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Cerebral blood flow as a mechanistic framework across neurological disease

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Abstract

Impaired cerebral blood flow (CBF) and cerebral autoregulation are central features in a range of neurological conditions including Alzheimer's disease, traumatic brain injury, epilepsy, schizophrenia, ischaemic stroke, cerebral small vessel disease, vascular dementia, multiple sclerosis, and other neurodegenerative diseases. By exploring the complex mechanisms of neurovascular dysfunction, such as endothelial cell damage, blood–brain barrier disruption, and altered neurovascular coupling, we highlight how these disruptions contribute to disease pathogenesis, progression, and clinical outcomes. The review underscores the significant challenges in managing these conditions, as current therapeutic options remain limited and often inadequate. We advocate for a shift towards targeted research focused on restoring cerebrovascular homeostasis, proposing that therapeutic modulation of CBF could mitigate disease progression and improve patient outcomes. This work aims to provide clinicians, researchers, and students with an integrated understanding of the intersection between vascular dysfunction and neurological disorders, fostering interdisciplinary collaboration and innovation in treatment strategies. By synthesising contemporary research, we hope to inspire new avenues for translational research aimed at developing novel therapies for cerebrovascular-related neurological diseases.

Keywords Autoregulation, Cerebrovascular circulation, Neurodegeneration, Neurological disease, Neuropsychiatry, Neurosurgery

1 Introduction

Cerebral blood flow (CBF) is tightly regulated through neurovascular coupling and cerebral autoregulation, ensuring a precise balance between regional perfusion and the brain's high metabolic demands. The neurovascular unit (NVU), comprising endothelial cells, pericytes, vascular smooth muscle, astrocytic endfeet, neurons, and microglia, functions as a coordinated interface that couples neural activity to local perfusion demands (Fig. 1) [1]. Through integrated endothelial-astrocytic-pericytic signalling, the NVU maintains blood–brain barrier (BBB) integrity, modulates cerebrovascular tone, and stabilises CBF in response to metabolic and synaptic activity [2]. These mechanisms preserve the delicate homeostasis essential for optimal cognitive, motor, and autonomic function. The integrity of the NVU, BBB, and the glial-lymphatic (glymphatic) clearance

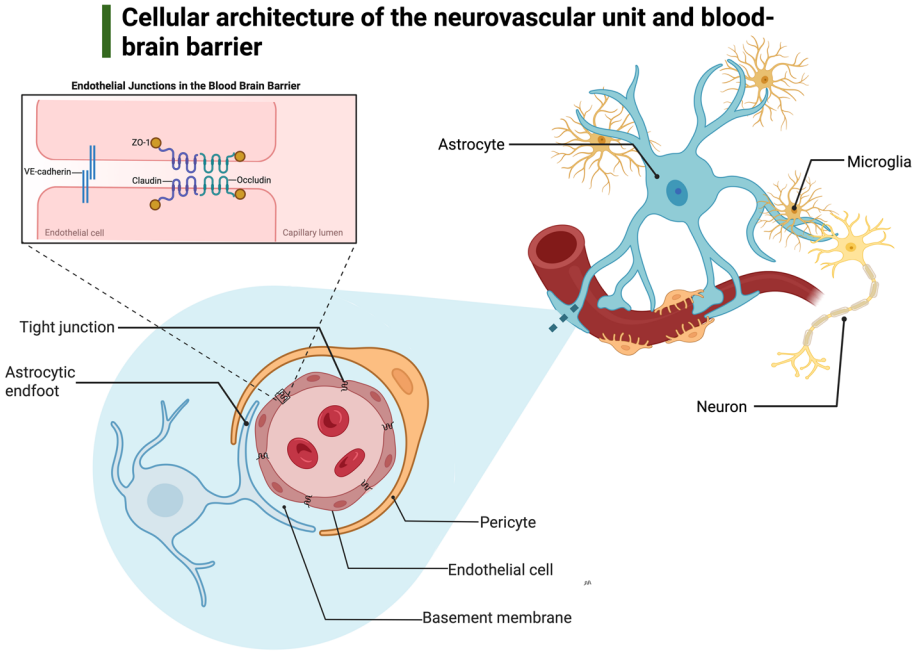

Fig. 1 Cellular architecture of the neurovascular unit and blood–brain barrier. The neurovascular unit (NVU) comprises neurons, endothelial cells joined by tight and adherens junctions, pericytes embedded within a shared basement membrane, astrocytic endfeet, and microglia. Together, these elements regulate cerebral blood flow (CBF), metabolic exchange, and immune signalling to maintain the integrity of the blood–brain barrier (BBB). Apical/luminally-located tight junctions (claudins, occludins, Zonula Occludens (ZO) proteins) and basal/peripherally adherens junctions (VE-cadherin) are formed exclusively between endothelial cells and constitute the physical BBB, while astrocytes, pericytes, neurons, and microglia modulate these junctions through signalling rather than forming barrier complexes themselves. Under homeostatic conditions, endothelial junctional complexes restrict paracellular diffusion, while astrocytic endfeet and pericytes modulate barrier permeability and neurovascular coupling (the coupling of neural activity to vascular tone). Astrocytes are depicted here in their physiological (non-reactive) state, as reactivity emerges only under pathological settings such as inflammation or ischaemia. The schematic provides a general depiction of the NVU framework rather than a disease-specific representation (Created in BioRender. Patel (2025) https://BioRender.com/6xo50my)

system is integral to this regulation, and any disruption can initiate or exacerbate pathological processes within the central nervous system (CNS).

Autoregulation operates through four interacting control axes (myogenic, metabolic, neurogenic, and NVU-mediated coupling), each with distinct stimuli, effectors, and timescales (Fig. 2) [3, 4]. The myogenic response stabilises flow across changes in cerebral perfusion pressure (CPP) through pressure-dependent smooth muscle constriction or dilation. Metabolic regulation adjusts vascular tone according to local biochemical signals, including carbon dioxide (CO_2), pH, nitric oxide (NO), adenosine, lactate, and endothelin-1 (ET_1), enabling tight coupling between oxidative demand and perfusion [5]. Neurogenic influences arising from autonomic and intracerebral neuronal pathways further refine regional tone [6]. NVU-mediated coupling integrates endothelial, astrocytic, and pericytic signalling with BBB and glymphatic function to align perfusion with neural activity at the microvascular scale. Together, these mechanisms maintain global CBF within a physiological plateau and dynamically redistribute regional perfusion according to metabolic need. Dysfunction in this system, due to either hypo- or hyperperfusion, can lead to critical outcomes like ischaemia, infarction, cerebral oedema, and increased intracranial pressure. Chronic hypertension and loss of circadian blood pressure variability further impair autoregulatory capacity through vascular remodelling and

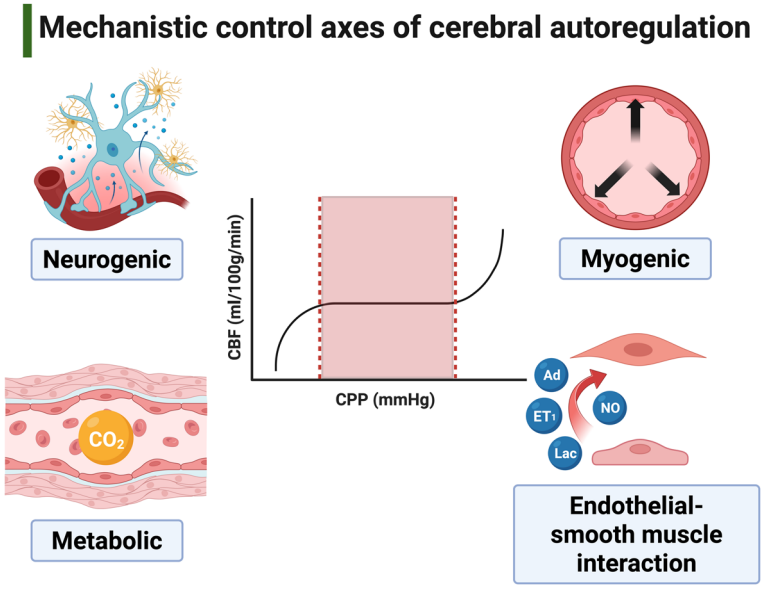

Fig. 2 Mechanistic control axes of cerebral autoregulation. Cerebral blood flow (CBF) is maintained within a physiological plateau (depicted on the autoregulatory curve as the flat segment between the lower and upper limits, red dashed lines) through four interacting control axes: myogenic, metabolic, neurogenic, and endothelial-smooth muscle regulation. Myogenic smooth muscle reflexes to transmural pressure stabilise flow across a range of cerebral perfusion pressures (CPPs). Metabolic mediators, including carbon dioxide (CO_2)/pH-driven vasodilation via nitric oxide (NO), adenosine, and lactate, opposed by endothelin-1 (ET_1), fine-tune vascular tone. Neurogenic inputs from neurons and astrocytes modulate regional arteriolar tone setpoints, while endothelial-smooth muscle interactions integrate these signals to sustain autoregulatory balance. Abbreviations: CBF. cerebral blood flow; CPP, cerebral perfusion pressure; CO_2, carbon dioxide; ET_1, endothelin-1; NO, nitric oxide. (Created in BioRender. Patel (2025) https://BioRender.com/yuzkvnl)

increased stiffness, shifting the autoregulatory curve and elevating the risk for cerebrovascular diseases and neurodegenerative decline [3].

Increasingly, impaired CBF is recognised as a common pathological denominator across a wide spectrum of neurodegenerative, neurosurgical, neuropsychiatric, and neurological disorders. In Alzheimer's disease, regional hypoperfusion measured by arterial-spin labelling magnetic resonance imaging (ASL-MRI) predicts cognitive decline and correlates with progression from mild cognitive impairment (MCI) to dementia [7, 8]. In traumatic brain injury, thresholds of critical low perfusion (< 20 mL/100 g/min) are tightly linked to secondary ischaemic injury and poorer long-term functional outcomes [9, 10]. Similarly, in acute ischaemic stroke, reduced cerebrovascular reserve and impaired dynamic autoregulation independently predict infarct expansion and diminished recovery [11, 12]. Across concussion, small vessel disease, and neuropsychiatric disorders, even subtle reductions in CBF are associated with cognitive slowing, attentional deficits, and impaired executive functions. These associations underscore the centrality of CBF as both a mechanistic and prognostic biomarker across a variety of neurological disciplines.

Given its broad clinical implications, there is a critical need to integrate insights from across the clinical neurosciences into a cohesive framework. This review synthesises contemporary research on CBF dysfunction across multiple disease states, identifying shared and distinct mechanisms while exploring potential therapeutic targets. By bridging perspectives from neurology, psychiatry, and neurosurgery, we aim to provide clinicians, researchers, and students with a comprehensive understanding of how vascular

dysfunction intersects with disease processes, fostering interdisciplinary dialogue and innovation in neurological diagnosis and treatment.

1.1 Clinical monitoring of cerebral blood flow

Clinical monitoring of CBF translates the mechanistic axes of autoregulation into measurable physiological signals using both cross-sectional and bedside modalities [13]. For a more detailed technical overview of contemporary CBF monitoring approaches and their clinical applications, refer to Nischal and Patel*et al.* [14].

Recent advances have markedly expanded the precision and clinical utility of cerebrovascular imaging, enabling more granular assessment of autoregulation and neurovascular health. Radionuclide and magnetic resonance imaging (MRI)-based techniques quantify perfusion and metabolism through diverse principles. Functional MRI (fMRI) employs blood-oxygenation-level-dependent (BOLD) contrast as an activity-linked surrogate [15, 16]. Positron emission tomography (PET) and single photon emission computed tomography (SPECT) enable tracer-based mapping, with integrated PET/MRI improving registration and longitudinal assessment [17]. Xenon-enhanced computed tomography (Xe-CT) remains a validated quantitative benchmark [18, 19].

ASL-MRI and its advanced variant, pseudocontinous ASL (pCASL-MRI), provide endogenous, radiation-free alternatives for repeatable perfusion measurements [20]. Dynamic susceptibility contrast MRI (DSC-MRI) [21] and dynamic contrast-enhanced MRI (DCE-MRI) [22] offer complementary approaches for assessing both perfusion and microvascular permeability, while contrast-based computed tomography (CT) perfusion is widely available for stroke workflows but yield variable absolute CBF estimates without standardised post-processing [23].

Beyond static mapping, multimodal paradigms integrating fMRI with electroencephalography (EEG) allow simultaneous assessment of neurovascular coupling and electrophysiological activity [24]. Portable methods, in contrast, emphasise continuous trend monitoring. Transcranial Doppler ultrasound (TCDU) estimates large-artery velocity to assess autoregulatory reactivity but is operator-dependent and assumes constant vessel diameter [25, 26]. Near-infrared spectroscopy (NIRS) tracks cortical oxygenation and, with contrast or frequency-domain paradigms, can approximate haemodynamic change despite extracranial contamination [27]. Ultrasound-tagged NIRS directly measures erythrocyte velocity [28], while laser Doppler flowmetry (LDF) and diffuse correlation spectroscopy (DCS) extend optical monitoring to microvascular flow [29–31], offering non-invasive, repeatable bedside trends with limited penetration depth [32].

In clinical practice, modality selection should align with investigative goal, be it quantitative mapping for diagnostic and longitudinal assessment, portable indices for continuous reactivity, and therapy titration, or multimodal integration for robust, patient-specific evaluation across acute, operative, and chronic neurovascular settings [33].

2 Neurodegenerative diseases

Dysregulated CBF represents a unifying hallmark of major neurodegenerative disorders, including Alzheimer's disease, Parkinson's disease, Huntington's disease, multiple sclerosis, and amyotrophic lateral sclerosis. Despite their distinct clinical presentations, these disorders exhibit common features such as impaired CBF, BBB dysfunction, and

disrupted neurovascular coupling. In Alzheimer's disease, reduced CBF and BBB breakdown contribute to β-amyloid accumulation, while Parkinson's disease and Huntington's disease are characterised by regional hypoperfusion associated with neurodegeneration and motor deficits. Multiple sclerosis involves hypoperfusion-driven inflammation and increased BBB permeability, whereas amyotrophic lateral sclerosis demonstrates progressive CBF reductions affecting both motor and cognitive function. Recognising the role of vascular dysfunction across these diseases underscores the potential for therapeutic strategies aimed at restoring CBF regulation and improving neurovascular health to mitigate disease progression (Table 1). Key neuroimaging studies reporting CBF deficits and impaired cerebrovascular reactivity in neurodegenerative disorders are summarised (Table 2), while region-specific patterns of CBF dysfunction and barrier breakdown are illustrated schematically (Fig. 3).

2.1 Alzheimer's disease

Alzheimer's disease (AD), the most common type of neurodegenerative dementia, is characterised by an accumulation of β-amyloid (Aβ) and tau neurofibrillary tangles within cerebral parenchyma, and subsequent memory loss and cognitive decline [34]. The two-hit vascular hypothesis of AD mechanistically describes its complex and multifactorial pathogenesis, with hit one corresponding to early cerebrovascular damage due to genetic, lifestyle, and vascular risk factors. Subsequent dysfunction of the cerebrovasculature, BBB, and CBF leads to the accumulation of Aβ (i.e. hit two) secondary to impaired glymphatic clearance. The net result of this is synaptic dysfunction, neuronal injury, neurodegeneration, and ultimately loss of function and structural connectivity [35]. Impaired cerebral autoregulation, a key proponent for the development of AD, has additionally been identified in transgenic mice overexpressing mutant amyloid precursor protein (APP). Increased APP expression, the protein precursor of Aβ, contributes to reduced CBF via dysfunctional endothelium-dependent vasodilation and exaggerated vasoconstrictor responses [36]. Evidence from human studies is largely congruent with these findings, such as Roher *et al.* (2012) who measured CBF within the internal carotid, basilar, and middle cerebral arteries by means of phase-contrast MRI and found that total CBF is 20% lower in AD patients relative to age-matched non-demented controls [37]. The dynamic interplay between dysfunctional waste clearance and cerebral hypoperfusion therefore provides a mechanistic foundation for understanding the development of AD (Table 1). These regional hypoperfusion patterns are characteristic of temporal and hippocampal vulnerability seen in AD (Fig. 3).

Dysfunction at the level of the NVU (Fig. 1) is of key importance in the pathogenesis of AD [38, 39]. Vascular smooth muscle cells and contractile pericytes regulate blood vessel diameter and vasomotility, while other components of the NVU maintain the integrity of the BBB [1]. Various groups have demonstrated increased hippocampal, cortical, and subcortical BBB permeability in patients with MCI and early-stage AD, as well as an increased CSF concentration of soluble platelet-derived growth factor receptor-β (PDGFR-β), a biomarker for pericyte degeneration and loss [40–42]. Kisler *et al.* (2017) showed that pericyte-deficient mice (PDGFR-$\beta^{-/-}$) have decreased cerebral oxygenation and neurovascular coupling relative to controls, as well as increased levels of subsequent neuronal death [43]. Overall, NVU pathology results in reduced CBF and increased Aβ accumulation in brain parenchyma [44]. Studies in apolipoprotein E4 positive patients,

Table 1 Disease-specific cerebral blood flow phenotypes with representative mechanistic evidence and clinical relevance

Disease	CBF phenotype	Key evidence	Clinical relevance
AD	Global hypoperfusion with mesial-temporal/posterior-cortical emphasis	APP/Aβ cause endothelial dysfunction and exaggerated vasoconstriction; ~ 20% ↓ total CBF versus controls (phase-contrast MRI) [22–24]	Use ASL/phase-contrast CBF and CO_2 reactivity to stage vascular involvement
	Impaired vasoreactivity		
	Early BBB/pericyte injury	PDGFR-β ↑/pericyte loss; CAA impairs neurovascular coupling and glymphatic outflow [28–30, 32, 42, 43, 46, 48–51]	Optimise vascular risk factors and slow-wave sleep
	CAA-related vasomotion loss	Slow-wave sleep and nocturnal dipping regulate Aβ clearance [50, 52, 56, 57, 59–61]	Consider vasomodulatory, BBB- and glymphatic-supportive adjuncts alongside anti-Aβ therapy
VD/SVD	WM-predominant hypoperfusion	Shared CAA and autoregulatory failure with AD	Use ASL for WM perfusion and ABPM for dipping profile to stage risk
	Impaired autoregulation	WM hypoperfusion on ASL [62, 64–66]	
	Nocturnal non-dipping	Non-dipping ↔ ↑WMH [67, 68]	Adopt CBF-sparing BP management and avoid excessive MAP reduction
	CAA overlap	Reduced cardiac output ↔ ↑subcortical WMH and cognitive impairment in older adults [69]	Optimise cardiac output to slow WM injury and vascular cognitive decline
MS	Diffuse WM-predominant hypoperfusion	Astrocytic ET_1 ↑ in plaques [78, 79]	Use ASL-CBF/ CO_2 reactivity to stage activity and anticipate BBB breach
			Tighten vascular risk and avoid hypocapnia
	Blunted CO_2 reactivity in plaques and normal-appearing WM	ASL/TCDU show ↓CBF and ↓CO_2 vasoreactivity [71–75, 87, 88, 271, 272]	Consider perfusion-guided rehabilitation
	ET_1/NVU dysfunction	Bosentan normalises CBF in small relapsing–remitting MS observational cohorts, larger randomised-controlled trials mixed [78, 80]	Evaluate vasoactive/BBB-stabilising adjuncts
HD	Bilateral striatal (caudate/putamen) and frontotemporal hypoperfusion	ASL shows reduced CBF in striatum and multimodal cortex; deficits correlate with Stroop [90, 91, 95]	ASL-CBF supports staging/prognosis, trial enrichment for neurovascular–metabolic therapies, and perfusion-aware cognitive/rehab planning
	Can precede clinical onset and parallels cognitive-motor decline	PET hypometabolism co-localizes; premanifest carriers show early CBF loss [91, 92, 98, 99]	
PD	Cortical and precuneus hypoperfusion	ASL shows ↓CBF (including non-demented PD) [102, 104, 248, 249, 250, 251]	Use ASL-CBF and CO_2 reactivity/dynamic autoregulation to stage non-motor risk and prognosis
		TCDU/CO_2 and dynamic autoregulation show dysregulation [102, 104, 248, 249, 250, 251]	Tighten vascular risk and avoid hypocapnia
	Blunted CO_2 reactivity and impaired dynamic autoregulation (worst in akinetic-rigid)	α-synuclein overexpression causes hypoperfusion and motor/olfactory deficits [108]	Consider perfusion-guided rehabilitation
	Limbic hypoperfusion in PD-depression	Pericyte loss → NVU uncoupling	Evaluate vasomodulatory/NVU-supportive trials

Table 1 (continued)

Disease	CBF phenotype	Key evidence	Clinical relevance
ALS	Frontotemporal and motor-system hypoperfusion	ASL/PET show early frontoparietal and thalamofrontal deficits (pre-cognitive) [109–114, 252, 25]	Perfusion to stage ALS-frontotemporal dementia and track progression
	Progressive cortical/subcortical involvement		Enrich trials for MMP/BBB-stabilising strategies
	BBB injury in advanced stages	SOD1/TDP-43 → MMP dysregulation → endothelial mitochondrial dysfunction, capillary narrowing, tight-junction loss [115–118]	Guide perfusion-aware rehab and respiratory/cognition monitoring

Summary of major neurodegenerative diseases highlighting characteristic CBF phenotypes, supporting mechanistic evidence, and actionable clinical implications. These findings illustrate how vascular dysfunction, impaired autoregulation, and neurovascular unit injury contribute to disease progression and therapeutic opportunity across the neurodegenerative spectrum

ABPM ambulatory blood pressure monitoring, *Aββ*-amyloid, *AD* Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *ASL* arterial-spin labelling, *BBB* blood–brain barrier, *CAA* cerebral amyloid angiopathy, *CBF* cerebral blood flow, CO_2 carbon dioxide, ET_1 endothelin-1, *HD* Huntington's disease, *MAP* mean arterial pressure, *MMP* matrix metalloproteinase, *MS* multiple sclerosis, *NVU* neurovascular unit, *PD* Parkinson's disease, *PDGFR-β* platelet-derived growth factor receptor-β, *PET* positron emission tomography, *SOD1* superoxide dismutase 1, *SVD* small vessel disease, *TCDU* transcranial Doppler ultrasound, *TDP-43* TAR DNA-binding protein 43, *VD* vascular dementia, *WM* white matter, *WMH* white matter magnetic resonance hyperintensity

a major AD susceptibility gene, report hippocampal and medial temporal lobe BBB dysfunction and pericyte loss, demonstrating an alternative pathogenic pathway with the same outcome [41, 45]. Neurovascular coupling itself is facilitated by cholinergic signalling networks, where reduced CBF has been demonstrated in murine models of cholinergic neuronal loss and denervation, particularly in the cerebral cortex and hippocampus [46–48]. Evidence from human autopsy studies support these findings, with AD brains showing not only reduced cholinergic neuron density in the temporal lobe and hippocampus, but also increased tortuosity of arterioles and string vessels [49]. These anatomical vascular abnormalities also contribute to reduced vasomotility and BBB dysfunction [50–52].

Cerebral amyloid angiopathy (CAA), or the deposition of Aβ peptide in the tunica media and adventitia of the leptomeningeal and cortical cerebral arteries, is additionally prevalent amongst AD patients, and results in reduced vascular compliance and increased arterial wall stiffness [53–55]. Van Veluw *et al.* (2020) demonstrated a functional consequence of this in mice with CAA, who showed impaired vasodilatory responses to visual stimulation relative to healthy controls [56]. CAA is also associated with perivascular space enlargement, which hinders glymphatic clearance of interstitial fluid (ISF) and soluble Aβ from white matter (WM), predisposing to Aβ accumulation and deposition in blood vessel walls (Fig. 4) [57–61]. More broadly, the role of the glymphatic system in AD has been demonstrated in genetically modified models, where aquaporin-4 knockout mice exhibit decreased Aβ clearance [62]. In humans, slow wave, non-rapid eye movement (non-REM) sleep, has been shown to be a key regulator of glymphatic Aβ clearance, with arterial pulsations of CBF via cortical pial arteries driving unidirectional clearance and increasing interstitial concentrations of Aβ by 60% [63, 64]. Of note, non-REM sleep states with low-frequency EEG delta waves and low noradrenaline tone are associated with increased glymphatic flow relative to wakefulness states and high noradrenaline status, and these synchronise with CBF oscillations via intracranial pressure B waves (also termed "slow waves") (Fig. 5) [65–68]. Beyond noradrenaline, several neurotransmitter systems critically modulate neurovascular coupling and are increasingly implicated in AD. Glutamate-driven NMDA receptor activation

Table 2 Studies reporting cerebral blood flow deficits and impaired cerebrovascular reactivity in neurodegenerative disorders using neuroimaging

Disease	Affected CNS regions	Study design	Sample size	Neuroimaging method(s)	References
CBF reductions					
AD	Internal carotid, basilar, and middle cerebral arteries	Cross-sectional	AD (n = 9); HC (n = 9)	2D-phase contrast MRI	[37]
	Hippocampus, posterior cingulate cortex, and precuneus	Cross-sectional	AD (n = 20); HC (n = 23)	ASL-MRI	[296]
	Hippocampus, posterior cingulate cortex, and precuneus	Cross-sectional	MCI (n = 54); AD (n = 23); HC (n = 180)	3D-pCASL MRI	[297]
	Hippocampus and prefrontal cortex	Longitudinal	MCI (n = 74); AD (n = 25); HC (n = 41)	ASL-MRI	[298]
	Hippocampus, frontal, temporal, and occipital grey matter	Cross-sectional	Huang*et al*. AD (n = 40); HC (n = 40) Mak *et al*. AD (n = 13); HC (n = 15)	3D-pCASL MRI	[299, 300]
VD	Frontal and temporal cortices	Cross-sectional	VD (n = 23); AD (n = 26)	ASL-MRI	[301]
	Frontal and parietal cortices	Cross-sectional	VD (n = 8); AD (n = 14); HC (n = 18)	ASL-MRI	[89]
HD	Sensorimotor, paracentral, inferior temporal, and lateral occipital cortices	Cross-sectional	HD (n = 17); HC (n = 41)	ASL-MRI	[123]
	Caudate and putamen	Cross-sectional	HD (n = 39); HC (n = 16)	pCASL-MRI	[118]
PD	Posterior parieto-occipital cortex, posterior cingulate, precuneus and cuneus, supramarginal middle frontal and superior temporal gyri	Cross-sectional	Melzer *et al*. PD (n = 61); HC (n = 29) Syrimi *et al*. PD (n = 22); HC (n = 16) Fernandez-Seara *et al*. PD (n = 25); HC (n = 34) Cheng *et al*. PD (n = 20); Parkinson-Plus (n = 16); HC (n = 17)	ASL-MRI	[130, 132, 302, 303]
	Prefrontal cortex	Longitudinal	PD (n = 49); HC (n = 37)	ASL-MRI	[304]
	Basal ganglia and cuneus	Cross-sectional	PD (n = 90); HC (n = 90)	ASL-MRI	[305]

Table 2 (continued)

Disease	Affected CNS regions	Study design	Sample size	Neuroimaging method(s)	References
ALS	Frontal and parietal cortices	Cross-sectional	ALS (n = 16)	ASL-MRI	[138]
	All cortical lobes, and subcortical grey and WM	Longitudinal	ALS (n = 14); HC (n = 11)	CT perfusion	[137]
	Frontal and temporal lobes	Cross-sectional	ALS (n = 55); HC (n = 20)	ASL-MRI	[141]
	Frontal, temporal, parietal, occipital cortices, and sensorimotor area	Cross-sectional	ALS (n = 21); ALS with dementia (n = 10); HC (n = 17)	PET	[306]
	Prefrontal	Cross-sectional	ALS (n = 15); ALS with dementia (n = 5)	SPECT	[307]
MS	WM including lesions and grey matter	Cross-sectional	MS (n = 39); HC (n = 19)	DCE-MRI	[115]
	WM including lesions	Cross-sectional	Ingrisch *et al.* MS (n = 19)	DSC-MRI	[99, 101, 308]
			Adhya *et al.* Relapse remitting MS (n = 11); Primary-progressive MS (n = 11); HC (n = 11)		
			Law *et al.* Relapse-remitting MS (n = 17); HC (n = 17)		
	Grey matter lesions	Cross-sectional	Peruzzo *et al.* Relapse-remitting MS (n = 44)	DSC-MRI	[309, 310]
			Francis *et al.* Secondary-progressive MS (n = 45)		
	Thalamus and right frontal regions	Cross-sectional	MS (n = 27); HC (n = 24)	ASL-MRI	[116]
AD	Occipital cortex	Cross-sectional	AD (n = 25); HC (n = 12)	fMRI + visual stimulation	[311]
	Middle cerebral artery	Cross-sectional	AD (n = 26); HC (n = 19)	TCDU + hypercapnia	[312]
	Whole brain	Cross-sectional	AD (n = 9); MCI (n = 7); HC (n = 11)	fMRI + hypercapnia	[313]
	Precuneus	Cross-sectional	AD (n = 53); MCI (n = 38); HC (n = 39)	fMRI + hypercapnia	[314]
	Temporal and parietal cortices	Cross-sectional	AD (n = 6); MCI (n = 11); HC (n = 13)	fMRI + hypercapnia	[315]
	Frontal, temporal and parietal cortices	Cross-sectional	SCI (n = 10); MCI (n = 10); AD (n = 18)	TCDU	[316]

Table 2 (continued)

Disease	Affected CNS regions	Study design	Sample size	Neuroimaging method(s)	References
VD	Middle cerebral artery	Cross-sectional	VD (n = 58); AD (n = 60); HC (n = 62)	TCDU	[317]
SVD	Subcortical grey matter, normal-appearing WM, and WMH	Cross-sectional	SVD (n = 182)	3 T MRI + hypercapnia	[318]
	Basal ganglia, frontal lobe and temporal lobe	Cross-sectional	SVD (n = 21); HC (n = 10)	ASL-MRI + intravenous dipyridamole injection	[319]
HD	Corpus callosum and subcortical WM including anterior cingulate, middle frontal, insular, middle temporal and posterior cingulate regions	Cross-sectional	HD (n = 12); HC (n = 11)	fMRI + hypercapnia	[320]
	Occipital cortex	Cross-sectional	HD (n = 23); HC (n = 16)	3D-Triple-acquisition-after-Inversion-Preparation MRI + visual stimulation	[321]
PD	Cuneus, precuneus, and parietal regions	Cross-sectional	PD (n = 25); HC (n = 17)	fMRI + hypercapnia	[322]
	Middle cerebral artery territory	Cross-sectional	PD (n = 22); HC (n = 11)	TCDU + orthostatic pressure test	[323]
	Basal ganglia, thalamus sensorimotor, supplementary motor, and visual cortices	Cross-sectional	PD (n = 26); HC (n = 16)	fMRI + hypercapnia	[324]
MS	Grey matter lesions	Cross-sectional	MS (n = 19); HC (n = 19)	pCASL-MRI + hypercapnia	[325]
	Default mode, frontoparietal, somatomotor, visual, limbic, dorsal and ventral attention networks	Cross-sectional	MS (n = 28); HC (n = 28)	pCASL-MRI + hypercapnia	[326]

This table summarises cross-sectional and longitudinal neuroimaging studies assessing cerebral blood flow reductions and cerebrovascular reactivity impairment across major neurodegenerative diseases. Modalities include arterial-spin labelling MRI (ASL-MRI), pseudocontinuous ASL-MRI (pCASL-MRI), dynamic susceptibility contrast MRI (DSC-MRI), dynamic contrast-enhanced MRI (DCE-MRI), positron emission tomography (PET), single-photon emission computed tomography (SPECT), computed tomography (CT) perfusion, and transcranial Doppler ultrasound (TCDU)

AD Alzheimer's disease, *ALS* amyotrophic lateral sclerosis, *ASL-MRI* arterial-spin labelling magnetic resonance imaging, *CBF* cerebral blood flow, *CT* computed tomography, *DSC-MRI* dynamic susceptibility contrast MRI, *DCE-MRI* dynamic contrast-enhanced MRI, *fMRI* functional MRI, *HD* Huntington's disease, *HC* healthy control, *MCI* mild cognitive impairment, *MRI* magnetic resonance imaging, *MS* multiple sclerosis, *pCASL-MRI* pseudocontinuous arterial-spin labelling MRI, *PD* Parkinson's disease, *PET* positron emission tomography, *SCI* subjective cognitive impairment, *SPECT* single photon emission CT, *SVD* small vessel disease, *VD* vascular dementia, *TCDU* transcranial Doppler ultrasound

initiates astrocytic calcium ion (Ca^{2+}) waves that trigger activity-dependent vasodilation, linking excitatory synaptic signalling to rapid perfusion shifts [38], γ-aminobutyric acid (GABA) interneurons, including NO-producing subtypes, further regulate local perfusion through subtype-specific vasoactive signalling [69]. Dopaminergic and serotonergic

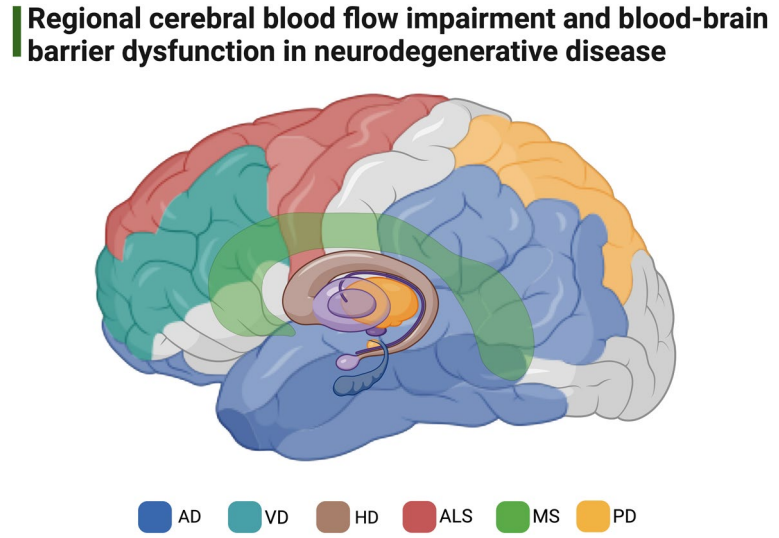

Fig. 3 Regional cerebral blood flow impairment and blood–brain barrier dysfunction in neurodegenerative disease. Representative cortical and subcortical territories most affected by cerebral blood flow (CBF) reduction and/or blood–brain barrier (BBB) breakdown are shown for Alzheimer's disease (AD), vascular dementia (VD), Huntington's disease (HD), amyotrophic lateral sclerosis (ALS), multiple sclerosis (MS), and Parkinson's disease (PD). Overlapping regions highlight shared vulnerability of frontotemporal, parietal, and hippocampal networks. Regional CBF alterations are closely associated with disease-specific pathological processes (such as amyloid and tau deposition in AD, demyelination in MS, neuronal loss in ALS, and microvascular injury in VD), which are discussed in the corresponding sections of the text. Abbreviations: AD, Alzheimer's disease; ALS, amyotrophic lateral sclerosis; BBB, blood–brain barrier; CBF, cerebral blood flow; HD, Huntington's disease; MS, multiple sclerosis; PD, Parkinson's disease; VD, vascular dementia (Created in BioRender. Patel (2025) https://BioRender.com/u0njv7z)

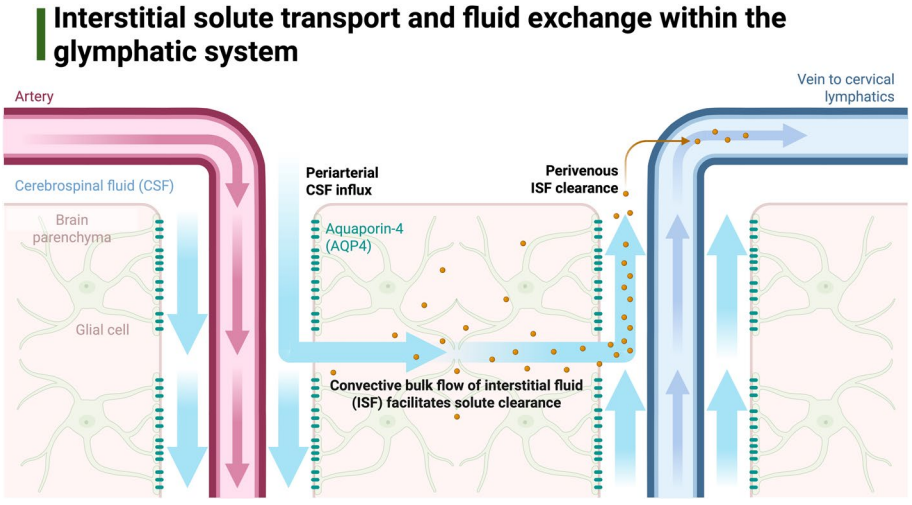

Fig. 4 Interstitial solute transport and fluid exchange within the glymphatic system. Cerebrospinal fluid (CSF) enters periarterial spaces surrounding penetrating arteries, where it exchanges with interstitial fluid (ISF) via aquaporin-4 (AQP4) channels on astrocytic endfeet. The resulting convective bulk flow of ISF drives solute clearance through perivenous pathways toward the cervical lymphatics, supporting metabolic waste removal and extracellular homeostasis. It is important to note that a parallel intramural periarterial drainage (IPAD) pathway exists (not depicted on the schematic), which clears solute along basement membranes of arterial walls and also contributes to waste removal, with its role and impairment in Alzheimer's disease, cerebral amyloid angiopathy, and sporadic cerebral small vessel disease becoming increasingly recognised. Abbreviations: AQP4, aquaporin-4; CSF, cerebrospinal fluid; ISF, interstitial fluid (Created in BioRender. Patel (2025) https://BioRender.com/0kn18kv)

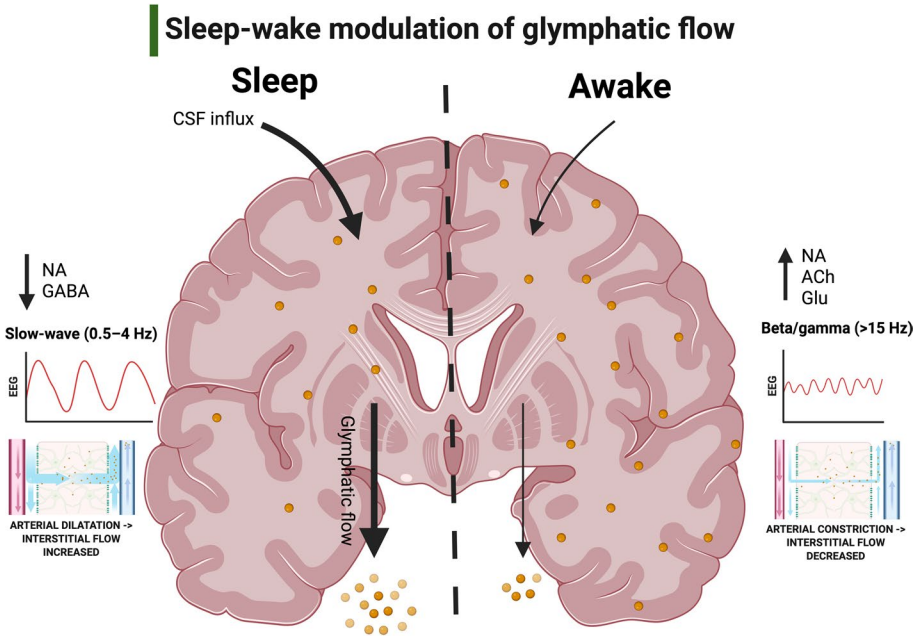

Fig. 5 Sleep–wake modulation of glymphatic flow. During non-rapid eye-movement (non-REM) sleep, reduced noradrenergic tone and increased γ-aminobutyric acid (GABA) tone accompany high-amplitude, low-frequency (0.5–4 Hz) slow-wave electroencephalography (EEG) activity. These conditions enhance cerebrospinal fluid (CSF) fluid influx into perivascular spaces and promote convective glymphatic flow, driven in part by arterial pulsations of cerebral blood flow (CBF), which facilitates interstitial solute clearance. In wakefulness, elevated noradrenaline, acetylcholine (ACh), and glutamate (Glu), together with beta/gamma EEG activity (> 15 Hz) increase vascular tone and reduce perivascular compliance. This suppresses glymphatic transport by limiting CSF-ISF exchange and attenuating interstitial solute clearance. Sleep–wake transitions therefore modulate neurovascular coupling, integrating neuronal activity, vascular pulsatility, and ISF dynamics to maintain metabolic homeostasis. Abbreviations: ACh, acetylcholine; CSF, cerebrospinal fluid; EEG, electroencephalography; GABA, γ-aminobutyric acid; Glu, glutamate; ISF, interstitial fluid; NA, noradrenaline; REM, rapid-eye movement (Created in BioRender. Patel (2025) https://BioRender.com/2g1y2tp)

projections to cortical microvessels modulate microvascular responsiveness and are disrupted in prodromal AD, contributing to cognitive slowing and impaired regional perfusion [70, 71]. Cholinergic dysfunction, particularly degeneration of basal forebrain cholinergic neurons in AD, reduces acetylcholine-mediated vasodilation and compromises cortical perfusion regulation [35]. Additionally, vasoactive neuropeptides, including VIP/PACAP (potent vasodilators) and neuropeptide-Y (strong vasoconstrictor), fine-tune microvascular responses under both physiological and pathological conditions [72, 73]. Importantly, in AD, these disturbances occur alongside elevated CSF noradrenaline, reflecting compensatory locus coeruleus hyperactivation that may degrade neurovascular coupling and exacerbate Aβ deposition [74].

Loss, attenuation, or reversal of nocturnal systemic blood pressure dipping may also provide an additional explanation for the observed accumulation of Aβ in AD. Tan *et al.* (2021) conducted a longitudinal study of 1000 Swedish men and proposed that reverse dipping represents an independent risk factor for developing AD in older men [75]. Tarumi *et al.* (2015) noted impaired dynamic CBF regulation and subsequent Aβ accumulation in the posterior cingulate cortex of age-corrected non-dippers with MCI [76]. Non-dipping has been shown to impact quality of sleep, with patients exhibiting reduced levels of slow wave (non-REM) sleep, higher microarousal rates, and increased wakefulness [77]. The role of sleep disruption as a cause or consequence of AD remains

controversial, though some hypotheses suggest that the aforementioned sleep phenotypes may suppress glymphatic system function, additionally predisposing to Aβ accumulation and subsequent neurodegeneration [78–80]. Intramural periarterial drainage (IPAD) represents a second, parallel clearance pathway that operates independently of the glymphatic system and becomes critically impaired in ageing and cerebrovascular disease [81]. Unlike glymphatic flow, which relies on CSF-ISF exchange through astrocytic AQP4 channels, IPAD drives solute movement within the basement membrane of cerebral arteries, using arterial wall pulsatility as its primary motive force [82, 83]. Experimental and human studies demonstrate that IPAD failure selectively promotes the accumulation of insoluble proteins, particularly Aβ, within arterial walls, forming the pathological substrate of CAA and contributing to downstream neurovascular dysfunction [84]. Although the relative contribution and pathophysiology of IPAD impairment in the pathogenesis of AD remains debated, reduced arterial compliance and age-related extracellular matrix stiffening further hinder perivascular drainage [85, 86]. In AD and CAA, convergent dysfunction of both glymphatic flow and IPAD likely amplifies Aβ retention WM injury, cognitive decline. Targeting vasomotility. glymphatic clearance, and IPAD pathways during early stages of AD, in combination with therapies that increase the solubility and breakdown of Aβ, may therefore provide an efficacious therapeutic approach in the future (Table 2).

2.2 Cerebral small vessel disease and vascular dementia

Cerebral small vessel disease (SVD) refers to a set of vascular pathologies affecting the arterioles, venules, and capillaries of the brain [87]. Associated with an increased propensity for cerebral ischaemia, cerebral SVD is a major contributing factor to the development of vascular dementia (VD) [88]. Cerebral SVD and VD are characterised by similar pathophysiological mechanisms to AD, where CAA and impaired cerebral autoregulation result in impaired neurological function via loss of WM structural integrity [89–91]. A recent systematic review and meta-analysis identified an association between dysfunctional nocturnal blood pressure dipping and increased WM magnetic resonance hyperintensity (WMH) volume, an imaging biomarker for cerebral SVD [92]. Chesebro *et al.* (2020) further demonstrated that this association predisposes to impaired cognition and memory, as seen in AD and VD [93]. Reductions in cardiac output may also be implicated in cerebral SVD due to its association with increased subcortical WMH volume secondary to chronic cerebral hypoperfusion, particularly in elderly patients [94]. The overlapping frontoparietal and subcortical perfusion deficits observed in VD and AD are illustrated (Fig. 3).

Emerging evidence suggests that IPAD dysfunction plays an important role in sporadic SVD. Age-related arterial stiffening and basement membrane thickening impede perivascular clearance, promoting retention of Aβ (among other proteins) and accelerating WM damage—mechanisms shared with ADD and CAA [84, 86]. Impaired CBF therefore represents a convergent pathogenic driver mechanism across cerebral SVD, VD, and AD, contributing to cognitive decline and structural network disconnection. Therapeutic modulation of CBF may therefore confer a potentially fruitful avenue for improving prognosis and slowing disease progression in these closely related neurological diseases (Table 1). However, directly modulating CBF in cerebral SVD and VD remains challenging. Current guidelines emphasise rigorous blood pressure control, yet the

optimal target that reduces recurrent stroke risk without worsening hypoperfusion in already vulnerable WM is uncertain, particularly as cardiac output-CBF coupling deteriorates with ageing and comorbidity [95, 96]. Small vasodilator trials in lacunar stroke using agents such as cilostazol and isosorbide mononitrate have shown feasibility and signals of benefit on WMHs but remain underpowered and definitive outcome data are still awaited [97]. There is therefore a pressing need for microvascular-specific biomarkers, integrating advanced perfusion imaging, BBB permeability measures, and circulating markers of endothelial or pericyte injury, to stratify patients and identify those most likely to benefit from CBF-targeted interventions.

2.3 Multiple sclerosis

Multiple sclerosis (MS) is a chronic progressive autoimmune disease characterised by CNS inflammation, T-cell-mediated demyelination, and axonal degeneration [98]. Impaired CBF is thought to play a key role in the pathophysiology of most clinical subtypes of MS, including relapsing–remitting MS, primary progressive MS, and clinically-isolated MS syndromes [99–102]. Various mechanisms have been proposed to explain why cerebral hypoperfusion is observed in MS. Saindane *et al.* (2007) suggested that axonal degeneration and decreased metabolic demand is the key proponent, though experimental evidence supporting this claim is scarce [103]. De Keyser *et al.* (1999) posited that a lack of β2-adrenoceptor expression on astrocytes in MS results in dysregulation of energy metabolism, reduced metabolic demand, and reduced CBF [104, 105]. However, the most promising evidence comes from D'haeseleer *et al.* (2013) who investigated ET_1 as a potential mediator for arteriolar vasoconstriction and CBF dysfunction in MS, and found increased levels of ET_1, derived from reactive astrocytes of MS plaques, in WM autopsy specimens [106]. Administration of the ET_1 antagonist Bosentan returned CBF to normal levels in their small cohort of relapsing–remitting MS patients, though this effect has not been observed in data from larger randomised-controlled trials (such as ROCHIMS) [106–108]. Nonetheless, further study is warranted to ascertain whether targeting the ET_1 system could be of therapeutic benefit in the management of MS.

Impaired CBF is also thought to contribute to the pathogenesis of MS through damage to the BBB [109]. Evidence suggests that hypoxic ischaemia, a key consequence of impaired CBF, can activate inflammatory cascades and promote generation of reactive oxygen species (ROS), which damages the BBB and increases its permeability [110, 111]. This enables autoreactive T-cells to enter brain parenchyma, destroy myelin sheaths, and promote inflammation via myelin breakdown product-mediated activation of neighbouring microglia and astrocytes [112, 113]. The net result is a positive feedback loop, which further exacerbates inflammation and damage to the BBB. Additional contribution from impaired glymphatic clearance has also been implicated in MS, particularly during progressive stages [114]. Therefore, hypoperfusion may not only provide a mechanistic basis for the development of MS but may also accelerate disease progression. Evidence from neuroimaging studies support this hypothesis, where a negative correlation between CBF and MS lesion volumes has been noted, while other studies have detected early CBF reductions in both MS plaques and healthy-looking WM of relapsing–remitting MS patients [115, 116]. A study investigating serum-based neuroinflammatory biomarkers and neurofilament light chain (a biomarker for axonal damage) found that hypoperfusion in MS alters their proteomic profile, suggesting that hypoperfusion is key

to managing neuroinflammation in MS [117]. The complex interplay between various pathological features of MS appears to converge on impaired CBF dynamicity, suggesting that modulation of CBF may provide an opportunity to delay disease progression and improve patient outcomes in MS (Table 1). The periventricular and cortical areas most affected by hypoperfusion and BBB dysfunction in MS are highlighted (Fig. 3).

2.4 Huntington's disease

Huntington's disease (HD) is a progressive neurodegenerative disorder which causes severe cognitive dysfunction, psychiatric sequalae, and involuntary motor movements. Aberrant regional CBF has been documented in the basal ganglia (specifically caudate and putamen) bilaterally, striatum, and motor cortex of HD patients, and associated with subsequent parenchymal atrophy and worse motor symptomatology [118, 119]. These CBF reductions are also associated with striatal and cortical atrophy, which may precede overt clinical signs in pre-manifest HD gene carriers [120]. A study using arterial-spin labelling MRI (ASL-MRI) in HD patients found significant CBF reductions in the frontotemporal, sensorimotor, occipital and cingulate cortical areas, as well as the insular and precuneus [119]. The insular and precuneal regions are associated with memory and emotional processing, both of which are affected in HD, supporting a further role for decreased CBF in the cognitive and emotional deficits seen in HD [121, 122]. These anatomical disturbances are also correlated with poorer performance on the Stroop test, a tool for assessing cognitive function [123–125]. In addition, bilateral hypoperfusion in the striatum, cingulate and temporal regions coincides with decreased glucose metabolism as shown by positron emission tomography (PET), as well as a reduction in striatal glycolysis and creatinine kinase seen in HD patients [119, 126–128]. As such, regional hypoperfusion may be associated with metabolic impairments and be a causative mechanism in neuronal dysfunction found in HD. These findings highlight the intricate relationship between CBF, metabolic processes, and cognitive function, suggesting that targeting these pathways could offer new therapeutic strategies for managing HD (Table 1). These frontostriatal and cingulate perfusion deficits are localised schematically (Fig. 3).

2.5 Parkinson's disease

Parkinson's disease (PD) is caused by the degeneration of dopaminergic neurons in the substantia nigra pars compacta and the formation of Lewy bodies containing aggregated α-synuclein, resulting in the hallmark triad of rigidity, bradykinesia and resting pin-rolling tremor [129]. In PD patients, ASL-MRI demonstrated decreased CBF in the cortical and precuneus regions, with more pronounced dysfunction in older patients that may be associated with worse mental impairment and cortical atrophy [130, 131]. In addition, reductions in CBF were seen in non-demented patients with PD, suggesting that reduction in perfusion may be an early sub-clinical biomarker for cognitive impairment and neurodegeneration [132]. In PD patients with depression, reduced CBF was observed in the right occipital WM and the right cingulate gyrus, which suggests that hypoperfusion in the limbic system may play a role in the pathogenesis of depression associated with PD [133]. Transcranial colour-coded Doppler sonography has revealed impaired cerebrovascular reactivity in PD patients, particularly those with the akinetic-rigid phenotype, which is associated with worse functional outcomes and higher degrees of leukoaraiosis

on MRI [134]. Dynamic cerebral autoregulation, neurovascular coupling, and vasomotor reactivity were all additionally found to be impaired in PD populations, suggesting that impaired CBF regulation in PD may affect central responsiveness to alterations in blood pressure and neural activity [135]. A study demonstrated that in transgenic mice overexpressing human α-synuclein, there was a significant reduction in cortical CBF accompanied by motor coordination deficits and olfactory dysfunction, supporting a causative role for α-synucleinopathy in CBF deficits [136]. Moreover, pericyte degeneration has been linked to neurovascular uncoupling, which limits oxygen supply to the brain and may contribute to the cognitive decline observed in PD patients [43]. Therapeutic modulation of CBF may therefore prove efficacious in the management of cognitive impairment and motor dysfunction in PD (Table 1). Region-specific cortical and subcortical hypoperfusion associated with PD is illustrated (Fig. 3).

2.6 Amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterised by upper and lower motor neuron signs in the absence of sensory impairment. ALS patients have early perfusion deficits within the frontoparietal cortex, subcortical grey matter, and WM, prior to the clinical manifestation of cognitive impairment [137, 138]. Progressive reductions in blood flow and glucose metabolism have also been observed in spinal regions of ALS mice models, suggesting that a combination of local and global CNS hypoperfusion may contribute to motor deficits [139]. Later stage ALS patients with cognitive impairment demonstrate more pronounced CBF reductions in frontal and temporal regions, while PET studies have revealed dysfunction in the dorsolateral prefrontal cortex (PFC) and thalamo-frontal association pathways in these patients [140, 141]. These findings suggest that CBF impairments in ALS are not exclusively limited to motor areas and likely contribute to both motor and cognitive symptoms, and that CBF impairment may precede clinical symptomatology, indicating a need for early intervention strategies [137, 142].

ALS is strongly associated with mutations in superoxide dismutase 1 (SOD1), where subsequent accumulation and aggregation of TAR DNA-binding protein 43 (TDP-43) induces oxidative stress and increases serum levels of matrix metalloproteinases (including MMP-2 and -9). This pathway has been observed in human ALS patients and SOD1 animal models, where matrix metalloproteinase dysregulation is linked to endothelial mitochondrial dysfunction, reduced capillary diameter and progressive loss of perivascular components, including occludin and collagen IV. Further evidence from MMP-9 knockout mice overexpressing both TDP-43 and SOD1 supports this as these animals exhibit heightened motor neuron protection [143–145]. Of note, the integrity of the BBB is also affected, with mitochondrial dysfunction, astrocyte pathology, and neuroinflammation contributing to its impairment, which in turn increased barrier permeability and exacerbates the degeneration of motor neurons [146, 147]. These findings suggest that targeting MMPs may offer a therapeutic strategy to modulate the neurodegenerative processes associated with ALS by preserving BBB integrity and improving motor neuron survival, though further research is necessary to elucidate the specific mechanisms through which MMP modulation can influence neuroinflammatory responses and neuronal health (Table 1). The predominant frontotemporal and motor cortical perfusion deficits characteristic of ALS are summarised (Fig. 3).

3 Neurosurgical diseases

Cerebrovascular dysfunction plays a critical role in a range of neurosurgical diseases, including traumatic brain injury, subarachnoid haemorrhage, concussion, and cerebral glioma. Impaired CBF, disrupted cerebral autoregulation, and vascular pathology contribute to secondary injury cascades and long-term neurological complications. Key mechanisms such as cerebral vasospasm, BBB dysfunction, and neuroinflammation underly much of this dysfunction, while emerging therapeutic strategies aimed at restoring CBF and improving patient outcomes continue to evolve.

3.1 Traumatic brain injury and intracranial bleeds

Traumatic brain injury (TBI) remains a significant cause of morbidity and mortality globally [148]. Reduced CBF is a commonly reported complication of TBI, with several contributory mechanisms underpinning its pathophysiology [149–151]. In the acute phase, damage to cerebral blood vessels and acute inflammation predisposes to cerebral oedema, raising ICP and resulting in decreased CBF via direct mechanical compression of cerebral blood vessels [152, 153]. At this stage, TBI is characterised by early global hypoperfusion, impaired dynamic cerebral autoregulation, and pressure-passive flow, often accompanied by blunted CO2 reactivity [154, 155]. Additionally, the increased pressure can disrupt BBB function, causing increased fluid extravasation into brain parenchyma, exacerbation of cerebral oedema, and further CBF dysfunction [156–158]. Cerebral swelling can also lead to impaired cerebral autoregulation, which is associated with poorer patient outcomes and increased mortality following TBI [9, 159, 160]. Cerebral vasospasm is another key mechanism responsible for impaired cerebral autoregulation post-TBI and has been extensively studied in the context of subarachnoid haemorrhage (SAH) (please refer to SAH sub-section) [161–164].

SAH refers to blood accumulation within the subarachnoid space and is typically due to non-traumatic aetiology, but the pathophysiological principles which result in cerebral vasospasm are shared across traumatic and non-traumatic causes [165]. Aneurysmal SAH is defined by profound CBF instability, including early transient hypoperfusion followed by delayed large-artery vasospasm and microvascular constriction that precipitate delayed cerebral ischaemia [166, 167]. Acute inflammation and/or direct vascular trauma causes endothelial cell damage and release of the potent vasoconstrictor molecule ET_1, which promotes cerebral vasospasm and cerebral hypoperfusion secondary to a rightward shift of the autoregulatory curve, as proposed by Strandgaard *et al.* (1973) [168, 169]. ET_1 itself binds endothelin-A (ET_A) receptors located on the tunica media of blood vessels, inducing smooth muscle contraction and vasoconstriction, while also binding endothelin-B1 (ET_{B1}) receptors on endothelial cells to reduce endothelial NO synthase (eNOS) synthesis [170]. In the context of TBI, evidence suggests that the interaction of ET_1 with ET_A receptors is likely responsible for observed reductions in CBF since ET_A receptor levels are significantly elevated during periods of impaired cerebral autoregulation (4-h post-TBI) [162–164, 171]. Of note, ET_B receptor levels peak at 24- and 48-h post-TBI, which coincides with CBF normalisation, suggesting that ET_B may be necessary to restore cerebral autoregulation and adequate cerebral perfusion [171]. Elevated ET_1 levels have also been reported in the CSF and plasma of SAH patients, with ET_1 inhibition and ET_1 receptor antagonism (e.g. Clazosentan) showing clinical efficacy in reversing CBF reduction post-SAH [160, 172, 173]. Delayed cerebral ischaemia

(DCI) is a serious and feared complication of SAH that occurs several days after the initial bleeding event and permanent brain damage and death [174]. It has a complex and multifactorial pathogenesis, though the bulk of evidence suggests that ET_1-mediated cerebral vasospasm is most critical in the observed ischaemia and neuronal cell death [175–177]. Other relevant contributing factors include thromboxane A2 release, generation of free radicals, and activation of inflammatory cells [178–180]. Therapeutic targeting of cerebral autoregulation and CBF may serve as a key opportunity to improve the prognosis and outcomes for this set of pathologies commonly encountered by service providers in the clinical neurosciences.

Cerebrovascular dysfunction following TBI has also been studied in the context of neurodegeneration, with evidence suggesting it may be causally linked to Aβ and tau deposition, as well as early initiation of pathology similar to AD [181]. Acute cerebral hypoperfusion post-TBI has been proposed to impair local glymphatic clearance, with autopsy studies in young TBI patients supporting this hypothesis and demonstrating increased Aβ and tau accumulation in close proximity to the site of trauma [182–184]. This neurotoxin accumulation is thought to lead to an injury cascade consisting of oxidative stress, endothelial cell dysfunction, and chronic inflammation [181]. Of note, TBI and AD brains show homogeneity in terms of cerebral volume, with hippocampal atrophy being common in both and thought to give rise to the stereotypical AD presentation of cognitive impairment and memory loss [185, 186]. BBB dysfunction has also been demonstrated in clinical studies of mild TBI, including rugby players exhibiting BBB dysfunction at the depths of cortical sulci, suggesting that increased barrier permeability could also contribute to the accumulation of neurotoxic substances, as seen in the perivascular accumulation of phosphorylated tau at the depth of cerebral sulci in chronic traumatic encephalopathy [187]. This innovative association between TBI and neurodegeneration further exemplifies the need for research activity in this arena, and once again demonstrates that novel approaches to CBF modulation may play a role in future treatment.

3.2 Concussion

Concussion, a form of mild TBI, is highly prevalent in populations globally though clinical intervention remains largely suboptimal given a lack of treatment strategies existing beyond large-scale prevention campaigns [188]. This lack of therapeutic success is, in part, due to poor mechanistic insight into the neurological sequelae that result in the long-term symptomology following singular and repeated concussion, although changes in CBF are emerging as a convergent pathogenic pathway and promising therapeutic target. Concussion produces regional hypoperfusion, particularly within the frontal, insular, and temporal cortices, that correlates with symptom burden and delayed recovery [189, 190]. In a study investigating CBF in concussed athletes, a sustained reduction in CBF was observed in the dorsal mid-insular cortex and superior temporal cortex without recovery to baseline in a subset of study participants, which correlated with poorer sporting outcomes, and symptoms of anxiety and depression [190]. The severity and duration of initial insult may therefore serve as a useful metric for prognostication, with more significant and sustained reductions in CBF post-concussion correlating with poorer clinical outcomes and prolonged recovery times [189, 190]. Of note, elevated MMP levels (particularly MMP-2 and -3) are associated with decreased CBF in

the early symptomatic phase of concussion, likely via increased BBB permeability and vascular dysfunction as seen with more severe TBIs and some forms of neurodegenerative disease [191]. Hypoperfusion experienced following concussion has also been linked to cognitive deficits, including impaired memory and visuomotor coordination, in both the acute and chronic phase [192, 193]. For example, male football players with a history of heading the ball exhibit impaired CBF regulation and cognitive performance relative to healthy non-concussed controls [192]. These findings suggest that CBF impairment is a key physiological marker of concussion and may also explain the increased incidence of neurodegenerative disease in athletes with a history of chronic concussion.

3.3 Cerebral glioma

CBF is a key factor in understanding the pathophysiology of cerebral gliomas, as it reflects both tumour angiogenesis and metabolic demands. High-grade gliomas, particularly glioblastomas (grade IV), exhibit significantly higher CBF than lower-grade gliomas (grade III), a pattern closely associated with neovascularisation [194]. Relative cerebral blood flow (rCBF) indices derived from MRI serve as reliable markers of tumour angiogenesis, correlating positively with histopathological grading, with more aggressive gliomas demonstrating extensive vascular proliferation and increased perfusion [195]. Additionally, molecular markers such as isocitrate dehydrogenase (IDH) mutation and methylguanine-DNA methyltransferase (MGMT) methylation influence rCBF, with IDH-mutant and MGMT-methylated gliomas exhibiting lower perfusion than their wild-type counterparts [196, 197]. BBB integrity is also disrupted in gliomas, as infiltrating tumour cells impair astrocyte-vascular coupling, leading to increased vascular permeability and oedema [198]. Vascular endothelial growth factor (VEGF) plays a crucial role in tumour vascularisation by promoting endothelial proliferation and capillary formation, with elevated VEGF levels strongly correlating with higher glioma grades and increased microvascular density [199]. Notably, gliomas with high VEGF expression exhibit increased rCBF and relative cerebral blood volume (rCBV), reinforcing the link between angiogenesis and tumour aggressiveness.

4 Neuropsychiatric diseases

CBF dysregulation plays a key role in the pathophysiology of neuropsychiatric disorders, including major depressive disorder, schizophrenia, migraine, generalised anxiety disorder. Regional hypoperfusion disrupts neurovascular coupling, contributing to cognitive dysfunction, affective dysregulation, and progressive disease burden. Therapeutic strategies aimed at restoring CBF and enhancing neuroprotection offer promising avenues for improving clinical outcomes.

4.1 Major depressive disorder

Major depressive disorder (depression) is a debilitating mental health disorder projected to be the leading contributor to the global burden of disease by 2030 [200]. The pathogenesis of depression is complex and multifactorial, with input from biological, psychological, and social factors [201]. Reduced CBF is thought to contribute to the development of depression through regional and global hypoperfusion, particularly in the elderly [202–206]. Bench *et al.* (1995) and Navarro *et al.* (2002) demonstrated focal reductions in CBF during depressed states, as well as resolution of cerebral perfusion in

these regions during periods of remission [207, 208]. A similar effect has been observed experimentally following administration of antidepressants [209]. Of note, depression demonstrates reproducible hypoperfusion within the dorsolateral PFC, anterior cingulate cortex, and limbic networks, correlating with depressive severity and cognitive impairment [210, 211]. The PFC is of particular interest, with evidence demonstrating consistent structural impairment amongst patients with depression [212]. Impaired CBF can cause reduced metabolism within the PFC, resulting in dysfunction of serotonergic, noradrenergic, and dopaminergic signalling pathways, which may explain the associated functional deficits of the PFC in depression such as impaired emotion regulation, altered decision making, and dysfunctional reward processing [213]. Dysfunction in the amygdala, involved in emotional stimulus processing, and hippocampus, involved in long-term memory consolidation and working memory, have also been identified in depression, possibly due to impaired CBF [214–216]. Overall, differential impairment in regional cerebral perfusion may provide a mechanistic explanation for the wide spectrum of clinical phenotypes observed in depression.

The "Vascular Depression" hypothesis has gained traction in recent years for providing a mechanistic link between vascular disease and depression. Initially proposed by Alexopoulos *et al.* (1997), the hypothesis states that the presence of vascular risk factors (e.g. hypertension, diabetes, atherosclerosis, stroke) and associated damage to cerebral blood vessels may "predispose, precipitate, or perpetuate" depression, especially in geriatric populations [217]. Increased WMH volume has also been proposed as a diagnostic criterion for vascular depression, with late-life depression being particularly associated with more severe and larger WMHs [218–221]. Oda *et al.* (2003) characterised the breadth of structures affected by WMHs in depressed patients, with lesions affecting both cortical structures, such as the frontal lobe, temporal lobe, and anterior cingulate gyrus, to subcortical structures, such as the thalamus and basal ganglia [222]. The primary proponent for depression therefore seems to be cerebral SVD, where an associated reduction in CBF predisposes to more severe depressive symptoms later in life [223].

4.2 Schizophrenia

Schizophrenia is a functional psychotic disorder characterised by the presence of delusions, thought disorders, hallucinations (particularly auditory), and passivity phenomena [224]. Traditionally thought to be due to increased dopaminergic signalling in the mesolimbic pathway (responsible for positive symptoms) and decreased dopaminergic signalling in the mesocortical pathway (responsible for negative symptoms), research from the last two decades challenges this dogma and suggests that altered CBF may also play a critical role in determining the severity of clinical symptomatology. Schizophrenia is associated with temporo-parietal and prefrontal hypoperfusion, alongside impaired frontal neurovascular coupling that correlates with negative symptoms and cognitive deficits [225, 226]. Zhao *et al.* (2006) used single photon emission computed tomography (SPECT) imaging to demonstrate decreased regional CBF in the bilateral frontotemporal lobes of patients presenting with negative symptoms, while Pinkham *et al.* (2011) used ASL-MRI to specify the superior temporal gyrus, cingulate cortex, and left middle frontal gyrus as key regions of interest where the degree of hypoperfusion correlates with negative symptom severity [227, 228]. Decreased CBF in the precentral and middle frontal gyri and increased CBF in the cingulate cortex and superior frontal

gyrus is also associated with increased severity of positive symptoms [228]. Pharmacological interventions commonly used in the clinical management of psychotic disorders also seem to optimise CBF in addition to targeting dopaminergic signalling pathways. Peitl *et al*. (2021) showed that, in patients presenting with a first schizophrenic episode, administration of aripiprazole (atypical antipsychotic) increased right frontotemporal CBF, decreased symptom severity, and increased cognition indices [229]. Recent studies suggest that CBF may therefore serve as a useful biomarker for quantifying the therapeutic response of schizophrenics to antipsychotics, as well as being a potentially fruitful avenue to identify novel therapeutic interventions [230].

4.3 Generalised anxiety disorder

Generalised anxiety disorder (GAD) is the most common of the anxiety disorders and is classically associated with a triad of subjective fear (which is constant and unremitting), discomfort, and somatic symptomatology. Cerebral autoregulatory mechanisms are thought to collapse in GAD, with TCDU data demonstrating more profound decreases in CBF velocity in GAD patients upon postural change relative to healthy controls, suggesting an inability to maintain homeostatic levels of cerebral perfusion during periods of physical stress [231, 232]. Of note, this impairment in cerebral autoregulation was negatively correlated with anxiety clinical assessment scores, where poorer autoregulatory function was associated with elevated levels of anxiety [232]. In particular, GAD demonstrated altered limbic and fronto-parietal perfusion patterns, including reduced CBF within the insula, anterior cingulate, and amygdala, all regions central to emotional regulation [233, 234]. Global neurovascular coupling is also disrupted in GAD, with evidence from Chen *et al.* (2021) showing that GAD patients exhibit a decreased correlation between voxel-wise CBF and functional connectivity strength (FCS) (measure of neural activity). This decoupling suggests a disrupted balance between brain activity and perfusion, particularly in the right superior parietal gyrus, where an increased CBF-FCS ratio is negatively correlated with self-esteem (as measured by clinical assessment scores) in GAD patients [235]. Further studies have demonstrated altered neural activity amongst elderly patients with anxiety, where a failure to activate the PFC (involved in the downregulation of negative emotions) may provide an opportunity for clinical targeting in this sub-population of GAD patients [236].

5 Neurological diseases

CBF impairment underlies several conditions typically managed by neurologists, including epilepsy, migraine, ischaemic stroke, and post-cardiac arrest brain injury. Each disorder exhibits distinct patterns and mechanisms of CBF disruption, ranging from focal neurovascular dysregulation in migraine to global hypoperfusion following cardiac arrest. While some alterations in CBF are transient and potentially reversible, others contribute to persistent structural and functional deficits.

5.1 Epilepsy

Epilepsy is defined by recurrent, unprovoked seizures arising from abnormal electrical activity in the brain. Increasing evidence suggests that alterations in CBF are both a consequence and a potential driver of seizure activity, with important implications for seizure localisation and clinical prognosis. In temporal lobe epilepsy (TLE), reduced CBF

has been reported in frontotemporal regions, with more pronounced decreases ipsilateral to the seizure focus, reinforcing its utility in epileptogenic mapping [237]. In contrast, patients with idiopathic generalised epilepsy exhibit decreased interictal regional CBF in structures such as the cingulate gyrus, thalamus, brainstem, and cerebellum [238, 239]. Following seizures, a compensatory phase of post-ictal hyperperfusion can persist up to six hours, reflecting increased metabolic demand and functional recovery [240]. In TLE, hyperperfusion patterns evolve dynamically during seizure progression, initially affecting the ipsilateral temporal lobe before spreading to the contralateral hemisphere, insula, basal ganglia, and frontal cortex [241]. Of note, peri-ictal hypotension is a critical factor in sudden unexpected death in epilepsy (SUDEP), which occurs more frequently at night, aligning with disruptions in diurnal autonomic regulation. Epilepsy itself is associated with significant autonomic dysfunction, which correlates with impaired cerebral autoregulation, as measured by autonomic nervous system indices [242]. These findings highlight the need for therapeutic strategies aimed at restoring central autonomic function and cerebral autoregulation, particularly in patients at high risk for SUDEP. Further research is needed, however, to explore the potential of CBF as a biomarker for seizure severity, localisation, and treatment response more broadly.

BBB dysfunction is increasingly recognised as a key contributor to epileptogenesis and treatment resistance [243]. Disruption of BBB integrity can facilitate the extravasation of pro-inflammatory molecules, leukocytes, and serum proteins into cerebral parenchyma, exacerbating neuroinflammation and neuronal hyperexcitability [244–246]. Persistent BBB leakage has been reported in both focal and generalised epilepsies, suggesting a broader role in disease progression beyond seizure localisation [247]. Claudin-5, a critical tight junction protein, plays a central role in maintaining BBB integrity, and its downregulation has been observed in treatment-resistant epilepsy, with lower expression levels correlating with increased seizure frequency and prolonged seizure duration [248]. Experimental knockdown of claudin-5 exacerbates seizure severity, disrupts BBB function, and promotes neuroinflammation, whereas pharmacological upregulation reduces seizure activity, suggesting that BBB stabilisation may represent a novel therapeutic approach for refractory epilepsy [249]. Beyond claudin-5, other junctional proteins are also dysregulated in epilepsy, such as downregulation of occludin, associated with increased BBB permeability, and Zonula Occludens-1 (ZO-1), linked to increased endothelial permeability, infiltration of albumin into the brain, and subsequent activation astrocytes and triggering of epileptiform activity [250, 251]. These findings underscore the critical role of BBB integrity in epilepsy pathophysiology, where targeting BBB stabilisation and restoring cerebrovascular homeostasis could open new therapeutic avenues, offering renewed hope for improved seizure control and neuroprotection in patients with refractory epilepsy.

5.2 Migraine

Migraine is a complex headache disorder thought to be associated with neuronal hyperexcitability, trigeminal nerve-induced inflammation, meningeal vessel dilation, and nerve fibre sensitisation, manifesting clinically as severe pain in the presence (with aura) or absence (without aura) of headache-preceding symptoms [252]. Genetic variants are known to be play a key role in the pathophysiology of migraine by altering cerebral haemodynamics, though the relationship remains unclear and largely inconsistent, with

some variants associated with higher flow velocities and others with decreased cross-sectional areas of the carotid arteries and decreased CBF [253].

Various studies have investigated the impairment of CBF in migraineurs with aura, particularly in the ictal (during migraine attacks) and inter-ictal phases. Chen *et al.* (2024) used ASL-MRI to study the inter-ictal period of patients with vestibular migraines, and found increased CBF in the primary motor cortex, primary somatosensory cortex, bifrontal gyrus, and insular cortex [254]. Another study by Fu *et al.* (2022) found similar increases in CBF of migraine with aura patients localised to the bilateral superior frontal gyrus, bilateral postcentral gyrus, and cerebellum, with simultaneous decreased CBF levels in the bilateral middle frontal gyrus, thalamus, and medioventral occipital cortex [255]. Microvascular vasospasm in the cerebral cortex during prolonged aura migraine is also thought to contribute to CBF impairment, likely due to endothelial dysfunction and decreased NO availability [256, 257]. An area of active investigation is the clinical association between CBF impairment and increased stroke risk, with some studies suggesting that impaired cerebral vasomotor reactivity could contribute to the increased incidence of stroke amongst migraineurs [256]. Overall, these findings suggest that CBF impairment may simultaneously be a consequence and a contributing factor to migraine attacks.

5.3 Ischaemic stroke

Ischaemic cerebrovascular accidents or strokes are mechanistically described as a regional reduction in CBF, where acute ischaemic events disrupt cerebral autoregulation and neurovascular coupling. However, these functional deficits are known to recover over time, suggesting that interventions that coincide with these recovery phases could enhance therapeutic outcomes and accelerate return towards baseline [258]. The penumbra (parenchymal zone that encloses core infarcted tissue), or moderately hypoperfused cerebral tissue within the thresholds of functional impairment and morphologic integrity, may particularly benefit from such timely intervention given its potentially salvageability if reperfused within a reasonable timeframe. This delineation is characterised by a core-penumbra CBF gradient, where critically reduced perfusion defines the infarct core and moderately reduced flow delineates salvageable penumbral tissue [259, 260]. Widely accepted CBF thresholds help operationally define these regions: perfusion below ~ 10–12 mL/100 g/min is typically associated with irreversible infarction within the ischaemic core, whereas values of ~ 12–22 mL/100 g/min correspond to the metabolically compromised but potentially salvageable penumbral tissue [260]. An interesting study conducted by Bo *et al.* (2020) demonstrated that excitatory optogenetic stimulation of sensorimotor neurons decreased cerebral haemodynamic responses (as shown by laser speckle contrast imaging) in both healthy and ischaemic tissue. Of note, however, stimulation of penumbral region neurons promoted recovery of neurovascular coupling, with CBF responses being positively correlated with anatomical distance from the ischaemic core, but only if this peri-infarct excitation was delivered within 24 h of lesion onset [261]. Despite this observed effect in the acute phase, Steiner *et al.* (2021) found that ipsilateral and contralateral reductions in CBF persisted several years post-stroke, suggesting that although accelerated recovery of cerebral perfusion may be possible, this recovery may not be complete [262]. This chronic impairment can additionally contribute to ongoing cognitive deficits and functional limitations in stroke survivors,

underscoring the importance of long-term monitoring and rehabilitation strategies aimed at improving cerebral perfusion.

In contemporary clinical practice, early restoration of cerebral perfusion remains the central therapeutic objective. Intravenous thrombolysis with tissue plasminogen activator and endovascular mechanical thrombectomy represent the established standards of care for eligible patients with acute ischaemic stroke, with both interventions demonstrating improved neurological outcomes when rapid reperfusion and restoration of CBF are achieved. Several promising therapies are being explored to enhance CBF during acute ischaemic stroke. These include drug therapies such as heme-free soluble guanylate cyclase activators, remote ischaemic preconditioning, and sphenopalatine ganglion stimulation [263]. Pharmacological modulators of blood viscosity are also commonly used given that increased blood viscosity is associated with lower baseline CBF in acute ischaemic stroke due to endothelial dysfunction, reduced NO-mediated vasodilation, and increased risk of thrombosis [264]. Non-pharmacological approaches, such as normobaric oxygen therapy and hypothermia, aim to preserve penumbral tissue by modulating metabolic demands while awaiting reperfusion [265, 266]. However, large randomised clinical trials evaluating these approaches have yielded neutral or negative results, suggesting that challenges related to treatment timing, patient selection, and physiological heterogeneity may limit their clinical efficacy despite encouraging mechanistic rationale [267, 268]. Additionally, sensory stimulation therapies have shown promise in enhancing neuroplasticity and functional recovery in stroke patients, indicating that a multifaceted approach may yield better outcomes than relying solely on traditional revascularisation techniques [265, 269]. Emerging evidence also suggests that biological sex may influence cerebrovascular physiology and stroke pathophysiology, with studies demonstrating higher baseline CBF in women across the lifespan, differences in vascular reactivity, and potentially more favourable collateral circulation in acute ischaemic stroke, highlighting the importance of considering sex-specific cerebrovascular dynamics in future therapeutic strategies [270–273].

5.4 Post-cardiac arrest brain injury

Post-cardiac arrest brain injury (PCABI) describes the impact on cerebral parenchyma of cessation of systemic perfusion following cardiac arrest, where CBF becomes severely impaired and results in hypoxic ischaemia and potential infarction of parenchymal tissue. Cardiac resuscitation helps stimulate transient hyperaemia in the acute phase, but due to the "no-reflow" phenomenon, often cerebral hypoperfusion rapidly recommences and can exacerbate hypoxic-ischaemia [274, 275]. Evidence suggests that even in cases where return of spontaneous circulation (ROSC) occurs prior to resuscitation attempts, CBF does not always return to pre-arrest baseline, with many patients experiencing hypoperfusion for several hours to days following the event [274, 276]. A key sub-cellular consequence of PCABI is mitochondrial dysfunction, where global cerebral ischaemia results in decreased mitochondrial adenosine triphosphate (ATP) generation and increased release of ROS, which can subsequently induce cerebrovascular dysfunction (resulting in an incessant positive feedback loop) [277]. Of note, pre-clinical therapeutic interventions aimed at improving mitochondrial dysfunction in PCABI have shown promise, but wider clinical implementation is still pending [278]. Continuous non-invasive monitoring of cerebral oxygenation and CBF using techniques such as NIRS and

TCDU can provide valuable insights into the effectiveness of such interventions aimed at restoring CBF PCABI [279, 280].

In addition to the direct effects of PCABI, microglial activation and subsequent neuroinflammation further exacerbate neurological injury and CBF impairment [281, 282]. The NOD-, LRR-, and pyrin domain-containing protein 3 (NLRP3) inflammasome, in particular, has been implicated in the inflammatory cascade following cardiac arrest, and its inhibition has been shown to reduce brain injury in experimental models [281]. The use of therapeutic hypothermia is also thought to decrease neuroinflammation post-cardiac arrest, with great efficacy in improving CBF dynamics [283, 284]. Similarly, the activation of various protein kinase C (PKC) isoforms play a key role in modulating post-ischaemic CBF, including PKC isoform δ, shown to exacerbate ischaemic damage, and PKC isoform ε, shown to be neuroprotective via stabilisation of cerebral circulation [285, 286]. These findings highlight the utility in therapeutically targeting neuroinflammatory pathways in post-cardiac arrest patients to prevent adverse neurological sequelae and improve long-term clinical outcomes.

6 Current dilemmas and future directions

Despite major advances in characterising CBF dysregulation across neurological, neurosurgical, neuropsychiatric, and neurodegenerative disease, several unresolved challenges continue to limit translation. First, the mechanisms linking microvascular dysfunction to network-level cognitive decline remain incompletely defined, with competing models emphasising NVU injury, impaired vasoreactivity, and glymphatic/IPAD failure [1, 287]. Second, attempts to therapeutically modulate CBF have provide inconsistent results, in part because the optimal targets of restoring autoregulation, enhancing perfusion, reducing pressure-passivity, or supporting perivascular clearance, remain disease- and stage-specific. Vasodilator trials in SVD and MS have shown mixed efficacy, highlighting the difficulty of modifying downstream microvascular tone without exacerbating leakage or oedema [288, 289]. Third, reliable biomarkers of microvascular health are lacking. Emerging metrics such as cerebrovascular reactivity, dynamic autoregulation indices, ASL-based perfusion reserve, and NIRS/DCS markers of microvascular flow show promise but lack standardisation for clinical decision-making [290–294]. Finally, the interaction between vascular dysfunction and sleep, inflammation, and protein clearance remains an active area of uncertainty, with models of glymphatic and IPAD flow yet to be reconciled in humans [81, 295]. Addressing these gaps will be essential for convert mechanistic insights into targeted therapies and developing precision vascular phenotyping across neurological disciplines.

7 Conclusion

This review has examined the central role of CBF dysfunction across a broad spectrum of neurodegenerative, neuropsychiatric, neurological and neurosurgical disorders. By integrating insights from multiple disciplines, we have highlighted how regional and global hypoperfusion not only reflects underlying pathology but often contributes directly to disease progression, symptomatology, and long-term outcomes. Despite advances in our understanding, key mechanistic pathways—particularly those linking vascular dysfunction to neurodegeneration, inflammation, and impaired clearance—remain incompletely understood.

There is an urgent need for continued interdisciplinary research to unravel the complexities of CBF regulation and its disruption in disease. Identifying shared and distinct vascular mechanisms across conditions may unlock new diagnostic markers and therapeutic targets. Ultimately, we hope this synthesis encourages clinicians, researchers, and students to view CBF not as a peripheral factor, but as a core element in the pathogenesis and treatment of neurological disease, paving the way for novel strategies to restore cerebral perfusion and improve patient outcomes across the neurosciences.

Abbreviations

Aβ	β-Amyloid
ABPM	Ambulatory blood pressure monitoring
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
APP	Amyloid precursor protein
AQP4	Aquaporin-4
ASL-MRI	Arterial-spin labelling magnetic resonance imaging
ATP	Adenosine triphosphate
BBB	Blood–brain barrier
BOLD	Blood-oxygenation-level-dependent
CAA	Cerebral amyloid angiopathy
CBF	Cerebral blood flow
Ca^{2+}	Calcium ion
CNS	Central nervous system
CO_2	Carbon dioxide
CPP	Cerebral perfusion pressure
CSF	Cerebrospinal fluid
CT	Computed tomography
DCE-MRI	Diffusion contrast-enhanced magnetic resonance imaging
DCI	Delayed cerebral ischaemia
DCS	Diffuse correlation spectroscopy
DSC-MRI	Dynamic susceptibility contrast magnetic resonance imaging
EEG	Electroencephalography
eNOS	Endothelial nitric oxide synthase
ET	Endothelin
FCS	Functional connectivity strength
fMRI	Functional magnetic resonance imaging
GAD	Generalised anxiety disorder
GABA	γ-Aminobutyric acid
Glymphatic	Glial-lymphatic
HC	Healthy control
HD	Huntington's disease
ICP	Intracranial pressure
IDH	Isocitrate dehydrogenase
IPAD	Intramural periarterial drainage
ISF	Interstitial fluid
LDF	Laser Doppler flowmetry
MCI	Mild cognitive impairment
MMP	Matrix metalloproteinase
MGMT	Methylguanine-DNA methyltransferase
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
NVU	Neurovascular unit
NIRS	Near-infrared spectroscopy
NLRP3	NOD-, LRR-, and pyrin domain-containing protein 3
NO	Nitric oxide
PD	Parkinson's disease
PCABI	Post-cardiac arrest brain injury
PDGFR-β	Platelet-derived growth factor receptor-β
PFC	Prefrontal cortex
PET	Positron emission tomography
PKC	Protein kinase C
rCBF	Relative cerebral blood flow
rCBV	Relative cerebral blood volume
REM	Rapid eye movement
ROS	Reactive oxygen species
ROSC	Return of spontaneous circulation
SAH	Subarachnoid haemorrhage
SCI	Subjective cognitive impairment

SOD1	Superoxide dismutase 1
SPECT	Single photon emission computed tomography
SUDEP	Sudden unexpected death in epilepsy
SVD	Small vessel disease
TBI	Traumatic brain injury
TCDU	Transcranial Doppler ultrasound
TDP-43	TAR DNA-binding protein 43
TLE	Temporal lobe epilepsy
VD	Vascular dementia
VEGF	Vascular endothelial growth factor
WM	White matter
WMH	White matter magnetic resonance hyperintensity
Xe-CT	Xenon-enhanced computed tomography
ZO	Zonula occludens

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SP: Conceptualisation, Methodology, Formal Analysis, Writing- Original Draft, Writing – Review & Editing, Visualisation, Project Administration. SAN: Conceptualisation, Methodology, Formal Analysis, Writing – Original Draft, Writing – Review & Editing, Visualisation, Project Administration. NKP: Conceptualisation, Methodology, Formal Analysis, Writing – Review & Editing, Supervision, Project Administration.

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References

1. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron. 2017;96(1):17–42. https://doi.org/10.1016/j.neuron.2017.07.030.
2. Attwell D, Buchan AM, Charpak S, Lauritzen M, Macvicar BA, Newman EA. Glial and neuronal control of brain blood flow. Nature. 2010;468(7321):232–43. https://doi.org/10.1038/nature09613.
3. Silverman A, Petersen NH. Physiology, cerebral autoregulation. StatPearls. Treasure Island. 2025
4. Strandgaard S, Paulson OB. Cerebral autoregulation. Stroke. 1984;15(3):413–6. https://doi.org/10.1161/01.str.15.3.413.
5. Hoiland RL, Fisher JA, Ainslie PN. Regulation of the cerebral circulation by arterial carbon dioxide. Compr Physiol. 2019;9(3):1101–54. https://doi.org/10.1002/cphy.c180021.
6. Ainslie PN, Brassard P. Why is the neural control of cerebral autoregulation so controversial? F1000Prime Rep. 2014;6:14. https://doi.org/10.12703/P6-14
7. Dai W, Lopez OL, Carmichael OT, Becker JT, Kuller LH, Gach HM. Mild cognitive impairment and alzheimer disease: patterns of altered cerebral blood flow at MR imaging. Radiology. 2009;250(3):856–66. https://doi.org/10.1148/radiol.2503080751.
8. Chao LL, Buckley ST, Kornak J, Schuff N, Madison C, Yaffe K, *et al*. ASL perfusion MRI predicts cognitive decline and conversion from MCI to dementia. Alzheimer Dis Assoc Disord. 2010;24(1):19–27. https://doi.org/10.1097/WAD.0b013e3181b4f736.
9. Kelly DF, Martin NA, Kordestani R, Counelis G, Hovda DA, Bergsneider M, *et al*. Cerebral blood flow as a predictor of outcome following traumatic brain injury. J Neurosurg. 1997;86(4):633–41. https://doi.org/10.3171/jns.1997.86.4.0633.
10. Menon DK, Zahed C. Prediction of outcome in severe traumatic brain injury. Curr Opin Crit Care. 2009;15(5):437–41. https://doi.org/10.1097/MCC.0b013e3283307a26.
11. Markus H, Cullinane M. Severely impaired cerebrovascular reactivity predicts stroke and TIA risk in patients with carotid artery stenosis and occlusion. Brain. 2001;124(Pt 3):457–67. https://doi.org/10.1093/brain/124.3.457.

12. Reinhard M, Rutsch S, Lambeck J, Wihler C, Czosnyka M, Weiller C, *et al*. Dynamic cerebral autoregulation associates with infarct size and outcome after ischemic stroke. Acta Neurol Scand. 2012;125(3):156–62. https://doi.org/10.1111/j.1600-0404.2011.01515.x
13. Fantini S, Sassaroli A, Tgavalekos KT, Kornbluth J. Cerebral blood flow and autoregulation: current measurement techniques and prospects for noninvasive optical methods. Neurophotonics. 2016;3(3):031411. https://doi.org/10.1117/1.NPh.3.3.031411
14. Nischal SA, Patel S, Yuen J, Mortimer A, Patel NK. Cerebral blood flow and modern approaches for clinical assessment and monitoring: a view to the future. Br J Neurosurg. 2025:1–15. https://doi.org/10.1080/02688697.2025.2602629
15. Glover GH. Overview of functional magnetic resonance imaging. Neurosurg Clin N Am. 2011;22(2):133–9. https://doi.org/10.1016/j.nec.2010.11.001
16. Attwell D, Iadecola C. The neural basis of functional brain imaging signals. Trends Neurosci. 2002;25(12):621–5. https://doi.org/10.1016/s0166-2236(02)02264-6.
17. Cui B, Zhang T, Ma Y, Chen Z, Ma J, Ma L, *et al*. Simultaneous PET-MRI imaging of cerebral blood flow and glucose metabolism in the symptomatic unilateral internal carotid artery/middle cerebral artery steno-occlusive disease. Eur J Nucl Med Mol Imaging. 2020;47(7):1668–77. https://doi.org/10.1007/s00259-019-04551-w
18. Lassen NA, Munck O. The cerebral blood flow in man determined by the use of radioactive krypton. Acta Physiol Scand. 1955;33(1):30–49. https://doi.org/10.1111/j.1748-1716.1955.tb01191.x.
19. Kirkpatrick PJ, Bucknall R, Naylor P, Rudman S, Strong AJ. Digital imaging of umbelliferone clearance: a method for repeated measurements of cerebral cortical blood flow with high temporal and spatial resolution. J Cereb Blood Flow Metab. 1994;14(6):1062–9. https://doi.org/10.1038/jcbfm.1994.139.
20. Alsop DC, Detre JA, Golay X, Gunther M, Hendrikse J, Hernandez-Garcia L, *et al*. Recommended implementation of arterial spin-labeled perfusion MRI for clinical applications: a consensus of the ISMRM perfusion study group and the European consortium for ASL in dementia. Magn Reson Med. 2015;73(1):102–16. https://doi.org/10.1002/mrm.25197
21. Renshaw PF, Levin JM, Kaufman MJ, Ross MH, Lewis RF, Harris GJ. Dynamic susceptibility contrast magnetic resonance imaging in neuropsychiatry: present utility and future promise. Eur Radiol. 1997;7(Suppl 5):216–21. https://doi.org/10.1007/pl00006895.
22. Gordon Y, Partovi S, Muller-Eschner M, Amarteifio E, Bauerle T, Weber MA, *et al*. Dynamic contrast-enhanced magnetic resonance imaging: fundamentals and application to the evaluation of the peripheral perfusion. Cardiovasc Diagn Ther. 2014;4(2):147–64. https://doi.org/10.3978/j.issn.2223-3652.2014.03.01.
23. Demeestere J, Wouters A, Christensen S, Lemmens R, Lansberg MG. Review of perfusion imaging in acute ischemic stroke: from time to tissue. Stroke. 2020;51(3):1017–24. https://doi.org/10.1161/STROKEAHA.119.028337.
24. Warbrick T. Simultaneous EEG-fMRI: what have we learned and what does the future hold? Sensors. 2022. https://doi.org/10.3390/s22062262.
25. Blanco P, Abdo-Cuza A. Transcranial Doppler ultrasound in neurocritical care. J Ultrasound. 2018;21(1):1–16. https://doi.org/10.1007/s40477-018-0282-9.
26. Vik SD, Torp H, Jarmund AH, Kiss G, Follestad T, Stoen R, *et al*. Continuous monitoring of cerebral blood flow during general anaesthesia in infants. BJA Open. 2023;6:100144. https://doi.org/10.1016/j.bjao.2023.100144.
27. Cardim D, Griesdale DE. Near-infrared spectroscopy: unfulfilled promises. Br J Anaesth. 2018;121(3):523–6. https://doi.org/10.1016/j.bja.2018.05.058.
28. Caccioppola A, Carbonara M, Macri M, Longhi L, Magnoni S, Ortolano F, *et al*. Ultrasound-tagged near-infrared spectroscopy does not disclose absent cerebral circulation in brain-dead adults. Br J Anaesth. 2018;121(3):588–94. https://doi.org/10.1016/j.bja.2018.04.038.
29. Sutherland BA, Rabie T, Buchan AM. Laser Doppler flowmetry to measure changes in cerebral blood flow. Methods Mol Biol. 2014;1135:237–48. https://doi.org/10.1007/978-1-4939-0320-7_20.
30. Buckley EM, Parthasarathy AB, Grant PE, Yodh AG, Franceschini MA. Diffuse correlation spectroscopy for measurement of cerebral blood flow: future prospects. Neurophotonics. 2014. https://doi.org/10.1117/1.NPh.1.1.011009.
31. Durduran T, Yodh AG. Diffuse correlation spectroscopy for non-invasive, micro-vascular cerebral blood flow measurement. Neuroimage. 2014;85(0 1):51–63. https://doi.org/10.1016/j.neuroimage.2013.06.017.
32. Carp SA, Robinson MB, Franceschini MA. Diffuse correlation spectroscopy: current status and future outlook. Neurophotonics. 2023;10(1):013509. https://doi.org/10.1117/1.NPh.10.1.013509.
33. Wintermark M, Sesay M, Barbier E, Borbely K, Dillon WP, Eastwood JD, *et al*. Comparative overview of brain perfusion imaging techniques. J Neuroradiol. 2005;32(5):294–314. https://doi.org/10.1016/s0150-9861(05)83159-1.
34. Knopman DS, Amieva H, Petersen RC, Chetelat G, Holtzman DM, Hyman BT, *et al*. Alzheimer disease. Nat Rev Dis Primers. 2021;7(1):33. https://doi.org/10.1038/s41572-021-00269-y.
35. Kisler K, Nelson AR, Montagne A, Zlokovic BV. Cerebral blood flow regulation and neurovascular dysfunction in Alzheimer disease. Nat Rev Neurosci. 2017;18(7):419–34. https://doi.org/10.1038/nrn.2017.48.
36. Niwa K, Kazama K, Younkin SG, Carlson GA, Iadecola C. Alterations in cerebral blood flow and glucose utilization in mice overexpressing the amyloid precursor protein. Neurobiol Dis. 2002;9(1):61–8. https://doi.org/10.1006/nbdi.2001.0460.
37. Roher AE, Debbins JP, Malek-Ahmadi M, Chen K, Pipe JG, Maze S, *et al*. Cerebral blood flow in Alzheimer's disease. Vasc Health Risk Manag. 2012;8:599–611. https://doi.org/10.2147/VHRM.S34874
38. Iadecola C. Neurovascular regulation in the normal brain and in Alzheimer's disease. Nat Rev Neurosci. 2004;5(5):347–60. https://doi.org/10.1038/nrn1387.
39. Zlokovic BV. Neurovascular pathways to neurodegeneration in Alzheimer's disease and other disorders. Nat Rev Neurosci. 2011;12(12):723–38. https://doi.org/10.1038/nrn3114.
40. Starr JM, Farrall AJ, Armitage P, McGurn B, Wardlaw J. Blood-brain barrier permeability in Alzheimer's disease: a case-control MRI study. Psychiatry Res. 2009;171(3):232–41. https://doi.org/10.1016/j.pscychresns.2008.04.003.
41. Montagne A, Barnes SR, Sweeney MD, Halliday MR, Sagare AP, Zhao Z, *et al*. Blood-brain barrier breakdown in the aging human hippocampus. Neuron. 2015;85(2):296–302. https://doi.org/10.1016/j.neuron.2014.12.032.
42. van de Haar HJ, Burgmans S, Jansen JF, van Osch MJ, van Buchem MA, Muller M, *et al*. Blood-brain barrier leakage in patients with early Alzheimer disease. Radiology. 2016;281(2):527–35. https://doi.org/10.1148/radiol.2016152244.
43. Kisler K, Nelson AR, Rege SV, Ramanathan A, Wang Y, Ahuja A, *et al*. Pericyte degeneration leads to neurovascular uncoupling and limits oxygen supply to brain. Nat Neurosci. 2017;20(3):406–16. https://doi.org/10.1038/nn.4489.

44. Sweeney MD, Kisler K, Montagne A, Toga AW, Zlokovic BV. The role of brain vasculature in neurodegenerative disorders. Nat Neurosci. 2018;21(10):1318–31. https://doi.org/10.1038/s41593-018-0234-x.
45. Halliday MR, Rege SV, Ma Q, Zhao Z, Miller CA, Winkler EA, *et al*. Accelerated pericyte degeneration and blood-brain barrier breakdown in apolipoprotein E4 carriers with Alzheimer's disease. J Cereb Blood Flow Metab. 2016;36(1):216–27. https://doi.org/10.1038/jcbfm.2015.44.
46. Van Beek AH, Claassen JA. The cerebrovascular role of the cholinergic neural system in Alzheimer's disease. Behav Brain Res. 2011;221(2):537–42. https://doi.org/10.1016/j.bbr.2009.12.047.
47. Govindpani K, McNamara LG, Smith NR, Vinnakota C, Waldvogel HJ, Faull RL, *et al*. Vascular dysfunction in Alzheimer's disease: a prelude to the pathological process or a consequence of it? J Clin Med. 2019. https://doi.org/10.3390/jcm8050651.
48. Nizari S, Wells JA, Carare RO, Romero IA, Hawkes CA. Loss of cholinergic innervation differentially affects eNOS-mediated blood flow, drainage of Aβ and cerebral amyloid angiopathy in the cortex and hippocampus of adult mice. Acta Neuropathol Commun. 2021;9(1):12. https://doi.org/10.1186/s40478-020-01108-z.
49. Babic T. The cholinergic hypothesis of Alzheimer's disease: a review of progress. J Neurol Neurosurg Psychiatry. 1999;67(4):558. https://doi.org/10.1136/jnnp.67.4.558.
50. Challa VR, Thore CR, Moody DM, Anstrom JA, Brown WR. Increase of white matter string vessels in Alzheimer's disease. J Alzheimers Dis. 2004;6(4):379–83. https://doi.org/10.3233/jad-2004-6404.
51. Baloyannis SJ, Baloyannis IS. The vascular factor in Alzheimer's disease: a study in Golgi technique and electron microscopy. J Neurol Sci. 2012;322(1–2):117–21. https://doi.org/10.1016/j.jns.2012.07.010.
52. Hunter JM, Kwan J, Malek-Ahmadi M, Maarouf CL, Kokjohn TA, Belden C, *et al*. Morphological and pathological evolution of the brain microcirculation in aging and Alzheimer's disease. PLoS ONE. 2012;7(5):e36893. https://doi.org/10.1371/journal.pone.0036893.
53. Weller RO, Nicoll JA. Cerebral amyloid angiopathy: pathogenesis and effects on the ageing and Alzheimer brain. Neurol Res. 2003;25(6):611–6. https://doi.org/10.1179/016164103101202057.
54. Nicoll JA, Yamada M, Frackowiak J, Mazur-Kolecka B, Weller RO. Cerebral amyloid angiopathy plays a direct role in the pathogenesis of Alzheimer's disease. Pro-CAA position statement. Neurobiol Aging. 2004;25(5):589–97. https://doi.org/10.1016/j.neurobiolaging.2004.02.003.
55. Shin HK, Jones PB, Garcia-Alloza M, Borrelli L, Greenberg SM, Bacskai BJ, *et al*. Age-dependent cerebrovascular dysfunction in a transgenic mouse model of cerebral amyloid angiopathy. Brain. 2007;130(Pt 9):2310–9. https://doi.org/10.1093/brain/awm156.
56. van Veluw SJ, Hou SS, Calvo-Rodriguez M, Arbel-Ornath M, Snyder AC, Frosch MP, *et al*. Vasomotion as a driving force for paravascular clearance in the awake mouse brain. Neuron. 2020;105(3):549-61 e5. https://doi.org/10.1016/j.neuron.2019.10.033.
57. Iliff JJ, Wang M, Liao Y, Plogg BA, Peng W, Gundersen GA, *et al*. A paravascular pathway facilitates CSF flow through the brain parenchyma and the clearance of interstitial solutes, including amyloid beta. Sci Transl Med. 2012;4(147):147ra11. https://doi.org/10.1126/scitranslmed.3003748
58. Roher AE, Kuo YM, Esh C, Knebel C, Weiss N, Kalback W, *et al*. Cortical and leptomeningeal cerebrovascular amyloid and white matter pathology in Alzheimer's disease. Mol Med. 2003;9(3–4):112–22.
59. Nedergaard M. Neuroscience. garbage truck of the brain. Science. 2013;340(6140):1529–30. https://doi.org/10.1126/science.1240514.
60. Kimbrough IF, Robel S, Roberson ED, Sontheimer H. Vascular amyloidosis impairs the gliovascular unit in a mouse model of Alzheimer's disease. Brain. 2015;138(Pt 12):3716–33. https://doi.org/10.1093/brain/awv327.
61. Peng W, Achariyar TM, Li B, Liao Y, Mestre H, Hitomi E, *et al*. Suppression of glymphatic fluid transport in a mouse model of Alzheimer's disease. Neurobiol Dis. 2016;93:215–25. https://doi.org/10.1016/j.nbd.2016.05.015.
62. Iliff JJ, Wang M, Zeppenfeld DM, Venkataraman A, Plog BA, Liao Y, *et al*. Cerebral arterial pulsation drives paravascular CSF-interstitial fluid exchange in the murine brain. J Neurosci. 2013;33(46):18190–9. https://doi.org/10.1523/JNEUROSCI.1592-13.2013.
63. Xie L, Kang H, Xu Q, Chen MJ, Liao Y, Thiyagarajan M, *et al*. Sleep drives metabolite clearance from the adult brain. Science. 2013;342(6156):373–7. https://doi.org/10.1126/science.1241224.
64. Mestre H, Tithof J, Du T, Song W, Peng W, Sweeney AM, *et al*. Flow of cerebrospinal fluid is driven by arterial pulsations and is reduced in hypertension. Nat Commun. 2018;9(1):4878. https://doi.org/10.1038/s41467-018-07318-3
65. Fultz NE, Bonmassar G, Setsompop K, Stickgold RA, Rosen BR, Polimeni JR, *et al*. Coupled electrophysiological, hemodynamic, and cerebrospinal fluid oscillations in human sleep. Science. 2019;366(6465):628–31. https://doi.org/10.1126/science.aax5440.
66. Grubb S, Lauritzen M. Deep sleep drives brain fluid oscillations. Science. 2019;366(6465):572–3. https://doi.org/10.1126/science.aaz5191.
67. Lundberg N. Continuous recording and control of ventricular fluid pressure in neurosurgical practice. Acta Psychiatr Scand Suppl. 1960;36(149):1–193.
68. Newell DW, Nedergaard M, Aaslid R. Physiological mechanisms and significance of intracranial B waves. Front Neurol. 2022;13:872701. https://doi.org/10.3389/fneur.2022.872701
69. Uhlirova H, Kilic K, Tian P, Thunemann M, Desjardins M, Saisan PA, *et al*. Cell type specificity of neurovascular coupling in cerebral cortex. Elife. 2016;5. https://doi.org/10.7554/eLife.14315
70. Cohen Z, Bonvento G, Lacombe P, Hamel E. Serotonin in the regulation of brain microcirculation. Prog Neurobiol. 1996;50(4):335–62. https://doi.org/10.1016/s0301-0082(96)00033-0.
71. Choi JK, Chen YI, Hamel E, Jenkins BG. Brain hemodynamic changes mediated by dopamine receptors: Role of the cerebral microvasculature in dopamine-mediated neurovascular coupling. Neuroimage. 2006;30(3):700–12. https://doi.org/10.1016/j.neuroimage.2005.10.029
72. Dalsgaard T, Hannibal J, Fahrenkrug J, Larsen CR, Ottesen B. VIP and PACAP display different vasodilatory effects in rabbit coronary and cerebral arteries. Regul Pept. 2003;110(3):179–88. https://doi.org/10.1016/s0167-0115(02)00205-7.
73. Tuor UI, Kelly PA, Edvinsson L, McCulloch J. Neuropeptide Y and the cerebral circulation. J Cereb Blood Flow Metab. 1990;10(5):591–601. https://doi.org/10.1038/jcbfm.1990.110.

74. Raskind MA, Peskind ER, Holmes C, Goldstein DS. Patterns of cerebrospinal fluid catechols support increased central noradrenergic responsiveness in aging and Alzheimer's disease. Biol Psychiatry. 1999;46(6):756–65. https://doi.org/10.1016/s0006-3223(99)00008-6.
75. Tan X, Sundstrom J, Lind L, Franzon K, Kilander L, Benedict C. Reverse dipping of systolic blood pressure is associated with increased dementia risk in older men: a longitudinal study over 24 years. Hypertension. 2021;77(4):1383–90. https://doi.org/10.1161/HYPERTENSIONAHA.120.16711
76. Tarumi T, Harris TS, Hill C, German Z, Riley J, Turner M, *et al*. Amyloid burden and sleep blood pressure in amnestic mild cognitive impairment. Neurology. 2015;85(22):1922–9. Epub 20151104. https://doi.org/10.1212/WNL.0000000000002167. PubMed PMID: 26537049; PubMed Central PMCID: PMC4664127.
77. Pedulla M, Silvestri R, Lasco A, Mento G, Lanuzza B, Sofia L, *et al*. Sleep structure in essential hypertensive patients: differences between dippers and non-dippers. Blood Press. 1995;4(4):232–7. https://doi.org/10.3109/08037059509077600.
78. Musiek ES, Holtzman DM. Mechanisms linking circadian clocks, sleep, and neurodegeneration. Science. 2016;354(6315):1004–8. https://doi.org/10.1126/science.aah4968.
79. Cedernaes J, Osorio RS, Varga AW, Kam K, Schioth HB, Benedict C. Candidate mechanisms underlying the association between sleep-wake disruptions and Alzheimer's disease. Sleep Med Rev. 2017;31:102–11. https://doi.org/10.1016/j.smrv.2016.02.002
80. Lloret MA, Cervera-Ferri A, Nepomuceno M, Monllor P, Esteve D, Lloret A. Is Sleep Disruption a Cause or Consequence of Alzheimer's Disease? Reviewing Its Possible Role as a Biomarker. Int J Mol Sci. 2020;21(3). Epub 20200210. https://doi.org/10.3390/ijms21031168. PubMed PMID: 32050587; PubMed Central PMCID: PMC7037733.
81. Albargothy NJ, Johnston DA, MacGregor-Sharp M, Weller RO, Verma A, Hawkes CA, *et al*. Convective influx/glymphatic system: tracers injected into the CSF enter and leave the brain along separate periarterial basement membrane pathways. Acta Neuropathol. 2018;136(1):139–52. https://doi.org/10.1007/s00401-018-1862-7
82. Carare RO, Bernardes-Silva M, Newman TA, Page AM, Nicoll JA, Perry VH, *et al*. Solutes, but not cells, drain from the brain parenchyma along basement membranes of capillaries and arteries: significance for cerebral amyloid angiopathy and neuroimmunology. Neuropathol Appl Neurobiol. 2008;34(2):131–44. https://doi.org/10.1111/j.1365-2990.2007.00926.x
83. Aldea R, Weller RO, Wilcock DM, Carare RO, Richardson G. Cerebrovascular smooth muscle cells as the drivers of intramural periarterial drainage of the brain. Front Aging Neurosci. 2019;11:1. https://doi.org/10.3389/fnagi.2019.00001.
84. Weller RO, Subash M, Preston SD, Mazanti I, Carare RO. Perivascular drainage of amyloid-beta peptides from the brain and its failure in cerebral amyloid angiopathy and Alzheimer's disease. Brain Pathol. 2008;18(2):253–66. https://doi.org/10.1111/j.1750-3639.2008.00133.x.
85. Diem AK, MacGregor Sharp M, Gatherer M, Bressloff NW, Carare RO, Richardson G. Arterial pulsations cannot drive intramural periarterial drainage: significance for Aβ drainage. Front Neurosci. 2017;11:475. https://doi.org/10.3389/fnins.2017.00475.
86. Hawkes CA, Gatherer M, Sharp MM, Dorr A, Yuen HM, Kalaria R, *et al*. Regional differences in the morphological and functional effects of aging on cerebral basement membranes and perivascular drainage of amyloid-β from the mouse brain. Aging Cell. 2013;12(2):224–36. https://doi.org/10.1111/acel.12045.
87. Li Q, Yang Y, Reis C, Tao T, Li W, Li X, *et al*. Cerebral small vessel disease. Cell Transplant. 2018;27(12):1711–22. https://doi.org/10.1177/0963689718795148.
88. Bordes C, Sargurupremraj M, Mishra A, Debette S. Genetics of common cerebral small vessel disease. Nat Rev Neurol. 2022;18(2):84–101. https://doi.org/10.1038/s41582-021-00592-8.
89. Schuff N, Matsumoto S, Kmiecik J, Studholme C, Du A, Ezekiel F, *et al*. Cerebral blood flow in ischemic vascular dementia and Alzheimer's disease, measured by arterial spin-labeling magnetic resonance imaging. Alzheimers Dement. 2009;5(6):454–62. https://doi.org/10.1016/j.jalz.2009.04.1233.
90. Purkayastha S, Fadar O, Mehregan A, Salat DH, Moscufo N, Meier DS, *et al*. Impaired cerebrovascular hemodynamics are associated with cerebral white matter damage. J Cereb Blood Flow Metab. 2014;34(2):228–34. https://doi.org/10.1038/jcbfm.2013.180.
91. Brickman AM, Guzman VA, Gonzalez-Castellon M, Razlighi Q, Gu Y, Narkhede A, *et al*. Cerebral autoregulation, beta amyloid, and white matter hyperintensities are interrelated. Neurosci Lett. 2015;592:54–8. https://doi.org/10.1016/j.neulet.2015.03.005.
92. Chokesuwattanaskul A, Cheungpasitporn W, Thongprayoon C, Vallabhajosyula S, Bathini T, Mao MA, *et al*. Impact of circadian blood pressure pattern on silent cerebral small vessel disease: a systematic review and meta-analysis. J Am Heart Assoc. 2020;9(12):e016299. https://doi.org/10.1161/JAHA.119.016299.
93. Chesebro AG, Melgarejo JD, Leendertz R, Igwe KC, Lao PJ, Laing KK, *et al*. White matter hyperintensities mediate the association of nocturnal blood pressure with cognition. Neurology. 2020;94(17):e1803–10. https://doi.org/10.1212/WNL.0000000000009316.
94. Jefferson AL, Tate DF, Poppas A, Brickman AM, Paul RH, Gunstad J, *et al*. Lower cardiac output is associated with greater white matter hyperintensities in older adults with cardiovascular disease. J Am Geriatr Soc. 2007;55(7):1044–8. https://doi.org/10.1111/j.1532-5415.2007.01226.x.
95. Wardlaw JM, Chabriat H, de Leeuw FE, Debette S, Dichgans M, Doubal F, *et al*. European stroke organisation (ESO) guideline on cerebral small vessel disease, part 2, lacunar ischaemic stroke. Eur Stroke J. 2024;9(1):5–68. https://doi.org/10.1177/23969873231219416.
96. Wardlaw JM, Smith EE, Biessels GJ, Cordonnier C, Fazekas F, Frayne R, *et al*. Neuroimaging standards for research into small vessel disease and its contribution to ageing and neurodegeneration. Lancet Neurol. 2013;12(8):822–38. https://doi.org/10.1016/S1474-4422(13)70124-8.
97. Smith EE, Markus HS. New treatment approaches to modify the course of cerebral small vessel diseases. Stroke. 2020;51(1):38–46. https://doi.org/10.1161/STROKEAHA.119.024150.
98. Tafti D, Ehsan M, Xixis KL. Multiple sclerosis. StatPearls. Treasure Island. 2025
99. Law M, Saindane AM, Ge Y, Babb JS, Johnson G, Mannon LJ, *et al*. Microvascular abnormality in relapsing-remitting multiple sclerosis: perfusion MR imaging findings in normal-appearing white matter. Radiology. 2004;231(3):645–52. https://doi.org/10.1148/radiol.2313030996.
100. Rashid W, Parkes LM, Ingle GT, Chard DT, Toosy AT, Altmann DR. Abnormalities of cerebral perfusion in multiple sclerosis. J Neurol Neurosurg Psychiatry. 2004;75(9):1288–93. https://doi.org/10.1136/jnnp.2003.026021.

101. Adhya S, Johnson G, Herbert J, Jaggi H, Babb JS, Grossman RI, *et al*. Pattern of hemodynamic impairment in multiple sclerosis: dynamic susceptibility contrast perfusion MR imaging at 3.0 T. Neuroimage. 2006;33(4):1029–35. https://doi.org/10.1016/j.neuroimage.2006.08.008.
102. Varga AW, Johnson G, Babb JS, Herbert J, Grossman RI, Inglese M. White matter hemodynamic abnormalities precede subcortical gray matter changes in multiple sclerosis. J Neurol Sci. 2009;282(1–2):28–33. https://doi.org/10.1016/j.jns.2008.12.036.
103. Saindane AM, Law M, Ge Y, Johnson G, Babb JS, Grossman RI. Correlation of diffusion tensor and dynamic perfusion MR imaging metrics in normal-appearing corpus callosum: support for primary hypoperfusion in multiple sclerosis. AJNR Am J Neuroradiol. 2007;28(4):767–72.
104. De Keyser J, Wilczak N, Leta R, Streetland C. Astrocytes in multiple sclerosis lack beta-2 adrenergic receptors. Neurology. 1999;53(8):1628–33. https://doi.org/10.1212/wnl.53.8.1628.
105. Ouellette J, Lacoste B. From neurodevelopmental to neurodegenerative disorders: the vascular continuum. Front Aging Neurosci. 2021;13:749026. https://doi.org/10.3389/fnagi.2021.749026.
106. D'Haeseleer M, Beelen R, Fierens Y, Cambron M, Vanbinst AM, Verborgh C, *et al*. Cerebral hypoperfusion in multiple sclerosis is reversible and mediated by endothelin-1. Proc Natl Acad Sci USA. 2013;110(14):5654–8. https://doi.org/10.1073/pnas.1222560110.
107. D'Haeseleer M, Hostenbach S, Peeters I, Sankari SE, Nagels G, De Keyser J, *et al*. Cerebral hypoperfusion: a new pathophysiologic concept in multiple sclerosis? J Cereb Blood Flow Metab. 2015;35(9):1406–10. https://doi.org/10.1038/jcbfm.2015.131.
108. Hostenbach S, Raeymaekers H, Van Schuerbeek P, Vanbinst AM, Cools W, De Keyser J, *et al*. The Role of Cerebral Hypoperfusion in Multiple Sclerosis (ROCHIMS) Trial in multiple sclerosis: insights from negative results. Front Neurol. 2020;11:674. https://doi.org/10.3389/fneur.2020.00674.
109. Monti L, Morbidelli L, Rossi A. Impaired cerebral perfusion in multiple sclerosis: relevance of endothelial factors. Biomark Insights. 2018;13:1177271918774800. https://doi.org/10.1177/1177271918774800.
110. Cramer SP, Simonsen H, Frederiksen JL, Rostrup E, Larsson HB. Abnormal blood-brain barrier permeability in normal appearing white matter in multiple sclerosis investigated by MRI. Neuroimage Clin. 2014;4:182–9. https://doi.org/10.1016/j.nicl.2013.12.001.
111. Rajeev V, Fann DY, Dinh QN, Kim HA, De Silva TM, Lai MKP, *et al*. Pathophysiology of blood brain barrier dysfunction during chronic cerebral hypoperfusion in vascular cognitive impairment. Theranostics. 2022;12(4):1639–58. https://doi.org/10.7150/thno.68304.
112. Balasa R, Barcutean L, Mosora O, Manu D. Reviewing the significance of blood-brain barrier disruption in multiple sclerosis pathology and treatment. Int J Mol Sci. 2021. https://doi.org/10.3390/ijms22168370.
113. Kamma E, Lasisi W, Libner C, Ng HS, Plemel JR. Central nervous system macrophages in progressive multiple sclerosis: relationship to neurodegeneration and therapeutics. J Neuroinflammation. 2022;19(1):45. https://doi.org/10.1186/s12974-022-02408-y.
114. Carotenuto A, Cacciaguerra L, Pagani E, Preziosa P, Filippi M, Rocca MA. Glymphatic system impairment in multiple sclerosis: relation with brain damage and disability. Brain. 2022;145(8):2785–95. https://doi.org/10.1093/brain/awab454.
115. Hojjat SP, Kincal M, Vitorino R, Cantrell CG, Feinstein A, Zhang L, *et al*. Cortical perfusion alteration in normal-appearing gray matter is most sensitive to disease progression in relapsing-remitting multiple sclerosis. AJNR Am J Neuroradiol. 2016;37(8):1454–61. https://doi.org/10.3174/ajnr.A4737.
116. Ota M, Sato N, Nakata Y, Ito K, Kamiya K, Maikusa N, *et al*. Abnormalities of cerebral blood flow in multiple sclerosis: a pseudocontinuous arterial spin labeling MRI study. Magn Reson Imaging. 2013;31(6):990–5. https://doi.org/10.1016/j.mri.2013.03.016.
117. Jakimovski D, Gibney BL, Marr K, Ramasamy DP, Dwyer MG, Bergsland N, *et al*. Lower cerebral arterial blood flow is associated with greater serum neurofilament light chain levels in multiple sclerosis patients. Eur J Neurol. 2022;29(8):2299–308. https://doi.org/10.1111/ene.15374.
118. Rocha NP, Charron O, Colpo GD, Latham LB, Patino JE, Stimming EF, *et al*. Cerebral blood flow is associated with markers of neurodegeneration in Huntington's disease. Parkinsonism Relat Disord. 2022;102:79–85. https://doi.org/10.1016/j.parkreldis.2022.07.024.
119. Ma Y, Eidelberg D. Functional imaging of cerebral blood flow and glucose metabolism in Parkinson's disease and Huntington's disease. Mol Imaging Biol. 2007;9(4):223–33. https://doi.org/10.1007/s11307-007-0085-4.
120. Montoya A, Price BH, Menear M, Lepage M. Brain imaging and cognitive dysfunctions in Huntington's disease. J Psychiatry Neurosci. 2006;31(1):21–9
121. Ruocco HH, Bonilha L, Li LM, Lopes-Cendes I, Cendes F. Longitudinal analysis of regional grey matter loss in Huntington disease: effects of the length of the expanded CAG repeat. J Neurol Neurosurg Psychiatry. 2008;79(2):130–5. https://doi.org/10.1136/jnnp.2007.116244.
122. Walker FO. Huntington's disease. Lancet. 2007;369(9557):218–28. https://doi.org/10.1016/S0140-6736(07)60111-1.
123. Chen JJ, Salat DH, Rosas HD. Complex relationships between cerebral blood flow and brain atrophy in early Huntington's disease. Neuroimage. 2012;59(2):1043–51. https://doi.org/10.1016/j.neuroimage.2011.08.112.
124. Lemiere J, Decruyenaere M, Evers-Kiebooms G, Vandenbussche E, Dom R. Cognitive changes in patients with Huntington's disease (HD) and asymptomatic carriers of the HD mutation—a longitudinal follow-up study. J Neurol. 2004;251(8):935–42. https://doi.org/10.1007/s00415-004-0461-9.
125. Adleman NE, Menon V, Blasey CM, White CD, Warsofsky IS, Glover GH, *et al*. A developmental fMRI study of the Stroop color-word task. Neuroimage. 2002;16(1):61–75. https://doi.org/10.1006/nimg.2001.1046.
126. Ciarmiello A, Cannella M, Lastoria S, Simonelli M, Frati L, Rubinsztein DC, *et al*. Brain white-matter volume loss and glucose hypometabolism precede the clinical symptoms of Huntington's disease. J Nucl Med. 2006;47(2):215–22.
127. Powers WJ, Videen TO, Markham J, McGee-Minnich L, Antenor-Dorsey JV, Hershey T, *et al*. Selective defect of in vivo glycolysis in early Huntington's disease striatum. Proc Natl Acad Sci USA. 2007;104(8):2945–9. https://doi.org/10.1073/pnas.0609833104.
128. Kim J, Amante DJ, Moody JP, Edgerly CK, Bordiuk OL, Smith K, *et al*. Reduced creatine kinase as a central and peripheral biomarker in Huntington's disease. Biochim Biophys Acta. 2010;1802(7–8):673–81. https://doi.org/10.1016/j.bbadis.2010.05.001.

129. Spillantini MG, Schmidt ML, Lee VM, Trojanowski JQ, Jakes R, Goedert M. Alpha-synuclein in Lewy bodies. Nature. 1997;388(6645):839–40. https://doi.org/10.1038/42166.
130. Melzer TR, Watts R, MacAskill MR, Pearson JF, Rueger S, Pitcher TL, *et al*. Arterial spin labelling reveals an abnormal cerebral perfusion pattern in Parkinson's disease. Brain. 2011;134(Pt 3):845–55. https://doi.org/10.1093/brain/awq377.
131. Lavy S, Melamed E, Cooper G, Bentin S, Rinot Y. Regional cerebral blood flow in patients with Parkinson's disease. Arch Neurol. 1979;36(6):344–8. https://doi.org/10.1001/archneur.1979.00500420054005.
132. Syrimi ZJ, Vojtisek L, Eliasova I, Viskova J, Svatkova A, Vanicek J, *et al*. Arterial spin labelling detects posterior cortical hypoperfusion in non-demented patients with Parkinson's disease. J Neural Transm. 2017;124(5):551–7. https://doi.org/10.1007/s00702-017-1703-1.
133. Yang Y, Yang Y, Pan A, Xu Z, Wang L, Zhang Y, *et al*. Identifying depression in Parkinson's disease by using combined diffusion tensor imaging and support vector machine. Front Neurol. 2022;13:878691. https://doi.org/10.3389/fneur.2022.878691.
134. Brisson RT, Fernandes RCL, Arruda JFL, Rocha T, Santos NGD, Silva LD, *et al*. Altered cerebral vasoreactivity on transcranial color-coded sonography related to akinetic-rigid phenotype of Parkinson's disease: interim analysis of a cross-sectional study. Brain Sci. 2023. https://doi.org/10.3390/brainsci13050709.
135. Barnes SC, Panerai RB, Beishon L, Hanby M, Robinson TG, Haunton VJ. Cerebrovascular responses to somatomotor stimulation in Parkinson's disease: a multivariate analysis. J Cereb Blood Flow Metab. 2022;42(8):1547–58. https://doi.org/10.1177/0271678X211065204.
136. Biju KC, Shen Q, Hernandez ET, Mader MJ, Clark RA. Reduced cerebral blood flow in an alpha-synuclein transgenic mouse model of Parkinson's disease. J Cereb Blood Flow Metab. 2020;40(12):2441–53. https://doi.org/10.1177/0271678X19895432.
137. Murphy MJ, Grace GM, Tartaglia MC, Orange JB, Chen X, Rowe A, *et al*. Widespread cerebral haemodynamics disturbances occur early in amyotrophic lateral sclerosis. Amyotroph Lateral Scler. 2012;13(2):202–9. https://doi.org/10.3109/17482968.2011.625569.
138. Rule RR, Schuff N, Miller RG, Weiner MW. Gray matter perfusion correlates with disease severity in ALS. Neurology. 2010;74(10):821–7. https://doi.org/10.1212/WNL.0b013e3181d3e2dd.
139. Miyazaki K, Masamoto K, Morimoto N, Kurata T, Mimoto T, Obata T, *et al*. Early and progressive impairment of spinal blood flow-glucose metabolism coupling in motor neuron degeneration of ALS model mice. J Cereb Blood Flow Metab. 2012;32(3):456–67. https://doi.org/10.1038/jcbfm.2011.155.
140. Abrahams S, Goldstein LH, Kew JJ, Brooks DJ, Lloyd CM, Frith CD, *et al*. Frontal lobe dysfunction in amyotrophic lateral sclerosis. A PET study. Brain. 1996;119(Pt 6):2105–20. https://doi.org/10.1093/brain/119.6.2105.
141. Shen D, Hou B, Xu Y, Cui B, Peng P, Li X, *et al*. Brain structural and perfusion signature of amyotrophic lateral sclerosis with varying levels of cognitive deficit. Front Neurol. 2018;9:364. https://doi.org/10.3389/fneur.2018.00364.
142. Tanaka M, Ichiba T, Kondo S, Hirai S, Okamoto K. Cerebral blood flow and oxygen metabolism in patients with progressive dementia and amyotrophic lateral sclerosis. Neurol Res. 2003;25(4):351–6. https://doi.org/10.1179/016164103101201670.
143. Miyazaki K, Ohta Y, Nagai M, Morimoto N, Kurata T, Takehisa Y, *et al*. Disruption of neurovascular unit prior to motor neuron degeneration in amyotrophic lateral sclerosis. J Neurosci Res. 2011;89(5):718–28. https://doi.org/10.1002/jnr.22594.
144. Spiller KJ, Khan T, Dominique MA, Restrepo CR, Cotton-Samuel D, Levitan M, *et al*. Reduction of matrix metalloproteinase 9 (MMP-9) protects motor neurons from TDP-43-triggered death in rNLS8 mice. Neurobiol Dis. 2019;124:133–40. https://doi.org/10.1016/j.nbd.2018.11.013.
145. Kaplan A, Spiller KJ, Towne C, Kanning KC, Choe GT, Geber A, *et al*. Neuronal matrix metalloproteinase-9 is a determinant of selective neurodegeneration. Neuron. 2014;81(2):333–48. https://doi.org/10.1016/j.neuron.2013.12.009.
146. Steinruecke M, Lonergan RM, Selvaraj BT, Chandran S, Diaz-Castro B, Stavrou M. Blood-CNS barrier dysfunction in amyotrophic lateral sclerosis: proposed mechanisms and clinical implications. J Cereb Blood Flow Metab. 2023;43(5):642–54. https://doi.org/10.1177/0271678X231153281.
147. Schreiber S, Bernal J, Arndt P, Schreiber F, Muller P, Morton L, *et al*. Brain vascular health in ALS is mediated through motor cortex microvascular integrity. Cells. 2023. https://doi.org/10.3390/cells12060957.
148. Johnson WD, Griswold DP. Traumatic brain injury: a global challenge. Lancet Neurol. 2017;16(12):949–50. https://doi.org/10.1016/S1474-4422(17)30362-9.
149. Liu AA, Voss HU, Dyke JP, Heier LA, Schiff ND. Arterial spin labeling and altered cerebral blood flow patterns in the minimally conscious state. Neurology. 2011;77(16):1518–23. https://doi.org/10.1212/WNL.0b013e318233b229.
150. Doshi H, Wiseman N, Liu J, Wang W, Welch RD, O'Neil BJ, *et al*. Cerebral hemodynamic changes of mild traumatic brain injury at the acute stage. PLoS ONE. 2015;10(2):e0118061. https://doi.org/10.1371/journal.pone.0118061.
151. Jullienne A, Obenaus A, Ichkova A, Savona-Baron C, Pearce WJ, Badaut J. Chronic cerebrovascular dysfunction after traumatic brain injury. J Neurosci Res. 2016;94(7):609–22. https://doi.org/10.1002/jnr.23732.
152. Marmarou A, Fatouros PP, Barzo P, Portella G, Yoshihara M, Tsuji O, *et al*. Contribution of edema and cerebral blood volume to traumatic brain swelling in head-injured patients. J Neurosurg. 2000;93(2):183–93. https://doi.org/10.3171/jns.2000.93.2.0183.
153. Zusman BE, Kochanek PM, Jha RM. Cerebral edema in traumatic brain injury: a historical framework for current therapy. Curr Treat Options Neurol. 2020. https://doi.org/10.1007/s11940-020-0614-x.
154. Bouma GJ, Muizelaar JP. Cerebral blood flow, cerebral blood volume, and cerebrovascular reactivity after severe head injury. J Neurotrauma. 1992;9(Suppl 1):S333–48.
155. Aries MJ, Czosnyka M, Budohoski KP, Steiner LA, Lavinio A, Kolias AG, *et al*. Continuous determination of optimal cerebral perfusion pressure in traumatic brain injury. Crit Care Med. 2012;40(8):2456–63. https://doi.org/10.1097/CCM.0b013e3182514eb6.
156. Pop V, Badaut J. A neurovascular perspective for long-term changes after brain trauma. Transl Stroke Res. 2011;2(4):533–45. https://doi.org/10.1007/s12975-011-0126-9.
157. Alves JL. Blood-brain barrier and traumatic brain injury. J Neurosci Res. 2014;92(2):141–7. https://doi.org/10.1002/jnr.23300.
158. Jha RM, Kochanek PM, Simard JM. Pathophysiology and treatment of cerebral edema in traumatic brain injury. Neuropharmacology. 2019;145(Pt B):230–46. https://doi.org/10.1016/j.neuropharm.2018.08.004.
159. Muizelaar JP, Lutz HA 3rd, Becker DP. Effect of mannitol on ICP and CBF and correlation with pressure autoregulation in severely head-injured patients. J Neurosurg. 1984;61(4):700–6. https://doi.org/10.3171/jns.1984.61.4.0700.

160. Graves JC, Kreipke CW. Endothelin, cerebral blood flow, and traumatic brain injury: implications for a future therapeutic target. In: Kobeissy FH (ed) Brain neurotrauma: molecular, neuropsychological, and rehabilitation aspects. Frontiers in neuroengineering. Boca Raton. 2015.
161. Lang EW, Diehl RR, Mehdorn HM. Cerebral autoregulation testing after aneurysmal subarachnoid hemorrhage: the phase relationship between arterial blood pressure and cerebral blood flow velocity. Crit Care Med. 2001;29(1):158–63. https://doi.org/10.1097/00003246-200101000-00031.
162. Kreipke CW, Morgan R, Roberts G, Bagchi M, Rafols JA. Calponin phosphorylation in cerebral cortex microvessels mediates sustained vasoconstriction after brain trauma. Neurol Res. 2007;29(4):369–74. https://doi.org/10.1179/016164107X204684.
163. Rafols JA, Morgan R, Kallakuri S, Kreipke CW. Extent of nerve cell injury in Marmarou's model compared to other brain trauma models. Neurol Res. 2007;29(4):348–55. https://doi.org/10.1179/016164107X204657.
164. Armstead WM, Kreipke CW. Endothelin-1 is upregulated after traumatic brain injury: a cross-species, cross-model analysis. Neurol Res. 2011;33(2):133–6. https://doi.org/10.1179/016164111X12881719352174.
165. Ziu E, Khan Suheb MZ, Mesfin FB. Subarachnoid hemorrhage. StatPearls. Treasure Island. 2025.
166. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, *et al*. Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke. 2010;41(10):2391–5. https://doi.org/10.1161/STROKEAHA.110.589275.
167. Macdonald RL. Delayed neurological deterioration after subarachnoid haemorrhage. Nat Rev Neurol. 2014;10(1):44–58. https://doi.org/10.1038/nrneurol.2013.246.
168. Strandgaard S, Olesen J, Skinhoj E, Lassen NA. Autoregulation of brain circulation in severe arterial hypertension. Br Med J. 1973;1(5852):507–10. https://doi.org/10.1136/bmj.1.5852.507.
169. Kowalczyk A, Kleniewska P, Kolodziejczyk M, Skibska B, Goraca A. The role of endothelin-1 and endothelin receptor antagonists in inflammatory response and sepsis. Arch Immunol Ther Exp (Warsz). 2015;63(1):41–52. https://doi.org/10.1007/s00005-014-0310-1.
170. Yeung PK, Shen J, Chung SS, Chung SK. Targeted over-expression of endothelin-1 in astrocytes leads to more severe brain damage and vasospasm after subarachnoid hemorrhage. BMC Neurosci. 2013;14(1):131. https://doi.org/10.1186/1471-2202-14-131.
171. Dore-Duffy P, Wang S, Mehedi A, Katyshev V, Cleary K, Tapper A, *et al*. Pericyte-mediated vasoconstriction underlies TBI-induced hypoperfusion. Neurol Res. 2011;33(2):176–86. https://doi.org/10.1179/016164111X12881719352372.
172. Barth M, Capelle HH, Munch E, Thome C, Fiedler F, Schmiedek P, *et al*. Effects of the selective endothelin A (ET(A)) receptor antagonist Clazosentan on cerebral perfusion and cerebral oxygenation following severe subarachnoid haemorrhage—preliminary results from a randomized clinical series. Acta Neurochir (Wien). 2007;149(9):911–8. https://doi.org/10.1007/s00701-007-1249-3.
173. Macdonald RL. Endothelin antagonists in subarachnoid hemorrhage: what next? Crit Care. 2012;16(6):171. https://doi.org/10.1186/cc11822.
174. Ikram A, Javaid MA, Ortega-Gutierrez S, Selim M, Kelangi S, Anwar SMH, *et al*. Delayed cerebral ischemia after subarachnoid hemorrhage. J Stroke Cerebrovasc Dis. 2021;30(11):106064. https://doi.org/10.1016/j.jstrokecerebrovasdis.2021.106064.
175. Budohoski KP, Czosnyka M, Smielewski P, Kasprowicz M, Helmy A, Bulters D, *et al*. Impairment of cerebral autoregulation predicts delayed cerebral ischemia after subarachnoid hemorrhage: a prospective observational study. Stroke. 2012;43(12):3230–7. https://doi.org/10.1161/STROKEAHA.112.669788.
176. Budohoski KP, Czosnyka M, Kirkpatrick PJ, Reinhard M, Varsos GV, Kasprowicz M, *et al*. Bilateral failure of cerebral autoregulation is related to unfavorable outcome after subarachnoid hemorrhage. Neurocrit Care. 2015;22(1):65–73. https://doi.org/10.1007/s12028-014-0032-6.
177. Santos GA, Petersen N, Zamani AA, Du R, LaRose S, Monk A, *et al*. Pathophysiologic differences in cerebral autoregulation after subarachnoid hemorrhage. Neurology. 2016;86(21):1950–6. https://doi.org/10.1212/WNL.0000000000002696.
178. Pradilla G, Chaichana KL, Hoang S, Huang J, Tamargo RJ. Inflammation and cerebral vasospasm after subarachnoid hemorrhage. Neurosurg Clin N Am. 2010;21(2):365–79. https://doi.org/10.1016/j.nec.2009.10.008.
179. Castanares-Zapatero D, Hantson P. Pharmacological treatment of delayed cerebral ischemia and vasospasm in subarachnoid hemorrhage. Ann Intensive Care. 2011;1(1):12. https://doi.org/10.1186/2110-5820-1-12.
180. Naraoka M, Matsuda N, Shimamura N, Asano K, Ohkuma H. The role of arterioles and the microcirculation in the development of vasospasm after aneurysmal SAH. Biomed Res Int. 2014;2014:253746. https://doi.org/10.1155/2014/253746.
181. Ramos-Cejudo J, Wisniewski T, Marmar C, Zetterberg H, Blennow K, de Leon MJ, *et al*. Traumatic brain injury and Alzheimer's disease: the cerebrovascular link. EBioMedicine. 2018;28:21–30. https://doi.org/10.1016/j.ebiom.2018.01.021.
182. Johnson VE, Stewart W, Smith DH. Traumatic brain injury and amyloid-β pathology: a link to Alzheimer's disease? Nat Rev Neurosci. 2010;11(5):361–70. https://doi.org/10.1038/nrn2808.
183. Iadecola C. The pathobiology of vascular dementia. Neuron. 2013;80(4):844–66. https://doi.org/10.1016/j.neuron.2013.10.008.
184. Perry DC, Sturm VE, Peterson MJ, Pieper CF, Bullock T, Boeve BF, *et al*. Association of traumatic brain injury with subsequent neurological and psychiatric disease: a meta-analysis. J Neurosurg. 2016;124(2):511–26. https://doi.org/10.3171/2015.2.JNS14503.
185. Barnes J, Bartlett JW, van de Pol LA, Loy CT, Scahill RI, Frost C, *et al*. A meta-analysis of hippocampal atrophy rates in Alzheimer's disease. Neurobiol Aging. 2009;30(11):1711–23. https://doi.org/10.1016/j.neurobiolaging.2008.01.010.
186. Graham NS, Sharp DJ. Understanding neurodegeneration after traumatic brain injury: from mechanisms to clinical trials in dementia. J Neurol Neurosurg Psychiatry. 2019;90(11):1221–33. https://doi.org/10.1136/jnnp-2017-317557.
187. O'Keeffe E, Kelly E, Liu Y, Giordano C, Wallace E, Hynes M, *et al*. Dynamic blood-brain barrier regulation in mild traumatic brain injury. J Neurotrauma. 2020;37(2):347–56. https://doi.org/10.1089/neu.2019.6483.
188. Tator CH. Concussions and their consequences: current diagnosis, management and prevention. CMAJ. 2013;185(11):975–9. https://doi.org/10.1503/cmaj.120039.
189. Wang Y, Nelson LD, LaRoche AA, Pfaller AY, Nencka AS, Koch KM, *et al*. Cerebral blood flow alterations in acute sport-related concussion. J Neurotrauma. 2016;33(13):1227–36. https://doi.org/10.1089/neu.2015.4072.
190. Meier TB, Bellgowan PS, Singh R, Kuplicki R, Polanski DW, Mayer AR. Recovery of cerebral blood flow following sports-related concussion. JAMA Neurol. 2015;72(5):530–8. https://doi.org/10.1001/jamaneurol.2014.4778.

191. Churchill NW, Di Battista AP, Rhind SG, Richards D, Schweizer TA, Hutchison MG. Cerebral blood flow is associated with matrix metalloproteinase levels during the early symptomatic phase of concussion. PLoS ONE. 2021;16(11):e0253134. https://doi.org/10.1371/journal.pone.0253134.
192. Marley CJ, Owens TS, Tsukamoto H, Stacey BS, Corkill R, Bailey DM. Impaired cerebral blood flow regulation and cognition in male football players. Scand J Med Sci Sports. 2021;31(10):1908–13. https://doi.org/10.1111/sms.14018.
193. Li F, Lu L, Shang S, Chen H, Wang P, Haidari NA, *et al*. Cerebral blood flow and its connectivity deficits in mild traumatic brain injury at the acute stage. Neural Plast. 2020;2020:2174371. https://doi.org/10.1155/2020/2174371.
194. Calvo-Imirizaldu M, Solis-Barquero SM, Aramendia-Vidaurreta V, Garcia de Eulate R, Dominguez P, Vidorreta M, *et al*. Cerebrovascular reactivity mapping in brain tumors based on a breath-hold task using arterial spin labeling. NMR Biomed. 2025;38(3):e5317. https://doi.org/10.1002/nbm.5317.
195. Price SJ, Green HA, Dean AF, Joseph J, Hutchinson PJ, Gillard JH. Correlation of MR relative cerebral blood volume measurements with cellular density and proliferation in high-grade gliomas: an image-guided biopsy study. AJNR Am J Neuroradiol. 2011;32(3):501–6. https://doi.org/10.3174/ajnr.A2312.
196. Wang K, Li Y, Cheng H, Li S, Xiang W, Ming Y, *et al*. Perfusion CT detects alterations in local cerebral flow of glioma related to IDH, MGMT and TERT status. BMC Neurol. 2021;21(1):460. https://doi.org/10.1186/s12883-021-02490-4.
197. Lu J, Li X, Li H. Perfusion parameters derived from MRI for preoperative prediction of IDH mutation and MGMT promoter methylation status in glioblastomas. Magn Reson Imaging. 2021;83:189–95. https://doi.org/10.1016/j.mri.2021.09.005.
198. Watkins S, Robel S, Kimbrough IF, Robert SM, Ellis-Davies G, Sontheimer H. Disruption of astrocyte-vascular coupling and the blood-brain barrier by invading glioma cells. Nat Commun. 2014;5(1):4196. https://doi.org/10.1038/ncomms5196.
199. Pang H, Dang X, Ren Y, Zhuang D, Qiu T, Chen H, *et al*. 3D-ASL perfusion correlates with VEGF expression and overall survival in glioma patients: comparison of quantitative perfusion and pathology on accurate spatial location-matched basis. J Magn Reson Imaging. 2019;50(1):209–20. https://doi.org/10.1002/jmri.26562.
200. Hock RS, Or F, Kolappa K, Burkey MD, Surkan PJ, Eaton WW. A new resolution for global mental health. Lancet. 2012;379(9824):1367–8. https://doi.org/10.1016/S0140-6736(12)60243-8.
201. Li Z, Ruan M, Chen J, Fang Y. Major depressive disorder: advances in neuroscience research and translational applications. Neurosci Bull. 2021;37(6):863–80. https://doi.org/10.1007/s12264-021-00638-3.
202. Lesser IM, Mena I, Boone KB, Miller BL, Mehringer CM, Wohl M. Reduction of cerebral blood flow in older depressed patients. Arch Gen Psychiatry. 1994;51(9):677–86. https://doi.org/10.1001/archpsyc.1994.03950090009002.
203. Awata S, Ito H, Konno M, Ono S, Kawashima R, Fukuda H, *et al*. Regional cerebral blood flow abnormalities in late-life depression: relation to refractoriness and chronification. Psychiatry Clin Neurosci. 1998;52(1):97–105. https://doi.org/10.1111/j.1440-1819.1998.tb00980.x.
204. Navarro V, Gasto C, Lomena F, Mateos JJ, Marcos T. Frontal cerebral perfusion dysfunction in elderly late-onset major depression assessed by 99MTC-HMPAO SPECT. Neuroimage. 2001;14(1 Pt 1):202–5. https://doi.org/10.1006/nimg.2001.0787.
205. Ishizaki J, Yamamoto H, Takahashi T, Takeda M, Yano M, Mimura M. Changes in regional cerebral blood flow following antidepressant treatment in late-life depression. Int J Geriatr Psychiatry. 2008;23(8):805–11. https://doi.org/10.1002/gps.1980.
206. Liao W, Wang Z, Zhang X, Shu H, Wang Z, Liu D, *et al*. Cerebral blood flow changes in remitted early- and late-onset depression patients. Oncotarget. 2017;8(44):76214–22. https://doi.org/10.18632/oncotarget.19185.
207. Bench CJ, Frackowiak RS, Dolan RJ. Changes in regional cerebral blood flow on recovery from depression. Psychol Med. 1995;25(2):247–61. https://doi.org/10.1017/s0033291700036151.
208. Navarro V, Gasto C, Lomena F, Mateos JJ, Marcos T, Portella MJ. Normalization of frontal cerebral perfusion in remitted elderly major depression: a 12-month follow-up SPECT study. Neuroimage. 2002;16(3 Pt 1):781–7. https://doi.org/10.1006/nimg.2002.1051.
209. Wei W, Karim HT, Lin C, Mizuno A, Andreescu C, Karp JF, *et al*. Trajectories in cerebral blood flow following antidepressant treatment in late-life depression: support for the vascular depression hypothesis. J Clin Psychiatry. 2018;79(6). https://doi.org/10.4088/JCP.18m12106
210. Mayberg HS. Limbic-cortical dysregulation: a proposed model of depression. J Neuropsychiatry Clin Neurosci. 1997;9(3):471–81. https://doi.org/10.1176/jnp.9.3.471.
211. Drevets WC. Neuroimaging studies of mood disorders. Biol Psychiatry. 2000;48(8):813–29. https://doi.org/10.1016/s0006-3223(00)01020-9.
212. Pizzagalli DA, Roberts AC. Prefrontal cortex and depression. Neuropsychopharmacology. 2022;47(1):225–46. https://doi.org/10.1038/s41386-021-01101-7.
213. Fu C, Shi D, Gao Y, Xu J. Functional assessment of prefrontal lobes in patients with major depression disorder using a dual-mode technique of 3D-arterial spin labeling and (18)F-fluorodeoxyglucose positron emission tomography/computed tomography. Exp Ther Med. 2017;14(2):1058–64. https://doi.org/10.3892/etm.2017.4594.
214. Sheline YI, Gado MH, Price JL. Amygdala core nuclei volumes are decreased in recurrent major depression. NeuroReport. 1998;9(9):2023–8. https://doi.org/10.1097/00001756-199806220-00021.
215. Axmacher N, Elger CE, Fell J. Working memory-related hippocampal deactivation interferes with long-term memory formation. J Neurosci. 2009;29(4):1052–960. https://doi.org/10.1523/JNEUROSCI.5277-08.2009.
216. Baxter MG, Croxson PL. Facing the role of the amygdala in emotional information processing. Proc Natl Acad Sci USA. 2012;109(52):21180–1. https://doi.org/10.1073/pnas.1219167110.
217. Alexopoulos GS, Meyers BS, Young RC, Campbell S, Silbersweig D, Charlson M. "Vascular depression" hypothesis. Arch Gen Psychiatry. 1997;54(10):915–22. https://doi.org/10.1001/archpsyc.1997.01830220033006.
218. Coffey CE, Figiel GS, Djang WT, Cress M, Saunders WB, Weiner RD. Leukoencephalopathy in elderly depressed patients referred for ECT. Biol Psychiatry. 1988;24(2):143–61. https://doi.org/10.1016/0006-3223(88)90270-3.
219. Dolan RJ, Poynton AM, Bridges PK, Trimble MR. Altered magnetic resonance white-matter T1 values in patients with affective disorder. Br J Psychiatry. 1990;157:107–10. https://doi.org/10.1192/bjp.157.1.107.
220. Fujikawa T, Yamawaki S, Touhouda Y. Incidence of silent cerebral infarction in patients with major depression. Stroke. 1993;24(11):1631–4. https://doi.org/10.1161/01.str.24.11.1631.
221. Krishnan KR, Hays JC, Blazer DG. MRI-defined vascular depression. Am J Psychiatry. 1997;154(4):497–501. https://doi.org/10.1176/ajp.154.4.497.

222. Oda K, Okubo Y, Ishida R, Murata Y, Ohta K, Matsuda T, *et al*. Regional cerebral blood flow in depressed patients with white matter magnetic resonance hyperintensity. Biol Psychiatry. 2003;53(2):150–6. https://doi.org/10.1016/s0006-3223(02)01548-2.
223. Taylor WD, Aizenstein HJ, Alexopoulos GS. The vascular depression hypothesis: mechanisms linking vascular disease with depression. Mol Psychiatry. 2013;18(9):963–74. https://doi.org/10.1038/mp.2013.20.
224. Hany M, Rehman B, Rizvi A, Chapman J. Schizophrenia. StatPearls. Treasure Island. 2025
225. Ku HL, Wang JK, Lee HC, Lane TJ, Liu IC, Chen YC, *et al*. Cerebral blood flow autoregulation is impaired in schizophrenia: a pilot study. Schizophr Res. 2017;188:63–7. https://doi.org/10.1016/j.schres.2017.01.015.
226. Andreasen NC. Negative symptoms in schizophrenia. Definition and reliability. Arch Gen Psychiatry. 1982;39(7):784–8. https://doi.org/10.1001/archpsyc.1982.04290070020005.
227. Zhao J, He X, Liu Z, Yang D. The effects of clozapine on cognitive function and regional cerebral blood flow in the negative symptom profile schizophrenia. Int J Psychiatry Med. 2006;36(2):171–81. https://doi.org/10.2190/1AA0-UW9Q-1CNK-3E2N.
228. Pinkham A, Loughead J, Ruparel K, Wu WC, Overton E, Gur R. Resting quantitative cerebral blood flow in schizophrenia measured by pulsed arterial spin labeling perfusion MRI. Psychiatry Res. 2011;194(1):64–72. https://doi.org/10.1016/j.pscychresns.2011.06.013.
229. Peitl V, Badzim VA, Sisko Markos I, Rendulic A, Matesic K, Karlovic D. Improvements of frontotemporal cerebral blood flow and cognitive functioning in patients with first episode of schizophrenia treated with long-acting Aripiprazole. J Clin Psychopharmacol. 2021;41(6):638–43. https://doi.org/10.1097/JCP.0000000000001477.
230. Selvaggi P, Jauhar S, Kotoula V, Pepper F, Veronese M, Santangelo B, *et al*. Reduced cortical cerebral blood flow in antipsychotic-free first-episode psychosis and relationship to treatment response. Psychol Med. 2023;53(11):5235–45. https://doi.org/10.1017/S0033291722002288.
231. Zhang HL, Guo ZN, Yang G, Yang L, Han K, Wu J, *et al*. Compromised cerebrovascular modulation in chronic anxiety: evidence from cerebral blood flow velocity measured by transcranial Doppler sonography. Neurosci Bull. 2012;28(6):723–8. https://doi.org/10.1007/s12264-012-1282-y.
232. Guo ZN, Lv S, Liu J, Wang Z, Jin H, Qiu Q, *et al*. Compromised dynamic cerebral autoregulation in patients with generalized anxiety disorder: a study using transfer function analysis. BMC Psychiatry. 2018;18(1):164. https://doi.org/10.1186/s12888-018-1713-z.
233. O'Carroll RE, Moffoot AP, Van Beck M, Dougall N, Murray C, Ebmeier KP, *et al*. The effect of anxiety induction on the regional uptake of 99mTc-exametazime in simple phobia as shown by single photon emission tomography (SPET). J Affect Disord. 1993;28(3):203–10. https://doi.org/10.1016/0165-0327(93)90106-t.
234. Etkin A, Prater KE, Schatzberg AF, Menon V, Greicius MD. Disrupted amygdalar subregion functional connectivity and evidence of a compensatory network in generalized anxiety disorder. Arch Gen Psychiatry. 2009;66(12):1361–72. https://doi.org/10.1001/archgenpsychiatry.2009.104.
235. Chen Y, Cui Q, Sheng W, Tang Q, Lu F, Pang Y, *et al*. Anomalous neurovascular coupling in patients with generalized anxiety disorder evaluated by combining cerebral blood flow and functional connectivity strength. Prog Neuropsychopharmacol Biol Psychiatry. 2021;111:110379. https://doi.org/10.1016/j.pnpbp.2021.110379.
236. Andreescu C, Gross JJ, Lenze E, Edelman KD, Snyder S, Tanase C, *et al*. Altered cerebral blood flow patterns associated with pathologic worry in the elderly. Depress Anxiety. 2011;28(3):202–9. https://doi.org/10.1002/da.20799.
237. Chen G, Hu J, Ran H, Nie L, Tang W, Li X, *et al*. Alterations of cerebral perfusion and functional connectivity in children with idiopathic generalized epilepsy. Front Neurosci. 2022;16:918513. https://doi.org/10.3389/fnins.2022.918513.
238. Joo EY, Tae WS, Hong SB. Cerebral blood flow abnormality in patients with idiopathic generalized epilepsy. J Neurol. 2008;255(4):520–5. https://doi.org/10.1007/s00415-008-0727-8.
239. Sone D, Watanabe M, Ota M, Kimura Y, Sugiyama A, Maekawa T, *et al*. Thalamic hypoperfusion and disrupted cerebral blood flow networks in idiopathic generalized epilepsy: arterial spin labeling and graph theoretical analysis. Epilepsy Res. 2017;129:95–100. https://doi.org/10.1016/j.eplepsyres.2016.12.009.
240. Lee DS, Lee SK, Kim SK, Kang KW, Kang E, Lee KH, *et al*. Late postictal residual perfusion abnormality in epileptogenic zone found on 6-hour postictal SPECT. Neurology. 2000;55(6):835–41. https://doi.org/10.1212/wnl.55.6.835.
241. Shin WC, Hong SB, Tae WS, Kim SE. Ictal hyperperfusion patterns according to the progression of temporal lobe seizures. Neurology. 2002;58(3):373–80. https://doi.org/10.1212/wnl.58.3.373.
242. Chen SF, Pan HY, Huang CR, Huang JB, Tan TY, Chen NC, *et al*. Autonomic dysfunction contributes to impairment of cerebral autoregulation in patients with epilepsy. J Pers Med. 2021. https://doi.org/10.3390/jpm11040313.
243. Loscher W, Friedman A. Structural, molecular, and functional alterations of the blood-brain barrier during epileptogenesis and epilepsy: a cause, consequence, or both? Int J Mol Sci. 2020. https://doi.org/10.3390/ijms21020591.
244. Takata F, Nakagawa S, Matsumoto J, Dohgu S. Blood-brain barrier dysfunction amplifies the development of neuroinflammation: understanding of cellular events in brain microvascular endothelial cells for prevention and treatment of BBB dysfunction. Front Cell Neurosci. 2021;15:661838. https://doi.org/10.3389/fncel.2021.661838.
245. Sanz P, Rubio T, Garcia-Gimeno MA. Neuroinflammation and epilepsy: from pathophysiology to therapies based on repurposing drugs. Int J Mol Sci. 2024. https://doi.org/10.3390/ijms25084161.
246. Li W, Wu J, Zeng Y, Zheng W. Neuroinflammation in epileptogenesis: from pathophysiology to therapeutic strategies. Front Immunol. 2023;14:1269241. https://doi.org/10.3389/fimmu.2023.1269241.
247. van Vliet EA, da Costa Araujo S, Redeker S, van Schaik R, Aronica E, Gorter JA. Blood-brain barrier leakage may lead to progression of temporal lobe epilepsy. Brain. 2007;130(Pt 2):521–34. https://doi.org/10.1093/brain/awl318.
248. Greene C, Hanley N, Campbell M. Claudin-5: gatekeeper of neurological function. Fluids Barriers CNS. 2019;16(1):3. https://doi.org/10.1186/s12987-019-0123-z.
249. Greene C, Hanley N, Reschke CR, Reddy A, Mae MA, Connolly R, *et al*. Microvascular stabilization via blood-brain barrier regulation prevents seizure activity. Nat Commun. 2022;13(1):2003. https://doi.org/10.1038/s41467-022-29657-y. (**Epub 20220414.**).
250. Marchi N, Granata T, Ghosh C, Janigro D. Blood-brain barrier dysfunction and epilepsy: pathophysiologic role and therapeutic approaches. Epilepsia. 2012;53(11):1877–86. https://doi.org/10.1111/j.1528-1167.2012.03637.x.
251. Ivens S, Kaufer D, Flores LP, Bechmann I, Zumsteg D, Tomkins O, *et al*. TGF-beta receptor-mediated albumin uptake into astrocytes is involved in neocortical epileptogenesis. Brain. 2007;130(Pt 2):535–47. https://doi.org/10.1093/brain/awl317.

252. Ashina M, Hansen JM, Do TP, Melo-Carrillo A, Burstein R, Moskowitz MA. Migraine and the trigeminovascular system-40 years and counting. Lancet Neurol. 2019;18(8):795–804. https://doi.org/10.1016/S1474-4422(19)30185-1.
253. Knol MJ, Loehrer EA, Wen KX, Bos D, Ikram MK, Vernooij MW, *et al*. Migraine genetic variants influence cerebral blood flow. Headache. 2020;60(1):90–100. https://doi.org/10.1111/head.13651.
254. Chen H, Mirg S, Gaddale P, Agrawal S, Li M, Nguyen V, *et al*. Multiparametric brain hemodynamics imaging using a combined ultrafast ultrasound and photoacoustic system. Adv Sci. 2024;11(31):e2401467. https://doi.org/10.1002/advs.202401467.
255. Fu T, Liu L, Huang X, Zhang D, Gao Y, Yin X, *et al*. Cerebral blood flow alterations in migraine patients with and without aura: an arterial spin labeling study. J Headache Pain. 2022;23(1):131. https://doi.org/10.1186/s10194-022-01501-0.
256. Altamura C, Paolucci M, Vernieri F. Migraine, endothelium, hemodynamics. Neurol Sci. 2018;39(Suppl 1):87–9. https://doi.org/10.1007/s10072-018-3351-0.
257. Viola S, Viola P, Buongarzone MP, Fiorelli L, Cipulli M, Litterio P. Microvascular vasospasm of cerebral cortex in prolonged aura migraine. Neurol Sci. 2018;39(Suppl 1):95–6. https://doi.org/10.1007/s10072-018-3343-0.
258. Salinet AS, Panerai RB, Robinson TG. The longitudinal evolution of cerebral blood flow regulation after acute ischaemic stroke. Cerebrovasc Dis Extra. 2014;4(2):186–97. https://doi.org/10.1159/000366017.
259. Astrup J, Siesjo BK, Symon L. Thresholds in cerebral ischemia—the ischemic penumbra. Stroke. 1981;12(6):723–5. https://doi.org/10.1161/01.str.12.6.723.
260. Bandera E, Botteri M, Minelli C, Sutton A, Abrams KR, Latronico N. Cerebral blood flow threshold of ischemic penumbra and infarct core in acute ischemic stroke: a systematic review. Stroke. 2006;37(5):1334–9. https://doi.org/10.1161/01.STR.0000217418.29609.22.
261. Bo B, Li Y, Li W, Wang Y, Tong S. Neurovascular coupling impairment in acute ischemic stroke by optogenetics and optical brain imaging. Annu Int Conf IEEE Eng Med Biol Soc. 2020;2020:3727–30. https://doi.org/10.1109/EMBC44109.2020.9176641.
262. Steiner L, Federspiel A, Jaros J, Slavova N, Wiest R, Steinlin M, *et al*. Cerebral blood flow and cognitive outcome after pediatric stroke in the middle cerebral artery. Sci Rep. 2021;11(1):19421. https://doi.org/10.1038/s41598-021-98309-w.
263. Biose IJ, Oremosu J, Bhatnagar S, Bix GJ. Promising cerebral blood flow enhancers in acute ischemic stroke. Transl Stroke Res. 2023;14(6):863–89. https://doi.org/10.1007/s12975-022-01100-w.
264. Gyawali P, Lillicrap TP, Esperon CG, Bhattarai A, Bivard A, Spratt N. Whole blood viscosity and cerebral blood flow in acute ischemic stroke. Semin Thromb Hemost. 2024;50(4):580–91. https://doi.org/10.1055/s-0043-1775858.
265. Baron JC. Protecting the ischaemic penumbra as an adjunct to thrombectomy for acute stroke. Nat Rev Neurol. 2018;14(6):325–37. https://doi.org/10.1038/s41582-018-0002-2.
266. Groysman LI, Emanuel BA, Kim-Tenser MA, Sung GY, Mack WJ. Therapeutic hypothermia in acute ischemic stroke. Neurosurg Focus. 2011;30(6):E17. https://doi.org/10.3171/2011.4.FOCUS1154.
267. Chen Q, Wu Z, Chen F, Wang J, Ye X, Li H. Efficacy and safety of normobaric hyperoxia for acute ischemic stroke: a systematic review and meta-analysis of randomized controlled trials. EClinicalMedicine. 2026;91:103701. https://doi.org/10.1016/j.eclinm.2025.103701.
268. Kuczynski AM, Marzoughi S, Al Sultan AS, Colbourne F, Menon BK, van Es A, *et al*. Therapeutic hypothermia in acute ischemic stroke-a systematic review and meta-analysis. Curr Neurol Neurosci Rep. 2020;20(5):13. https://doi.org/10.1007/s11910-020-01029-3.
269. von Bornstadt D, Gertz K, Lagumersindez Denis N, Seners P, Baron JC, Endres M. Sensory stimulation in acute stroke therapy. J Cereb Blood Flow Metab. 2018;38(10):1682–9. https://doi.org/10.1177/0271678X18791073.
270. Meng Z, Ma Y, Zhang W, Zhuang H, Xu C, Zhang Y, *et al*. Age- and sex-specific cerebral blood flow atlases for healthy brain across the lifespan. Sci Data. 2025;12(1):1169. https://doi.org/10.1038/s41597-025-05406-w.
271. Lagebrant C, Ramgren B, Hassani Espili A, Maranon A, Kremer C. Sex differences in collateral circulation and outcome after mechanical thrombectomy in acute ischemic stroke. Front Neurol. 2022;13:878759. https://doi.org/10.3389/fneur.2022.878759.
272. Kremer C, Lorenzano S, Kruuse C. Editorial: sex differences in cerebrovascular diseases. Front Neurol. 2022;13:1128177. https://doi.org/10.3389/fneur.2022.1128177.
273. Turtzo LC, McCullough LD. Sex differences in stroke. Cerebrovasc Dis. 2008;26(5):462–74. https://doi.org/10.1159/000155983.
274. Iordanova B, Li L, Clark RSB, Manole MD. Alterations in cerebral blood flow after resuscitation from cardiac arrest. Front Pediatr. 2017;5:174. https://doi.org/10.3389/fped.2017.00174.
275. Schoenthal T, Hoiland R, Griesdale DE, Sekhon MS. Cerebral hemodynamics after cardiac arrest: implications for clinical management. Minerva Anestesiol. 2023;89(9):824–33. https://doi.org/10.23736/S0375-9393.23.17268-3.
276. van den Brule JMD, van der Hoeven JG, Hoedemaekers CWE. Cerebral perfusion and cerebral autoregulation after cardiac arrest. BioMed Res Int. 2018;2018:4143636. https://doi.org/10.1155/2018/4143636.
277. Wang P, Yao L, Zhou LL, Liu YS, Chen MD, Wu HD, *et al*. Carbon monoxide improves neurologic outcomes by mitochondrial biogenesis after global cerebral ischemia induced by cardiac arrest in rats. Int J Biol Sci. 2016;12(8):1000–9. https://doi.org/10.7150/ijbs.13222.
278. Tabassum S, Wu S, Lee CH, Yang BSK, Gusdon AM, Choi HA, *et al*. Mitochondrial-targeted therapies in traumatic brain injury: from bench to bedside. Neurotherapeutics. 2025;22(1):e00515. https://doi.org/10.1016/j.neurot.2024.e00515.
279. Jakkula P, Hastbacka J, Reinikainen M, Pettila V, Loisa P, Tiainen M, *et al*. Near-infrared spectroscopy after out-of-hospital cardiac arrest. Crit Care. 2019;23(1):171. https://doi.org/10.1186/s13054-019-2428-3.
280. Reichenbach A, Alteheld L, Henriksen J, Nakstad ER, Andersen GO, Sunde K, *et al*. Transcranial Doppler during the first week after cardiac arrest and association with 6-month outcomes. Front Neurol. 2023;14:1222401. https://doi.org/10.3389/fneur.2023.1222401.
281. Chang Y, Zhu J, Wang D, Li H, He Y, Liu K, *et al*. NLRP3 inflammasome-mediated microglial pyroptosis is critically involved in the development of post-cardiac arrest brain injury. J Neuroinflammation. 2020;17(1):219. https://doi.org/10.1186/s12974-020-01879-1.
282. Sekhon MS, Ainslie PN, Griesdale DE. Clinical pathophysiology of hypoxic ischemic brain injury after cardiac arrest: a "two-hit" model. Crit Care. 2017;21(1):90. https://doi.org/10.1186/s13054-017-1670-9.

283. Kim JC, Lee BK, Lee DH, Jung YH, Cho YS, Lee SM, *et al*. Association between lactate clearance during post-resuscitation care and neurologic outcome in cardiac arrest survivors treated with targeted temperature management. Clin Exp Emerg Med. 2017;4(1):10–8. https://doi.org/10.15441/ceem.16.149.
284. Nadir A, Kara D, Turkoz A. The effect of thermoelectric craniocerebral cooling device on protecting brain functions in post-cardiac arrest syndrome. Front Cardiovasc Med. 2024;11:1502173. https://doi.org/10.3389/fcvm.2024.1502173.
285. Lin HW, Della-Morte D, Thompson JW, Gresia VL, Narayanan SV, Defazio RA, *et al*. Differential effects of delta and epsilon protein kinase C in modulation of postischemic cerebral blood flow. Adv Exp Med Biol. 2012;737:63–9. https://doi.org/10.1007/978-1-4614-1566-4_10.
286. Della-Morte D, Raval AP, Dave KR, Lin HW, Perez-Pinzon MA. Post-ischemic activation of protein kinase C epsilon protects the hippocampus from cerebral ischemic injury via alterations in cerebral blood flow. Neurosci Lett. 2011;487(2):158–62. https://doi.org/10.1016/j.neulet.2010.10.013.
287. Wardlaw JM, Benveniste H, Nedergaard M, Zlokovic BV, Mestre H, Lee H, *et al*. Perivascular spaces in the brain: anatomy, physiology and pathology. Nat Rev Neurol. 2020;16(3):137–53. https://doi.org/10.1038/s41582-020-0312-z.
288. Webb AJS, Feakins K, Lawson A, Stewart C, Thomas J, Llwyd O. Optimal markers of treatment response to vasodilatory drugs in small vessel disease: an OxHARP trial analysis. Int J Stroke. 2025. https://doi.org/10.1177/17474930251360093.
289. Thrippleton MJ, Backes WH, Sourbron S, Ingrisch M, van Osch MJP, Dichgans M, *et al*. Quantifying blood-brain barrier leakage in small vessel disease: review and consensus recommendations. Alzheimers Dement. 2019;15(6):840–58. https://doi.org/10.1016/j.jalz.2019.01.013.
290. Wu LY, Chai YL, Cheah IK, Chia RSL, Hilal S, Arumugam TV, *et al*. Blood-based biomarkers of cerebral small vessel disease. Ageing Res Rev. 2024;95:102247. https://doi.org/10.1016/j.arr.2024.102247.
291. Panerai RB, White RP, Markus HS, Evans DH. Grading of cerebral dynamic autoregulation from spontaneous fluctuations in arterial blood pressure. Stroke. 1998;29(11):2341–6. https://doi.org/10.1161/01.str.29.11.2341.
292. Afkhami R, Walker FR, Ramadan S, Wong R, Johnson SJ. Indexing cerebrovascular health using near-infrared spectroscopy. Sci Rep. 2021;11(1):14812. https://doi.org/10.1038/s41598-021-94348-5
293. Durduran T, Zhou C, Edlow BL, Yu G, Choe R, Kim MN, *et al*. Transcranial optical monitoring of cerebrovascular hemodynamics in acute stroke patients. Opt Express. 2009;17(5):3884–902. https://doi.org/10.1364/oe.17.003884.
294. Jezzard P, Chappell MA, Okell TW. Arterial spin labeling for the measurement of cerebral perfusion and angiography. J Cereb Blood Flow Metab. 2018;38(4):603–26. https://doi.org/10.1177/0271678X17743240
295. Kress BT, Iliff JJ, Xia M, Wang M, Wei HS, Zeppenfeld D, *et al*. Impairment of paravascular clearance pathways in the aging brain. Ann Neurol. 2014;76(6):845–61. https://doi.org/10.1002/ana.24271
296. Yoshiura T, Hiwatashi A, Noguchi T, Yamashita K, Ohyagi Y, Monji A, *et al*. Arterial spin labelling at 3-T MR imaging for detection of individuals with Alzheimer's disease. Eur Radiol. 2009;19(12):2819–25. https://doi.org/10.1007/s00330-009-1511-6.
297. Taghvaei M, Dolui S, Sadaghiani S, Shakibajahromi B, Brown C, Khandelwal P, *et al*. Regional cerebral blood flow reflects both neurodegeneration and microvascular integrity across the Alzheimer's continuum. Alzheimers Dement. 2025;21(1):e14382. https://doi.org/10.1002/alz.14382
298. Camargo A, Wang Z. Alzheimer's disease neuroimaging I. Longitudinal cerebral blood flow changes in normal aging and the Alzheimer's disease continuum identified by arterial spin labeling MRI. J Alzheimers Dis. 2021;81(4):1727–35. https://doi.org/10.3233/JAD-210116
299. Huang Q, Cao X, Chai X, Wang X, Xu L, Xiao C. Three-dimensional pseudocontinuous arterial spin labeling and susceptibility-weighted imaging associated with clinical progression in amnestic mild cognitive impairment and Alzheimer's disease. Medicine (Baltimore). 2019;98(23):e15972. https://doi.org/10.1097/MD.0000000000015972.
300. Mak HK, Chan Q, Zhang Z, Petersen ET, Qiu D, Zhang L, *et al*. Quantitative assessment of cerebral hemodynamic parameters by QUASAR arterial spin labeling in Alzheimer's disease and cognitively normal elderly adults at 3-tesla. J Alzheimers Dis. 2012;31(1):33–44. https://doi.org/10.3233/JAD-2012-111877.
301. Gao YZ, Zhang JJ, Liu H, Wu GY, Xiong L, Shu M. Regional cerebral blood flow and cerebrovascular reactivity in Alzheimer's disease and vascular dementia assessed by arterial spinlabeling magnetic resonance imaging. Curr Neurovasc Res. 2013;10(1):49–53. https://doi.org/10.2174/1567202613804806016.
302. Fernandez-Seara MA, Mengual E, Vidorreta M, Aznarez-Sanado M, Loayza FR, Villagra F, *et al*. Cortical hypoperfusion in Parkinson's disease assessed using arterial spin labeled perfusion MRI. Neuroimage. 2012;59(3):2743–50. https://doi.org/10.1016/j.neuroimage.2011.10.033.
303. Cheng L, Wu X, Guo R, Wang Y, Wang W, He P, *et al*. Discriminative pattern of reduced cerebral blood flow in Parkinson's disease and Parkinsonism-Plus syndrome: an ASL-MRI study. BMC Med Imaging. 2020;20(1):78. https://doi.org/10.1186/s12880-020-00479-y
304. Wang J, Zhang W, Zhou Y, Jia J, Li Y, Liu K, *et al*. Altered prefrontal blood flow related with mild cognitive impairment in Parkinson's disease: a longitudinal study. Front Aging Neurosci. 2022;14:896191. https://doi.org/10.3389/fnagi.2022.896191
305. Wang S, Cai Y, Zhao Y, Yu Y, Chen X, Wang L. Altered resting-state cerebral blood flow and its relationship with molecular architecture in tremor dominant Parkinson's disease. Brain Res Bull. 2025;222:111237. https://doi.org/10.1016/j.brainresbull.2025.111237
306. Tanaka M, Kondo S, Hirai S, Sun X, Yamagishi T, Okamoto K. Cerebral blood flow and oxygen metabolism in progressive dementia associated with amyotrophic lateral sclerosis. J Neurol Sci. 1993;120(1):22–8. https://doi.org/10.1016/0022-510x(93)90019-u.
307. Ishikawa T, Morita M, Nakano I. Constant blood flow reduction in premotor frontal lobe regions in ALS with dementia—a SPECT study with 3D-SSP. Acta Neurol Scand. 2007;116(5):340–4. https://doi.org/10.1111/j.1600-0404.2007.00876.x.
308. Ingrisch M, Sourbron S, Morhard D, Ertl-Wagner B, Kumpfel T, Hohlfeld R, *et al*. Quantification of perfusion and permeability in multiple sclerosis: dynamic contrast-enhanced MRI in 3D at 3T. Invest Radiol. 2012;47(4):252–8. https://doi.org/10.1097/RLI.0b013e31823bfc97.
309. Peruzzo D, Castellaro M, Calabrese M, Veronese E, Rinaldi F, Bernardi V, *et al*. Heterogeneity of cortical lesions in multiple sclerosis: an MRI perfusion study. J Cereb Blood Flow Metab. 2013;33(3):457–63. https://doi.org/10.1038/jcbfm.2012.192
310. Francis PL, Jakubovic R, O'Connor P, Zhang L, Eilaghi A, Lee L, *et al*. Robust perfusion deficits in cognitively impaired patients with secondary-progressive multiple sclerosis. AJNR Am J Neuroradiol. 2013;34(1):62–7. https://doi.org/10.3174/ajnr.A3148.

311. Dumas A, Dierksen GA, Gurol ME, Halpin A, Martinez-Ramirez S, Schwab K, *et al*. Functional magnetic resonance imaging detection of vascular reactivity in cerebral amyloid angiopathy. Ann Neurol. 2012;72(1):76–81. https://doi.org/10.1002/ana.23566.
312. Gongora-Rivera F, Cordero-Perez A, Gonzalez-Aquines A, Anaya-Escamilla A, Villarreal-Garza E, Espinosa-Ortega M, *et al*. Impaired cerebral vasomotor reactivity in Alzheimer's disease. Int J Alzheimers Dis. 2018;2018:9328293. https://doi.org/10.1155/2018/9328293.
313. Cantin S, Villien M, Moreaud O, Tropres I, Keignart S, Chipon E, *et al*. Impaired cerebral vasoreactivity to CO_2 in Alzheimer's disease using BOLD fMRI. Neuroimage. 2011;58(2):579–87. https://doi.org/10.1016/j.neuroimage.2011.06.070.
314. Tang X, Wang L, Feng Q, Hu H, Zhu Y, Liao Z, *et al*. Resting-state functional magnetic resonance imaging study on cerebrovascular reactivity changes in the precuneus of Alzheimer's disease and mild cognitive impairment patients. Sci Rep. 2025;15(1):363. https://doi.org/10.1038/s41598-024-82769-x.
315. Holmes KR, Tang-Wai D, Sam K, McKetton L, Poublanc J, Crawley AP, *et al*. Slowed temporal and parietal cerebrovascular response in patients with Alzheimer's Disease. Can J Neurol Sci. 2020;47(3):366–73. https://doi.org/10.1017/cjn.2020.30.
316. Saka E, Atay LO, Akdemir UO, Yetim E, Balci E, Arsava EM, *et al*. Cerebral vasomotor reactivity across the continuum of subjective cognitive impairment, amnestic mild cognitive impairment and probable Alzheimer's dementia: a transcranial Doppler and PET/MRI study. J Cereb Blood Flow Metab. 2023;43(1):129–37. https://doi.org/10.1177/0271678X221124656.
317. Vicenzini E, Ricciardi MC, Altieri M, Puccinelli F, Bonaffini N, Di Piero V, *et al*. Cerebrovascular reactivity in degenerative and vascular dementia: a transcranial Doppler study. Eur Neurol. 2007;58(2):84–9. https://doi.org/10.1159/000103642.
318. Sleight E, Stringer MS, Clancy U, Arteaga C, Jaime Garcia D, Hewins W, *et al*. Cerebrovascular reactivity in patients with small vessel disease: a cross-sectional study. Stroke. 2023;54(11):2776–84. https://doi.org/10.1161/STROKEAHA.123.042656.
319. Lee BC, Tsai HH, Huang AP, Lo YL, Tsai LK, Chen YF, *et al*. Arterial spin labeling imaging assessment of cerebrovascular reactivity in hypertensive small vessel disease. Front Neurol. 2021;12:640069. Epub 20210630. https://doi.org/10.3389/fneur.2021.640069. PubMed PMID: 34276531; PubMed Central PMCID: PMC8278327.
320. Chan ST, Mercaldo ND, Kwong KK, Hersch SM, Rosas HD. Impaired cerebrovascular reactivity in Huntington's disease. Front Physiol. 2021;12:663898. https://doi.org/10.3389/fphys.2021.663898.
321. Klinkmueller P, Kronenbuerger M, Miao X, Bang J, Ultz KE, Paez A, *et al*. Impaired response of cerebral oxygen metabolism to visual stimulation in Huntington's disease. J Cereb Blood Flow Metab. 2021;41(5):1119–30. https://doi.org/10.1177/0271678X20949286.
322. Ryman SG, Shaff N, Dodd A, Nitschke S, Wertz C, Julio K, *et al*. Reduced and delayed cerebrovascular reactivity in patients with Parkinson's Disease. Mov Disord. 2023;38(7):1262–72. https://doi.org/10.1002/mds.29429.
323. Camargo CH, Martins EA, Lange MC, Hoffmann HA, Luciano JJ, Young Blood MR, *et al*. Abnormal cerebrovascular reactivity in patients with Parkinson's Disease. Parkinsons Dis. 2015;2015:523041. https://doi.org/10.1155/2015/523041.
324. van der Horn HJ, Vakhtin AA, Julio K, Nitschke S, Shaff N, Dodd AB, *et al*. Parkinson's disease cerebrovascular reactivity pattern: a feasibility study. J Cereb Blood Flow Metab. 2024;44(10):1774–86. https://doi.org/10.1177/0271678X241241895.
325. Marshall O, Lu H, Brisset JC, Xu F, Liu P, Herbert J, *et al*. Impaired cerebrovascular reactivity in multiple sclerosis. JAMA Neurol. 2014;71(10):1275–81. https://doi.org/10.1001/jamaneurol.2014.1668.
326. Marshall O, Chawla S, Lu H, Pape L, Ge Y. Cerebral blood flow modulation insufficiency in brain networks in multiple sclerosis: a hypercapnia MRI study. J Cereb Blood Flow Metab. 2016;36(12):2087–95. Epub 20160615. https://doi.org/10.1177/0271678X16654922. PubMed PMID: 27306754; PubMed Central PMCID:PMC5363669.

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