

Research Article

Neurovascular Coupling in Neurological Disorders: A Comprehensive Review

Zi Ye¹ , Yixiao Wang² , Qi Zhang^{2,*} 

¹Department of Clinical Medicine, 2nd Clinical Medical School, Shaanxi University of Chinese Medicine, Xianyang, China

²School of Basic Medical Science, Shaanxi University of Chinese Medicine, Xianyang, China

Abstract

This article provides a systematic review of current research on Neurovascular Coupling (NVC), covering its fundamental mechanisms, role in diseases, investigative technologies, and future directions. NVC describes the process where neuronal activity triggers localized changes in cerebral blood flow (CBF). This mechanism is orchestrated by the Neurovascular Unit (NVU), a functional complex comprising neurons, glial cells (e.g., astrocytes), and vascular cells (e.g., endothelial cells, pericytes, vascular smooth muscle cells). These components work in concert through intercellular signaling to co-regulate CBF. The regulation involves various vasoactive substances, including nitric oxide (NO) and prostaglandin E2 (PGE2). Dysfunction of NVC is a critical pathological mechanism in neurological disorders. In Alzheimer's disease, abnormalities across the NVU lead to blood-brain barrier disruption and impaired clearance of amyloid- β , exacerbating cognitive decline. Similarly, in cerebral small vessel disease, endothelial dysfunction manifesting as impaired NVC is a key feature, with severity correlating with structural damage like white matter hyperintensities. Following an ischemic stroke, NVU component abnormalities cause acute NVC decoupling, and the degree of functional recovery is closely associated with neurological prognosis. Technologies for studying NVC are evolving. Established methods include functional Magnetic Resonance Imaging (fMRI), which measures the blood-oxygen-level-dependent (BOLD) signal, and transcranial Doppler ultrasound. Recent advancements feature novel tools like high-speed, large-field-of-view photoacoustic/fluorescence hybrid microscopes (e.g., LiTA-HM), enabling cortex-wide imaging of neurovascular dynamics with subcellular resolution. Current research challenges include reliance on animal models. Future directions should integrate structural and functional neuroimaging techniques. Therapeutically, strategies aimed at enhancing endothelial function to restore NVC hold promise. Combining advanced imaging with omics technologies will likely deepen the understanding of the NVU and propel the field toward precise prevention and treatment of NVC-related diseases.

Keywords

Neurovascular Coupling, Neurovascular Unit, Alzheimer's Disease, Parkinson's Disease, Hypertension, Stroke

*Corresponding author: zhangqi@sntcm.edu.cn (Qi Zhang)

Received: 11 October 2025; **Accepted:** 29 October 2025; **Published:** 26 November 2025



Copyright: © The Author(s), 2025. Published by Science Publishing Group. This is an **Open Access** article, distributed under the terms of the Creative Commons Attribution 4.0 License (<http://creativecommons.org/licenses/by/4.0/>), which permits unrestricted use, distribution and reproduction in any medium, provided the original work is properly cited.

1. Introduction

1.1. Definition and Physiological Function of Neurovascular Coupling (NVC)

The neurovascular coupling (NVC) is the process linking neuronal activity to hemodynamic changes [1]. When neurons in a specific brain region are activated due to functional demands (such as sensation, movement and cognition), the corresponding brain region is accompanied by an increase in blood flow and volume. This change is usually triggered by neuromodulatory mechanisms to meet the oxygen and nutrient requirements of local neural activity. Conversely, when neuronal activity decreases, cerebral blood flow (CBF) decreases accordingly, thereby achieving precise regulation of CBF. Additionally, studies have shown that under different body states and in different brain regions, NVC may exhibit asynchronous changes, such as increased neural activity without a corresponding increase in CBF or increased CBF without increased neural activity [2].

The neurovascular unit (NVU) serves as the structural and functional foundation for NVC and is composed of neurons, glial cells (including astrocytes and microglia), brain microvascular endothelial cells (BMECs), pericytes, and the extracellular matrix [3]. NVC, a cell-to-cell signaling mechanism, involves nearly all cellular components of the NVU. Through coordinated intercellular signaling, these cells work together to form a dynamic regulatory system that precisely modulates CBF, vascular function, neuroimmune responses, and metabolic waste clearance [4, 5]. Dysfunction in NVU components leads to blood-brain barrier (BBB) breakdown, contributing to pathologies such as stroke, Alzheimer's disease, Parkinson's disease and traumatic brain injury by allowing inflammatory infiltration and edema [6-8].

In summary, the mechanisms and regulation of the NVC are crucial for maintaining normal brain function. They hold great significance in understanding brain function and developing relevant therapeutic strategies.

1.2. The Physiology of Neurovascular Coupling (NVC) Regulation

NVC is a complex process co-regulated by feedforward and feedback mechanisms [9]. The feedforward mechanism relies on non-metabolic signaling pathways (e.g., glutamatergic synaptic signaling) to directly activate intracellular calcium-dependent cascades, generating vasoactive messengers that increase CBF. In contrast, the feedback mechanism is modulated by metabolic factors (such as oxygen, glucose, and carbon dioxide), where decreased oxygen (O_2) or elevated carbon dioxide (CO_2) levels trigger vasodilation to adjust CBF. These two mechanisms act in concert to main-

tain homeostasis within the brain's internal environment [10, 11].

NVC involves a coordinated sequence in which neuronal activity (e.g., glutamate release) activates glial cells, leading to the release of vasoactive substances, such as nitric oxide (NO), prostaglandins, and epoxyeicosatrienoic acids. These mediators regulate vascular tone and local blood flow. NO acts as a key signaling molecule, produced by neuronal nitric oxide synthase (nNOS), which couples with N-methyl-D-aspartic acid (NMDA) receptors via the scaffolding postsynaptic density-95 (PSD95) to facilitate vasodilation. Additionally, CO_2 modulates NVC by inducing changes in extracellular pH and vascular tone. The renin-angiotensin system (RAS) also participates, where angiotensin II (Ang II) promotes vasoconstriction via AT1 receptors, potentially disrupting NVC under pathological conditions [12].

NVC is frequently impaired in disease states such as diabetic retinopathy, hypoxia, and neurodegenerative disorders. For instance, hypoxia triggers an initial reduction in CBF, followed by a compensatory increase, although neuronal activity may remain suppressed. In diabetes, hyperglycemia and elevated Ang II levels contribute to microvascular dysfunction and inflammatory responses, thereby attenuating functional hyperemia [13]. These alterations highlight the vulnerability of NVC mechanisms in disease and their role in exacerbating neurological injury.

1.3. Core Mechanisms of Neurovascular Coupling (NVC)

NVC clarifies how neuronal activation directly generates signals or transmits them to glial cells and interneurons, ultimately influencing microvessels and modulating CBF in response to metabolic demands. Neurons act as primary sensors of neural activity and transmit signals that initiate vascular responses. Astrocytes envelop blood vessels with their end-feet, secreting factors such as vascular endothelial growth factor (VEGF) to modulate BBB permeability [14, 15]. Microglia serve as immune sentinels, phagocytizing debris and releasing inflammatory mediators [16]. BMECs form the BBB's core through tight junctions, limiting paracellular transport [17]. Pericytes, embedded in the capillary basement membrane, contract to regulate blood flow and stabilize endothelial connections [18].

This integrative methodology, which focuses on vascular-neural interactions, offers a new paradigm for fully elucidating the neurovascular mechanisms implicated in brain pathologies.

2. NVC Impairment is a Shared Pathophysiological Mechanism in Multiple Neurological Diseases

2.1. The Role of Neurovascular Unit Dysfunction in the Pathophysiology of Alzheimer's Disease

In the pathological process of Alzheimer's disease (AD), all components of the NVU, including BMECs, pericytes, astrocytes, and microglia, undergo significant impairment, forming a self-reinforcing vicious cycle [19].

In the early stages of AD, the integrity of the BBB is compromised. In regions such as the hippocampus and cerebral cortex, the expression of tight junction proteins in endothelial cells is downregulated and the activity of matrix metalloproteinase-9 (MMP-9) is increased [20]. These changes lead to the degradation of basement membrane components and a significant reduction in pericyte coverage, which further results in the extravasation of plasma proteins (e.g., fibrinogen and thrombin) and the subsequent triggering of neuroinflammation.

Furthermore, impairment in the clearance function of A β can also exacerbate neuroinflammation through two mechanisms. First, transporter dysfunction impairs A β clearance via reduced A β efflux from LRP1 downregulation and increased A β influx from RAGE upregulation, both of which contribute to cerebral A β accumulation. Second, reduced expression of aquaporin-4 (AQP4) on astrocytic endfeet further impairs glymphatic system function, thereby compromising the clearance of toxic proteins such as A β and tau [21]. Beyond driving neuroinflammation, A β deposition impairs capillary blood flow regulation via aberrant pericyte contraction and downregulated microglial P2Y₁₂ receptors [22]. Chronic cerebral hypoperfusion upregulates the expression of beta-secretase 1 (BACE1) via hypoxia-inducible factor 1 subunit alpha (HIF-1 α) signaling, thereby promoting the production of A β and amplifying A β pathology [23].

Studies indicate that as early as 3 months of age, AD models exhibit attenuated and delayed NVC responses. This impaired hemodynamic regulation fails to meet the metabolic demands of neuronal activity, leading to deficient functional hyperemia, which in turn causes chronic metabolic deficits and local tissue hypoxia. Furthermore, resting-state functional connectivity imaging reveals initial hyperconnectivity, followed by a progressive reduction in connectivity within the default mode network, reflecting impaired neurovascular synchronization [24]. These changes result in dysregulated capillary constriction, reduced capillary density, and microhemorrhages.

Microglia also play a key role in AD pathogenesis. A β accumulation prompts their polarization toward a pro-inflammatory M1 phenotype. Once activated, these microglia release inflammatory cytokines such as tumor necrosis

factor- α (TNF- α) and Interleukin - 1 β (IL-1 β), as well as reactive oxygen species, which further degrade tight junctions and promote the infiltration of peripheral immune cells [25]. Furthermore, they interact with astrocytes, inducing the formation of neurotoxic A1 reactive astrocytes, which further amplifies the neurodegenerative process [23]. Vascular risk factors such as hypertension, exacerbate this cascade via a pathway of oxidative stress involving Nicotinamide Adenosine Dinucleotide Phosphate (NADPH) oxidase activation [26].

Together, these mechanisms form a self-reinforcing cycle in which A β deposition intensifies NVU damage, and conversely, NVU dysfunction further obstructs A β clearance. This dysfunction manifests as a unified pathological axis in AD, encompassing BBB leakage leading to toxin accumulation, NVC impairment resulting in hypoperfusion, and pericyte loss coupled with neuroinflammation, collectively driving cognitive deterioration. Multi-target therapeutic strategies directed at the NVU demonstrate considerable potential. For instance, galantamine has been shown to partially restore NVC by enhancing cholinergic signaling. Other promising approaches include targeting the PDGF-BB pathway to protect pericytes, inhibiting MMP-9 activity to repair BBB integrity, and modulating AQP4 function to improve glymphatic clearance [27, 28].

2.2. The Role of Neurovascular Unit Dysfunction in the Pathophysiology of Parkinson's Disease

Parkinson's disease (PD), the second most common neurodegenerative disorder, is characterized by the progressive loss of dopaminergic neurons in the substantia nigra pars compacta and the presence of Lewy bodies [29, 30].

The reduced expression and mislocalization of AQP4 on astrocytic end-feet compromises glymphatic clearance of toxic solutes and disrupts vasodilatory signaling. Concurrently, activated astrocytes release pro-inflammatory cytokines such as interleukin-6 (IL-6), which further exacerbate endothelial injury and BBB disruption. These inflammatory processes also impair the normal regulatory functions of astrocytes on pericytes, leading to dysregulation of capillary contractility [31, 32]. In the early stages, impaired NVC manifests as reduced functional connectivity and CBF within visual and sensorimotor networks, correlating with diverse motor and non-motor symptoms. As the disease progresses to advanced stages, this deficit evolves into critical hypoperfusion, culminating in the rapid and pronounced deterioration of cognitive and motor functions [33, 34].

Endothelial dysfunction is a central pathophysiological event in NVC impairment in PD. In the brains of patients with PD, decreased expression of tight junction proteins increases BBB permeability, resulting in the extravasation of serum albumin, fibrinogen, and other macromolecules, thereby triggering local inflammation and tissue injury. Concurrently, the accumulation of neurotoxic substances

results from dysfunction of endothelial transporters, including diminished P-glycoprotein (P-gp) function in advanced stages. Furthermore, upregulation of the receptor for advanced glycation end products facilitates the entry of α -synuclein (α -syn) into the brain and promotes pro-inflammatory signaling. Additionally, cerebrovascular remodeling occurs in PD, exemplified by increased "string vessels" in the substantia nigra and endothelial cell loss, which further compromises CBF regulation [35].

Subsequently, C3 binds to C3a receptors (C3aR) on the neuronal surface, which in turn activates glycogen synthase kinase 3 β (GSK3 β), thereby exacerbating neuronal apoptosis and the pathological aggregation of α -syn [31]. Meanwhile, loss-of-function of PD-associated DJ1 gene impairs lysosomal proteolytic function in astrocytes, leading to the accumulation of advanced glycation end products. This further exacerbates the phosphorylation and aggregation of α -syn. Additionally, DJ1 deficiency reduces the anti-inflammatory capacity of astrocytes and increases the release of pro-inflammatory cytokines such as interleukin-18 (IL-18) [36]. Furthermore, the expression of excitatory amino acid transporter 2 (EAAT2), a glutamate transporter in astrocytes, is downregulated by the influence of PD-associated gene mutations, such as those in LRRK2 and DJ1. This leads to impaired glutamate clearance and subsequent induction of excitotoxicity [37]. It also abnormally activates the NLRP3 inflammasome, mediating the release of IL-1 β via Caspase-1 and thereby amplifying neuroinflammation [38]. However, healthy astrocytes can exert neuroprotective effects through multiple mechanisms, including the secretion of neurotrophic factors such as glial cell line-derived neurotrophic factor and mesencephalic astrocyte-derived neurotrophic factor, transfer of healthy mitochondria to damaged neurons, and clearance of extracellular α -syn [39].

In PD, the accumulation of α -syn activates microglia, inducing their polarization toward the proinflammatory M1 phenotype. These activated M1 microglia release cytokines such as TNF- α and IL-1 β , as well as reactive oxygen species (ROS). These factors degrade tight junction proteins and promote the infiltration of peripheral immune cells, thereby exacerbating BBB damage. Furthermore, activated microglia interact with astrocytes, inducing the generation of neurotoxic A1 reactive astrocytes. This forms an inflammatory amplification loop that further impairs NVC [40].

In summary, in the pathogenesis of PD, functional dysregulation across various components of the NVU collectively contributes to impairments in NVC. This interplay ultimately establishes a self-perpetuating pathological cycle, beginning with inflammatory initiation, leading to NVC dysfunction, and culminating in neuronal injury. Targeting this mechanism, intervention strategies aimed at restoring NVU functionality, including preserving pericyte function, modulating transporter activity in endothelial cells, and inhibiting microglial overactivation, hold promise as potential therapeutic avenues to block or delay the progression of PD.

2.3. The Role of Neurovascular Unit Dysfunction in the Pathophysiology of Hypertension-induced Cognitive Impairment

Hypertension induces multifaceted alterations in the NVU that drive the pathogenesis of cognitive impairment. Initially, hypertension promotes structural and functional disturbances of the NVU. Endothelial dysfunction emerges as an early event [41], characterized by increased BBB permeability, downregulation of tight junction proteins, and reduced NO bioavailability, leading to microvascular rarefaction and cerebral hypoperfusion [42, 43].

Aberrant Ca²⁺ signaling in astrocytic end-feet, such as enhanced activation of TRPV4 channels, triggers the release of inflammatory mediators, exacerbating vasoconstriction and neuroinflammation. Pericyte loss and capillary constriction further compromise microcirculation, limiting oxygen and nutrient delivery. Collectively, these changes contribute to chronic cerebral hypoperfusion and oxidative stress, promoting neuronal injury and white matter lesions [44]. Mechanistically, overactivation of the RAS is a central driver of these changes. Ang II, via AT1 receptors, stimulates NADPH oxidase to generate ROS, inducing oxidative and nitrosative stress that disrupts endothelial and astrocytic function [45]. NVC is impaired, manifesting as attenuated functional hyperemic responses; for instance, elevated pulse pressure increases arterial stiffness and pulsatility index, compromising vascular regulation. Furthermore, aberrant VNC prevents vascular signals from effectively modulating neuronal activity, further undermining cognitive processing [46]. Inflammatory cascades, including microglial activation and cytokine release, amplify damage, establishing a positive feedback loop that accelerates neurodegeneration.

As a pressure-sensing and signal-integrating hub, the NVU plays a central role in the pathogenesis of hypertension-related cognitive decline. Its dysfunction directly leads to cerebral hypoperfusion, metabolic imbalance, and dysregulation of neuronal networks, resulting in deficits in memory, processing speed, and executive functioning. Targeting NVU components, such as using ARBs to block AT1 receptors or antioxidant therapies, may restore blood flow regulation and cognitive performance, highlighting the NVU as a critical target for therapeutic intervention. In summary, hypertension disrupts NVU homeostasis through multiple pathways, driving cognitive impairment progression. Future studies should focus on elucidating the mechanisms of intercellular communication within the NVU to develop precise therapeutic strategies.

2.4. The Role of Neurovascular Unit Dysfunction in the Pathophysiology of Stroke

Following a stroke, significant abnormalities emerge in the

components of NVU and the function of NVC. During the acute phase of injury, impairment of NVU components leads to uncoupling of neuronal activity from CBF regulation. For instance, following subarachnoid hemorrhage, a phenomenon termed "inverted NVC" has been observed, in which neuronal activation paradoxically induces vasoconstriction. In the chronic phase, NVC may exhibit partial recovery in certain brain regions, particularly within the ischemic penumbra. The extent of functional restoration is closely associated with neurological prognosis.

Ischemia rapidly induces functional abnormalities in cerebral microvascular endothelial cells. This is characterized by the downregulation of tight junction proteins, such as Claudin-5, Occludin, and Zonula Occludens-1 (ZO-1), resulting in increased BBB permeability. The subsequent extravasation of high-molecular-weight substances, such as serum albumin and fibrinogen, triggers localized inflammation and tissue damage. Concurrently, dysfunction of endothelial transporters contributes to the accumulation of neurotoxic substances. For example, upregulation of RAGE can facilitate the influx of α -syn into the brain, thereby activating pro-inflammatory signaling pathways. Furthermore, cerebrovascular remodeling occurs, marked by an increase in "string vessels" and endothelial cell loss within the substantia nigra region, which further compromises the regulation of CBF [47-49].

In the early phase of stroke, pericytes may contribute to capillary occlusion through vasoconstriction, and later, they shift toward a pro-inflammatory phenotype that exacerbates cerebral edema by increasing BBB permeability. Pericyte loss leads to blunted capillary dilation responses, impairing cerebral autoregulation and disrupting BBB integrity. Additionally, pericyte deficiency compromises the normal regulatory control of astrocytes over capillary constriction, ultimately disrupting the dynamic coupling between CBF and neuronal metabolic demand [50].

Under ischemic conditions, astrocytes undergo significant pathological alterations characterized by mitochondrial dysfunction, disruption of ionic homeostasis, and aberrant activation of AQP4, collectively triggering cellular swelling.

Concurrently, the maldistribution of AQP4 at astrocytic end-feet impairs vasodilatory signaling and compromises CBF regulation. Furthermore, activated astrocytes release pro-inflammatory cytokines, including IL-6 and IL-1 β , which exacerbate endothelial injury and BBB disruption. Notably, these astrocytes can be polarized into neurotoxic A1-type reactive astrocytes by activated microglia, thereby establishing a self-amplifying inflammatory cycle that perpetuates ischemic damage [51].

Microglia are rapidly activated following ischemic stroke. The accumulation of α -syn can polarize these cells towards a pro-inflammatory M1 phenotype, prompting the release of cytokines such as TNF- α and IL-1 β , as well as ROS. This response contributes to the degradation of tight junction proteins within the BBB, facilitating the infiltration of peripheral immune cells. The interaction between activated microglia and astrocytes further amplifies the inflammatory cascade, compromising the structural and functional integrity of NVU. Notably, NLRP3 inflammasome activation is particularly prominent in microglia, where it mediates the cleavage and release of mature IL-1 β , significantly exacerbating neuroinflammation and contributing to NVU injury [52].

In the early phase of cerebral ischemia, neurons undergo apoptosis and necrosis due to excitotoxicity mediated by glutamate, intracellular calcium overload and severe oxidative stress. This ischemic insult leads to a temporal dissociation between CBF dynamics and neuronal activity, a phenomenon described as NVC "uncoupling". In its initial stages, this dysregulation primarily manifests as NVC impairment within the visual and sensorimotor networks. As the condition progresses to later phases, persistent cerebral hypoperfusion accelerates the deterioration of both cognitive and motor functions [53-55].

Furthermore, abnormalities in intercellular communication within NVU exacerbate injury. This is exemplified by dysregulated inflammatory signaling between microglia and astrocytes and a mismatch in metabolic demand between neurons and endothelial cells [56].

Table 1. NVC Pathology in Neurological Disorders.

disease	common pathological changes	specific pathological changes	Relevant targets	References
AD	BBB impairment (decreased expression of tight junction proteins, pericyte loss), Astrocytes (abnormal distribution of AQP4 in endfeet, release of proinflammatory factors by activated cells), Microglial activation induces the release of cytokines such as TNF- α and IL-1 β , as well as the production of ROS.	Increased amyloid-beta (A β) production combined with impaired clearance leads to neuroinflammation, vascular dysregulation, tau protein pathology, and extensive loss of cholinergic neurons.	APP, Tau, AGER, BACE1, PDGF-BB pathway, TLR4 pathway, GSK-3 β kinase, CDK5 kinase, AChE, NMDA, BDNF	[19-28]
PD		Pathological aggregation of α -syn directly impairs synaptic structure and function, and induces inflammatory responses as well as dopaminergic	eNOS, AT1R/AT2R, PDGFR β , BDNF, GFAP, Nrf2/ARE pathway	[29-40]

disease	common pathological changes	specific pathological changes	Relevant targets	References
Hyperten- sion-induced cognitive impairment		neuron degeneration.		
		Overactivation of the ren- in-angiotensin system (RAS) and im- pairment of the myogenic contraction response.	eNOS, AT1R/AT2R, PDGFR β , BDNF, GFAP, Nrf2/ARE pathway	[41-46]
stroke		Glutamate-mediated excitotoxicity, intracellular calcium overload, and severe oxidative stress lead to exten- sive neuronal apoptosis and necrosis, as well as the "inverted NVC" phe- nomenon.	tPA, uPA, GP II b/IIIaR, P2Y12R, TLR4/NF- κ B path- way, Notch pathway, NLRP3, VEGF, PDGFR β , BDNF	[47-56]

3. The Critical Role of Technology in Advancing Research on NVC Dysfunction

NVC refers to the close relationship between neuronal activity and CBF, which is crucial for understanding brain function and dysfunction. Various neuroimaging techniques have been developed to study NVC, each with unique advantages and limitations.

Functional magnetic resonance imaging (fMRI), particularly blood oxygenation level-dependent (BOLD) fMRI, emerged in the early 1990s as a non-invasive tool for indirectly mapping brain activity via hemodynamic changes. It offers high spatial resolution (mm-level) but suffers from low temporal resolution (seconds) and indirect measurement of neural activity, often requiring complex modeling to infer NVC [57]. Electroencephalography (EEG) provides milli-second temporal resolution for direct neural recording but has poor spatial resolution and is susceptible to artifacts when combined with MRI, such as gradient-induced noise, which limits its use in simultaneous EEG-fMRI studies. Transcranial Doppler ultrasound (TCD), used since the 1990s, measures cerebral blood velocity in real time with portability but is limited to large vessels (e.g., middle cerebral artery) and has low spatial resolution, making it unsuitable for capillary-level NVC assessment [58].

To overcome these limitations, multimodal approaches gained prominence in the 2000s. Simultaneous EEG-fMRI combines EEG's temporal precision with fMRI's spatial detail, allowing direct correlation of neural and hemodynamic signals. However, it requires artifact correction for EEG data and careful synchronization, and physiological confounds (e.g., heart rate, blood pressure) can affect results if not controlled [59, 60]. Functional near-infrared spectroscopy (fNIRS) paired with TCD offers a portable alternative for measuring oxygenation and blood flow with moderate tem-

poral resolution (1 Hz); however, it is restricted to superficial cortical regions and has a lower spatial resolution than fMRI [61]. These methods excel in clinical settings for studying epilepsy and cognitive tasks but require rigorous physiological monitoring to ensure validity.

Recent advances include photoacoustic microscopy (PAM), which integrates optical and acoustic imaging to achieve high-resolution (μ m) mapping of blood oxygenation and flow without labels. For example, a linear transducer array-based hybrid microscope (LiTA-HM) enables cortex-wide imaging in awake mice at 0.8 s temporal resolution, capturing detailed NVC dynamics during hypoxia and epilepsy [62]. Its advantages include high spatial resolution and simultaneous neural-vascular imaging; however, it is invasive and requires surgical preparation. Similarly, head-mounted microscopes combine PAM and fluorescence microscopy for freely behaving animals, providing real-time data on neuronal and hemodynamic activities with minimal restraint artifacts, although their weight and size can limit natural behavior [63, 64]. The wireless integrated sensing detector (WISDEM) allows simultaneous EEG and fMRI by encoding signals on sidebands, eliminating cables and reducing artifacts during MRI sequences. It facilitates NVC studies in rodents with optogenetic stimulation but has reduced signal-to-noise ratio compared to wired systems [63, 65]. In humans, adaptive optics rolling slit ophthalmoscopy (AO-RSO) non-invasively images retinal NVC with micrometer resolution, serving as a window into brain health. It detects vasodilation responses to flicker stimuli with high precision but is limited to the retina and requires complex instrumentation [66].

NVC neuroimaging has evolved from single-modality techniques to integrated, multimodal systems that provide comprehensive insights into brain function. In the field of medical neuroimaging and neural monitoring technologies, every approach is accompanied by inherent tradeoffs. For instance, fMRI, a widely used non-invasive neuroimaging modality, offers excellent spatial resolution, enabling precise

localization of brain regions involved in specific functions; however, it is limited by relatively poor temporal resolution, which restricts its ability to capture rapid neural activity dynamics. Similarly, wireless neural monitoring systems provide significant advantages in terms of convenience, as they allow for ambulatory monitoring of patients without the constraints of wired connections. However, this convenience often comes at the cost of a reduced signal-to-noise ratio (SNR), which may compromise the accuracy and reliability of the collected neural data. Despite these existing limitations, the future development directions of these technologies are clearly oriented toward three key goals: first, the miniaturization of devices to enhance patient comfort and expand the scope of applicable scenarios (e.g., long-term wearable monitoring); second, the development and optimization of advanced artifact handling algorithms and techniques to minimize the impact of interference factors (such as motion artifacts or environmental electromagnetic noise) on data quality; and third, the expansion of their clinical application spectrum, with a particular focus on addressing unmet needs in the diagnosis, prognosis assessment, and treatment monitoring of neurodegenerative diseases (including AD, PD, and amyotrophic lateral sclerosis).

4. Conclusions and Future Directions

NVC dysfunction has been recognized as a core pathophysiological mechanism shared by multiple brain disorders. NVC refers to the precise matching of regional CBF to the metabolic demands of active neurons. Its dysregulation can be attributed to several factors, including vascular risk factor-induced endothelial dysfunction, neuroinflammation-mediated BBB disruption, and impaired clearance of toxic metabolites such as β -amyloid. These processes collectively establish a self-perpetuating vicious cycle that exacerbates neuronal injury and accelerates disease progression.

As an early and sensitive biomarker of neurological diseases, NVC dysfunction offers a unique window for early diagnosis and intervention before significant neuronal loss. Currently, a range of noninvasive techniques are widely employed to assess NVC integrity. These include functional MRI methods, such as BOLD-fMRI and dynamic contrast-enhanced (DCE) MRI, which evaluate hemodynamic responses and BBB permeability, respectively; diffusion tensor imaging (DTI) to assess white matter integrity; TCD to measure CBF velocity; and dynamic vascular analysis (DVA) to evaluate cerebrovascular reactivity. These tools provide critical means for disease diagnosis, monitoring of disease progression, and evaluation of therapeutic efficacy.

However, current research faces several challenges. There remains an overreliance on animal models and non-physiological conditions, limited sample sizes in clinical studies, and, notably, frequent neglect of key structural factors, such as cerebrovascular anatomical architecture, in the regulation of CBF. Future investigations should integrate

structural and functional neuroimaging modalities. Utilizing standardized software to analyze larger-scale human datasets will help bridge species differences and establish clinically meaningful cerebrovascular outcomes.

Therapeutically, interventions aimed at restoring NVC function represent a novel approach. Promising strategies include enhancing eNOS function with medications such as cilostazol or statins, employing anti-inflammatory agents such as TNF- α inhibitors to mitigate neuroinflammation, utilizing analogs of vasoactive neuropeptides such as pituitary adenylate cyclase-activating polypeptide (PACAP) to modulate vascular tone, and applying endothelin receptor antagonists (e.g., macitentan) to reverse pathological vasoconstriction. Preclinical studies suggest that combination therapies can synergistically improve the matching between CBF and neuronal activity.

Looking ahead, the integration of advanced imaging technologies with single-cell transcriptomics and proteomics has the potential to map spatiotemporal interactions at the neurovascular interface. This approach will deepen our understanding of NVU development and homeostasis. The expanding molecular framework is expected to ultimately pioneer innovative strategies for the prevention, precise diagnosis, and therapeutic management of NVC-related disorders, offering new hope for improving outcomes in patients with brain diseases.

Abbreviations

NVC	Neurovascular Coupling
NVU	Neurovascular Unit
CBF	Cerebral Blood Flow
BMECs	Brain Microvascular Endothelial Cells
BBB	Blood-Brain Barrier
NMDA	N-methyl-D-aspartic acid
RAS	Renin-Angiotensin System
VEGF	Vascular Endothelial Growth Factor
AD	Alzheimer's Disease
NADPH	Nicotinamide Adenosine Dinucleotide Phosphate
PD	Parkinson's Disease
ROS	Reactive Oxygen Species
Fmri	functional Magnetic Resonance Imaging
TCD	Transcranial Doppler Ultrasound
PAM	Photoacoustic Microscopy
LiTA-HM	Linear Transducer Array-based Hybrid Microscope

Author Contributions

Zi Ye: Conceptualization, Data curation, Formal Analysis, Funding acquisition, Investigation, Resources, Writing – original draft

Yixiao Wang: Supervision

Qi Zhang: Methodology, Project administration, Writing –

review & editing

Conflicts of Interest

The authors declare no conflicts of interest.

References

- [1] Novak V, Hajjar I. The relationship between blood pressure and cognitive function [J]. *Nature Reviews Cardiology*, 2010, 7(12): 686-698. <https://doi.org/10.1016/j.jacc.2022.01.045>
- [2] Drew P J. Neurovascular coupling: motive unknown [J]. *Trends in neurosciences*, 2022, 45(11): 809-819. <https://doi.org/10.1016/j.tins.2022.08.004>
- [3] Liu L, Liu J, Bao J, et al. Interaction of microglia and astrocytes in the neurovascular unit [J]. *Frontiers in immunology*, 2020, 11: 1024. <https://doi.org/10.3389/fimmu.2020.01024>
- [4] Grubb S, Lauritzen M, Aalkjær C. Brain capillary pericytes and neurovascular coupling [J]. *Comparative Biochemistry and Physiology Part A: Molecular & Integrative Physiology*, 2021, 254: 110893. <https://doi.org/10.1016/j.cbpa.2020.110893>
- [5] Martineau É, Malescot A, Elmkjss N, et al. Distal activity patterns shape the spatial specificity of neurovascular coupling [J]. *Nature Neuroscience*, 2024, 27(11): 2101-2114. <https://doi.org/10.1038/s41593-024-01756-7>
- [6] Tiedt S, Buchan A M, Dichgans M, et al. The neurovascular unit and systemic biology in stroke—implications for translation and treatment [J]. *Nature Reviews Neurology*, 2022, 18(10): 597-612. <https://doi.org/10.1038/s41582-022-00703-z>
- [7] Li T, Wang L, Piao Z, et al. Altered neurovascular coupling for multidisciplinary intensive rehabilitation in Parkinson's disease [J]. *Journal of Neuroscience*, 2023, 43(7): 1256-1266. <https://doi.org/10.1523/jneurosci.1204-22.2023>
- [8] Magyar-Sumegi Z D, Csendes M, Lendvai-Emmert D, et al. Chronic impairment of neurovascular coupling and cognitive decline in young survivors of severe traumatic brain injury [J]. *GeroScience*, 2025: 1-13. <https://doi.org/10.1007/s11357-025-01683-w>
- [9] Meng L, Rasmussen M, Meng D M, et al. Integrated feedforward and feedback mechanisms in neurovascular coupling [J]. *Anesthesia & Analgesia*, 2024, 139(6): 1283-1293. <https://doi.org/10.1213/ane.0000000000006891>
- [10] Hosford P S, Gourine A V. What is the key mediator of the neurovascular coupling response? [J]. *Neuroscience & Biobehavioral Reviews*, 2019, 96: 174-181. <https://doi.org/10.1016/j.neubiorev.2018.11.011>
- [11] Roy R K, Althammer F, Seymour A J, et al. Inverse neurovascular coupling contributes to positive feedback excitation of vasopressin neurons during a systemic homeostatic challenge [J]. *Cell reports*, 2021, 37(5). <https://doi.org/10.1016/j.celrep.2021.109925>
- [12] Attwell D, Buchan A M, Charpak S, et al. Glial and neuronal control of brain blood flow [J]. *Nature*, 2010, 468(7321): 232-243. <https://doi.org/10.1038/nature09613>
- [13] Vermeulen T D, Benbaruj J, Brown C V, et al. Acute intermittent hypercapnic hypoxia and cerebral neurovascular coupling in males and females [J]. *Experimental Neurology*, 2020, 334: 113441. <https://doi.org/10.1016/j.expneurol.2020.113441>
- [14] Du C, Park K, Hua Y, et al. Astrocytes modulate cerebral blood flow and neuronal response to cocaine in prefrontal cortex [J]. *Molecular psychiatry*, 2024, 29(3): 820-834. <https://doi.org/10.21203/rs.3.rs-2626090/v1>
- [15] Institoris A, Vandal M, Peringod G, et al. Astrocytes amplify neurovascular coupling to sustained activation of neocortex in awake mice [J]. *Nature communications*, 2022, 13(1): 7872. <https://doi.org/10.1038/s41467-022-35383-2>
- [16] Császár E, Lénárt N, Cserép C, et al. Microglia modulate blood flow, neurovascular coupling, and hypoperfusion via purinergic actions [J]. *Journal of Experimental Medicine*, 2022, 219(3): e20211071. <https://doi.org/10.1084/jem.20211071>
- [17] Alarcon-Martinez L, Villafranca-Baughman D, Quintero H, et al. Interpericyte tunnelling nanotubes regulate neurovascular coupling [J]. *Nature*, 2020, 585(7823): 91-95. <https://doi.org/10.1038/s41586-020-2589-x>
- [18] Meza-Resillas J, O'Hara F, Kaushik S, et al. Systemic nimodipine affects pericyte calcium signaling, resting hemodynamics and neurovascular coupling in healthy mouse brain [J]. *Neurotherapeutics*, 2025: e00614. <https://doi.org/10.1016/j.neurot.2025.e00614>
- [19] Divecha Y A, Rampes S, Tromp S, et al. The microcirculation, the blood-brain barrier and the neurovascular unit in health and Alzheimer's Disease. The aberrant pericyte is a central player [J]. *Pharmacological Reviews*, 2025: 100052. <https://doi.org/10.1016/j.pharmr.2025.100052>
- [20] Zhu W M, Neuhaus A, Beard D J, et al. Neurovascular coupling mechanisms in health and neurovascular uncoupling in Alzheimer's disease [J]. *Brain*, 2022, 145(7): 2276-2292. <https://doi.org/10.1093/brain/awac174>
- [21] Zimmer A R, Bourourou M, Lesage F, et al. Neurovascular coupling and functional connectivity changes through the Alzheimer's disease spectrum: Effects of simvastatin treatment [J]. *Alzheimer's & Dementia*, 2025, 21(8): e70402. <https://doi.org/10.1002/alz.70402>
- [22] Kisler K, Nelson A R, Montagne A, et al. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease [J]. *Nature Reviews Neuroscience*, 2017, 18(7): 419-434. <https://doi.org/10.1038/nrn.2017.48>
- [23] Shang J, Yamashita T, Zhai Y, et al. Strong Impact of Chronic Cerebral Hypoperfusion on Neurovascular Unit, Cerebrovascular Remodeling, and Neurovascular Trophic Coupling in Alzheimer's Disease Model Mouse [J]. *Journal of Alzheimer's Disease*, 2016, 52(1): 113-26. <https://doi.org/10.3233/jad-151126>

- [24] Nelson A R. Peripheral pathways to neurovascular unit dysfunction, cognitive impairment, and Alzheimer's disease [J]. *Frontiers in aging neuroscience*, 2022, 14: 858429. <https://doi.org/10.3389/fnagi.2022.858429>
- [25] Huang W, Xia Q, Zheng F, et al. Microglia-mediated neurovascular unit dysfunction in Alzheimer's disease [J]. *Journal of Alzheimer's Disease*, 2023, 94(s1): S335-S354. <https://doi.org/10.3233/jad-221064>
- [26] Csiszar A, Tarantini S, Fülöp G A, et al. Hypertension impairs neurovascular coupling and promotes microvascular injury: role in exacerbation of Alzheimer's disease [J]. *Geroscience*, 2017, 39(4): 359-372. <https://doi.org/10.1007/s11357-017-9991-9>
- [27] Liu X, Hou D R, Lin F B, et al. The role of neurovascular unit damage in the occurrence and development of Alzheimer's disease [J]. *Reviews in the Neurosciences*, 2019, 30(5): 477-484. <https://doi.org/10.1515/revneuro-2018-0056>
- [28] Zhao T, Pan P, Jia Y, et al. Crossing Pathological Boundaries: Multi-Target Restoration of the Neurovascular Unit in Alzheimer's and Vascular Dementia-From Modern Therapeutics to Traditional Chinese Medicine [J]. *Aging and disease*. <https://doi.org/10.14336/ad.2025.0801>
- [29] Alshibani A A K. Parkinson's Disease: An Integrative Analysis of Pathophysiology, Genetic Susceptibility, Diagnosis, Therapeutic Strategies, and Emerging Researches [J]. *Bani Waleed University Journal of Humanities and Applied Sciences*, 2025, 10(2): 520-536. <https://doi.org/10.58916/jhas.v10i2.773>
- [30] De Lau L M L, Breteler M M B. Epidemiology of Parkinson's disease [J]. *The Lancet Neurology*, 2006, 5(6): 525-535. <https://doi.org/10.1007/s00702-017-1686-y>
- [31] Miyazaki I, Asanuma M. Neuron-astrocyte interactions in Parkinson's disease [J]. *Cells*, 2020, 9(12): 2623. <https://doi.org/10.3390/cells9122623>
- [32] Si X, Dai S, Fang Y, et al. Matrix metalloproteinase-9 inhibition prevents aquaporin-4 depolarization-mediated glymphatic dysfunction in Parkinson's disease [J]. *Journal of advanced research*, 2024, 56: 125-136. <https://doi.org/10.1016/j.jare.2023.03.004>
- [33] Morrone Parfitt G, Coccia E, Goldman C, et al. Disruption of lysosomal proteolysis in astrocytes facilitates midbrain organoid proteostasis failure in an early-onset Parkinson's disease model [J]. *Nature Communications*, 2024, 15(1): 447. <https://doi.org/10.1038/s41467-024-44732-2>
- [34] Shang S, Ye J, Wu J, et al. Early disturbance of dynamic synchronization and neurovascular coupling in cognitively normal Parkinson's disease [J]. *Journal of Cerebral Blood Flow & Metabolism*, 2022, 42(9): 1719-1731. <https://doi.org/10.1177/0271678x221098503>
- [35] Lau K, Kotzur R, Richter F. Blood-brain barrier alterations and their impact on Parkinson's disease pathogenesis and therapy [J]. *Translational neurodegeneration*, 2024, 13(1): 37. <https://doi.org/10.1186/s40035-024-00430-z>
- [36] Wang T, Sun Y, Dettmer U. Astrocytes in Parkinson's disease: from role to possible intervention [J]. *Cells*, 2023, 12(19): 2336. <https://doi.org/10.3390/cells12192336>
- [37] Zhu H, Xiao F, Xiao Y, et al. Targeting CB2R in astrocytes for Parkinson's disease therapy: unraveling the Foxg1-mediated neuroprotective mechanism through autophagy-mediated NLRP3 degradation [J]. *Journal of Neuroinflammation*, 2023, 20(1): 304. <https://doi.org/10.1186/s12974-023-02989-2>
- [38] Garcia R, Zarate S, Srinivasan R. [J]. *Astrocyte-Neuron Interactions in Health and Disease. The role of astrocytes in parkinson's disease: astrocytes in parkinson's disease*, 2024: 319-343. https://link.springer.com/chapter/10.1007/978-3-031-64839-7_13
- [39] Jiang S Y, Tian T, Yao H, et al. The cGAS-STING-YY1 axis accelerates progression of neurodegeneration in a mouse model of Parkinson's disease via LCN2-dependent astrocyte senescence [J]. *Cell Death & Differentiation*, 2023, 30(10): 2280-2292. <https://doi.org/10.1038/s41418-023-01216-y>
- [40] Kam T I, Hinkle J T, Dawson T M, et al. Microglia and astrocyte dysfunction in parkinson's disease [J]. *Neurobiology of disease*, 2020, 144: 105028. <https://doi.org/10.1016/j.nbd.2020.105028>
- [41] de Montgolfier O, Thorin-Trescases N, Thorin E. Pathological continuum from the rise in pulse pressure to impaired neurovascular coupling and cognitive decline [J]. *American journal of hypertension*, 2020, 33(5): 375-390. <https://doi.org/10.1093/ajh/hpaa001>
- [42] Dunn K M, Nelson M T. Neurovascular signaling in the brain and the pathological consequences of hypertension [J]. *American Journal of Physiology-Heart and Circulatory Physiology*, 2014, 306(1): H1-H14. <https://doi.org/10.1152/ajpheart.00364.2013>
- [43] Iadecola C, Gottesman R F. Neurovascular and cognitive dysfunction in hypertension: epidemiology, pathobiology, and treatment [J]. *Circulation research*, 2019, 124(7): 1025-1044. <https://doi.org/10.1161/CIRCRESAHA.118.313260>
- [44] Monteiro A, Castro P, Pereira G, et al. Cerebral blood flow regulation and cognitive performance in hypertension [J]. *Journal of Cerebral Blood Flow & Metabolism*, 2024, 44(11): 1277-1287. <https://doi.org/10.1177/0271678x241254680>
- [45] Wu H, Sun Q, Yuan S, et al. AT1 receptors: their actions from hypertension to cognitive impairment [J]. *Cardiovascular Toxicology*, 2022, 22(4): 311-325. <https://doi.org/10.1007/s12012-022-09730-0>
- [46] Presa J L, Saravia F, Bagi Z, et al. Vascular-neuronal coupling and neurovascular coupling at the neurovascular unit: impact of hypertension [J]. *Frontiers in physiology*, 2020, 11: 584135. <https://doi.org/10.3389/fphys.2020.584135>
- [47] Stamatovic S M, Phillips C M, Martinez-Revollar G, et al. Involvement of epigenetic mechanisms and non-coding RNAs in blood-brain barrier and neurovascular unit injury and recovery after stroke [J]. *Frontiers in neuroscience*, 2019, 13: 864. <https://doi.org/10.3389/fnins.2019.00864>

- [48] Steliga A, Kowiański P, Czuba E, et al. Neurovascular unit as a source of ischemic stroke biomarkers—limitations of experimental studies and perspectives for clinical application [J]. *Translational stroke research*, 2020, 11(4): 553-579. <https://doi.org/10.1007/s12975-019-00744-5>
- [49] Li Z, McConnell H L, Stackhouse T L, et al. Increased 20-HETE signaling suppresses capillary neurovascular coupling after ischemic stroke in regions beyond the infarct [J]. *Frontiers in Cellular Neuroscience*, 2021, 15: 762843. <https://doi.org/10.3389/fncel.2021.762843>
- [50] Su E J, Fredriksson L, Schielke G P, et al. Tissue plasminogen activator-mediated PDGF signaling and neurovascular coupling in stroke [J]. *Journal of Thrombosis and Haemostasis*, 2009, 7: 155-158. <https://doi.org/10.1111/j.1538-7836.2009.03402.x>
- [51] Sun J, Chi L, He Z, et al. NLRP3 inflammasome contributes to neurovascular unit damage in stroke [J]. *Journal of drug targeting*, 2019, 27(8): 866-875. <https://doi.org/10.1080/1061186x.2018.1564925>
- [52] Wang L, Xiong X, Zhang L, et al. Neurovascular unit: a critical role in ischemic stroke [J]. *CNS Neuroscience & Therapeutics*, 2021, 27(1): 7-16. <https://doi.org/10.1111/cns.13561>
- [53] Wierońska J M, Cieślik P, Kalinowski L. Nitric oxide-dependent pathways as critical factors in the consequences and recovery after brain ischemic hypoxia [J]. *Biomolecules*, 2021, 11(8): 1097. <https://doi.org/10.3390/biom11081097>
- [54] Qin C, Yang S, Chu Y H, et al. Signaling pathways involved in ischemic stroke: molecular mechanisms and therapeutic interventions [J]. *Signal transduction and targeted therapy*, 2022, 7(1): 215. <https://doi.org/10.1038/s41392-022-01064-1>
- [55] Chamorro Á, Dirnagl U, Urra X, et al. Neuroprotection in acute stroke: targeting excitotoxicity, oxidative and nitrosative stress, and inflammation [J]. *The Lancet Neurology*, 2016, 15(8): 869-881. [https://doi.org/10.1016/s1474-4422\(16\)00114-9](https://doi.org/10.1016/s1474-4422(16)00114-9)
- [56] Gao X, Liu D, Yue K, et al. Revolutionizing ischemic stroke diagnosis and treatment: the promising role of neurovascular unit-derived extracellular vesicles [J]. *Biomolecules*, 2024, 14(3): 378. <https://doi.org/10.3390/biom14030378>
- [57] Logothetis N K, Pauls J, Augath M, et al. Neurophysiological investigation of the basis of the fMRI signal [J]. *nature*, 2001, 412(6843): 150-157. <https://doi.org/10.1038/35084005>
- [58] Burma J S, Bailey D M, Johnson N E, et al. Physiological influences on neurovascular coupling: A systematic review of multimodal imaging approaches and recommendations for future study designs [J]. *Experimental Physiology*, 2025, 110(1): 23-41. <https://doi.org/10.1113/ep092060>
- [59] Shahsavarani S, Thibodeaux D N, Xu W, et al. Cortex-wide neural dynamics predict behavioral states and provide a neural basis for resting-state dynamic functional connectivity [J]. *Cell reports*, 2023, 42(6). <https://doi.org/10.1016/j.celrep.2023.112527>
- [60] Liu L, Xu Z, Lai Z, et al. Photoacoustic and fluorescence hybrid microscope for cortex-wide imaging of neurovascular dynamics with subcellular resolution [J]. *Science Advances*, 2025, 11(30): eadw5275. <https://doi.org/10.1126/sciadv.adw5275>
- [61] Wan X, Yin X, Chai X, et al. Evaluation of neurovascular coupling in early-onset and late-onset epilepsy of unknown etiology [J]. *Journal of Magnetic Resonance Imaging*, 2025, 61(6): 2489-2500. <https://doi.org/10.1002/jmri.29678>
- [62] Ball J D, Hills E, Altaf A, et al. Neurovascular coupling methods in healthy individuals using transcranial doppler ultrasonography: A systematic review and consensus agreement [J]. *Journal of Cerebral Blood Flow & Metabolism*, 2024, 44(12): 1409-1429. <https://doi.org/10.1177/0271678x241270452>
- [63] Sen é P, Krafft L, Loukili I, et al. Revealing neurovascular coupling at a high spatial and temporal resolution in the living human retina [J]. *Science Advances*, 2025, 11(26): eadx2941. <https://doi.org/10.1126/sciadv.adx2941>
- [64] Chen N, Xu Z, Song Z, et al. Simultaneous head-mounted imaging of neural and hemodynamic activities at high spatio-temporal resolution in freely behaving mice [J]. *Science Advances*, 2025, 11(12): eadu1153. <https://doi.org/10.1126/sciadv.adu1153>
- [65] Chen Y, Qian W, Razansky D, et al. WISDEM: a hybrid wireless integrated sensing detector for simultaneous EEG and MRI [J]. *Nature Methods*, 2025: 1-10. <https://doi.org/10.1038/s41592-025-02798-w>
- [66] Burma J S, Oni I K, Lapointe A P, et al. Quantifying neurovascular coupling through a concurrent assessment of arterial, capillary, and neuronal activation in humans: A multimodal EEG-fNIRS-TCD investigation [J]. *Neuroimage*, 2024, 302: 120910. <https://doi.org/10.1016/j.neuroimage.2024.120910>