Journal of Integrative Neuroscience

J. Integr. Neurosci. **2026**; 25(2): 42796
https://doi.org/10.31083/JIN42796

Review

Physiological Regulatory Mechanisms of Neurovascular Coupling and the Role of Its Dysfunction in Neurological Diseases

Aili Wang[1,2], Jing Li[1,2], Huaie Liu[2,3,*], Dongxu Yue[4,*]

[1]Department of Infectious Diseases, The First Affiliated Hospital of Kunming Medical University, 650000 Kunming, Yunnan, China
[2]Department of Pathology and Pathophysiology, Faculty of Basic Medical Sciences, Kunming Medical University, 650000 Kunming, Yunnan, China
[3]Department of Geriatric Gastroenterology, The First Affiliated Hospital of Kunming Medical University, 650000 Kunming, Yunnan, China
[4]Department of Pathology, The First People's Hospital of Yunnan Province, Kunming University of Science and Technology Affiliated Hospital, 650000 Kunming, Yunnan, China
*Correspondence: liuhuaie@163.com (Huaie Liu); drydx@foxmail.com (Dongxu Yue)
Academic Editor: Hahn Young Kim
Submitted: 31 May 2025 Revised: 12 August 2025 Accepted: 19 August 2025 Published: 26 February 2026

Abstract

Neurovascular coupling (NVC) is a fundamental physiological process that regulates cerebral blood flow in response to neuronal activity. This mechanism ensures the efficient delivery of oxygen and glucose to active brain regions while clearing metabolic byproducts, thus maintaining brain homeostasis and supporting optimal neural function. Disruptions in NVC are linked to complex molecular and cellular alterations and contribute significantly to a range of both acute and chronic neurological disorders, including Alzheimer's disease, ischemic stroke, cerebral small vessel disease, migraines, epilepsy, and cognitive deficits associated with diabetes. Gaining a deeper understanding of the pathological mechanisms underlying NVC dysfunction in these conditions is critical for developing novel diagnostic biomarkers and targeted therapeutic strategies. This review aims to provide a comprehensive exploration of the physiological basis of NVC in a healthy brain, alongside the methods used to study it. Additionally, it offers a detailed analysis of the molecular and cellular mechanisms driving NVC dysfunction in major neurological diseases, presenting a theoretical framework and new insights for the development of innovative diagnostic and therapeutic interventions.

Keywords: neurovascular coupling; blood-brain barrier; signaling pathways; nervous system diseases; targeted therapy

1. Introduction

Neurovascular coupling (NVC) refers to the close temporal and spatial association between transient neural activity in the brain and subsequent changes in local cerebral blood flow (CBF), cerebral blood volume, and cerebral oxygen metabolism rate [1]. Despite accounting for only 2% of body weight, the brain consumes over 20% of the body's resting energy, with nearly all of this energy derived from aerobic glucose metabolism [2]. However, the brain's ability to store energy is highly limited. Therefore, to meet the dynamic and substantial energy demands of neural activity, the brain has evolved a highly efficient and precise regulatory mechanism, NVC, to allocate blood supply in real time and on demand, ensuring timely delivery of oxygen, glucose, and other energy substrates while effectively clearing metabolic waste products [2].

As early as 1890, Roy and Sherrington [3] proposed the existence of an intrinsic mechanism in the brain that regulates local blood supply based on changes in local functional activity. They hypothesized that metabolic byproducts of neuronal activity diffuse to local blood vessels, leading to increased blood flow. This pioneering concept laid the foundation for NVC research. The initial "metabolic hypothesis" posited that functional hyperemia was driven by byproducts of energy consumption, such as CO_2, lactate, H^+, adenosine, or oxygen debt [4,5]. However, increasing evidence suggests that while such byproducts do have vasoactive properties, acute and rapid CBF responses under physiological conditions are primarily modulated by vasoactive signaling molecules associated with neuronal signaling, such as nitric oxide (NO), prostaglandins and potassium ions, rather than simple metabolic feedback [6,7]. This shift from passive metabolic feedback to active signaling regulation has greatly enhanced understanding of the complexity of NVC. In 2001, the National Institute of Neurological Disorders and Stroke introduced the concept of the "Neurovascular Unit" (NVU) [8]. The NVU emphasizes the unique structural and functional connections between brain cells and blood vessels, tightly integrating the fields of neuroscience and cerebrovascular biology [9]. The NVU is a multicellular structural and functional module composed of neurons, astrocytes, endothelial cells, pericytes and vascular smooth muscle cells, along with the basement membrane and extracellular matrix that surrounds them [10]. These components interact through complex signaling pathways to maintain the integrity of the blood-brain barrier (BBB) and precisely regulate CBF to meet the brain's energy needs [11].

The integrity of NVC function is crucial for maintaining brain health. However, increasing evidence sug-

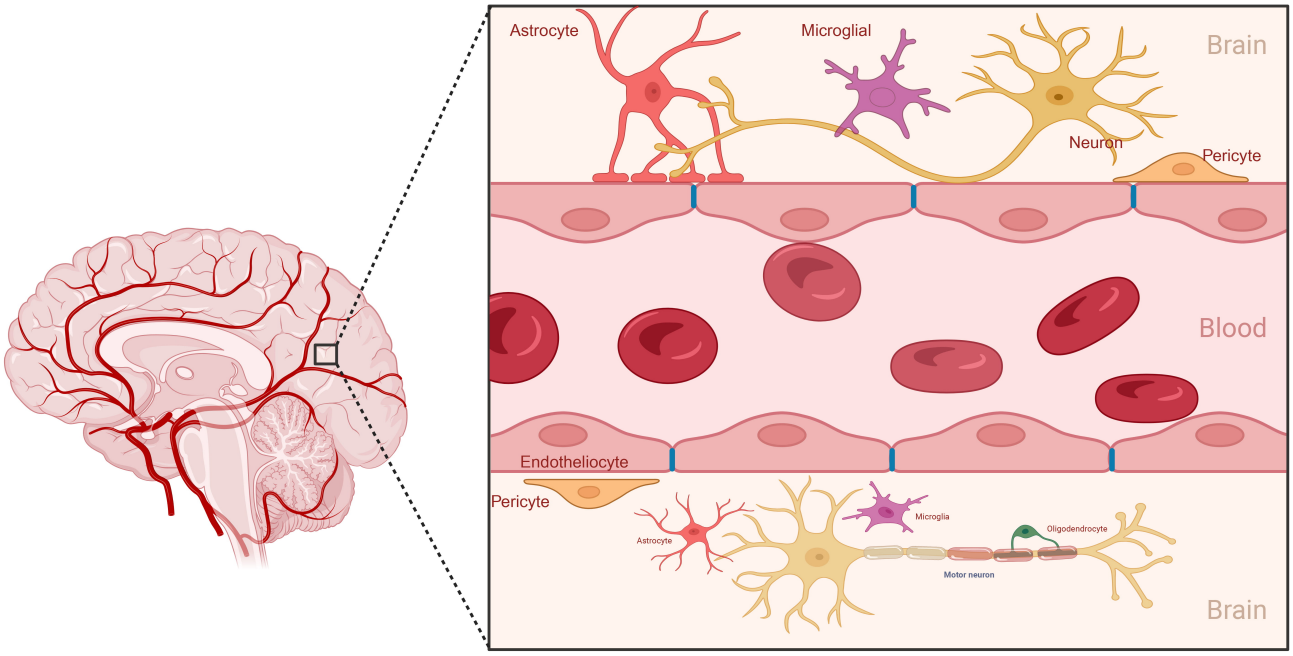

Fig. 1. Schematic illustration of the neurovascular unit (NVU) and its cellular components. The NVU is a multicellular functional unit that maintains brain homeostasis and regulates the blood-brain barrier. The magnified view displays the core cellular components, including endothelial cells, pericytes, astrocytes, microglia, neurons, and oligodendrocytes, highlighting their spatial organization around a cerebral blood vessel. Created with BioRender (https://www.biorender.com/).

gests that impairment or "decoupling" of NVC is an early pathological feature of various cerebrovascular and neurodegenerative diseases, potentially occurring before clinical symptoms or structural damage [9]. These disease spectra are broad and include Alzheimer's disease (AD), ischemic stroke, cerebral small vessel disease (CSVD), migraine, epilepsy, and diabetes with cognitive impairment [12–15]. Given the central role of NVC in brain physiology and pathology, a deeper understanding of its regulatory mechanisms, the causes of functional impairment and its role in disease is essential. This review aims to comprehensively overview the physiological basis of NVC in a healthy brain and its assessment techniques, systematically explore the molecular and cellular mechanisms of NVC dysfunction in major brain diseases and provide a comprehensive reference for research in neuroscience and related clinical fields, while also looking ahead to future research directions.

2. Cellular and Structural Basis of Neurovascular Coupling

2.1 Core Components and Physiological Significance of the Neurovascular Unit

The NVU is the core structural platform for realizing NVC functions. Rather than being a simple cell collection, it is a highly integrated, multi-cellular functional module whose integrity is essential for maintaining brain homeostasis, regulating BBB permeability and accurately matching local CBF with neuronal metabolic demands [11]. Core cellular members of the NVU include neurons, astrocytes, endothelial cells, pericytes and vascular smooth muscle cells, as well as microglial cells, the basement membrane and the extracellular matrix that encases these cells (Fig. 1). The precise cellular composition, structural arrangement and complex intercellular interactions together form the physiological foundation for NVC. Structural or functional abnormalities in any NVU component can disrupt overall coordination, leading to NVC dysfunction and BBB integrity disruption.

2.2 Physiological Functions of Each Cellular Component in the Neurovascular Unit

Within the NVU, different cells play unique and coordinated roles (Table 1, Ref. [16–24]). Neurons, as initiators of NVC, release neurotransmitters such as glutamate, directly activating neuronal-type nitric oxide synthase (nNOS) to generate NO, or by indirectly acting on astrocytes via metabotropic glutamate receptors to trigger vasodilation. Neurons also release adenosine triphosphate (ATP) and prostaglandins (PGE) (e.g., PGE_2), which further regulate vascular tone [16]. Specific gamma-aminobutyric acid (GABA) interneurons also release NO or vasoactive peptides to assist in blood flow regulation [25]. Astrocytes, as integrators, surround blood vessels with their vascular end-feet. They respond to glutamate released by neurons, raising intracellular calcium (Ca^{2+}) levels and releasing vasoactive substances such as potassium ions (K^+), arachidonic acid (AA) metabolites and ATP, finely regulat-

Table 1. Cellular Composition of the Neurovascular Unit and its key role in NVC.

Cell type	Key functions in NVC	Key signaling molecules	Main reference
Neuron	Initiate NVC signals; Sense metabolic demand; Direct vasodilation/vasoconstriction	Glutamate, NO, ATP, PGE_2, GABA, NPY, VIP	[16]
Astrocyte	Integrate neuronal signals; Transduce signals to vessels via endfeet; Modulate vascular tone	Ca^{2+} signaling, K^+, AA metabolites: PGE_2, EETs, 20-HETE, ATP	[21]
Endotheliocyte	Maintain BBB; Synthesize & release vasoactive factors; Propagate vasodilatory signals	NO, PGI_2, EDHF, ET-1, Endothelial Ca^{2+} signaling, TRP channels	[17,22]
Pericyte	Regulate capillary diameter & blood flow; Maintain BBB integrity	Glutamate, ATP, NO, K^+, AA metabolites, Contractile proteins	[23,24]
Microglia	Immune surveillance; Modulate CBF and NVC via purinergic signaling	P2Y12 receptors, CD39 (ATP/ADP→adenosine)	[18]
Oligodendrocyte	Myelination; Axonal metabolic support; Indirectly influence NVC via K^+ buffering	Kir4.1 channels, Metabolite transport, e.g., lactate	[19]
VSMCs	Integrate vasoactive signals; Regulate arteriole diameter & blood flow	Response to NO, prostaglandins, K^+, EETs, 20-HETE, ET-1, Ca^{2+} signaling, K^+ channels	[20]

Footnotes: 20-HETE, 20-hydroxyeicosatetraenoic acid; AA, arachidonic acid; ATP, adenosine triphosphate; ADP, adenosine diphosphate; BBB, blood-brain barrier; CBF, cerebral blood flow; EETs, epoxyeicosatrienoic acids; ET-1, endothelin-1; EDHF, endothelium-derived hyperpolarizing factor; GABA, gamma-aminobutyric acid; NO, nitric oxide; NVC, neurovascular coupling; NVU, neurovascular unit; NPY, neuropeptide Y; PGE_2, prostaglandin E2; PGI_2, prostacyclin; P2Y12, purinergic receptor Y12; TRP, transient receptor potential; VSMCs, vascular smooth muscle cells; VIP, vasoactive intestinal peptide; CD39, Cluster of Differentiation 39.

ing vascular contraction and dilation. Astrocytic signal integration is influenced by local oxygen concentrations and vascular tone, allowing dynamic vascular responses according to the microenvironment [26].

Brain microvascular endothelial cells not only form the BBB but also actively participate in NVC by producing NO through endothelial nitric oxide synthase (eNOS), synthesizing prostacyclin 2 (PGI_2), and mediating vasodilation through the endothelium-derived hyperpolarizing factor (EDHF) pathway [17]. Additionally, endothelial cells produce the vasoconstrictor endothelin-1 (ET-1), with its release forming a dynamic balance with vasodilatory substances [27]. Endothelial cell Ca^{2+} signal integration comes from neuronal and astrocytic signals that responds to various stimuli through transient receptor potential (TRP) channels, coordinating and propagating vasodilation signals upstream along the vascular tree [28]. Pericytes envelop capillaries and respond to signals such as glutamate, ATP, norepinephrine and AA metabolites with their contractile proteins, directly regulating capillary diameter, potentially reacting before small arteries in NVC [29]. Microglial cells, as immune sentinels, sense ATP/adenosine diphosphate (ADP) through their purinergic receptor Y12 (P2Y12) receptors and hydrolyze ATP/ADP to adenosine via Cluster of Differentiation 39 (CD39) ectonucleotidase, thus regulating local CBF and NVC, partially independent of the NO pathway [18]. Oligodendrocytes mainly promote NVC indirectly by forming myelin and providing metabolic support to axons, maintaining neuronal function and the normal demands of NVC [19]. Finally, vascular smooth muscle cells (VSMCs), as the primary effector cells of small artery walls, integrate various vasodilation and vasoconstriction signals from the NVU components, precisely regulating CBF by changing their contraction state and vascular diameter, with their reactivity significantly influenced by pre-existing vascular tension [20].

2.3 Structure of the Neurovascular Unit and Blood-Brain Barrier

The NVU's structure shows high specificity along the vascular tree (Fig. 1). Small arterial walls consist of endothelial cells, a basement membrane, multi-layered VSMCs and astrocyte end-feet, with the possibility of a perivascular space. By contrast, the capillary wall is simpler, composed of endothelial cells, a shared basement membrane, embedded pericytes and tightly surrounding astrocyte end-feet, without the VSMC layer [30]. This precise structural arrangement facilitates efficient signal transmission within the NVU. The BBB is a critical manifestation of the NVU's structure and function, with the core being the physical barrier formed by tight junctions between brain microvascular endothelial cells. Pericytes and astrocytes induce and maintain the endothelial cell barrier through signaling molecules or direct contact [31]. BBB integrity is crucial for maintaining CNS homeostasis, protecting neurons from harmful substances, and ensuring proper NVC function [32].

3. Physiological Mechanism of Neurovascular Coupling

NVC is a complex process involving interactions between multiple cell types and signaling pathways (Fig. 2). Neuronal activity serves as the initiating signal, which, through the coordinated actions of the components of the

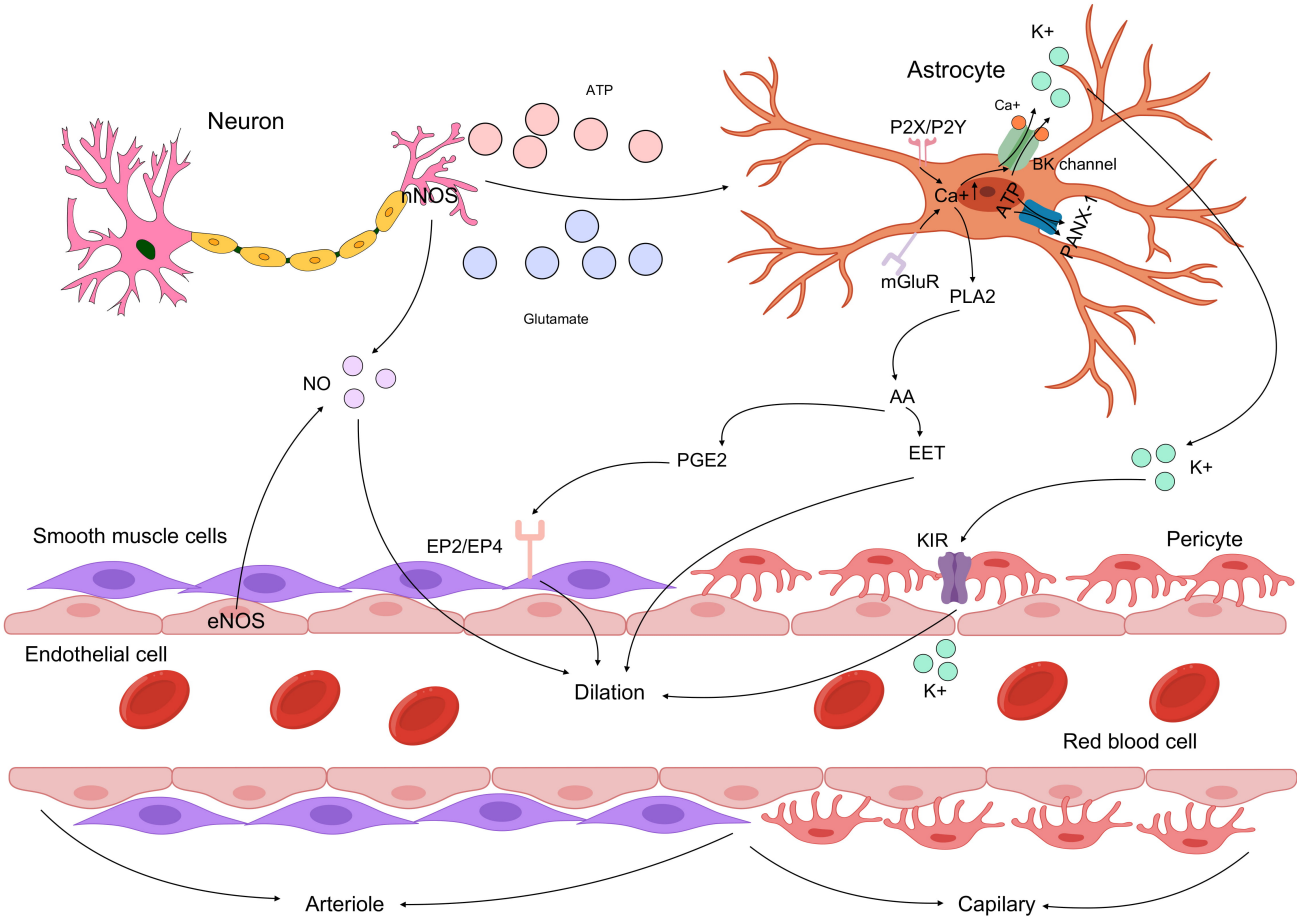

Fig. 2. Core signaling pathways of neurovascular coupling. Neurovascular coupling is mediated by parallel neuronal and astrocytic signaling pathways that converge on vascular cells. Neuron-derived NO from nNOS directly induces vasodilation of arteriolar SMCs. Concurrently, astrocyte activation by neurotransmitters (glutamate, ATP) triggers a Ca^{2+}-dependent release of vasoactive agents, including K^+, PGE2, and EETs. These messengers target SMCs and pericytes via specific receptors and channels (e.g., EP2/EP4, Kir) to promote a coordinated increase in local blood flow. BK channel, large-conductance Ca^{2+}-activated K^+ channel; eNOS, endothelial nitric oxide synthase; EP2/EP4, prostaglandin E2 receptors 2/4; Kir, inwardly rectifying K^+ channel; mGluR, metabotropic glutamate receptor; nNOS, neuronal nitric oxide synthase; PANX-1, pannexin-1; PLA2, phospholipase A2; P2X/P2Y, purinergic receptor; SMC, smooth muscle cell. Created with MedPeer (https://www.medpeer.cn/).

NVU, ultimately leads to vasomotor responses in vascular smooth muscle or pericytes, thereby regulating local CBF. Unlike the earlier belief in metabolic feedback (e.g., decreased oxygen concentration driving increased blood flow), the prevailing view is that NVC is primarily regulated by feedforward signaling molecules released by neurons and glial cells [11].

3.1 Signal Initiation: Neuronal Activity

NVC is initiated by neuronal electrical activity and synaptic transmission. Neurons release a variety of neurotransmitters and neuromodulators, which trigger a complex signaling cascade that regulates local CBF [33]. Glutamate, released by excitatory neurons, is one of the primary triggers for NVC. Glutamate acts on N-methyl-D-aspartate receptors on postsynaptic neurons, leading to Ca^{2+} influx. This activation subsequently triggers nNOS to produce the vasodilator NO, or catalyzes the synthesis of PGE_2 via cyclooxygenase-2, both of which promote vasodilation [34]. Inhibitory interneurons also play a complex role in NVC regulation, mediating both vasodilation and vasoconstriction. For instance, interneurons expressing somatostatin release neuropeptide Y (NPY), which induces vasoconstriction via Y1 receptors, while neurons expressing vasoactive intestinal peptide (VIP) or nNOS promote vasodilation [35]. Recent studies have identified a specific type of cortical GABAergic neuron, co-expressing nNOS and tachykinin receptor 1, that plays a critical role in mediating CBF increases through feedforward excitatory pathways and the release of signaling molecules such as NO. Their axons project both locally and over long distances, regulating pericyte relaxation [36]. Additionally, neurons with subcortical regions (such as the basal ganglia and locus coeruleus) directly project to cortical microvessels, influ-

encing local blood flow through the release of acetylcholine (ACh), norepinephrine and serotonin (5-HT) [37]. Recent research has further demonstrated that in deeper brain regions, glutamatergic axons cross the gaps in astrocytic end-feet, forming tight "synaptic-like" structures with arteriolar smooth muscle cells, mediating direct and rapid neuronal control over blood vessels, thereby providing a new direct pathway for NVC [10]. Neurons utilize various vasoactive molecules through different signaling pathways to ensure the robustness and precision of the NVC response [38].

In addition to classical neurotransmitter signaling, ion concentration changes induced by neuronal activity are also key signals in initiating NVC. During neuronal firing, intracellular K^+ rapidly effluxes through delayed rectifier potassium channels, causing a rapid increase in the K^+ concentration in the synaptic cleft. This elevated K^+ concentration can be directly detected by nearby vascular smooth muscle cells and inward rectifier potassium (Kir) channels 2.1 on pericyte membranes. The activation of Kir channels leads to hyperpolarization of the vascular cell membrane, closing voltage-dependent Ca^{2+} channels, which ultimately results in vasodilation. This "neuron-K^+-Kir channel" pathway bypasses complex intermediate signaling cascades and is considered one of the fastest feedforward mechanisms for initiating functional hyperemia [39]. However, the efficiency of this signaling pathway is tightly regulated by the precise microstructural organization of the neurovascular unit. Computational model studies suggest that the dense, sheath-like structure formed by the terminal astrocytic end-feet around blood vessels acts as a physical barrier, restricting the diffusion of K^+ from the synapse to the blood vessel, thereby limiting the propagation of the K^+ signal. Consequently, the ability of the K^+ signal to effectively trigger vasodilation may depend on the geometric configuration of the astrocytic end-feet or their dynamic changes during physiological processes [40].

3.2 Signal Transmission and Regulation: The Contribution of Astrocytes

Astrocytes are key integrators in the transmission of signals between neurons and blood vessels in NVC. They regulate vascular responses through complex Ca^{2+} signal transduction and the release of various vasoactive substances. Neuronal activity, particularly glutamatergic signaling, activates metabotropic glutamate receptors on astrocytic membranes, promoting the release of Ca^{2+} from intracellular stores via the inositol trisphosphate (InsP3) pathway, leading to an increase in intracellular Ca^{2+} levels. These Ca^{2+} signals spread within the cell and potentially are transferred to neighboring cells, ultimately reaching the astrocytic end-feet surrounding blood vessels [41]. Elevated intracellular Ca^{2+} levels in astrocytes initiate the synthesis and/or release of various vasoactive substances, including PGE_2, epoxyeicosatrienoic acids (EETs) and K^+ efflux, all of which induce vasodilation. PGE_2 and EETs act on corresponding receptors or channels on VSMCs, while increased extracellular K^+ concentration induces vasodilation by activating Kir channels on VSMCs. Alternatively, astrocyte-derived 20-hydroxyeicosatetraenoic acid (20-HETE) and released ATP cause vasoconstriction [42]. The net effect of astrocyte-derived signals (vasodilation or vasoconstriction) is dynamically regulated by current vascular tone and the local microenvironment, positioning astrocytes as "gatekeepers" [16].

3.3 Signal Propagation and Execution: Response of Vascular Cells

The ultimate effectors of NVC are vascular cells — endothelial cells, pericytes and VSMCs — which integrate upstream signals and regulate vessel diameter to control CBF [38]. Endothelial cells are located on the inner surface of blood vessels, serving as a critical interface between blood flow and brain tissue. These cells play a central role in sensing, integrating, and transmitting NVC signals to smooth muscle cells. They produce and release various vasoactive factors, promoting signal propagation along the vessel wall. Endothelial-derived vasodilators include NO, prostacyclin (PGI_2) and EDHFs, while ET-1 primarily acts as a vasoconstrictor [43]. Pericytes, which closely encase the outer walls of capillaries between endothelial cells and astrocyte end-feet, actively regulate capillary diameter, thus precisely modulating microcirculatory blood flow [44]. The relative contribution of pericytes and upstream small artery smooth muscle in regulating local CBF remains a core controversy in the field of NVC. One perspective proposes that pericytes serve as the primary regulatory site in NVC. Pioneering research from Attwell's lab [23] has demonstrated that pericytes possess potent contractile abilities, with their diameter changes sufficiently altering the vascular resistance of the entire capillary network, thereby controlling local CBF. In contrast, an alternative view challenges this notion, suggesting that the primary regulation of blood flow occurs in the upstream small arteries, which possess stronger contractile capacity. Research from Grutzendler's lab [45] provides opposing evidence, arguing that under physiological conditions, the contractile force of pericytes is insufficient to significantly alter overall blood flow, while the dilation and constriction of small artery smooth muscle are the key determinants of regional blood flow responses. Pericytes express a range of receptors and ion channels, enabling them to respond to signals from neurons and astrocytes, and regulate their contraction through Ca^{2+} signaling [46]. Recent research has highlighted the critical role of thin-strand pericytes in NVC. These cells detect increased neuronal activity and changes in local metabolic states, generating electrical signals via ATP-sensitive potassium (KATP) channels. These signals propagate retrogradely to upstream arterioles, causing vasodilation and increasing local blood supply [46,47]. Optogenetic activation of individual thin-strand pericytes is

sufficient to regulate arteriolar diameter remotely, confirming their importance in signal transmission [46]. VSMCs, which surround the walls of arterioles, are the final effector cells in the NVC pathway. They regulate local cerebral blood flow by altering vessel diameter through contraction and relaxation [11]. VSMCs integrate a variety of vasodilatory signals, including NO, PGI_2, EDHFs/hyperpolarization signals from endothelial cells and signals from neurons or astrocytes (e.g., PGE_2, K^+, adenosine). Potassium channels play a key role in VSMC relaxation. Their opening leads to potassium efflux, membrane hyperpolarization and inhibition of voltage-dependent Ca^{2+} channel opening, reducing intracellular Ca^{2+} concentrations and resulting in smooth muscle relaxation [48].

3.4 Integration and Regulation of Neurovascular Coupling

NVC is a dynamically integrated multi-loop control system, whose regulation depends on the precise coordination of feedforward and feedback mechanisms. The feedforward loop, primarily driven by neuronal activity, involves rapid signal transmission processes, including glutamate-mediated neurotransmitter release, calcium wave propagation in astrocytes, and the swift generation of vasoactive molecules such as K^+, NO, and PGE_2. These processes enable the early dilation of the local microvascular bed before there is a significant increase in metabolic demand, resulting in "predictive" perfusion. This can even lead to a temporary, excessive increase in regional cerebral blood flow that exceeds metabolic needs [49]. In contrast, the feedback loop operates at a slower pace and includes not only traditional metabolic by-products such as CO_2, O_2, lactate, and adenosine, but more critically, a series of active negative feedback mechanisms. These mechanisms fine-tune vascular tone in response to changes in local metabolic load, ensuring that CBF is restored to baseline levels with precision [16,49].

In these negative feedback mechanisms, endothelial cells detect shear stress induced by congestion through mechanosensitive ion channels, activating vasoconstriction signals to actively modulate the magnitude and duration of the congestion response, thereby preventing excessive shear stress from disrupting the microenvironment. Concurrently, vascular smooth muscle cells restore basal vascular tone through contraction, protecting downstream microvessels from damage due to pressure fluctuations [50]. Furthermore, several key molecules regulate the balance between vasodilation and vasoconstriction: when neuronal activity decreases and NO levels decline, the inhibition of 20-HETE synthesis is lifted, resulting in an increase in its concentration, which actively drives vasoconstriction to restore blood flow [51]. Notably, functional congestion can lead to local CO_2 depletion, causing transient hypocapnia, which subsequently triggers rebound vasoconstriction. Metabolites, such as adenosine, also play a role in regulating vascular tone, thereby maintaining tissue homeostasis [52]. Hence, the dynamic integration and balance of feedforward and feedback mechanisms collectively constitute the "fail-safe" system of NVC, ensuring rapid response and precise matching.

Additionally, NVC characteristics are significantly influenced by the brain's overall functional state and diffuse neuromodulatory systems. Different types of anesthetics and depths of anesthesia profoundly impact the baseline, response amplitude, and spatiotemporal dynamics of NVC through multiple pathways, including alterations in neuronal excitability, ion channel function, receptor sensitivity and systemic physiological parameters [53,54]. Research has shown that during "sleep inertia" following sleep deprivation, electroencephalography-functional magnetic resonance imaging (EEG-fMRI) coupling patterns, used as an alternative NVC index, exhibit dynamic changes, suggesting that NVC may not remain constant across varying states of alertness [55]. Additionally, ascending neuromodulatory systems originating from the brainstem or basal forebrain, including ACh, Norepinephrine, 5-HT, and dopamine, project widely to the cerebral cortex and other regions, modulating NVU components to regulate their signal pathways, ion channel activities and receptor sensitivities [56]. This higher-level regulation endows NVC with enhanced adaptability, allowing it to dynamically adjust based on the brain's varying physiological and behavioral demands.

4. Neurovascular Coupling Assessment Techniques

The evaluation of NVC is essential for understanding brain physiology and the pathophysiological mechanisms of various neurological disorders. A range of neuroimaging and physiological monitoring techniques have been developed to indirectly or directly assess this complex process. Each method offers unique advantages and limitations, making it suitable for specific research objectives and clinical contexts, thus providing valuable insights into NVC across multiple levels.

4.1 Functional Magnetic Resonance Imaging

Blood-oxygen-level-dependent functional magnetic resonance imaging (BOLD-fMRI) is one of the most widely used non-invasive techniques for brain functional imaging. It provides an indirect reflection of the NVC process by detecting dynamic changes in local brain oxygenation levels driven by neuronal activity [57]. The underlying principle is that neural activity induces functional hyperemia, which lowers the local concentration of deoxygenated hemoglobin, leading to an increase in MRI signals (T2 signals) [58]. The key advantages of BOLD-fMRI include its high spatial resolution (down to millimeters), its ability to cover the entire brain, and its completely non-invasive nature [59]. However, BOLD signals do not directly measure neuronal firing and are susceptible to various sources

of interference, such as head motion, physiological noise, and the effects of large blood vessels [60]. In particular, in the presence of brain diseases, pathological changes in the NVU result in a phenomenon known as "neurovascular uncoupling", where BOLD signals no longer accurately reflect neural activity [61]. Consequently, BOLD-fMRI results often need to be validated using other techniques that directly measure neural activity or more directly assess CBF.

BOLD-fMRI remains a cornerstone in cognitive neuroscience research, extensively applied to assess brain functional activation patterns and NVC characteristics in both healthy individuals and those with various diseases. For example, in migraine research, fMRI has not only highlighted dynamic blood oxygen level changes in the visual cortex at different stages of the migraine cycle but also revealed that even during the interictal phase without prodromal symptoms, patients with migraines may exhibit persistent abnormalities or dysfunction in baseline cortical activity, particularly in the visual cortex, which may be linked to migraine susceptibility [62]. Recently, the evaluation of cerebrovascular reactivity (CVR) using BOLD-fMRI has attracted increasing attention [63]. CVR is typically assessed by inducing global vasodilation through techniques such as inhaling carbon dioxide or breath-holding and then measuring changes in the BOLD signal. Since both CVR and task-induced NVC depend on the vasomotor function of blood vessels, CVR assessment provides critical insight into the degree to which observed BOLD signal changes during tasks are due to variations in neural activity versus the vascular functional state, thus offering valuable information for a more accurate interpretation of BOLD-fMRI results.

4.2 Transcranial Doppler Ultrasonography

Transcranial Doppler ultrasonography (TCD) is a non-invasive, portable diagnostic tool that uses a low-frequency ultrasound probe (usually $\leq$2 MHz), placed on specific acoustic windows of the skull (such as the temporal, occipital, or ocular windows), to emit ultrasound waves and receive Doppler-shifted signals reflected from red blood cells flowing through intracranial vessels. Based on the Doppler effect, TCD allows for real-time, continuous measurement of blood flow velocity in the intracranial large arteries, indirectly reflecting changes in CBF [64]. Functional TCD is the main method for assessing NVC, by recording dynamic changes in the blood flow velocity of target arteries during tasks or stimuli (e.g., the maximum percentage increase in blood flow velocity after stimulation or changes in specific frequency components observed in spectral analysis) [65]. TCD's primary advantages include its non-invasive nature, real-time monitoring, portability and low cost, making it suitable for bedside use with a high temporal resolution during detection of rapid hemodynamic changes [66]. However, its accuracy depends on the operator's experience and about 10–15% of individuals may not achieve satisfactory signals due to suboptimal acoustic windows. Additionally, TCD primarily measures the blood flow velocity in the main arteries at the skull base, which indirectly reflects the status of downstream microcirculation and lacks precise spatial localization. Furthermore, blood flow velocity is influenced by various systemic physiological changes [67].

Despite these limitations, TCD is widely used in both clinical and research settings to assess NVC function, cerebral vascular reactivity, and cerebral autoregulation in healthy individuals and patients with cerebrovascular diseases [68,69]. For example, functional TCD studies have shown hemodynamic abnormalities and impaired NVC in the posterior cerebral artery in migraine patients during both the aura and attack phases [70]. TCD reflects the integrative response of upstream large arteries to downstream microcirculation NVC, making it valuable for assessing overall cerebrovascular function. To explore the mechanisms of NVC at the microvascular level, however, it is necessary to combine TCD with other techniques capable of directly detecting microcirculation or neural activity [71].

4.3 Near-Infrared Spectroscopy

Near-infrared spectroscopy (NIRS) is a non-invasive optical imaging technique that uses near-infrared light at specific wavelengths to penetrate biological tissues, exploiting the differing absorption properties of oxygenated and deoxygenated hemoglobin. This allows for the estimation of relative changes in the concentrations of these two hemoglobin types in local cortical tissue, indirectly reflecting NVC [72]. The primary advantage of NIRS in assessing NVC is its non-invasive nature, portability and lower cost compared to larger devices like fMRI, as well as its greater tolerance to motion artifacts, making it ideal for use in natural environments or with specific populations (such as infants, children, the elderly, and patients with movement disorders) [60]. NIRS has high temporal resolution, theoretically down to the millisecond level, though practical resolution is limited by the inherent slow hemodynamic response (in the seconds range) [73]. Additionally, functional NIRS can be synchronized with other techniques, enabling multimodal NVC research [74].

Despite its limitations, such as lower spatial resolution (typically at the centimeter level), limited depth penetration (mainly reflecting superficial cortical regions) and potential interference from blood flow changes in extra-cranial tissues [62], NIRS offers significant advantages in terms of portability, cost-effectiveness and suitability for specific populations [73]. It has been widely applied in NVC research related to cognitive functions, motor control, emotional regulation and language and its use in studying NVC in various neurological conditions such as stroke, neurodegenerative diseases, psychiatric disorders and pediatric developmental disorders has been increasing [10,75]. For example, one study using synchronous NIRS and EEG record-

ings has found that in AD patients, the coupling between neural activity in certain brainwave frequencies and corresponding cortical blood oxygen signals is significantly weaker than in healthy controls, indicating that impaired NVC may be a key factor in the pathophysiological process of AD [75]. This capability to assess cortical NVC in settings where fMRI is not feasible constitutes NIRS's core application value.

4.4 Electrophysiological Technology and Multimodal Techniques

The NVC process is inherently complex, involving various components such as neuronal activity, glial cell signaling and vascular responses. Due to this complexity, no single technique fully captures the scope of NVC. Multimodal evaluation strategies combine two or more complementary methods, such as electrophysiology with hemodynamics, or macro with micro techniques, to collect data from different levels, either synchronously or in a close sequential manner. The approach enables a more comprehensive and accurate understanding of the underlying mechanisms of NVC and its dynamic alterations in both healthy and diseased brain states [76].

EEG records the cumulative synaptic potentials of numerous neurons through electrodes placed on the scalp. It offers direct insights into cortical neural activity and provides excellent temporal resolution (in the millisecond range) to capture fast dynamic changes in neural function. However, its spatial resolution is relatively low, making it difficult to precisely pinpoint the subcortical origins of the signals [77]. To overcome the limitations of single-modality approaches, combining EEG with hemodynamic techniques that offer higher spatial resolution, such as fMRI, TCD, or NIRS, has emerged as an ideal strategy for NVC research [76].

For instance, the EEG-fMRI integration leverages EEG's high temporal resolution and fMRI's high spatial resolution, enabling the study of the region-specific and dynamic properties of NVC by analyzing the correlation between specific EEG events and subsequent BOLD signal changes. This combination has been widely used to investigate NVC in conditions such as epilepsy, sleep disorders, stroke, and AD [78]. The EEG-TCD technique allows for simultaneous monitoring of neural activity and blood flow dynamics. During cognitive tasks, neuronal activity typically precedes blood flow changes, with a slight delay. By combining the high temporal resolution of EEG and TCD, this delay can be accurately measured, providing insight into how blood flow responds to neural activity [71]. Finally, EEG-NIRS, owing to its portability, low cost, and insensitivity to motion, is especially useful in NVC assessments across diverse populations, such as infants, elderly, or patients with mobility limitations, and natural settings, such as bedside monitoring or during rehabilitation [79].

5. Neurovascular Coupling Dysfunction in Brain Diseases

Dysfunction in NVC is a common feature in various neurological diseases. It is not only a consequence of the disease but may also participate in its onset and progression, exacerbating neuronal damage and functional decline. Table 2 (Ref. [14,80–84]) shows the comparison of neurovascular coupling dysfunction in major neurological diseases.

5.1 Alzheimer's Disease

Alterations in cerebral hemodynamics, including reduced resting CBF and impaired functional hyperemia, are core pathological features of AD. These changes often precede clinical symptoms and correlate with the severity of dementia, potentially accelerating disease progression [9]. According to the "vascular hypothesis" of AD, vascular risk factors and dysfunction of the NVU serve as initial triggers, leading to chronic brain hypoxia. This, in turn, decreases the clearance of β-amyloid (Aβ) and increases its production, ultimately exacerbating neurodegeneration [85]. Aβ pathology impairs NVC through various mechanisms, including inhibiting tissue plasminogen activator (tPA) activity via upregulation of plasminogen activator inhibitor-1. This disruption of the tPA-NO signaling pathway weakens N-methyl-D-aspartate (NMDA) receptor-dependent vasodilation [86]. Additionally, Aβ induces vascular oxidative stress, which is toxic to endothelial cells and leads to the deposition of amyloid in blood vessel walls, forming cerebral amyloid angiopathy and irreversibly impairing vascular function [87]. Tau protein pathology also contributes by interfering with the coupling of NMDA receptors and nNOS, reducing NO production, and impairing functional hyperemia. These effects occur before neuronal degeneration and neurofibrillary tangles form. Tau may also inhibit the phosphorylation of nNOS and eNOS [88]. Importantly, both Aβ and Tau independently and synergistically disrupt NVC through interference with NO-mediated vasodilation, suggesting that the NO signaling pathway is a common pathological convergence point.

Furthermore, dysfunction of various NVU components plays an important role in AD pathology. Pericyte degeneration, shedding and impaired metabolic sensing and vasodilation are early events in AD, leading to BBB breakdown and reduced CBF [9]. Loss of pericyte-derived laminin and abnormal capillary pericyte contraction also contribute to insufficient brain perfusion [23]. Endothelial dysfunction is marked by oxidative stress, decreased NO bioavailability, increased BBB permeability and loss of cholinergic innervation, resulting in weakened eNOS-dependent NVC [89]. Astrocytes in AD models exhibit abnormal calcium signaling, particularly in their end-feet and their decoupling from vascular reactivity weakens NVC. This persists even when vascular elasticity remains intact. Dysfunction of their aquaporin-4 may exacerbate Aβ accumulation [90]. This multifaceted NVU damage collectively

Table 2. Comparison of NVC dysfunction in major neurological diseases.

Neurological diseases	Main NVC dysfunction manifestation	Key affected NVU cells	Major implicated signaling pathways/Molecules	Core NVC pathological mechanism	Main reference
Alzheimer's Disease	Impaired functional hyperemia; Reduced CBF	Pericytes; Endothelial cells; Astrocytes; Neurons	Aβ/Tau toxicity; NO pathway impairment; ET-1 signaling abnormality; Oxidative stress; Inflammation; Ca^{2+} signaling abnormality	Aβ deposition; Tau pathology	[83]
Ischemic Stroke	Ischemic penumbra NVC decoupling; Capillary no-reflow; Impaired functional hyperemia	Pericytes; Endothelial cells; Astrocytes; Microglia	NO/20-HETE imbalance; Glutamate excitotoxicity; Inflammatory cytokines; Ca^{2+} signaling abnormality	Ischemia/reperfusion injury; Spreading depolarizations	[80]
Cerebral Small Vessel Disease	Reduced CBF; Impaired vasoreactivity; Impaired functional hyperemia	Endothelial cells; Pericytes; SMCs	ET-1 signaling abnormality; NO pathway impairment; Oxidative stress; Inflammation; BBB breakdown signaling	Hypertension; Aging, Cerebral Amyloid Angiopathy	[84]
Migraine with Aura	CSD-induced initial hyperperfusion followed by sustained hypoperfusion; Impaired functional hyperemia	Pericytes; Astrocytes; Endothelial cells	Cortical Spreading Depression; NO; K^{+}; Glutamate	Cortical Spreading Depression	[81]
Epilepsy	Ictal hyperemia; Interictal hypoperfusion; Dynamic and spatially heterogeneous NVC changes	Astrocytes; Pericytes; Endothelial cells; Neurons	NO pathway impairment; K^{+} channel dysfunction; Ca^{2+} signaling abnormality; ET-1 signaling abnormality; Inflammation; BBB breakdown	Neuronal hyperexcitability; Ion channel dysfunction; BBB breakdown	[14]
Diabetes with Cognitive Impairment	Impaired functional hyperemia; Reduced CBF	Endothelial cells; Astrocytes; Pericytes	Hyperglycemic toxicity; Insulin resistance signaling; ALFF-RAGE pathway; Oxidative stress; Inflammation; NO pathway impairment	Chronic hyperglycemia; Insulin resistance; AGEs accumulation	[82]

Footnotes: Aβ, β-amyloid; AGEs, advanced glycation end-products; ALFF, amplitude of low-frequency fluctuation; RAGE, receptor for advanced glycation end-products.

leads to chronic cerebral hypoperfusion and hypoxia in AD patients, further worsening neuronal dysfunction and cognitive decline. Hypoxic conditions also stimulate Aβ production and inhibit its clearance, creating a damaging cycle.

5.2 Ischemic Stroke

In ischemic stroke, acute ischemia leads to severe NVC impairment, particularly in the ischemic penumbra, where residual neuronal activity cannot adequately trigger CBF increases, thus exacerbating energy mismatch and tissue damage [80]. Although reperfusion therapy is essential, it also results in reperfusion injury due to incomplete microvascular reperfusion (no-reflow phenomenon) and ongoing NVC dysfunction [91]. Even when large vessels are reperfused, high capillary transit time heterogeneity may lead to "reperfusion failure", which results in low oxygen extraction efficiency. In some cases, sudden restoration of blood flow may trigger "hyperperfusion syndrome", accompanied by tissue hypoxia. NVC failure accelerates the transition from the ischemic penumbra to the infarct core [92]. Under ischemic conditions, astrocytes fail to efficiently uptake glutamate, exacerbating excitotoxicity. Other NVU cells, such as oligodendrocytes, endothelial cells, and pericytes, also express glutamate receptors and are susceptible to damage [80]. Ischemia triggers a robust inflammatory response, including activation of microglia and astrocytes, infiltration of peripheral immune cells, and the release of pro-inflammatory cytokines and damage-associated molecules. This leads to BBB breakdown, further exacerbating NVU damage and NVC dysfunction [93].

Post-stroke recovery involves neurogenesis and angiogenesis, two closely linked processes that are critical for functional improvement. Activated endothelial cells and neural stem cells promote each other through growth factor secretion. Neuroinflammation plays a complex role during recovery, being harmful during the acute phase but beneficial in later stages, with certain inflammatory mediators (e.g., short-term interleukin-6 (IL-6)) promoting repair [58]. Recovery of NVC is crucial for the support of the metabolic needs of regenerating tissues and new synapses. Persistent NVC dysfunction outside the infarct zone may result in long-term neurological deficits [94]. Thus, stroke treatment should not only focus on reperfusing large vessels but also aim to improve microvascular dysfunction and restore NVC, ensuring effective tissue reperfusion and supporting recovery.

5.3 Cerebral Small Vessel Disease

CSVD refers to a heterogeneous group of disorders affecting small arteries, arterioles, capillaries and small veins in the brain [95]. Common causes include hypertensive vascular disease and cerebral amyloid angiopathy. The primary pathological change is arteriosclerosis, characterized by thickening and hardening of vascular walls and lipid-laden degeneration. These structural changes underlie NVC dysfunction and lead to endothelial dysfunction, impaired vascular reactivity, reduced CBF and disruption of the BBB [96,97]. Endothelial damage is an early event in CSVD, resulting in an imbalance of vasoactive substances and a reduction in NO bioavailability, directly affecting NVC. Thakore *et al*. [67] reported that in a CSVD mouse model, depletion of phosphatidylinositol 4,5-bisphosphate in capillary endothelial cells led to the loss of activity in inward-rectifying potassium channel Kir2.1, impairing the dilation signal from capillaries to arterioles and causing functional cerebral hyperperfusion. Furthermore, carotid hemodynamic parameters, such as reduced wall shear stress and increased pulsatility index, were associated with impaired NVC in CSVD patients, suggesting that hemodynamic changes in large arteries directly affect NVC function in brain microvasculature [98]. This "large vessel to microvessel" pathological influence highlights the complexity of CSVD pathophysiology.

A clinical study showed that NVC function declines with the severity of CSVD imaging biomarkers, such as white matter hyperintensities and cerebral microbleeds [70]. Impaired NVC results in chronic cerebral underperfusion, particularly in the deep white matter regions. This underperfusion, together with BBB disruption, exacerbates white matter damage and is closely associated with cognitive decline [99]. A study using resting-state fMRI with local consistency and CBF ratio analysis has revealed early NVC abnormalities in patients with subcortical ischemic vascular disease that correlate with the degree of cognitive impairment [100]. NVC assessment is considered a potential biomarker for monitoring CSVD severity and progression. Current treatments focus primarily on controlling vascular risk factors, especially hypertension, but there is a great need for specific therapies targeting NVU dysfunction [73].

5.4 Migraine With Aura

NVC dysfunction in migraine with aura is primarily associated with cortical spreading depression (CSD). CSD is a large-scale, slowly propagating depolarization wave involving neurons and glial cells, followed by neural activity suppression, and is considered the neurophysiological basis of migraine aura [62]. CSD induces significant changes in CBF: an initial brief local increase in blood flow (hyperemia), followed by a prolonged and gradually spreading decrease in blood flow (hypoperfusion). This biphasic blood flow response represents a transient and severe disturbance in NVC, with the hypoperfusion phase lasting for several hours and associated with NVC impairment [81]. During CSD, all components of the NVU participate in the dynamic changes in NVC. Pericytes in capillaries play an active regulatory role, with prolonged vasoconstriction after CSD being associated with sustained increases in calcium concentration in pericytes. After CSD, sensory stim-

uli no longer induce normal capillary dilation or calcium responses in pericytes, suggesting that pericyte dysfunction contributes to NVC impairment following CSD [101]. Astrocytes also exhibit intense calcium wave activity during CSD and pharmacologically inhibiting astrocyte function blocks CSD-induced meningeal afferent nerve sensitization, indicating that astrocytes may contribute to harmful information processing downstream of CSD via calcium-independent signaling pathways [78]. Calcitonin gene-related peptide (CGRP) release increases during CSD, possibly contributing to the initiation and propagation of CSD and its vascular effects. CGRP receptor antagonists inhibit the occurrence of CSD *in vitro* [102]. Additionally, abnormalities in KATP channel function are also linked to NVC dysfunction in migraine. Global regulation of KATP channel activity significantly interferes with NVC. Mice with Cantú syndrome show diminished baseline NVC and increased sensitivity to KATP channel openers, suggesting that KATP channel dysfunction may play a key role in the pathogenesis of migraine with aura [103].

5.5 Epilepsy

Epilepsy is characterized by abnormal synchronous high-frequency discharges of neurons, with NVC dysfunction playing a crucial role in its pathophysiology. Both early-onset and late-onset idiopathic epilepsy patients show lower global NVC coefficients and reduced CBF/"Amplitude of Low-Frequency Fluctuation" (ALFF) ratios in specific brain regions, such as the precentral and postcentral gyri, when compared to healthy controls [104]. During seizures, epileptic foci typically exhibit marked increases in local CBF and metabolic rates, with fMRI revealing heightened BOLD signals at the seizure sites. However, one study has reported transient vasoconstriction or more complex biphasic perfusion patterns at the onset of seizures [105]. During the interictal period, abnormal discharges, such as spikes, also affect NVC. One to five seconds prior to a seizure, vasoconstriction may be observed in the cortical region surrounding an epileptic focus, potentially due to blood shunting in response to imminent high metabolic activity or a reduction in local metabolism [106]. Post-seizure, localized brain tissue often experiences severe and persistent hypoxia, accompanied by reduced CBF and sustained microarterial constriction, which is closely linked to fluctuations in Ca^{2+} levels in vascular smooth muscle cells and astrocytes. Astrocytic Ca^{2+} signaling increases sharply during seizures, possibly triggering both vasodilation and vasoconstriction, leading to complex vascular responses [14].

Components of the NVU contribute to epilepsy-associated NVC dysfunction, with neuronal hyperexcitability being the primary initiating factor. Endothelial cells and the integrity of the BBB may be compromised during epileptic seizures, exacerbating inflammation and NVU dysfunction [107]. The ET-1 signaling pathway plays a significant role, with endothelin receptor type A (ETA) receptor activation causing local ischemia and excitotoxic damage, while endothelin receptor type B (ETB) receptor activation drives non-ischemic seizures through inflammatory pathways. NVC dysfunction leads to energy failure, hypoxia, and neuronal damage in the epileptic focus and surrounding regions, promoting the propagation of epileptic discharges and resulting in neurological deficits and long-term secondary brain damage after a seizure [14]. Notably, persistent post-seizure vasoconstriction and severe local hypoxia represent critical periods for secondary brain damage and may significantly contribute to cognitive and neurological dysfunction associated with epilepsy [14].

5.6 Diabetes With Cognitive Impairment

Diabetes, particularly Type 2 diabetes, results in metabolic disturbances, such as chronic hyperglycemia, insulin resistance, dyslipidemia, and low-grade chronic inflammation, leading to cerebrovascular pathology and NVC dysfunction, ultimately contributing to cognitive impairment [108]. One study has shown regional reductions in the coupling between neuronal activity and CBF in specific brain areas, such as the hippocampus, fusiform gyrus and amygdala, in diabetic patients, although global gray matter NVC may remain unchanged [109]. The degree of NVC impairment correlates with the severity of cognitive deficits, particularly in executive function, memory, and processing speed. Research also indicates that reduced ALFF-CBF coupling in the left hippocampus and amygdala is associated with poorer executive function in diabetic patients [109].

Several key mechanisms contribute to NVC dysfunction in diabetes. Endothelial dysfunction, induced by hyperglycemia, is a central factor, involving impaired eNOS function, reduced NO production and excessive reactive oxygen species (ROS) generation, which damage endothelial cells, decrease NO clearance and promote inflammation [110]. Advanced glycation end-products (AGEs) accumulate in the brain's microvasculature, leading to vascular sclerosis and the triggering of oxidative stress and inflammation through interactions with the "Receptor for Advanced Glycation End-products" (RAGE), thereby impairing NVC [108]. Chronic inflammation and insulin resistance further damage endothelial NO production, glucose transport and neuronal function, leading to NVC dysregulation [82]. Diabetes-associated microvascular changes, including basal membrane thickening, pericyte loss/dysfunction, endothelial cell damage, capillary rarefaction and astrocyte activation and dysfunction, all directly impair the vascular response to neuronal activity [82]. Additionally, the dysfunction of specific signaling molecules and ion channels contributes to NVC impairment [111]. These combined mechanisms underscore NVC dysfunction as a key link between diabetes and cognitive decline.

6. Targeted Therapeutic Strategies for Neurovascular Coupling

NVC dysfunction is a central pathological mechanism in numerous neurological disorders. Consequently, restoring or modulating NVC function has emerged as a promising therapeutic avenue. Current treatment strategies are primarily categorized into pharmacological interventions, non-pharmacological interventions, and emerging cutting-edge approaches.

6.1 Pharmacological Interventions

6.1.1 Targeting Key Molecular Signaling Pathways

Multiple signaling pathways precisely regulate NVC, with NO acting as a crucial vasodilator. Strategies to enhance NO bioavailability include supplementation with NO precursors such as L-arginine and L-citrulline, the latter being regarded as more effective [112]. Preclinical studies have demonstrated that L-citrulline improves retinal vasodilation in diabetic rats and enhances CBF in a cerebral diffusion restriction model, while L-arginine has been successfully used to restore NVC in patients with MELAS (mitochondrial myopathy, encephalomyopathy, lactic acidosis, and stroke-like episodes). Dietary nitrates/nitrites, independent of NOS, also show potential for improving CBF in elderly individuals [105]. Furthermore, modulating the AA metabolic pathway to balance the production of vasodilators and vasoconstrictors remains a crucial therapeutic focus [113]. ET-1, a potent vasoconstrictor, is implicated in NVC dysfunction in several neurological disorders, making ET-1 antagonists a promising therapeutic strategy [114].

6.1.2 Modulating Neuroinflammation and Oxidative Stress

Oxidative stress and inflammation are common mechanisms underlying NVU damage and NVC dysfunction [102]. Consequently, antioxidants and anti-inflammatory agents hold therapeutic promise. Resveratrol, a polyphenolic compound with antioxidant properties, clears ROS by activating sirtuin 1, inhibiting pro-inflammatory enzymes, and downregulating nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, thereby rescuing NVC function in aged mice and improving CBF and cognitive function in some human trials [115]. Mitochondria are a major source of ROS and mitochondrial-targeted antioxidants show promise in treating conditions like brain injury and AD, although gender differences in efficacy may exist [116]. Inhibitors targeting specific cytokines, such as IL-1 and tumor necrosis factor-α (TNF-α), exhibit therapeutic potential in reducing neuroinflammation. IL-1, a key mediator of neuronal damage, reduces CBF, and blocking its action exerts neuroprotective effects [117]. TNF-α inhibitors have also been shown to improve cognition in AD animal models, although their direct impact on NVC requires further investigation [118].

6.1.3 Targeting Cellular Components of the Neurovascular Unit

Protecting the structural and functional integrity of the cellular components within the NVU has become an important therapeutic strategy for various brain diseases. Given the central role of pericytes in maintaining the BBB and regulating blood flow, as well as their vulnerability in multiple pathological states, targeting pericytes has garnered considerable attention. Strategies include inhibiting pericyte apoptosis, promoting their proliferation and migration, regulating their contractile state, or restoring their function by targeting specific receptors such as platelet-derived growth factor receptor β and Tie2 [119]. However, the specificity of drug delivery remains a challenge [120]. Enhancing endothelial function is another central strategy, including the use of antioxidants (e.g., vitamin C, coenzyme Q10 and α-lipoic acid) to mitigate ROS damage and enhance NO bioavailability [121]. Targeting molecules such as Caveolin-1 or poly (ADP-ribose) polymerase 1 (PARP-1) may also improve NVC. Caveolin-1 can be restored through gene therapy to enhance NVC, whereas excessive activation of PARP-1 leads to endothelial dysfunction through nicotinamide adenine dinucleotide (NAD^+) depletion, while inhibiting PARP-1 has been shown to improve NVC and cognitive function in aged mice [122]. Moreover, neuroprotective agents indirectly safeguard NVC by reducing neuronal damage and excitotoxicity. Anti-inflammatory and immunomodulatory agents protect NVC by inhibiting excessive activation of microglia and astrocytes, reducing inflammatory factor release, for example, by polarizing microglia towards an M2 anti-inflammatory phenotype [123]. Statins, beyond their lipid-lowering effects, improve endothelial function, exhibit anti-inflammatory and antioxidant properties and show potential for NVU protection in experimental stroke models, although clinical evidence remains inconsistent [124].

6.2 Non-Pharmacological Interventions

6.2.1 Lifestyle Interventions

Regular physical exercise and healthy dietary habits are crucial for maintaining vascular health and improving NVC. Regular physical exercise enhances NO bioavailability, increases CBF and improves brain function by upregulating eNOS and nuclear factor erythroid 2-related factor 2, a key regulatory factor in the antioxidant pathway [125]. In AD animal models, exercise alleviates cerebrovascular dysfunction and enhances NVC [126]. For post-concussion syndrome, some rehabilitation programs explicitly target NVC by combining fMRI-guided training with cognitive challenges, reporting both subjective and objective improvements [126,127]. In terms of dietary adjustments, foods rich in nitrates (e.g., leafy vegetables, beets) and polyphenols (e.g., resveratrol in fruits and cocoa) directly convert to NO or enhance its bioavailability [128].

The Mediterranean diet is associated with better post-stroke outcomes, possibly by reducing insulin resistance, increasing the mobilization of circulating endothelial progenitor cells and exerting anti-inflammatory effects [129]. Caloric restriction and intermittent fasting alleviate neuroinflammation and oxidative stress, thereby improving endothelial function [130].

6.2.2 Neuromodulation Technologies

Neuromodulation technologies provide novel pathways for regulating NVC by directly or indirectly influencing neuronal activity and vascular function. Photobiomodulation, using specific wavelengths of light (red to near-infrared), targets mitochondrial cytochrome C oxidase to enhance ATP synthesis, increase CBF and reduce oxidative stress and inflammation [131]. Transcranial direct current stimulation (tDCS) modulates cortical excitability through weak direct currents, with anodal tDCS shown to increase CBF, proving beneficial for chronic stroke or brain hypoperfusion [132]. Deep brain stimulation, such as stimulation of the thalamic subthalamic nucleus in Parkinson's disease patients, improves motor symptoms and reverses microvascular density reduction, thereby enhancing microvascular integrity [133]. Vagus nerve stimulation indirectly modulates central nervous system activity and has shown promise in reducing infarct volume, increasing CBF and decreasing inflammation in preclinical stroke models [134]. Focused ultrasound (FUS), an emerging technology, induces hemodynamic responses by modulating neural activity with low-intensity stimulation. When combined with microbubbles to open the BBB, it may temporarily suppress neurovascular responses, suggesting that its impact on NVC is dependent on parameters such as intensity, duration, and frequency [135]. Even when applied locally, these technologies may engage broader network modulation, influencing NVC on a larger scale.

6.3 Emerging Treatment Models

Emerging therapeutic modalities represent cutting-edge strategies for repairing NVC, aiming to utilize advanced biotechnologies for more precise interventions. However, their path toward clinical application is complex, commonly involving significant challenges in safety, efficacy, and targeted delivery. Gene therapy seeks to correct the molecular defects causing NVC dysfunction through the long-term introduction of therapeutic genes, such as those encoding NOS or neuroprotective factors [136]. For instance, targeting cyclin-dependent kinase 5, which is aberrantly activated in AD and disrupts the function of NVU cells, represents a promising gene therapy approach to restore NVU integrity [137]. Despite slow progress in clinical translation, there has been some momentum. The core challenge lies in selecting the ideal viral vector (such as adeno-associated virus, AAV), avoiding immune responses, and ensuring precise and stable gene expression. In the field of Parkinson's disease, some early clinical trials have shown promise, such as a phase 1b trial delivering adeno-associated virus serotype 2 carrying glial cell line-derived neurotrophic factor to the striatum, which confirmed the safety of the therapy and the effectiveness of targeting, marking a key step in repairing neural circuits [138]. Stem cell-based therapies primarily support neurorepair by leveraging endogenous paracrine effects, such as the release of growth factors and anti-inflammatory molecules, promoting angiogenesis, alleviating inflammation, strengthening the BBB, and enhancing synaptic plasticity, which collectively enhance the NVU microenvironment and restore NVC [139]. Clinically, mesenchymal stem cells (MSCs) have been widely evaluated in clinical trials for diseases such as ischemic stroke and AD due to their immunomodulatory properties. A meta-analysis of stroke indicated that MSC transplantation is safe and may improve functional outcomes. However, there remain core issues to address, such as cell source, survival, functional integration, and risks of immune rejection and tumorigenicity [140]. Nanomedicine, utilizing nanomaterials as targeted delivery systems for drugs or genes, particularly those crossing the BBB, or for direct neuroprotection and the construction of nanofiber scaffolds to support neural regeneration, holds potential to enhance the specificity and efficacy of pharmacological interventions [141]. However, the clinical translation of nanomedicine in neurology is still in its early stages, mainly due to the formidable challenge of efficiently and safely crossing the BBB. Most nanomedicine applications for central nervous system diseases remain at the preclinical stage. However, some concepts are approaching clinical reality, such as the development of nanoparticle-based systems for more effective delivery of antioxidants, anti-inflammatory agents, or thrombolytics to ischemic brain tissue following stroke [142]. Optogenetics, a research tool that precisely modulates the activity of specific neurons using genetic engineering, has advanced our understanding of NVC mechanisms. In stroke animal models, it has shown potential to enhance NVC responses and promote functional recovery by regulating nNOS expression, providing a foundation for the development of new therapies [143]. However, its clinical translation remains distant. The primary barrier is that this technology requires invasive gene delivery via viral vectors (for implanting light-sensitive proteins) and surgical implantation of fiber-optic devices for light delivery. These procedures raise significant safety concerns regarding immunogenicity, potential neurotoxicity, and long-term stability of the equipment, making it more distant for clinical application compared to gene and cell therapies [144].

7. Conclusion and Future Perspectives

NVC is a fundamental process that supports normal brain function. It enables the rapid and precise adjustment of cerebral blood flow to meet the metabolic demands

of neurons through the coordinated action of multiple cell types and signaling molecules within the NVU. A deeper understanding of the physiological mechanisms underlying NVC has revealed the complex functions and coordination among NVU components, such as neurons, astrocytes, pericytes and endothelial cells, in the sensing, transmission and execution of signals. However, this nuanced regulatory system is susceptible to disruption under pathological conditions, such as aging, oxidative stress, inflammation, metabolic disorders and hypertension, which lead to NVC dysfunction. The uncoupling of NVC is a common pathological feature of various brain diseases, including AD, stroke, CSVD, epilepsy and migraines and is considered a key mechanism underlying cognitive decline and neuronal damage associated with these conditions.

With the advancement of imaging technologies such as fMRI, positron emission tomography (PET), TCD, NIRS and high-resolution optical imaging, the ability to assess NVC has both greatly improved and deepened understanding of its role in both health and disease. Although the precise roles of astrocytes and pericytes remain debated, the targeting of NVC dysfunction is emerging as a promising therapeutic strategy. Preclinical studies suggest that interventions such as modulating NO signaling, antioxidant therapies, anti-inflammatory approaches, ion channel regulation, targeted cell-type therapies and metabolic improvements may help restore impaired NVC function. Notably, enhancing endothelial health and maintaining redox balance seem to be central mechanisms shared by many interventions.

Future research should focus on resolving the complex regulatory network of NVC with higher spatiotemporal resolution, elucidating the causal role of NVC dysfunction in disease pathogenesis and the development of reliable clinical assessment tools and biomarkers. Translating these findings into effective clinical strategies will be essential to overcoming current challenges and achieving breakthroughs in the prevention and treatment of brain diseases associated with NVC dysfunction.

Author Contributions

ALW, HEL and DXY conceptualized the study and designed the overall structure of the review. ALW, JL, and LW performed the extensive literature search and drafted the initial manuscript. ALW, JL and DXY prepared the figures and tables. DXY and HEL supervised the project and provided financial support. 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.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

Not applicable.

Funding

This work was supported by the Joint Special Project of Kunming Medical University-General Project (202401AY070001-245).

Conflict of Interest

The authors declare no conflict of interest.

References

[1] Sten S, Podéus H, Sundqvist N, Elinder F, Engström M, Cedersund G. A quantitative model for human neurovascular coupling with translated mechanisms from animals. PLoS Computational Biology. 2023; 19: e1010818. https://doi.org/10.1371/journal.pcbi.1010818.

[2] Raichle ME, Gusnard DA. Appraising the brain's energy budget. Proceedings of the National Academy of Sciences of the United States of America. 2002; 99: 10237–10239. https://doi.org/10.1073/pnas.172399499.

[3] Roy CS, Sherrington CS. On the Regulation of the Blood-supply of the Brain. The Journal of Physiology. 1890; 11: 85–158.17. https://doi.org/10.1113/jphysiol.1890.sp000321.

[4] Huneau C, Benali H, Chabriat H. Investigating Human Neurovascular Coupling Using Functional Neuroimaging: A Critical Review of Dynamic Models. Frontiers in Neuroscience. 2015; 9: 467. https://doi.org/10.3389/fnins.2015.00467.

[5] Iadecola C, Nedergaard M. Glial regulation of the cerebral microvasculature. Nature Neuroscience. 2007; 10: 1369–1376. https://doi.org/10.1038/nn2003.

[6] Hosford PS, Wells JA, Nizari S, Christie IN, Theparambil SM, Castro PA, *et al*. CO_2 signaling mediates neurovascular coupling in the cerebral cortex. Nature Communications. 2022; 13: 2125. https://doi.org/10.1038/s41467-022-29622-9.

[7] Chen Y, Wang L, Zhou Y, Wang Y, Qin W, Wang M, *et al*. Exendin-4 improves cerebral ischemia by relaxing microvessels, rapidly increasing cerebral blood flow after reperfusion. Basic Research in Cardiology. 2025; 120: 423–441. https://doi.org/10.1007/s00395-025-01096-y.

[8] Schaeffer S, Iadecola C. Revisiting the neurovascular unit. Nature Neuroscience. 2021; 24: 1198–1209. https://doi.org/10.1038/s41593-021-00904-7.

[9] Iadecola C. The Neurovascular Unit Coming of Age: A Journey through Neurovascular Coupling in Health and Disease. Neuron. 2017; 96: 17–42. https://doi.org/10.1016/j.neuron.2017.07.030.

[10] Zhang D, Ruan J, Peng S, Li J, Hu X, Zhang Y, *et al*. Synaptic-like transmission between neural axons and arteriolar smooth muscle cells drives cerebral neurovascular coupling. Nature Neuroscience. 2024; 27: 232–248. https://doi.org/10.1038/s41593-023-01515-0.

[11] Yang L, Zhao W, Kan Y, Ren C, Ji X. From Mechanisms to Medicine: Neurovascular Coupling in the Diagnosis and Treatment of Cerebrovascular Disorders: A Narrative Review. Cells. 2024; 14: 16. https://doi.org/10.3390/cells14010016.

[12] Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nature Reviews. Neuroscience. 2017; 18: 419–434. https://doi.org/10.1038/nrn.2017.48.

[13] Fabjan A, Zaletel M, Žvan B. Is there a persistent dysfunction of neurovascular coupling in migraine? BioMed Research International. 2015; 2015: 574186. https://doi.org/10.1155/2015/574186.

[14] Liu X, Zhang Y, Zhao Y, Zhang Q, Han F. The Neurovascular Unit Dysfunction in the Molecular Mechanisms of Epileptogenesis and Targeted Therapy. Neuroscience Bulletin. 2024; 40: 621–634. https://doi.org/10.1007/s12264-024-01193-3.

[15] Yu Y, Hu B, Yu XW, Cui YY, Cao XY, Ni MH, *et al*. Neurovascular decoupling of frontoparietal cortex-putamen-cerebellum network in type 2 diabetes patient: Potential biomarker for abnormal eating patterns. Diabetes Research and Clinical Practice. 2025; 224: 112175. https://doi.org/10.1016/j.diabres.2025.112175.

[16] Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. Nature. 2010; 468: 232–243. https://doi.org/10.1038/nature09613.

[17] Guerra G, Lucariello A, Perna A, Botta L, De Luca A, Moccia F. The Role of Endothelial Ca^{2+} Signaling in Neurovascular Coupling: A View from the Lumen. International Journal of Molecular Sciences. 2018; 19: 938. https://doi.org/10.3390/ijms19040938.

[18] Császár E, Lénárt N, Cserép C, Környei Z, Fekete R, Pósfai B, *et al*. Microglia modulate blood flow, neurovascular coupling, and hypoperfusion via purinergic actions. The Journal of Experimental Medicine. 2022; 219: e20211071. https://doi.org/10.1084/jem.20211071.

[19] Looser ZJ, Faik Z, Ravotto L, Zanker HS, Jung RB, Werner HB, *et al*. Oligodendrocyte-axon metabolic coupling is mediated by extracellular K^+ and maintains axonal health. Nature Neuroscience. 2024; 27: 433–448. https://doi.org/10.1038/s41593-023-01558-3.

[20] Blanco VM, Stern JE, Filosa JA. Tone-dependent vascular responses to astrocyte-derived signals. American Journal of Physiology. Heart and Circulatory Physiology. 2008; 294: H2855–H2863. https://doi.org/10.1152/ajpheart.91451.2007.

[21] Lia A, Di Spiezio A, Speggiorin M, Zonta M. Two decades of astrocytes in neurovascular coupling. Frontiers in Network Physiology. 2023; 3: 1162757. https://doi.org/10.3389/fnetp.2023.1162757.

[22] Negri S, Faris P, Soda T, Moccia F. Endothelial signaling at the core of neurovascular coupling: The emerging role of endothelial inward-rectifier K^+ ($K_{ir}2.1$) channels and N-methyl-d-aspartate receptors in the regulation of cerebral blood flow. The International Journal of Biochemistry & Cell Biology. 2021; 135: 105983. https://doi.org/10.1016/j.biocel.2021.105983.

[23] Hall CN, Reynell C, Gesslein B, Hamilton NB, Mishra A, Sutherland BA, *et al*. Capillary pericytes regulate cerebral blood flow in health and disease. Nature. 2014; 508: 55–60. https://doi.org/10.1038/nature13165.

[24] Hartmann DA, Coelho-Santos V, Shih AY. Pericyte Control of Blood Flow Across Microvascular Zones in the Central Nervous System. Annual Review of Physiology. 2022; 84: 331–354. https://doi.org/10.1146/annurev-physiol-061121-040127.

[25] Cauli B, Tong XK, Rancillac A, Serluca N, Lambolez B, Rossier J, *et al*. Cortical GABA interneurons in neurovascular coupling: relays for subcortical vasoactive pathways. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2004; 24: 8940–8949. https://doi.org/10.1523/JNEUROSCI.3065-04.2004.

[26] Stackhouse TL, Mishra A. Neurovascular Coupling in Development and Disease: Focus on Astrocytes. Frontiers in Cell and Developmental Biology. 2021; 9: 702832. https://doi.org/10.3389/fcell.2021.702832.

[27] Sandoo A, van Zanten JJCSV, Metsios GS, Carroll D, Kitas GD. The endothelium and its role in regulating vascular tone. The Open Cardiovascular Medicine Journal. 2010; 4: 302–312. https://doi.org/10.2174/1874192401004010302.

[28] Harraz OF, Longden TA, Dabertrand F, Hill-Eubanks D, Nelson MT. Endothelial GqPCR activity controls capillary electrical signaling and brain blood flow through PIP_2 depletion. Proceedings of the National Academy of Sciences of the United States of America. 2018; 115: E3569–E3577. https://doi.org/10.1073/pnas.1800201115.

[29] Sweeney MD, Ayyadurai S, Zlokovic BV. Pericytes of the neurovascular unit: key functions and signaling pathways. Nature Neuroscience. 2016; 19: 771–783. https://doi.org/10.1038/nn.4288.

[30] Muoio V, Persson PB, Sendeski MM. The neurovascular unit - concept review. Acta Physiologica (Oxford, England). 2014; 210: 790–798. https://doi.org/10.1111/apha.12250.

[31] Sweeney MD, Zhao Z, Montagne A, Nelson AR, Zlokovic BV. Blood-Brain Barrier: From Physiology to Disease and Back. Physiological Reviews. 2019; 99: 21–78. https://doi.org/10.1152/physrev.00050.2017.

[32] Gong Y, Wu M, Huang Y, He X, Yuan J, Dang B. Research developments in the neurovascular unit and the blood brain barrier (Review). Biomedical Reports. 2025; 22: 88. https://doi.org/10.3892/br.2025.1966.

[33] Shetty PK, Galeffi F, Turner DA. Cellular Links between Neuronal Activity and Energy Homeostasis. Frontiers in Pharmacology. 2012; 3: 43. https://doi.org/10.3389/fphar.2012.00043.

[34] Peretin JM, Cover CG, Vazquez AL. Contributions of synaptic glutamate versus neuronal spiking activity to cerebral vascular responses in awake mice. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2025. https://doi.org/10.1177/0271678X251338407. (online ahead of print)

[35] Uhlirova H, Kılıç K, Tian P, Thunemann M, Desjardins M, Saisan PA, *et al*. Cell type specificity of neurovascular coupling in cerebral cortex. eLife. 2016; 5: e14315. https://doi.org/10.7554/eLife.14315.

[36] Ruff CF, Juarez Anaya F, Dienel SJ, Rakymzhan A, Altamirano-Espinoza A, Couey JJ, *et al*. Long-range inhibitory neurons mediate cortical neurovascular coupling. Cell Reports. 2024; 43: 113970. https://doi.org/10.1016/j.celrep.2024.113970.

[37] Meyer-Baese L, Jaeger D, Keilholz S. Neurovascular coupling: a review of spontaneous neocortical dynamics linking neuronal activity to hemodynamics and what we have learned from the rodent brain. Journal of Neurophysiology. 2025; 133: 644–660. https://doi.org/10.1152/jn.00418.2024.

[38] McConnell HL, Kersch CN, Woltjer RL, Neuwelt EA. The Translational Significance of the Neurovascular Unit. The Journal of Biological Chemistry. 2017; 292: 762–770. https://doi.org/10.1074/jbc.R116.760215.

[39] Zaritsky JJ, Eckman DM, Wellman GC, Nelson MT, Schwarz TL. Targeted disruption of kir2.1 and kir2.2 genes reveals the essential role of the inwardly rectifying k(+) current in k(+)-mediated vasodilation. Circulation Research. 2000; 87: 160–166. https://doi.org/10.1161/01.res.87.2.160.

[40] Djurich S, Secomb TW. Analysis of potassium ion diffusion from neurons to capillaries: Effects of astrocyte endfeet geometry. The European Journal of Neuroscience. 2024; 59: 323–332. https://doi.org/10.1111/ejn.16232.

[41] Muñoz MF, Puebla M, Figueroa XF. Control of the neurovascular coupling by nitric oxide-dependent regulation of astrocytic Ca(2+) signaling. Frontiers in Cellular Neuroscience. 2015; 9: 59. https://doi.org/10.3389/fncel.2015.00059.

[42] Le Gac B, Tournissac M, Belzic E, Picaud S, Dusart I, Soula H, *et al*. Elevated pyramidal cell firing orchestrates arteriolar vasoconstriction through COX-2-derived prostaglandin E2 signaling. eLife. 2025; 13: RP102424. https://doi.org/10.7554/eLife.102424.

[43] Rubanyi GM. Endothelium-derived relaxing and contracting factors. Journal of Cellular Biochemistry. 1991; 46: 27–36. https://doi.org/10.1002/jcb.240460106.

[44] Peppiatt CM, Howarth C, Mobbs P, Attwell D. Bidirectional control of CNS capillary diameter by pericytes. Nature. 2006; 443: 700–704. https://doi.org/10.1038/nature05193.

[45] Hill RA, Tong L, Yuan P, Murikinati S, Gupta S, Grutzendler J. Regional Blood Flow in the Normal and Ischemic Brain Is Controlled by Arteriolar Smooth Muscle Cell Contractility and Not by Capillary Pericytes. Neuron. 2015; 87: 95–110. https://doi.org/10.1016/j.neuron.2015.06.001.

[46] Longden TA, Isaacs D. Pericyte Electrical Signalling and Brain Haemodynamics. Basic & Clinical Pharmacology & Toxicology. 2025; 136: e70030. https://doi.org/10.1111/bcpt.70030.

[47] Mughal A, Hennig GW, Heppner T, Tsoukias NM, Hill-Eubanks D, Nelson MT. Electrocalcium coupling in brain capillaries: Rapidly traveling electrical signals ignite local calcium signals. Proceedings of the National Academy of Sciences of the United States of America. 2024; 121: e2415047121. https://doi.org/10.1073/pnas.2415047121.

[48] Dunn KM, Nelson MT. Potassium channels and neurovascular coupling. Circulation Journal: Official Journal of the Japanese Circulation Society. 2010; 74: 608–616. https://doi.org/10.1253/circj.cj-10-0174.

[49] Meng L, Rasmussen M, Meng DM, White FA, Wu LJ. Integrated Feedforward and Feedback Mechanisms in Neurovascular Coupling. Anesthesia and Analgesia. 2024; 139: 1283–1293. https://doi.org/10.1213/ANE.0000000000006891.

[50] Lim XR, Abd-Alhaseeb MM, Ippolito M, Koide M, Senatore AJ, Plante C, *et al*. Endothelial Piezo1 channel mediates mechanofeedback control of brain blood flow. Nature Communications. 2024; 15: 8686. https://doi.org/10.1038/s41467-024-52969-0.

[51] Hirunpattarasilp C, Barkaway A, Davis H, Pfeiffer T, Sethi H, Attwell D. Hyperoxia evokes pericyte-mediated capillary constriction. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2022; 42: 2032–2047. https://doi.org/10.1177/0271678X221111598.

[52] Mangia S, DiNuzzo M, Ponticorvo S, Dienel GA, Behar KL, Benveniste H, *et al*. Reduced removal of waste products from energy metabolism takes center stage in human brain aging. Scientific Reports. 2025; 15: 8127. https://doi.org/10.1038/s41598-025-90342-3.

[53] Franceschini MA, Radhakrishnan H, Thakur K, Wu W, Ruvinskaya S, Carp S, *et al*. The effect of different anesthetics on neurovascular coupling. NeuroImage. 2010; 51: 1367–1377. https://doi.org/10.1016/j.neuroimage.2010.03.060.

[54] Masamoto K, Kanno I. Anesthesia and the quantitative evaluation of neurovascular coupling. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2012; 32: 1233–1247. https://doi.org/10.1038/jcbfm.2012.50.

[55] Wang ZJ, Lee HC, Chuang CH, Hsiao FC, Lee SH, Hsu AL, *et al*. Traces of EEG-fMRI coupling reveals neurovascular dynamics on sleep inertia. Scientific Reports. 2024; 14: 1537. https://doi.org/10.1038/s41598-024-51694-4.

[56] Natsubori A, Kwon S, Honda Y, Kojima T, Karashima A, Masamoto K, *et al*. Serotonergic regulation of cortical neurovascular coupling and hemodynamics upon awakening from sleep in mice. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2024; 44: 1591–1607. https://doi.org/10.1177/0271678X241238843.

[57] Hall CN, Howarth C, Kurth-Nelson Z, Mishra A. Interpreting BOLD: towards a dialogue between cognitive and cellular neuroscience. Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences. 2016; 371: 20150348. https://doi.org/10.1098/rstb.2015.0348.

[58] Ruan Z, Sun D, Zhou X, Yu M, Li S, Sun W, *et al*. Altered neurovascular coupling in patients with vascular cognitive impairment: a combined ASL-fMRI analysis. Frontiers in Aging Neuroscience. 2023; 15: 1224525. https://doi.org/10.3389/fnagi.2023.1224525.

[59] Sharpee TO, Destexhe A, Kawato M, Sekulić V, Skinner FK, Wójcik DK, *et al*. 25th Annual Computational Neuroscience Meeting: CNS-2016. BMC Neuroscience. 2016; 17 Suppl 1: 54. https://doi.org/10.1186/s12868-016-0283-6.

[60] Yang L, Wang Z. Applications and advances of combined fMRI-fNIRs techniques in brain functional research. Frontiers in Neurology. 2025; 16: 1542075. https://doi.org/10.3389/fneur.2025.1542075.

[61] Stadlbauer A, Kinfe TM, Zimmermann M, Eyüpoglu I, Brandner N, Buchfelder M, *et al*. Association between tissue hypoxia, perfusion restrictions, and microvascular architecture alterations with lesion-induced impairment of neurovascular coupling. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2022; 42: 526–539. https://doi.org/10.1177/0271678X20947546.

[62] Pikor D, Banaszek-Hurla N, Drelichowska A, Hurla M, Dorszewska J, Wolak T, *et al*. fMRI Insights into Visual Cortex Dysfunction as a Biomarker for Migraine with Aura. Neurology International. 2025; 17: 15. https://doi.org/10.3390/neurolint17020015.

[63] Williams RJ, Macdonald ME, Mazerolle EL, Pike GB. The relationship between cognition and cerebrovascular reactivity: implications for task-based fMRI. Frontiers in Physics. 2021; 9: 645249. https://doi.org/10.3389/fphy.2021.645249.

[64] Naqvi J, Yap KH, Ahmad G, Ghosh J. Transcranial Doppler ultrasound: a review of the physical principles and major applications in critical care. International Journal of Vascular Medicine. 2013; 2013: 629378. https://doi.org/10.1155/2013/629378.

[65] Ferreira J, Ferreira P, Azevedo E, Castro P. Assessment of Neurovascular Coupling by Spectral Analysis of Cerebral Blood Flow Velocity With Transcranial Doppler. Ultrasound in Medicine & Biology. 2024; 50: 751–759. https://doi.org/10.1016/j.ultrasmedbio.2024.02.003.

[66] Pan Y, Wan W, Xiang M, Guan Y. Transcranial Doppler Ultrasonography as a Diagnostic Tool for Cerebrovascular Disorders. Frontiers in Human Neuroscience. 2022; 16: 841809. https://doi.org/10.3389/fnhum.2022.841809.

[67] Thakore P, Yamasaki E, Ali S, Sanchez Solano A, Labelle-Dumais C, Gao X, *et al*. PI3K block restores age-dependent neurovascular coupling defects associated with cerebral small vessel disease. Proceedings of the National Academy of Sciences of the United States of America. 2023; 120: e2306479120. https://doi.org/10.1073/pnas.2306479120.

[68] D'Andrea A, Conte M, Cavallaro M, Scarafile R, Riegler L, Cocchia R, *et al*. Transcranial Doppler ultrasonography: From methodology to major clinical applications. World Journal of Cardiology. 2016; 8: 383–400. https://doi.org/10.4330/wjc.v8.i7.383.

[69] Wolf ME, Held VE, Förster A, Griebe M, Szabo K, Gass A, *et al*. Pearls & oy-sters: dynamics of altered cerebral perfusion and neurovascular coupling in migraine aura. Neurology. 2011; 77: e127–e128. https://doi.org/10.1212/WNL.0b013e31823a0ceb.

[70] Yang S, Webb AJS. Associations between neurovascular coupling and cerebral small vessel disease: A systematic review and meta-analysis. European Stroke Journal. 2023; 8: 895–903. https://doi.org/10.1177/23969873231196981.

[71] Rojas-Pescio H, Beishon L, Panerai R, Chacón M. Statistical Complexity Analysis of Neurovascular Coupling with Cognitive Stimulation in Healthy Participants. Journal of Cognitive Neuroscience. 2024; 36: 1995–2010. https://doi.org/10.1162/jocn_a_02200.

[72] Chiarelli AM, Zappasodi F, Di Pompeo F, Merla A. Simultaneous functional near-infrared spectroscopy and electroencephalography for monitoring of human brain activity and oxygenation: a review. Neurophotonics. 2017; 4: 041411. https://doi.org/10.1117/1.NPh.4.4.041411.

[73] Sun Y, Song X, Jin C, Peng Y, Zhou J, Zheng X. Cerebral Small Vessel Disease: Current and Emerging Therapeutic Strategies. Aging and Disease. 2025. https://doi.org/10.14336/AD.2024.1515. (online ahead of print)

[74] Muñoz V, Muñoz-Caracuel M, Angulo-Ruiz BY, Gómez CM. Neurovascular coupling during auditory stimulation: event-related potentials and fNIRS hemodynamic. Brain Structure & Function. 2023; 228: 1943–1961. https://doi.org/10.1007/s00429-023-02698-9.

[75] Chiarelli AM, Perpetuini D, Croce P, Filippini C, Cardone D, Rotunno L, *et al*. Evidence of Neurovascular Un-Coupling in Mild Alzheimer's Disease through Multimodal EEG-fNIRS and Multivariate Analysis of Resting-State Data. Biomedicines. 2021; 9: 337. https://doi.org/10.3390/biomedicines9040337.

[76] Zhong J, Li G, Lv Z, Chen J, Wang C, Shao A, *et al*. Neuromodulation of Cerebral Blood Flow: A Physiological Mechanism and Methodological Review of Neurovascular Coupling. Bioengineering (Basel, Switzerland). 2025; 12: 442. https://doi.org/10.3390/bioengineering12050442.

[77] Mele G, Cavaliere C, Alfano V, Orsini M, Salvatore M, Aiello M. Simultaneous EEG-fMRI for Functional Neurological Assessment. Frontiers in Neurology. 2019; 10: 848. https://doi.org/10.3389/fneur.2019.00848.

[78] Zhao J, Blaeser AS, Levy D. Astrocytes mediate migraine-related intracranial meningeal mechanical hypersensitivity. Pain. 2021; 162: 2386–2396. https://doi.org/10.1097/j.pain.0000000000002229.

[79] Tang YW, Lin YD. Brain activity monitoring system based on EEG-NIRS measurement system. Applied Mechanics and Materials. 2017; 870: 351–356. https://doi.org/10.4028/www.scientific.net/AMM.870.351.

[80] Terasaki Y, Liu Y, Hayakawa K, Pham LD, Lo EH, Ji X, *et al*. Mechanisms of neurovascular dysfunction in acute ischemic brain. Current Medicinal Chemistry. 2014; 21: 2035–2042. https://doi.org/10.2174/09298673216613228223400.

[81] Schain AJ, Melo-Carrillo A, Strassman AM, Burstein R. Cortical Spreading Depression Closes Paravascular Space and Impairs Glymphatic Flow: Implications for Migraine Headache. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2017; 37: 2904–2915. https://doi.org/10.1523/JNEUROSCI.3390-16.2017.

[82] Feng L, Gao L. The role of neurovascular coupling dysfunction in cognitive decline of diabetes patients. Frontiers in Neuroscience. 2024; 18: 1375908. https://doi.org/10.3389/fnins.2024.1375908.

[83] Saiyasit N, Butlig EAR, Chaney SD, Traylor MK, Hawley NA, Randall RB, *et al*. Neurovascular Dysfunction in Diverse Communities With Health Disparities-Contributions to Dementia and Alzheimer's Disease. Frontiers in Neuroscience. 2022; 16: 915405. https://doi.org/10.3389/fnins.2022.915405.

[84] Moretti R, Caruso P. Small Vessel Disease-Related Dementia: An Invalid Neurovascular Coupling? International Journal of Molecular Sciences. 2020; 21: 1095. https://doi.org/10.3390/ijms21031095.

[85] Soto-Rojas LO, Pacheco-Herrero M, Martínez-Gómez PA, Campa-Córdoba BB, Apátiga-Pérez R, Villegas-Rojas MM, *et al*. The Neurovascular Unit Dysfunction in Alzheimer's Disease. International Journal of Molecular Sciences. 2021; 22: 2022. https://doi.org/10.3390/ijms22042022.

[86] Park L, Zhou J, Koizumi K, Wang G, Anfray A, Ahn SJ, *et al*. tPA Deficiency Underlies Neurovascular Coupling Dysfunction by Amyloid-β. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2020; 40: 8160–8173. https://doi.org/10.1523/JNEUROSCI.1140-20.2020.

[87] Zhu WM, Neuhaus A, Beard DJ, Sutherland BA, DeLuca GC. Neurovascular coupling mechanisms in health and neurovascular uncoupling in Alzheimer's disease. Brain: a Journal of Neurology. 2022; 145: 2276–2292. https://doi.org/10.1093/brain/awac174.

[88] Canepa E, Fossati S. Impact of Tau on Neurovascular Pathology in Alzheimer's Disease. Frontiers in Neurology. 2020; 11: 573324. https://doi.org/10.3389/fneur.2020.573324.

[89] Sagare AP, Bell RD, Zlokovic BV. Neurovascular defects and faulty amyloid-β vascular clearance in Alzheimer's disease. Journal of Alzheimer's Disease: JAD. 2013; 33 Suppl 1: S87–100. https://doi.org/10.3233/JAD-2012-129037.

[90] Shekhar S, Wang S, Mims PN, Gonzalez-Fernandez E, Zhang C, He X, *et al*. Impaired Cerebral Autoregulation-A Common Neurovascular Pathway in Diabetes may Play a Critical Role in Diabetes-Related Alzheimer's Disease. Current Research in Diabetes & Obesity Journal. 2017; 2: 555587.

[91] Eltzschig HK, Eckle T. Ischemia and reperfusion–from mechanism to translation. Nature Medicine. 2011; 17: 1391–1401. https://doi.org/10.1038/nm.2507.

[92] Camara R, Matei N, Zhang JH. Evolution of the stroke paradigm: A review of delayed recanalization. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2020; 41: 945–957. https://doi.org/10.1177/0271678X20978861.

[93] Rahman AA, Amruta N, Pinteaux E, Bix GJ. Neurogenesis After Stroke: A Therapeutic Perspective. Translational Stroke Research. 2021; 12: 1–14. https://doi.org/10.1007/s12975-020-00841-w.

[94] Li Z, McConnell HL, Stackhouse TL, Pike MM, Zhang W, Mishra A. Increased 20-HETE Signaling Suppresses Capillary Neurovascular Coupling After Ischemic Stroke in Regions Beyond the Infarct. Frontiers in Cellular Neuroscience. 2021; 15: 762843. https://doi.org/10.3389/fncel.2021.762843.

[95] Chojdak-Łukasiewicz J, Dziadkowiak E, Zimny A, Paradowski B. Cerebral small vessel disease: A review. Advances in Clinical and Experimental Medicine: Official Organ Wroclaw Medical University. 2021; 30: 349–356. https://doi.org/10.17219/acem/131216.

[96] Blevins BL, Vinters HV, Love S, Wilcock DM, Grinberg LT, Schneider JA, *et al*. Brain arteriolosclerosis. Acta Neuropathologica. 2021; 141: 1–24. https://doi.org/10.1007/s00401-020-02235-6.

[97] Bai T, Yu S, Feng J. Advances in the Role of Endothelial Cells in Cerebral Small Vessel Disease. Frontiers in Neurology. 2022; 13: 861714. https://doi.org/10.3389/fneur.2022.861714.

[98] Ruan L, Wang B, ZhuGe Q, Jin K. Coupling of neurogenesis and angiogenesis after ischemic stroke. Brain Research. 2015; 1623: 166–173. https://doi.org/10.1016/j.brainres.2015.02.042.

[99] Vlegels N, van den Brink H, Kopczak A, Arts T, Pham SDT, Siero JCW, *et al*. The relation between cerebral small vessel function and white matter microstructure in monogenic and sporadic small vessel disease - the ZOOM@SVDs study. Cerebral Circulation - Cognition and Behavior. 2025; 8: 100383. https://doi.org/10.1016/j.cccb.2025.100383.

[100] Liu X, Cheng R, Chen L, Gong J, Luo T, Lv F. Altered Neurovascular Coupling in Subcortical Ischemic Vascular Disease. Frontiers in Aging Neuroscience. 2021; 13: 598365. https://doi.org/10.3389/fnagi.2021.598365.

[101] Khennouf L, Gesslein B, Brazhe A, Octeau JC, Kutuzov N, Khakh BS, *et al*. Active role of capillary pericytes during stimulation-induced activity and spreading depolarization. Brain: a Journal of Neurology. 2018; 141: 2032–2046. https:

//doi.org/10.1093/brain/awy143.
[102] Romozzi M, Calabresi P. Is there a role of calcitonin gene-related peptide in cortical spreading depression mechanisms?-Argument pro. The Journal of Headache and Pain. 2025; 26: 90. https://doi.org/10.1186/s10194-025-02011-5.
[103] Bowen RM, York NW, Padawer-Curry J, Bauer AQ, Lee JM, Nichols CG. Control of neurovascular coupling by ATP-sensitive potassium channels. Journal of Cerebral Blood Flow and Metabolism: Official Journal of the International Society of Cerebral Blood Flow and Metabolism. 2025; 45: 1130–1143. https://doi.org/10.1177/0271678X251313906.
[104] Welton T, Tan YL, Chan LL. Editorial for "Evaluation of Neurovascular Coupling in Early-Onset and Late-Onset Epilepsy of Unknown Etiology". Journal of Magnetic Resonance Imaging: JMRI. 2025; 61: 2501–2502. https://doi.org/10.1002/jmri.29683.
[105] Zhao M, Nguyen J, Ma H, Nishimura N, Schaffer CB, Schwartz TH. Preictal and ictal neurovascular and metabolic coupling surrounding a seizure focus. The Journal of Neuroscience: the Official Journal of the Society for Neuroscience. 2011; 31: 13292–13300. https://doi.org/10.1523/JNEUROSCI.2597-11.2011.
[106] Prince DA, Connors BW. Mechanisms of interictal epileptogenesis. Advances in Neurology. 1986; 44: 275–299.
[107] Swissa E, Serlin Y, Vazana U, Prager O, Friedman A. Blood-brain barrier dysfunction in status epileptics: Mechanisms and role in epileptogenesis. Epilepsy & Behavior: E&B. 2019; 101: 106285. https://doi.org/10.1016/j.yebeh.2019.04.038.
[108] Cade WT. Diabetes-related microvascular and macrovascular diseases in the physical therapy setting. Physical Therapy. 2008; 88: 1322–1335. https://doi.org/10.2522/ptj.20080008.
[109] Hu B, Yan LF, Sun Q, Yu Y, Zhang J, Dai YJ, *et al*. Disturbed neurovascular coupling in type 2 diabetes mellitus patients: Evidence from a comprehensive fMRI analysis. NeuroImage. Clinical. 2019; 22: 101802. https://doi.org/10.1016/j.nicl.2019.101802.
[110] Mekala A, Qiu H. Interplay Between Vascular Dysfunction and Neurodegenerative Pathology: New Insights into Molecular Mechanisms and Management. Biomolecules. 2025; 15: 712. https://doi.org/10.3390/biom15050712.
[111] Jia G, Bai H, Mather B, Hill MA, Jia G, Sowers JR. Diabetic Vasculopathy: Molecular Mechanisms and Clinical Insights. International Journal of Molecular Sciences. 2024; 25: 804. https://doi.org/10.3390/ijms25020804.
[112] Lourenço CF, Laranjinha J. Nitric Oxide Pathways in Neurovascular Coupling Under Normal and Stress Conditions in the Brain: Strategies to Rescue Aberrant Coupling and Improve Cerebral Blood Flow. Frontiers in Physiology. 2021; 12: 729201. https://doi.org/10.3389/fphys.2021.729201.
[113] Kleinfeld D, Blinder P, Drew PJ, Driscoll JD, Muller A, Tsai PS, *et al*. A guide to delineate the logic of neurovascular signaling in the brain. Frontiers in Neuroenergetics. 2011; 3: 1. https://doi.org/10.3389/fnene.2011.00001.
[114] Tsenov G, Vondrakova K, Otahal J, Burchfiel J, Kubova H. Activation of either the ETA or the ETB receptors is involved in the development of electrographic seizures following intrahippocampal infusion of the endothelin-1 in immature rats. Experimental Neurology. 2015; 265: 40–47. https://doi.org/10.1016/j.expneurol.2014.12.017.
[115] Cicero AFG, Ruscica M, Banach M. Resveratrol and cognitive decline: a clinician perspective. Archives of Medical Science: AMS. 2019; 15: 936–943. https://doi.org/10.5114/aoms.2019.85463.
[116] Olatona OA, Sterben SP, Kansakar SBS, Symes AJ, Liaudanskaya V. Mitochondria: the hidden engines of traumatic brain injury-driven neurodegeneration. Frontiers in Cellular Neuroscience. 2025; 19: 1570596. https://doi.org/10.3389/fncel.2025.1570596.
[117] Murray KN, Parry-Jones AR, Allan SM. Interleukin-1 and acute brain injury. Frontiers in Cellular Neuroscience. 2015; 9: 18. https://doi.org/10.3389/fncel.2015.00018.
[118] Ekert JO, Gould RL, Reynolds G, Howard RJ. TNF alpha inhibitors in Alzheimer's disease: A systematic review. International Journal of Geriatric Psychiatry. 2018; 33: 688–694. https://doi.org/10.1002/gps.4871.
[119] Uemura MT, Maki T, Ihara M, Lee VMY, Trojanowski JQ. Brain Microvascular Pericytes in Vascular Cognitive Impairment and Dementia. Frontiers in Aging Neuroscience. 2020; 12: 80. https://doi.org/10.3389/fnagi.2020.00080.
[120] Cheng J, Korte N, Nortley R, Sethi H, Tang Y, Attwell D. Targeting pericytes for therapeutic approaches to neurological disorders. Acta Neuropathologica. 2018; 136: 507–523. https://doi.org/10.1007/s00401-018-1893-0.
[121] Girouard H, Iadecola C. Neurovascular coupling in the normal brain and in hypertension, stroke, and Alzheimer disease. Journal of Applied Physiology (Bethesda, Md.: 1985). 2006; 100: 328–335. https://doi.org/10.1152/japplphysiol.00966.2005.
[122] Tarantini S, Yabluchanskiy A, Csipo T, Fulop G, Kiss T, Balasubramanian P, *et al*. Treatment with the poly(ADP-ribose) polymerase inhibitor PJ-34 improves cerebromicrovascular endothelial function, neurovascular coupling responses and cognitive performance in aged mice, supporting the NAD+ depletion hypothesis of neurovascular aging. GeroScience. 2019; 41: 533–542. https://doi.org/10.1007/s11357-019-00101-2.
[123] Chen C, Li P. Neurovascular unit protection—novel therapeutic targets and strategies. CNS Neuroscience & Therapeutics. 2021; 27: 5–6. https://doi.org/10.1111/cns.13588.
[124] Posada-Duque RA, Barreto GE, Cardona-Gomez GP. Protection after stroke: cellular effectors of neurovascular unit integrity. Frontiers in Cellular Neuroscience. 2014; 8: 231. https://doi.org/10.3389/fncel.2014.00231.
[125] Nation DA, Hong S, Jak AJ, Delano-Wood L, Mills PJ, Bondi MW, *et al*. Stress, exercise, and Alzheimer's disease: a neurovascular pathway. Medical Hypotheses. 2011; 76: 847–854. https://doi.org/10.1016/j.mehy.2011.02.034.
[126] White D, John CS, Kucera A, Truver B, Lepping RJ, Kueck PJ, *et al*. A methodology for an acute exercise clinical trial called dementia risk and dynamic response to exercise. Scientific Reports. 2021; 11: 12776. https://doi.org/10.1038/s41598-021-92177-0.
[127] Willie CK, Cowan EC, Ainslie PN, Taylor CE, Smith KJ, Sin PYW, *et al*. Neurovascular coupling and distribution of cerebral blood flow during exercise. Journal of Neuroscience Methods. 2011; 198: 270–273. https://doi.org/10.1016/j.jneumeth.2011.03.017.
[128] Zhang R, Zhang M, Wang P. The intricate interplay between dietary habits and cognitive function: insights from the gut-brain axis. Frontiers in Nutrition. 2025; 12: 1539355. https://doi.org/10.3389/fnut.2025.1539355.
[129] Armeli F, Bonucci A, Maggi E, Pinto A, Businaro R. Mediterranean Diet and Neurodegenerative Diseases: The Neglected Role of Nutrition in the Modulation of the Endocannabinoid System. Biomolecules. 2021; 11: 790. https://doi.org/10.3390/biom11060790.
[130] van Rooij JRA, van den Berg M, Vasilkovska T, Van Audekerke J, Kosten L, Bertoglio D, *et al*. Short-term caloric restriction or resveratrol supplementation alters large-scale brain network connectivity in male and female rats. Frontiers in Nutrition. 2025; 12: 1440373. https://doi.org/10.3389/fnut.2025.1440373.
[131] Yan B, Zhou J, Yan F, Gao M, Tang J, Huang L, *et al*. Unlocking the potential of photobiomodulation therapy for brain neurovascular coupling: The biological effects and medical applications. Journal of Cerebral Blood Flow and Metabolism: Offi-

cial Journal of the International Society of Cerebral Blood Flow and Metabolism. 2025; 45: 800–830. https://doi.org/10.1177/0271678X241311695.

[132] Gunduz ME, Kocahasan M, Keser Z. Transcranial Direct Current Stimulation to Provide Neuroprotection and Enhance Cerebral Blood Flow in Stroke: A Comprehensive Review. Medicina (Kaunas, Lithuania). 2024; 60: 2061. https://doi.org/10.3390/medicina60122061.

[133] Pienaar IS, Lee CH, Elson JL, McGuinness L, Gentleman SM, Kalaria RN, *et al*. Deep-brain stimulation associates with improved microvascular integrity in the subthalamic nucleus in Parkinson's disease. Neurobiology of Disease. 2015; 74: 392–405. https://doi.org/10.1016/j.nbd.2014.12.006.

[134] Andalib S, Divani AA, Ayata C, Baig S, Arsava EM, Topcuoglu MA, *et al*. Vagus Nerve Stimulation in Ischemic Stroke. Current Neurology and Neuroscience Reports. 2023; 23: 947–962. https://doi.org/10.1007/s11910-023-01323-w.

[135] Song H, Chen R, Ren L, Zeng Y, Sun J, Tong S. Low intensity transcranial ultrasound stimulation induces hemodynamic responses through neurovascular coupling. iScience. 2024; 27: 110269. https://doi.org/10.1016/j.isci.2024.110269.

[136] Weihl C, Macdonald RL, Stoodley M, Lüders J, Lin G. Gene therapy for cerebrovascular disease. Neurosurgery. 1999; 44: 239–52; discussion 253. https://doi.org/10.1097/00006123-199902000-00001.

[137] Posada-Duque RA, Cardona-Gómez GP. CDK5 Targeting as a Therapy for Recovering Neurovascular Unit Integrity in Alzheimer's Disease. Journal of Alzheimer's Disease: JAD. 2021; 82: S141–S161. https://doi.org/10.3233/JAD-200730.

[138] Bartus RT, Weinberg MS, Samulski RJ. Parkinson's disease gene therapy: success by design meets failure by efficacy. Molecular Therapy: the Journal of the American Society of Gene Therapy. 2014; 22: 487–497. https://doi.org/10.1038/mt.2013.281.

[139] Lyu Z, Park J, Kim KM, Jin HJ, Wu H, Rajadas J, *et al*. A neurovascular-unit-on-a-chip for the evaluation of the restorative potential of stem cell therapies for ischaemic stroke. Nature Biomedical Engineering. 2021; 5: 847–863. https://doi.org/10.1038/s41551-021-00744-7.

[140] Xue P, Wang M, Yan G. Mesenchymal stem cell transplantation as an effective treatment strategy for ischemic stroke in Asia: a meta-analysis of controlled trials. Therapeutics and Clinical Risk Management. 2018; 14: 909–928. https://doi.org/10.2147/TCRM.S161326.

[141] Toader C, Dumitru AV, Eva L, Serban M, Covache-Busuioc RA, Ciurea AV. Nanoparticle Strategies for Treating CNS Disorders: A Comprehensive Review of Drug Delivery and Theranostic Applications. International Journal of Molecular Sciences. 2024; 25: 13302. https://doi.org/10.3390/ijms252413302.

[142] Saraiva C, Praça C, Ferreira R, Santos T, Ferreira L, Bernardino L. Nanoparticle-mediated brain drug delivery: Overcoming blood-brain barrier to treat neurodegenerative diseases. Journal of Controlled Release: Official Journal of the Controlled Release Society. 2016; 235: 34–47. https://doi.org/10.1016/j.jconrel.2016.05.044.

[143] Cheng MY, Aswendt M, Steinberg GK. Optogenetic Approaches to Target Specific Neural Circuits in Post-stroke Recovery. Neurotherapeutics: the Journal of the American Society for Experimental NeuroTherapeutics. 2016; 13: 325–340. https://doi.org/10.1007/s13311-015-0411-5.

[144] Walker MC, Kullmann DM. Optogenetic and chemogenetic therapies for epilepsy. Neuropharmacology. 2020; 168: 107751. https://doi.org/10.1016/j.neuropharm.2019.107751.