Berkeley Pharma Tech
Journal of Medicine

The Pulse of Cognition: Investigating Neurovascular Coupling's Role in Cognition and Therapeutic Promise for Alzheimer's, Parkinson's, and Dementia

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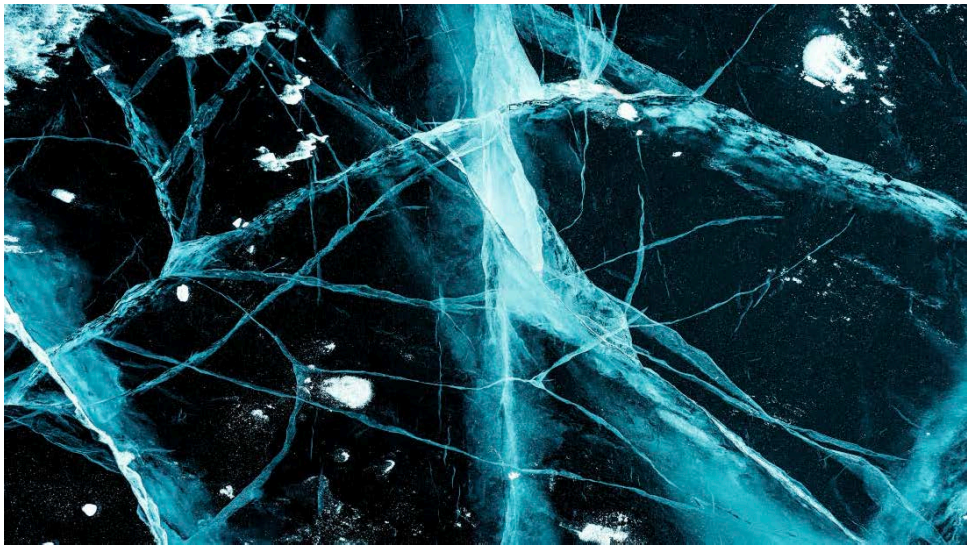

Keywords:
Neurovascular coupling
Dementia
Alzheimer's disease
Parkinson's disease
Vascular dysfunction

Abstract

Cognitive decline—including dementia, Alzheimer's disease, and Parkinson's disease—is a growing global health concern. These neurodegenerative disorders affect approximately 50 million people worldwide. In the United States, nearly two out of three seniors experience some form of cognitive impairment. Since the 1990s, the prevalence of mild cognitive impairment has been rising in the U.S. and is projected to continue increasing for future decades. These alarming trends underscore the urgent need for more effective methods of early detection and treatment that address the physical, emotional, and cognitive needs of affected individuals. Emerging evidence suggests that neurovascular coupling (NVC)—the critical process linking brain activity to dynamic blood flow—plays an essential role in regulating brain energetics and function, and may contribute to cognitive dysfunction when impaired. This review delves into the characteristics of NVC and the neurovascular unit (NVU), examines early detection strategies targeting NVC-related biomarkers, and discusses current and investigational treatments for NVC-associated cognitive disorders.

Published July 31, 2025

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1. Introduction

1.1 Cognitive Decline

Cognitive decline is an escalating public health concern, driven in part by the aging global population. Data show that nearly 20% of adults aged 50 and older worldwide experience some degree of cognitive decline.[1] In the United States, approximately two out of three adults aged 70 or older have some form of cognitive impairment, while one in three individuals aged 85 or older suffers from more severe conditions such as Alzheimer's disease.[2,3] These statistics highlight the urgent need for comprehensive interventions. Effective strategies include pharmacological treatments, nutraceutical approaches, and vascular-targeted therapies aimed at addressing both the underlying causes and the consequences of cognitive decline.

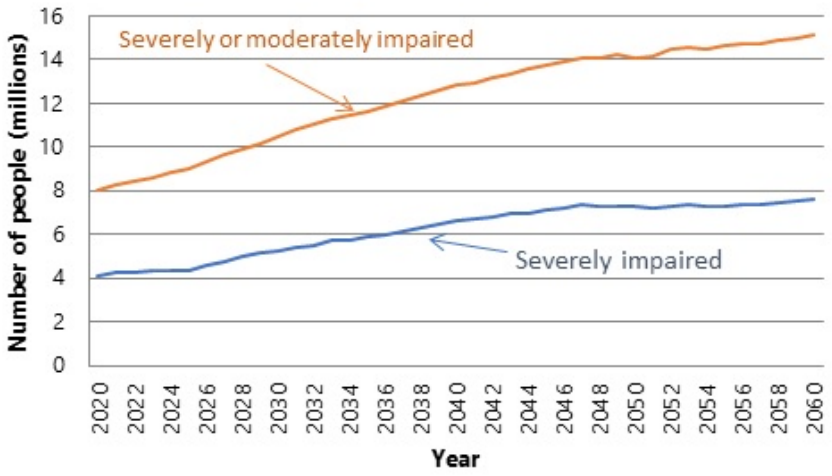

Figure 1: DYNASIM Projection of Adults with Cognitive Impairments from 2020 to 2060

Cognitive decline encompasses a range of conditions, including common neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson's disease, and various forms of dementia. AD, for example, involves impairments across multiple cognitive domains, affecting memory, reasoning, language, coordination, mood, and behavior.[4] Similarly, Parkinson's disease presents a range of non-motor and motor symptoms, including a diminished sense of smell, digestive issues, and drooling,

alongside difficulties in executing normal movements, experiencing tremors, and maintaining a stable walking posture.[5] Dementia is a broader term that refers to the progressive deterioration of memory and other cognitive functions, significantly interfering with an individual's ability to perform daily activities. [6] Collectively, these conditions underscore the multifaceted nature of cognitive decline and emphasize the need to address these diseases.

As cognitive decline progresses, impairments in neuronal activity can lead to inadequate perfusion of vital brain regions, one of the main causes of neuronal damage and cognitive impairments. Therefore, understanding the interplay between cognitive decline and neurovascular coupling is crucial for developing effective strategies to preserve brain function and slow the progression of neurodegenerative diseases.

1.2 Neurovascular Coupling

NVC refers to the process by which the metabolic demands of active neurons trigger localized changes in cerebrovascular blood flow (CBF). This mechanism ensures that the brain receives adequate oxygen and nutrients during periods of increased neural activity, thereby maintaining optimal perfusion in response to fluctuating neuronal demands.[7]

1.2.1 Neurovascular Unit

The regulation of NVC is coordinated by the neurovascular unit (NVU), a complex assembly of neurons, glial cells, and vascular cells. Glial cells—such as astrocytes and microglia—play essential roles in supporting and protecting neurons. They also contribute to vasculogenesis (the formation of new blood vessels from endothelial progenitor cells) and the development of synapses.[8] Vascular cells, including endothelial cells, help maintain the blood-brain barrier (BBB), sense mechanical and hormonal signals to regulate CBF. These cells also release substances, like proteoglycans and glycoproteins, to adapt blood flow accordingly. Vascular smooth muscle cells adjust CBF by modulating vascular tone and capillary diameter in response to signals from endothelial cells. Likewise, pericytes influence CBF by altering capillary diameter in response to neurotransmitters such as noradrenaline and glutamate. This interconnected network ensures the delivery of essential nutrients, such asglucose and oxygen, to sustain the

energy-demanding brain activity, while also maintaining cerebrovascular homeostasis.[9]

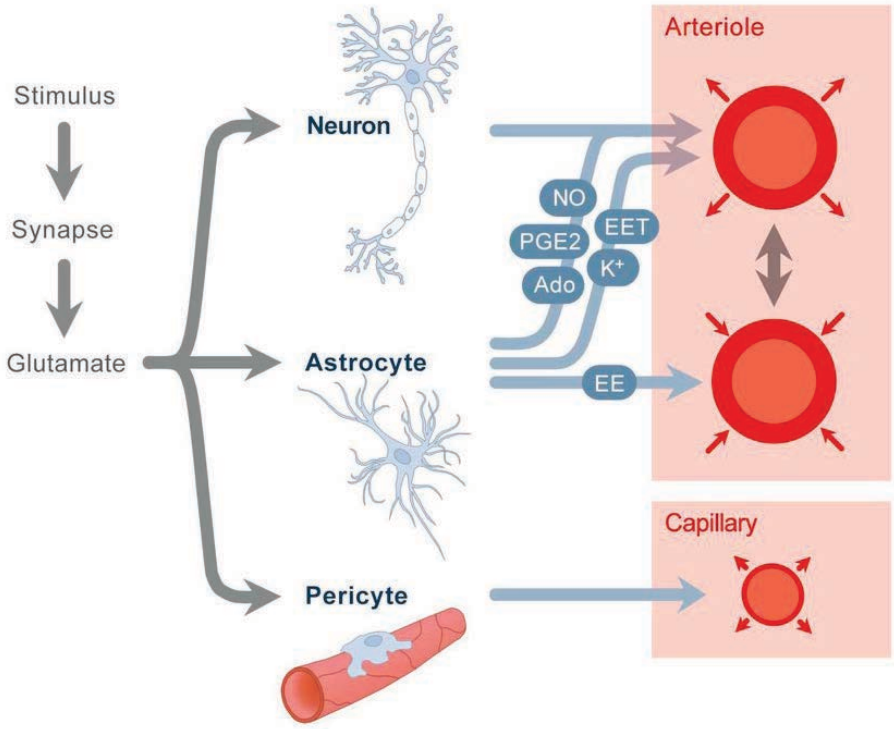

Figure 2: Neurovascular Coupling Mechanism. *Stimulation triggers glutamate secretion, activating neurons and astrocytes to release nitric oxide (NO), potassium (K+), adenosine (Ado), epoxyeicosatrienoic acids (EET), and prostaglandins (PGE2), leading to arteriolar vasodilation. Astrocytes also release arachidonic acid (AA), causing vasoconstriction, and pericytes are stimulated separately, leading to capillary dilation.*

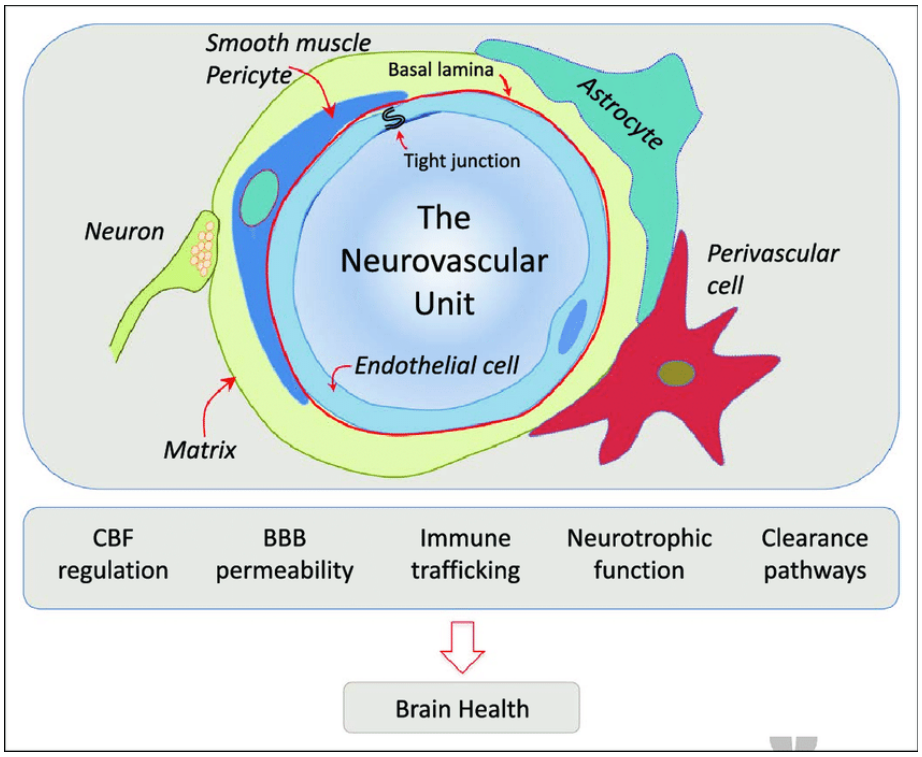

Figure 3: The Neurovascular Unit. *The neurovascular unit (NVU) consists of endothelial cells, pericytes, astrocytes, neurons, and the extracellular matrix. The NVU balances the brain microenvironment, regulates cerebral blood flow, facilitates immune cell movement, produces growth factors for cell survival, and aids in clearing harmful brain byproducts, crucial for brain health.*

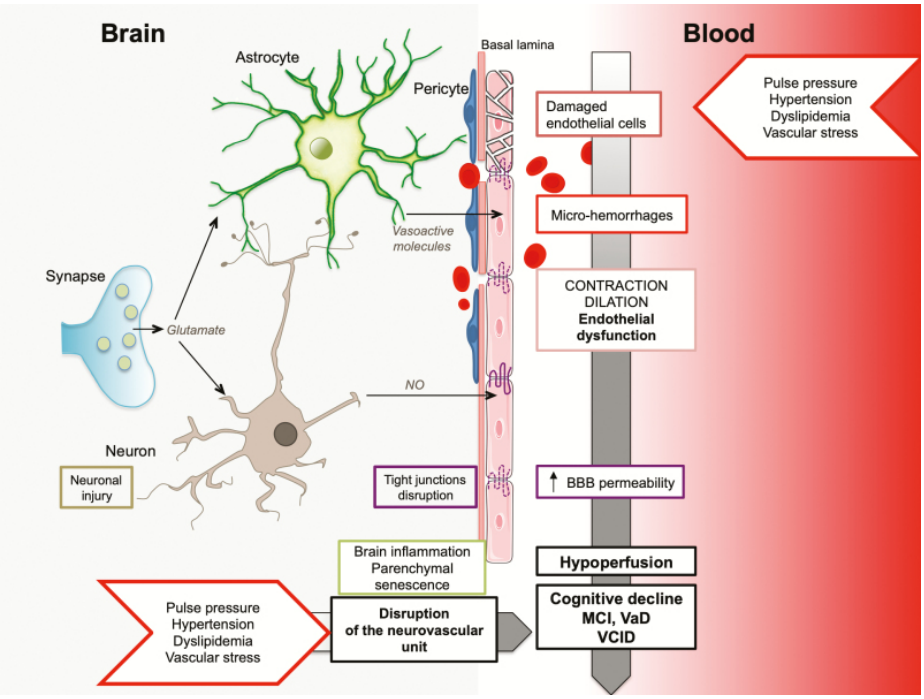

Figure 4: The Blood-Brain Barrier. *Vascular stresses affect the blood-brain barrier, which regulates brain perfusion. Conditions like hypertension damage the endothelium, disrupting the blood-brain barrier, causing microhemorrhages, inflammation, and neuronal injury. This process contributes to cognitive decline and dementia.*

1.3 Purpose of Study

Building upon our review of cognitive decline, we propose that NVC plays a critical regulatory role in neurovascular diseases associated with cognitive impairment. This study aims to identify early signs of cognitive decline by targeting relevant biomarkers and to explore treatment options for conditions linked to NVC dysfunction. Specifically, we seek to understand how changes in neuronal activity affect blood vessel function and cerebral blood flow (CBF) in cognitive disorders such as AD, Parkinson's disease, and dementia.

2. Histopathological Features of NVC-related Diseases

Histopathological markers of NVC-related diseases, including Alzheimer's and vascular dementia, can be observed through tissue imaging techniques. Particularly, the well-known biomarkers of neurofibrillary tangles and β-amyloid plaque is associated with Alzheimer's, while neuronal tissue death and myelin breakdown is associated with vascular dementia.[10] It is

hypothesized that vascular abnormalities contribute to the early progression of cognitive disorders and precede the emergence of these histopathological features.[11] For instance, one study found that patients with vascular dementia have significant hippocampal neuronal loss due to microvascular pathology.[12] These findings support a correlation between vascular dysfunction and development of key features of cognitive disorders.

2.1 Associated Biomarkers

2.1.1 Pericyte detachment

Pericytes are instrumental in maintaining the NVU, as they are positioned in the unit between endothelial cells, astrocytes, and neurons. They contribute not only to the structural maintenance of blood vessels but also to the regulation of molecular waste clearance, cell signaling, and cerebral blood flow. For example, pericytes influence the activity of proteins that preserve the tight junctions of the blood–brain barrier (BBB) and modulate the transport of fluid-filled vesicles across it.12 In the cases of higher blood pressure, which can stretch the vein and weaken it, pericyte detachment from the unit is promoted. Pericyte detachment from around the circumference of the vein can lead to BBB permeability, neuroinflammation, and issues with neuronal communication, ultimately resulting in cognitive dysfunction. Additionally, recent studies have implicated pericyte detachment with hypoxia and loss of myelination, which leads to the loss of essential connections within the brain.[13]

2.1.2 Genetic factors

The APOEε4 allele, located on chromosome 19, has often been described as the greatest genetic risk factor for Alzheimer's. Although its exact role in disease pathology remains incompletely understood, it is known to be involved in lipid transport within the brain and the production of β-amyloid and tau proteins—key biomarkers of Alzheimer's disease. Emerging research suggests that APOEε4 also disrupts neurovascular regulation and exacerbates cognitive decline. Individuals carrying this allele exhibit marked pericyte deficiency—approximately 50% fewer pericytes compared to individuals without the allele—and increased blood–brain barrier breakdown.[14] The correlation between APOEε4 with protein

aggregate formation and NVC regulation supports our hypothesis that the NVC contributes to cognitive decline.[15]

2.1.3 Vascular dysfunction

Given the NVU's intimate relationship with brain function, vascular dysfunction as a whole can act as a root for brain dysfunction. The "2-hit vascular hypothesis model", proposed by Berislav V. Zlokovic, implicates vascular dysfunction in exacerbating cognitive decline.[16] The "first hit" are risk factors such as aging, atherosclerosis, hypertension, diabetes, or stroke, all of which jeopardize or breakdown vascular integrity and alter cerebral blood flow. The "second hit" refers to the increased Aβ protein levels, inflammation, and tau protein levels that result, which causes even further decline. This model describes a positive feedback loop between vascular and brain dysfunction: injury to the vascular system can accelerate neurodegeneration, while neuronal damage can, in turn, worsen vascular health.[17] Consequently, vascular markers may serve as valuable early indicators for the prevention and early-stage intervention of neurodegenerative diseases.

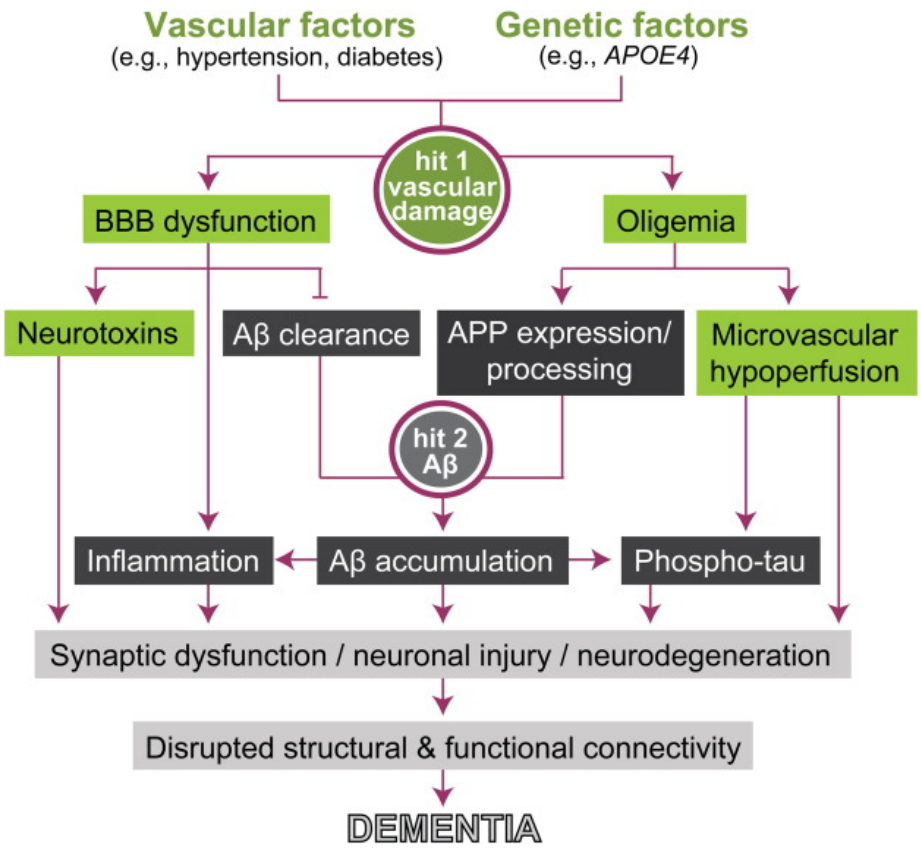

Figure 5: 2-Hit Hypothesis. *2-hit hypothesis model shows that vascular factors and genetic factors discussed before serve as predisposing factors to 'hit 1 vascular damage,' which causes BBB breakdown and 'hit 2': physiological manifestations of cognitive decline such as protein aggregation and inflammation. These hits cause significant neurodegeneration and also (not pictured) a positive feedback loop of brain and vascular damage.*

2.1.4 Blood-brain barrier breakdown

The blood-brain barrier (BBB) regulates the exchange of compounds between the blood and the brain by selectively transporting solutes through active transport mechanisms and passive diffusion.

These include organic compounds such as vitamins, hormones, and macromolecules necessary for brain neuron functions. Different levels of stress such as hypertension or vascular recanalization can cause the breakdown of the barrier. Not only does the breakdown of the barrier result in the loss of its functions, but it also allows for the release of neurodegenerative compounds such as protein aggregates and pathogens that are absorbed by the blood to the brain which leads to neurovascular coupling-related diseases. BBB breakdown is also associated with aging,

which progressively alters its permeability. Given the BBB's close functional relationship with pericytes, astrocytes, and neurons, its failure is often accompanied by dysfunction in these associated cells—providing a broader pathological context for detection and diagnosis.

3. Novel Neuroimaging Techniques

Recent advances in medical imaging have paved the way for the detection of biomarkers and early disease indicators. Neuroimaging plays a critical role in diagnosing neurodegenerative diseases, enabling clinicians to detect early signs of cognitive impairment, abnormalities in cerebral blood flow, and evidence of stroke, while also facilitating ongoing disease monitoring. This section explores several state-of-the-art techniques, including in-vivo photon imaging, Dynamic Vessel Analyzer (DVA), multimodal imaging platforms, fMRI, and fNIRS.

3.1 In-Vivo Photon Imaging

In-vivo photon imaging is a powerful technique that allows for deep-tissue visualization beyond the superficial layers of the dorsal brain. It has been instrumental in identifying correlations between external factors—such as dietary salt intake—and internal biomarkers, like elevated tau protein levels, a potential indicator of neurodegeneration. Two-Photon Imaging is a specific type of In-Vivo Photon Imaging technique. This specific technique uses two photons of lower energy to excite a fluorescent molecule. Compared to single photon imaging techniques, it allows deeper tissue penetration and provides high-resolution images with less photodamage. Researchers employ two-photon microscopy to track changes in blood vessel diameter, blood flow, and oxygenation levels in response to neuronal activity.[18]

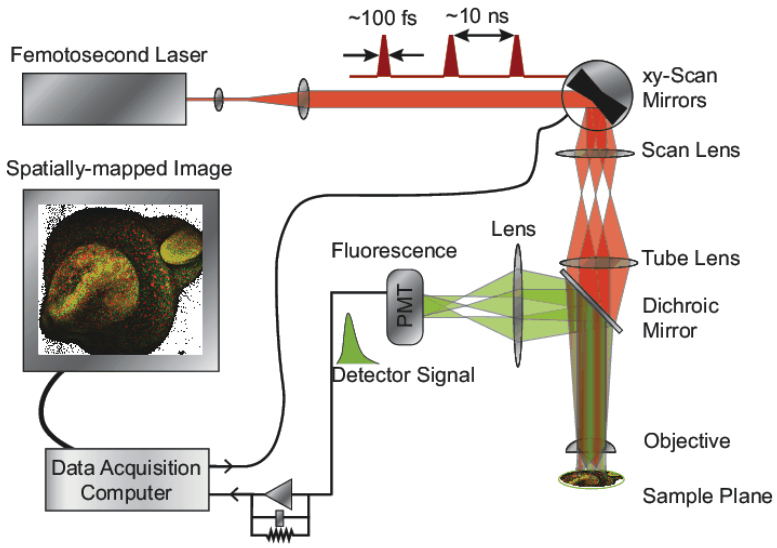

Figure 6: Schematic of a 2PF microscope. *A two-photon fluorescence microscope utilizes a femtosecond laser to send light through xy-scan mirrors, scan and tube lenses, focusing on a sample with an objective lens. This induces fluorescence in the sample, which is then collected back through the objective lens, filtered by a dichroic mirror, and detected by a photomultiplier tube, ultimately translating into an image by a computer.*

3.2 Dynamic Vessel Analyzer

In one study, patients with varying degrees of Alzheimer's disease were compared to controls by assessing the retinal blood vessel response to flickering lights. Retinal vasculature is a valid proxy for cerebral blood flow since they share anatomical and physiological features that stem from a shared embryonic origin. To assess these responses, scientists used the Dynamic Vessel Analyzer (DVA)—a novel imaging tool that captures microvascular dynamics in the eye. As a non-invasive proxy for cerebral vasculature, the DVA provides valuable insights into neurovascular function. Results revealed that patients with moderate or mild dementia from Alzheimer's had emphasized arterial and venous dilation, as well as delayed arterial reaction to the flickering lights. These findings suggest that increased and delayed retinal neurovascular coupling, perhaps caused by damaged feedback loops or excessive activity of retinal neurons, is associated with Alzheimer's. As a non-invasive and accessible diagnostic tool, the DVA

holds promise for monitoring retinal and vascular changes linked to Alzheimer's disease and may aid in tracking disease progression.[19]

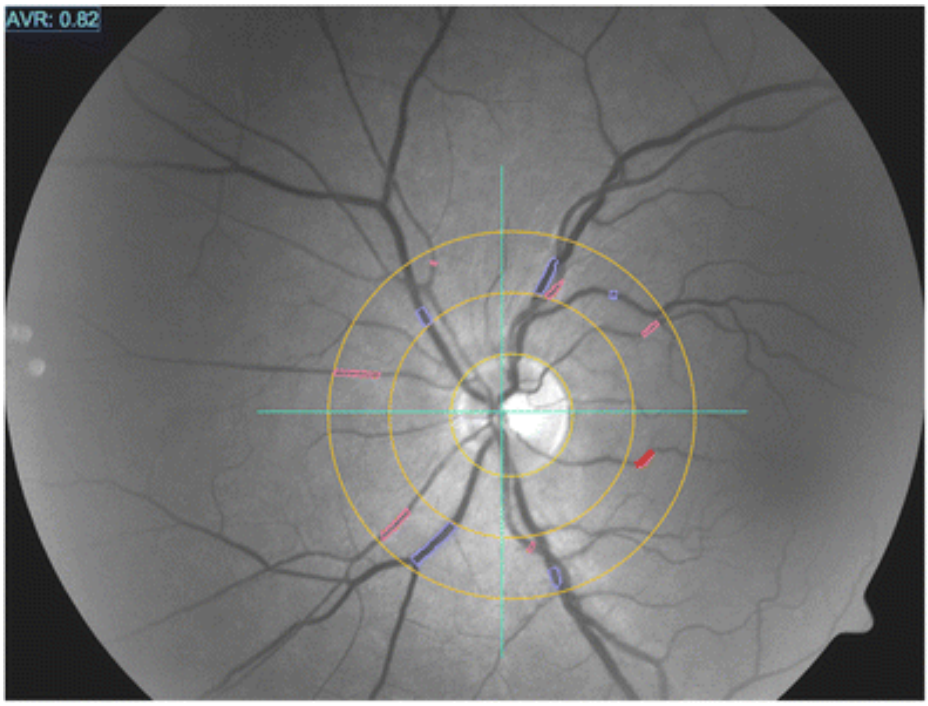

Figure 7: Static analysis performed by the Dynamic Vessel Analyzer.
The technology gives valuable glimpses into arterioles (red segments) and venules (blue segments)

3.3 Multimodality Imaging Platforms

Traditional high-resolution microscopy offers excellent detail but is limited by its small field of view. To overcome this limitation, researchers in one study employed a multimodality imaging approach to investigate the role of calcium ion (Ca^{2+}) fluctuations in astrocytes, key glial cells involved in maintaining the NVU. Using electrical stimulation in mice, researchers observed that astrocytes exhibited a delayed response to stimulation, while cerebral blood flow increased rapidly. This finding suggests that astrocytes contribute to the coupling between neuronal activity and blood flow. Additionally, the stimulation induced vasoconstriction—the narrowing of blood vessels—indicating that astrocytes may regulate blood flow not only during periods of high neural activity but also at rest. By integrating multiple imaging modalities, the study provided a more comprehensive

understanding of astrocytic function in cerebral perfusion and cognitive maintenance.[20]

3.4 fMRI (Functional Magnetic Resonance Imaging)

fMRI is a widely used, non-invasive technique for visualizing brain activity by measuring changes in blood oxygenation levels. It relies on BOLD (blood-oxygen-level-dependent) contrast, which detects variations in the magnetic properties of oxygenated and deoxygenated hemoglobin. fMRI is repeatable, widely available, and offers superior spatial resolution compared to other neuroimaging methods. It enables in-depth, whole-brain analysis of functional activity. However, fMRI has limitations: it is contraindicated for individuals with metal implants or devices from prior medical procedures, and its sensitivity to movement makes it less suitable for use during physical activity or with populations such as infants.

3.5 fNIRS (Functional Near-Infrared Spectroscopy)

Although fMRI is considered one of the most advanced neuroimaging modalities, functional near-infrared spectroscopy (fNIRS) has emerged as a promising alternative or complementary technique. Like fMRI, fNIRS is non-invasive and measures hemodynamic responses in the brain, but it does so using near-infrared light instead of magnetic fields. fNIRS is relatively inexpensive, portable, and tolerant to motion, making it suitable for dynamic settings and use in young or mobile populations. However, it has limitations in terms of probe placement and depth of measurement, typically capturing data only from the frontal cortex and superficial cortical areas.

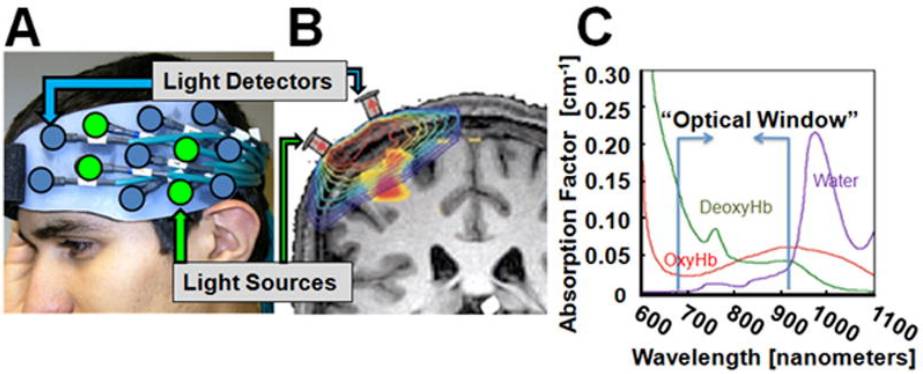

Figure 8: Functional near-infrared spectroscopy. *Functional near-infrared spectroscopy (fNIRS) is used for non-invasive monitoring of changes in oxy- and deoxy-hemoglobin levels within the brain. It involves a configuration of fiber optic-based light sources and detectors arranged on a flexible head cap worn by the participant.*

4. Neurovascular Coupling Targeted Market Therapeutics

Exploring new treatments for brain health is essential in addressing cognitive decline. This article introduces several options, including Cocoa Flavonoids (CF), Nicotinamide Mononucleotide(NMN), i-NO Pericyte Relaxant, Inorganic nitrate supplementation, and Nicotinamide Adenine Dinucleotide (NAD) supplementation. Each offers potential benefits, but future research is required to confirm their safety and effectiveness.

4.1 Cocoa Flavonoids (CF)

Cocoa flavonoids (CF) are recognized for their neuroprotective attributes, antioxidant and vasodilatory properties, and their ability to inhibit cholinesterase and tau formation. Despite these promising attributes, their effects appear limited in scope. Current evidence suggests that CF primarily increases BOLD (blood-oxygen-level-dependent) responses in specific brain regions—namely the supramarginal gyrus of the parietal lobe and the inferior frontal gyrus.[21] The effects of CF intake are not well understood, and clinical studies are required to further investigate their impact.

4.2 Nicotinamide Mononucleotide (NMN)

Nicotinamide Mononucleotide (NMN) is another treatment option that enhances endothelial NO-mediated vasodilation and serves as an NAD+ intermediate. It is also recognized for improving spatial working memory and movement coordination. However, most research has focused on its vascular effects in large arteries, such as the aorta, leaving its broader systemic and neurological interactions underexplored. Moreover, some clinical trials have reported adverse effects, raising concerns about the safety and long-term efficacy of NAD^+ intermediates like NMN. These findings underscore the need for further investigation to better understand its therapeutic viability.[22]

4.3 i-NO Pericyte Relaxant

i-NO Pericyte Relaxant demonstrates potential as treatment by opening constricted blood vessels, becoming neuroprotective in other mammals, and assisting in recanalization and pretreatment.

While showing strength as a neuroprotective agent and in aiding blood flow, this presents certain challenges. For example, its efficacy can be compromised by interactions with other chemicals such as adenosine triphosphate, norepinephrine, angiotensin II, and intracellular reactive oxygen species. These chemicals can potentially reduce its therapeutic benefits. Additionally, there are reported side effects that could be detrimental to patients. Given these issues, it is clear that extensive human clinical trials are required to verify the treatment's safety and to ensure its therapeutic efficacy is consistent and reliable.

4.4 Inorganic nitrate supplementation

Inorganic nitrate supplementation is a non-pharmaceutical approach used to support cerebral vascular health. It is available over the counter in supplement form and naturally occurs in dietary sources such as beetroot juice. Inorganic nitrates are known to reduce blood pressure, enhance endothelial function, and potentially improve athletic performance.

While generally well-tolerated and being a non-pharmaceutical option, some individuals may experience side effects such as stomach discomfort, changes

in bowel movements, or colored urine. A notable concern is the potential for drug interactions, particularly with medications that affect nitric oxide pathways, which may increase the risk of conditions like methemoglobinemia. Despite its benefits, the long-term effects of inorganic nitrate supplementation remain unclear. Further research is necessary to fully understand its efficacy and safety for prolonged use.

4.5 Nicotinamide Adenine Dinucleotide (NAD) supplementation

Nicotinamide adenine dinucleotide (NAD) supplementation has emerged as a promising strategy to mitigate age-related cognitive decline. NAD is a coenzyme essential for cellular metabolism and energy production, but its levels naturally decline with age, which may contribute to reduced brain function and vascular integrity. Supplementation typically involves the use of NAD precursors, such as nicotinamide riboside (NR) and nicotinamide mononucleotide (NMN), which are intended to boost intracellular NAD^+ levels. This, in turn, may enhance mitochondrial function and promote neurovascular health. However, side effects such as nausea, fatigue, headaches, and diarrhea have been reported. Although these supplements are generally considered safe at recommended doses, the long-term effects remain uncertain. Further clinical trials are needed to evaluate the full therapeutic potential and safety profile of NAD supplementation for cognitive health.

Currently, researchers are conducting two ongoing significant clinical trials, NCT03617302 and NCT05483465, related to the Neurovascular Coupling in cognitive decline. These studies aim to understand how changes in the interaction between neuronal activity and cerebral blood flow contribute to cognitive impairments associated with aging. By investigating different interventions, these studies aim to identify interventions that may slow or mitigate cognitive decline in older adults.

4.6 Inorganic Nitrate Supplementation on Cerebrovascular Aging and Arterial Stiffness

The first ongoing clinical study "Inorganic Nitrate Supplementation on Cerebrovascular Aging and Arterial Stiffness" focuses on examining the effects of inorganic nitrate supplementation, particularly from beetroot

juice, on aging cerebrovascular systems and arterial stiffness.[23] Launched on November 1, 2018, the study is expected to conclude on June 30, 2024. This randomized, double-blind, crossover study enrolled 53 community-dwelling older adults, randomly assigned to either an experimental or control group. The experimental group received nitrate-rich beetroot juice, while the control group consumed nitrate-depleted beetroot juice. The primary outcomes measured were the acute changes in carotid artery stiffness, assessed through ultrasonography and applanation tonometry, and changes in cerebral blood flow which were measured using 4D pc VIPR MRI technology. The 4D pc VIPR MRI is an advanced imaging technique that generates detailed, dynamic images of blood flow in cerebral arteries, allowing researchers to visualize circulation patterns throughout the brain. Carotid artery stiffness is a critical biomarker of cerebrovascular aging, as reduced compliance in these vessels can impair cerebral perfusion. This study underscores the potential role of dietary nitrate supplementation in supporting vascular function and mitigating cognitive decline associated with aging.

4.7 The Effect of NAD Supplementation on Brain Vascular Health in Aging

The second study "The Effect of NAD Supplementation on Brain Vascular Health in Aging," delves into its effects on brain vascular health in aging individuals.[24] The objective is to ascertain whether Nicotinamide Riboside, a precursor to NAD, can enhance brain health and memory in older adults by replenishing NAD levels. The trial began on May 3, 2023 and is scheduled for completion in December 2027. This randomized, double-blind, placebo-controlled parallel study involves 214 community-dwelling older adults with normal cognitive function. Participants in the experimental group receive oral nicotinamide riboside (1 gram per day) for 8 weeks, while the control group receives an indistinguishable placebo. Primary outcomes include changes in neurovascular coupling, assessed using functional near-infrared spectroscopy, and alterations in neuronal activity, measured through EEG. EEG provides spectral data through power spectral density analysis, enabling researchers to assess brain activity before and after treatment, reported as a percentage change from baseline. This study is particularly

significant as it explores the direct impact of NAD^+ replenishment on brain vascular health, with the potential to prevent or delay cognitive decline in the aging population.

5. Future Directions

Future directions of research on NVC-associated cognitive decline could include conducting longitudinal studies spanning 5-10 years to track the efficacy of interventions targeting NVC in individuals with cognitive impairments. This could also include the development of combination therapies, such as medicinal treatments and lifestyle interventions to investigate the benefits of improving overall well-being on brain health. In addition, genetic factors play a critical role in cognitive decline and warrant deeper investigation. While the APOEε4 allele is a well-known genetic risk factor, emerging evidence suggests that other genes—such as CLDN5, which is associated with blood–brain barrier integrity—may also be implicated in NVC dysfunction.[21] Future research could explore epigenetic approaches, including gene expression modulation, as a potential therapeutic strategy for NVC-related diseases.

6. Conclusion

As discussed, the growing prevalence of cognitive decline, including Alzheimer's, Parkinson's, and dementia, presents a significant challenge to public health systems worldwide. This review highlights the important role of NVC in regulating cerebral blood flow and brain health, both of which are essential in mitigating cognitive decline and managing neurodegenerative diseases.

Innovations in biomarkers–pericyte detachment, APOEε4 gene expression, vascular dysfunction in accordance with the 2-hit hypothesis model, and BBB breakdown–and advanced neuroimaging techniques–in-vivo photon imaging, Dynamic Vessel Analyzer, multimodality imaging platforms, fMRI, fNIRS–can be the key for the early detection and combating of NVC-related diseases. Additionally, NVC-targeting market therapeutics provide a look into future treatment. Substances like cocoa flavonoids and inorganic nitrate supplementation are being explored for their potential benefits in improving brain vascular health and cognitive function. With

continued research, these market therapies could be developed into effective treatments for both early and late stages of NVC-related symptoms. Ongoing research is necessary to refine these therapies to ensure both effectiveness and safety across various stages of disease progression. Although many of these interventions are still in early-stage research and suffer from limited funding and clinical validation, they show promise for future therapeutic development. In summary, the integration of advanced neuroimaging techniques with targeted biomarker detection holds considerable promise for improving the early diagnosis, monitoring, and treatment of cognitive decline. Focusing on the neurovascular unit as a therapeutic target may pave the way for more effective and personalized interventions in the fight against neurodegenerative diseases.

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