronic hypoperfusion models (BCAS). A novel erythropoietin-derived peptide (DEPO) enhanced remyelination, reduced gliosis, and improved cognition by activating EPOR–JAK2/STAT5/AKT signaling and attenuating neuroinflammation, with behavioral benefits in spatial learning tasks [65]. High-frequency rTMS exerts cognitive benefits in rodent models of cerebral ischemia (tMCAO) by enhancing hippocampal synaptic plasticity and upregulating BDNF signaling. These effects were associated with increased dendritic spine density and improved learning and memory in behavioral tasks, supporting its role as a non-pharmacological BDNF mimetic [49].

5.3 Translational Barriers and Opportunities

Despite robust preclinical efficacy, clinical translation remains limited. One major obstacle is age disparity—most rodent models use young, healthy animals, whereas VaD and PSD primarily affect elderly individuals with comorbidities (e.g., diabetes, hypertension, immunosenescence) that influence drug responsiveness [71,72]. Second, popular models such as MCAO and BCAS simulate discrete, reproducible injuries, which contrast with the multifocal, heterogeneous, and progressive pathology in human cerebrovascular disease [73]. Third, pathological overlap with neurodegenerative diseases complicates model validity. In humans, VaD often coexists with Alzheimer-type changes, including β-amyloid and tau deposition. However, animal models frequently isolate vascular mechanisms, thereby missing key synergistic pathologies [74,75]. For instance, while Notch signaling dysregulation is well-demonstrated in BCAS models, its role in human VaD is less established. A recent mouse study shows that Notch suppression is associated with BBB breakdown and microglial activation, warranting translational validation in postmortem tissues [47]. To enhance translational validity, several strategies have been proposed: (1) incorporation of aged or comorbid rodent models, including transgenic lines that mimic human metabolic and vascular risk factors (e.g., hypertensive, diabetic, or ApoE4 transgenic rodents); (2) multimodal outcome assessments that integrate behavioral testing with MRI, molecular, and transcriptomic profiling; and (3) longitudinal study designs that better reflect disease progression and therapeutic windows in clinical populations. Addressing these limitations will be essential for the development of effective, disease-modifying therapies for VaD and PSD, as summarized in Fig. 2 that illustrates how each major obstacle in preclinical VaD/PSD research corresponds to a specific opportunity for refinement, providing a roadmap for enhancing translational relevance.

6. Therapeutic Strategies

Despite the continued reliance on symptomatic treatment and vascular risk control in VaD and PSD, emerging molecular insights have paved the way for disease-modifying approaches. These include precision-based interventions tailored to individual genetic and biomarker profiles, strategies to restore BBB integrity, combinatory neurovascular–cognitive therapies, and regenerative cell-based treatments. The following subsections highlight key advances in these domains.

6.1 Precision Medicine and Stratified Therapies

Precision medicine offers the potential for individualized intervention by integrating a patient's genetic background, neuroimaging features, and fluid biomarker profiles. This approach is particularly relevant in VaD and PSD, given their etiological and clinical heterogeneity. Recent genome-wide association studies (GWAS) and targeted sequencing have identified several variants associated with small vessel disease and vascular cognitive impairment. *NOTCH3* mutations, traditionally linked to CADASIL, have also been implicated in sporadic forms of small vessel disease. These mutations impair vascular smooth muscle integrity and promote perivascular degeneration. Rodent models carrying *Notch3* mutations exhibit white matter vacuolization and reactive gliosis [76]. Similarly, *COL4A1* and *COL4A2* mutations compromise basement membrane stability in cerebral microvessels, leading to spontaneous microbleeds and white matter lesions. Murine models harboring *COL4A1* variants demonstrate cognitive dysfunction accompanied by vascular fragility [77]. The APOE ε4 allele, a well-established genetic risk factor for Alzheimer's disease, also contributes to vascular cognitive decline by promoting BBB breakdown, impairing amyloid clearance, and exacerbating white matter degeneration [78]. In clinical settings, integrative polygenic risk scores—such as iPRS-DEM—have been developed to incorporate both vascular and neurodegenerative loci, thereby improving risk stratification [79]. Advanced neuroimaging modalities, including diffusion tensor imaging (DTI), enable the quantification of early microstructural white matter injury [80]. In parallel, plasma biomarkers such as glial fibrillary acidic protein (GFAP) and neurofilament light chain (NfL) serve as non-invasive indicators of neurovascular injury and axonal degeneration [81]. In summary, precision medicine provides a powerful framework for early diagnosis, individualized risk assessment, and targeted therapeutic strategies in VaD and PSD. Future efforts should focus on longitudinal validation in diverse cohorts and the implementation of adaptive clinical trials stratified by genetic and imaging biomarkers.

6.2 Targeting NVU Dysfunction

Disruption of the NVU—a dynamic interface composed of endothelial cells, astrocytes, pericytes, and the basement membrane—plays a central role in the pathogene-

sis of VaD and PSD [82]. Among NVU components, BBB breakdown allows serum proteins and peripheral immune cells to infiltrate the parenchyma, initiating glial activation and progressive neuronal dysfunction.

6.2.1 Pharmacological Targeting of BBB and Endothelial Stability

Preclinical studies using rodent models of ischemic injury, such as MCAO or chronic hypoperfusion (e.g., BCAS), have identified several pharmacologic strategies for NVU preservation. Sphingosine-1-phosphate receptor (S1PR) modulators, such as fingolimod, preserve tight junction proteins (claudin-5, occludin), suppress astrocytic and microglial activation, and reduce extravasation of immunoglobulin (Ig) G and albumin in peri-infarct regions [83,84]. MMP-9 inhibitors and angiopoietin-1 mimetics contribute to endothelial integrity by preventing degradation of the extracellular matrix [85–87]. These agents are particularly effective during the acute post-ischemic phase, although there is growing evidence of their potential in slowing chronic NVU deterioration in models of VaD.

6.2.2 Biological Approaches: Mesenchymal Stem (MSC)-Derived Exosomes and NVU Restoration

MSC–derived extracellular vesicles (EVs) have gained attention as a cell-free regenerative strategy for NVU repair. In aged rat models subjected to bilateral common carotid artery occlusion, both intravenous and intracerebroventricular administration of MSC-EVs reduced levels of IL-1β and TNF-α, restored AQP4 polarity in astrocytic endfeet, and promoted endothelial regeneration, collectively improving spatial memory performance [88].

6.2.3 Integration and Translational Outlook

Current NVU-targeted therapies converge on three mechanistic axes: (1) BBB stabilization, through structural reinforcement and inhibition of paracellular leakage [78,83]; (2) Suppression of neuroinflammation, by modulating astrocytic and microglial reactivity [82,89]; and (3) Restoration of neurovascular coupling, improving cerebral perfusion to metabolically active neurons [90]. Translational challenges remain significant, notably the lack of aged and comorbid animal models, and the absence of real-time *in vivo* biomarkers for NVU integrity. Emerging imaging tools such as dynamic contrast-enhanced MRI (DCE-MRI) now allow longitudinal assessment of BBB permeability in human trials [91]. Future research should aim to integrate such imaging with molecular biomarkers and individualized NVU-modifying interventions.

6.3 Combined Vascular–Cognitive Interventions

Therapeutic approaches that concurrently target vascular pathology and neuroplasticity deficits are gaining increasing attention in the management of VaD and PSD. This dual strategy reflects the interdependence of cerebrovascular integrity and cognitive function. Several pharmacological agents demonstrate pleiotropic actions on both vascular and neural systems. Citicoline supports phospholipid synthesis and stimulates neurotrophic pathways, leading to cognitive enhancement in patients and improved hippocampal synaptic plasticity in ischemic rodent models [61]. Cilostazol, a phosphodiesterase-3 inhibitor, has been shown to preserve memory function in 2VO rat models by increasing nitric oxide bioavailability and suppressing neuroinflammatory responses [66]. Resveratrol, a polyphenolic compound, modulates the STING/TBK1/IRF3 inflammatory axis and protects cholinergic neurons in models of chronic cerebral hypoperfusion [64,65]. Non-pharmacological interventions also play a critical role. Aerobic exercise and rTMS have demonstrated cognitive benefits in preclinical settings. In rat models of global ischemia, high-frequency rTMS upregulated brain-derived neurotrophic factor (BDNF) expression in the hippocampus and significantly improved working memory [49]. In summary, combined vascular–cognitive strategies offer synergistic benefits by targeting both underlying pathology and functional decline. Future clinical trials should emphasize early-stage, multimodal implementation guided by individualized risk profiles and supported by molecular and imaging biomarkers.

6.4 Regenerative Therapies: iPSC and EV Approaches

Regenerative therapies aim to reverse neurovascular degeneration in VaD and PSD by restoring cellular structure and function. Two promising approaches—induced pluripotent stem cell (iPSC)-derived neural precursors and MSC-derived EVs—are gaining traction in preclinical research. iPSC-derived NPCs exhibit multipotency and secrete a broad range of neurotrophic factors, making them attractive for neurorestorative applications in VaD and PSD. In adult rodent models of ischemia, including MCAO and bilateral carotid artery stenosis, transplanted NPCs demonstrated robust survival and integration, particularly within the hippocampal and cortical regions [92].

6.4.1 iPSC-Derived NPCs

These NPCs were capable of differentiating into both neuronal and glial lineages and actively secreted vascular endothelial growth factor (VEGF), glial cell line–derived neurotrophic factor (GDNF), and thrombospondins (TSPs), facilitating neurovascular repair and synaptic remodeling [93,94]. Functionally, NPC transplantation mitigated white matter atrophy and improved cognitive outcomes, as assessed by Y-maze alternation and novel object recognition tasks [95]. In addition, iPSC-derived vascular endothelial cells (iVECs) have been shown to enhance regulatory T cell (Treg) recruitment and suppress microglial activation, thereby supporting remyelination and vascular remodeling [96]. However, translational application of iPSC-derived therapies remains limited by potential tumorigenicity, im-

Table 6. Regenerative and NVU-targeted therapies in VaD and PSD with mechanisms and supporting references.

Therapy	Cell type/Origin	Model type	Mechanism of action	Outcome	Supporting references
iPSC-NPCs	Human iPSC-derived neural precursor cells	MCAO, chronic hypoperfusion (rats, pigs)	Neuronal/glial differentiation; VEGF, GDNF, TSP secretion	Improved memory, synaptic density	[92–95]
Endothelial iPSCs	Human iPSC-derived vascular endothelial cells	Chronic hypoperfusion (mice)	Treg cell recruitment, WMI protection	Enhanced white matter recovery	[96]
MSC-EVs	Bone marrow– or adipose–derived MSCs	Chronic hypoperfusion (rats, mice)	miRNA transfer (e.g., miR-132-3p), BBB repair, M1→M2 microglia shift	Cognitive rescue, BBB integrity restored	[52,88]
NVU-targeted drugs	Various (resveratrol, citicoline, cilostazol)	Stroke, hypoperfusion (rodents, humans)	BBB stabilization, anti-inflammatory, neurovascular coupling	Improved CBF, reduced inflammation, memory enhancement	[61,64–66]

→ indicates leads to or results in. Abbreviations: iPSC, induced pluripotent stem cell; NPC, neural precursor cell; VEGF, vascular endothelial growth factor; GDNF, glial cell-derived neurotrophic factor; TSP, thrombospondin; WMI, white matter injury; MSC, mesenchymal stem cell; EV, extracellular vesicle; CBF, cerebral blood flow.

munogenicity, and the lack of long-term safety data—particularly in aged or comorbid populations who most frequently develop VaD or PSD.

6.4.2 MSC-Derived EVs

MSC-derived EVs represent a cell-free, low-immunogenicity alternative to stem cell transplantation. In rat models of chronic cerebral hypoperfusion, EVs enriched in miR-132-3p have been shown to restore tight junction protein expression, enhance cerebral perfusion, and reverse spatial memory deficits [52]. Nonetheless, significant challenges remain, including: (1) Standardization of EV isolation protocols; (2) Optimization of dosage and delivery methods; and (3) Comprehensive characterization of bioactive cargo. Innovative strategies such as scaffold-assisted delivery and engineered synthetic vesicles may help overcome these limitations and improve clinical translation. A summary of regenerative and NVU-targeted strategies is provided in Table 6 (Ref. [52,61,64–66,88,92–96]).

7. Conclusion and Future Directions

VaD and PSD represent clinically overlapping but mechanistically distinct subtypes within the broader spectrum of vascular cognitive impairment. VaD is predominantly driven by chronic cerebral hypoperfusion, leading to white matter degeneration, glial activation, and NVU disruption. In contrast, PSD typically follows acute ischemic events, where excitotoxicity, oxidative stress, and BBB breakdown dominate the early phase, followed by secondary neurodegeneration and disconnection of cognitive networks [82–84]. While both disorders share common features—such as BBB impairment, neuroinflammation, and synaptic dysfunction—their temporal evolution, regional vulnerability, and triggering mechanisms differ, necessitating differential diagnostic and therapeutic strategies. Despite substantial insights gained from animal models such as BCAS and MCAO, translational challenges persist. These include species-specific differences in cerebrovascular anatomy, immune responses, and behavioral phenotypes [89,90]. Future preclinical research must increasingly incorporate models that reflect aging, comorbid conditions (e.g., hypertension, diabetes), and longitudinal disease progression, to improve clinical relevance. From a clinical standpoint, there is a pressing need to refine diagnostic criteria by integrating dynamic molecular biomarkers alongside structural neuroimaging. Promising candidates include endothelial injury markers (MMP-9, S100β), neuroinflammatory markers (IL-6, TNF-α), and neurodegeneration markers (NfL, tau). In parallel, advanced neuroimaging modalities, such as dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) and functional MRI (fMRI), can assess cerebrovascular reactivity and track disease progression [78–91]. Longitudinal, multimodal biomarker studies combined with standardized cognitive assessments will be pivotal in identifying high-risk individuals, monitoring progression, and evaluating therapeutic efficacy. Emerging regenerative approaches, including stem cell–based neural repair and MSC-derived extracellular vesicles, have demonstrated potential to restore both structural and functional integrity in VaD and PSD. However, clinical translation requires rigorous validation through well-powered trials with mechanistic endpoints [88–92]. Ultimately, a precision medicine paradigm—integrating vascular, neuroimmune, and synaptic biomarkers—may enable the development of tailored therapeutic strategies, targeting the specific pathophysiological context of each dementia subtype.

Abbreviations

2VO, two-vessel occlusion; 4VO, four-vessel occlusion; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; AQP4, aquaporin-4; BBB, blood–brain barrier; BCAS, bilateral common carotid artery stenosis; BDNF, brain-derived neurotrophic factor; DCE-MRI, dynamic contrast-enhanced magnetic resonance imaging; DMN, default mode network; EVs, extracellular vesicles; fMRI, functional MRI; GDNF, glial cell line–derived neurotrophic factor; GFAP, glial fibrillary acidic protein; GWAS, genome-wide association studies; I/R, ischemia-reperfusion; Ig, immunoglobulin; IL, Interleukin; iNOS, inducible nitric oxide synthase; iPSC, induced pluripotent stem cell; iVECs, vascular endothelial cells; MMPs, matrix metalloproteinases; MSC, Mesenchymal stem cell; NADPH, nicotinamide adenine dinucleotide phosphate hydrogen; NfL, neurofilament light chain; NMDA, N-methyl-D-aspartate; NPCs, neural precursor cells; NVU, neurovascular unit; OPC, oligodendrocyte precursor cell; PSD, post-stroke dementia; ROS, reactive oxygen species; rTMS, repetitive transcranial magnetic stimulation; S1PR, sphingosine-1-phosphate receptor; SVD, small vessel disease; tMCAO, transient middle cerebral artery occlusion; TNF-α, tumor necrosis factor alpha; Treg, regulatory T cell; TSPs, thrombospondins; VaD, vascular dementia; VCI, vascular cognitive impairment; VEGF, vascular endothelial growth factor.

Availability of Data and Materials

All data reported in this paper will also be shared by the lead contact upon request.

Author Contributions

JHA and M-HW designed the research study. JHA, MCS, DWK, K-YY, and M-HW wrote the manuscript. All authors contributed to the study's design, manuscript preparation, and revision. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

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During the preparation of this work the authors used ChatGPT-3.5 in order to check spell and grammar. After using this tool, the authors reviewed and edited the content as needed and takes full responsibility for the content of the publication.

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