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Review Article

Blood-Brain Barrier Disruption and Post-Stroke Cognitive Impairment

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Abstract

Background: Cognitive impairment affects a large proportion of ischaemic stroke survivors, often out of proportion to infarct size, and mounting evidence implicates disruption of the blood-brain barrier (BBB) as a shared driver.

Objective: To review evidence linking BBB disruption to post-stroke cognitive impairment (PSCI), spanning pathophysiology, imaging, small vessel disease and therapeutics.

Methods: Narrative synthesis of mechanistic, neuroimaging, longitudinal cohort and therapeutic literature.

Findings: Ischaemia triggers tight-junction breakdown, matrix metalloproteinase activation and neuroinflammatory leukocyte trafficking, producing measurable permeability on dynamic contrast-enhanced MRI and PET. Elevated BBB leakage correlates with white matter hyperintensity progression, microbleeds and steeper cognitive decline across multi-year cohorts, independent of infarct volume. Pericyte loss and endothelial injury sustain chronic leakage, while emerging therapies target junctional repair and neurovascular inflammation.

Conclusions: BBB integrity is a plausible, imageable and potentially modifiable determinant of PSCI, warranting incorporation into risk stratification and trial design.

Keywords: Blood-brain barrier; Post-stroke cognitive impairment; Cerebral small vessel disease; Neuroinflammation; Dynamic contrast-enhanced MRI

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Introduction

Stroke remains one of the leading causes of acquired cognitive impairment worldwide, and impairment frequently persists or emerges well beyond the acute period, affecting attention, processing speed and executive function even in patients with good motor recovery [1]. Meta-analytic estimates place the pooled risk of dementia after stroke at roughly one in ten patients over the following years, rising substantially with recurrent events [2]. Because the severity of cognitive

decline correlates poorly with infarct volume alone, attention has turned to processes that extend beyond the visible lesion, and the blood-brain barrier (BBB) has emerged as a candidate mechanistic link.

The BBB is a specialised interface of endothelial tight junctions, pericytes, astrocytic end-feet and basement membrane that normally restricts paracellular movement of solutes and immune cells into brain parenchyma [3]. Acute ischaemia disrupts this interface through oxidative stress, proteolytic degradation of junctional proteins and neuroinflammatory signalling, and the resulting leakage can persist long after the acute event, seeding a chronic neurovascular injury that is increasingly implicated in cognitive decline both after stroke and in cerebral small vessel disease (SVD) more broadly [4,5]. Because this leakage is now directly visualisable with modern neuroimaging, it has moved from a pathological curiosity to a candidate biomarker and treatment target, motivating a wave of cohort studies designed specifically to test whether barrier status predicts cognitive trajectory rather than merely correlating with it cross-sectionally.

This review synthesises evidence on BBB pathophysiology after ischaemic stroke, methods for imaging permeability, the relationship between BBB disruption and post-stroke cognitive impairment (PSCI), mechanistic links through neuroinflammation, white matter injury and microbleeds, longitudinal cohort evidence, and therapeutic strategies aimed at restoring barrier integrity. It is written as a narrative synthesis of mechanistic, neuroimaging and cohort literature identified through the sources cited throughout, rather than a systematic review with predefined search criteria, and it draws where possible on cohorts that followed patients over months to years so that temporal relationships between leakage and decline can be distinguished from simple association.

Pathophysiology of Blood-Brain Barrier Disruption After Ischaemic Stroke



Within minutes of vessel occlusion, energy failure disrupts ionic gradients and generates reactive oxygen species that degrade endothelial tight-junction proteins including claudin-5, occludin and zonula occludens-1 [6]. Matrix metalloproteinase-9, released by activated endothelium, astrocytes and infiltrating leukocytes, cleaves basal lamina components and junctional complexes, a process amplified by reperfusion after recanalisation [7]. Rapid reorganisation of the endothelial actin cytoskeleton appears to precede overt junctional loss, opening a paracellular route for plasma constituents and immune cells within the first hours of ischaemia and predicting long-term injury in experimental models [7].

Neuroinflammation sustains this process well beyond the acute window. Circulating neutrophils and monocytes adhere to activated endothelium and transmigrate into ischaemic tissue, while resident microglia and astrocytes release cytokines that further compromise junctional integrity [6,8]. Systemic inflammatory responses triggered by stroke, including gut-derived and cardiovascular signalling, can prolong BBB compromise and have been linked to a range of post-stroke comorbidities beyond the neurological deficit itself [5]. Pericytes, which stabilise the endothelial tube and regulate capillary tone, are particularly vulnerable to ischaemic injury; their loss or migration away from capillaries accompanies persistent leakage and impaired microvascular reactivity, and restoring pericyte coverage improves functional outcomes in animal models [9]. The clinical trajectory of permeability is not monophasic: studies tracking barrier function from the acute through subacute phase describe an early peak, partial resolution, and in some patients a secondary rise associated with hemorrhagic transformation risk, underscoring that BBB disruption evolves over a much longer timescale than the infarct itself [10,11,12]. This staged pattern has practical consequences for interpreting any single imaging time

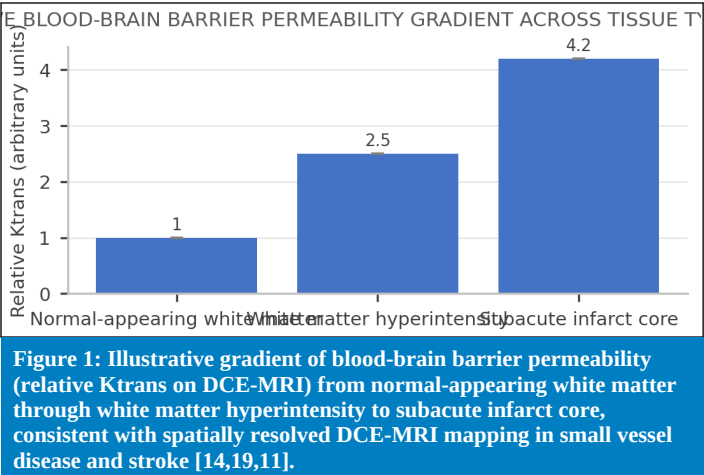
point: a scan obtained days after onset may capture very different biology from one obtained at presentation, and comparisons across studies that sample different windows should be made cautiously. It also implies that the therapeutic window for barrier-protective interventions may extend well beyond the hyperacute period targeted by reperfusion therapies, since secondary leakage phases appear open to modification days to weeks after the index event.

Imaging Blood-Brain Barrier Permeability

Quantifying BBB leakage in living patients has relied chiefly on dynamic contrast-enhanced MRI (DCE-MRI), in which serial imaging after gadolinium administration allows pharmacokinetic modelling of the transfer constant K_{trans} as a surrogate for permeability [13]. Consensus recommendations now specify acquisition parameters, tracer-kinetic models and reporting standards to allow cross-cohort comparison, reflecting how heterogeneous earlier protocols had been [13]. Applied to SVD populations, DCE-MRI has revealed that leakage is spatially heterogeneous, concentrating in white matter and around existing lesions rather than being uniformly distributed, which argues against a purely diffuse process [14,15].

Positron emission tomography (PET) offers a complementary, non-contrast route to permeability quantification using tracers whose brain uptake depends on barrier integrity, and recent total-body and kinetic-modelling approaches have improved the precision with which molecular permeability-surface-area products can be estimated non-invasively [16]. Post-treatment imaging after mechanical thrombectomy using arterial spin labelling and diffusion-based sequences has similarly shown measurable, spatially specific barrier disruption in the peri-infarct territory, supporting the feasibility of monitoring BBB status as a routine adjunct to structural stroke imaging [17].

Together, these modalities have converted BBB permeability from a largely histological concept into a quantifiable, longitudinally trackable imaging biomarker, one that can in principle be repeated at multiple time points in the same patient to chart the staged trajectory described above.



A practical limitation common to both modalities is spatial and temporal resolution relative to the subtlety of the signal: leakage in early SVD or the peri-infarct penumbra is often only marginally above the noise floor of standard sequences, which is precisely why consensus acquisition and modelling protocols have been prioritised over simply adopting whichever sequence a given centre already runs [13]. PET approaches face an analogous trade-off between tracer specificity for barrier transport and the practical burden of radiotracer production, which has so far limited PET-based permeability mapping to specialist centres rather than routine stroke pathways [16].

Blood-Brain Barrier Disruption, White Matter Injury and Cerebral Small Vessel Disease

Standardised neuroimaging criteria for SVD recognise white matter hyperintensities (WMH), lacunes, microbleeds and perivascular spaces as convergent markers of an underlying microvascular process, and BBB failure has been proposed as a core, unifying mechanism

linking these lesion types to cognitive decline [18,19]. In a prospective cohort, higher baseline BBB permeability, particularly within normal-appearing white matter, predicted greater WMH growth and lacune formation on follow-up imaging, implicating leakage as an early, potentially preventable step rather than a passive marker of established tissue damage [19]. Later work extending this cohort confirmed that leakage tends to cluster around, and precede radiological change at, discrete "hotspots" that colocalise with subsequent lesions in both sporadic and monogenic SVD [15].

Table 1: Cohort and imaging studies linking blood-brain barrier leakage to white matter injury, lacunes and microbleeds in cerebral small vessel disease [18,19,15,14,22,24].			
Study	Design	Imaging method	Key finding
Wardlaw 2013 (STRIVE)	Consensus statement	Neuroimaging criteria	Standardised SVD lesion definitions
Wardlaw 2017	Prospective cohort	DCE-MRI	Baseline BBB leakage predicts WMH/lacune progression
Rudilosso 2023	Multicentre cohort	DCE-MRI	Leakage hotspots colocalise with incident lesions
Verstappen 2025	Cross-sectional	DCE-MRI	Leakage concentrated in white matter, not diffuse
Li 2023	Cross-sectional	DCE-MRI	Microbleeds linked to widespread BBB leakage
Wong 2019	Cross-sectional	DCE-MRI, ASL	BBB impairment coexists with white matter hypoperfusion

Cognitive relevance is reinforced by studies linking hippocampal barrier breakdown to memory impairment independent of amyloid and neurodegenerative markers, suggesting a vascular contribution to cognitive dysfunction distinct from classical Alzheimer pathology [20,21]. Broader physiological reviews of the BBB integrate these observations with the pericyte-endothelial

signalling pathways thought to underlie age- and vascular risk-related barrier failure [3]. (See Table 1.)

Blood-Brain Barrier Disruption, Microbleeds and Post-Stroke Cognitive Impairment: Cohort Evidence

Cerebral microbleeds, a hallmark SVD lesion visible on susceptibility-weighted imaging, are consistently associated with more widespread BBB leakage than seen in microbleed-free individuals of similar vascular risk, implicating barrier failure in their genesis rather than treating microbleeds as an incidental finding [22]. Longitudinal cohort data directly connect baseline leakage to subsequent cognitive trajectory: in a two-year follow-up of patients with SVD, greater baseline BBB permeability predicted steeper decline in processing speed and executive function, even after adjustment for WMH volume and vascular risk factors [23]. Complementary work has shown that BBB impairment coexists with reduced cerebral perfusion in the same white matter regions, suggesting that leakage and hypoperfusion act together rather than as independent insults on cognition [24].

These associations are not confined to chronic SVD; they extend into the post-stroke period specifically. Because BBB permeability after acute ischaemic stroke follows a protracted, multiphase course, patients with the most pronounced or persistent leakage during the subacute period appear to be those at greatest risk of adverse functional and cognitive outcomes, as tracked by serial imaging and biomarker studies [25,11]. Taken together with epidemiological data showing that a substantial minority of stroke survivors develop measurable cognitive impairment or dementia within several years [2,1], the cohort evidence positions BBB disruption as a mechanistically plausible and imageable contributor to PSCI, rather than a bystander phenomenon confined to the infarct core. (See Figure 1 and Figure 2.)

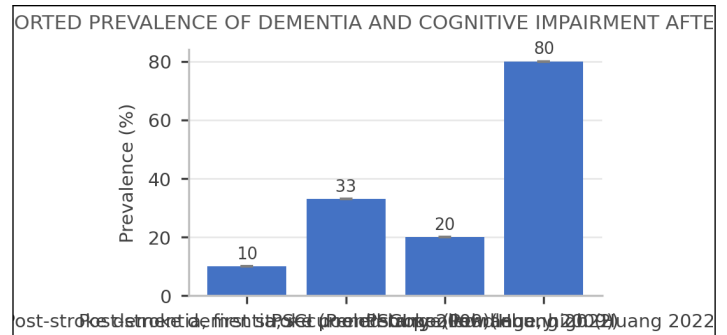


Figure 2: Reported prevalence of dementia and cognitive impairment after stroke: pooled post-stroke dementia after first-ever versus recurrent stroke [2] and the low-high pooled range for post-stroke cognitive impairment across heterogeneous case definitions [1].

Therapeutic Strategies Targeting Blood-Brain Barrier Integrity

No therapy specifically targeting the BBB is yet in routine clinical use for PSCI, but several strategies are under active investigation. Approaches aimed at limiting acute junctional breakdown include matrix metalloproteinase inhibition and antioxidant strategies intended to blunt the early proteolytic and oxidative injury described above, alongside efforts to stabilise pericyte coverage of capillaries to prevent chronic leakage and support microvascular repair [9]. Cell- and vesicle-based approaches, including stem-cell and exosome therapies designed to promote endothelial and junctional regeneration, have shown barrier-restorative effects in preclinical stroke models and are among the more actively developed tissue-repair strategies [26].

Immune-directed strategies constitute a second avenue, given the central role of neutrophil and monocyte trafficking in sustaining leakage; targeting specific adhesion and cytokine pathways involved in immune-mediated barrier disruption is proposed as a way to limit secondary injury without broadly immunosuppressing patients during a vulnerable recovery period [8]. Because systemic inflammatory signalling after stroke appears to prolong BBB compromise, interventions addressing this axis, rather

than the cerebral vasculature alone, may also carry cognitive benefit [5]. More broadly, the therapeutic challenges long recognised in cerebral SVD, including the difficulty of targeting a diffuse, slowly evolving microvascular process with conventional pharmacology, apply directly to BBB-directed treatment of PSCI and will likely require imaging-based patient selection using the DCE-MRI and PET methods described above [27,13]. (See Table 2.)

Table 2: Therapeutic strategies under investigation for restoring blood-brain barrier integrity after ischaemic stroke [9,26,8,5,27].			
Strategy	Target	Stage of evidence	Source
Pericyte stabilisation	Capillary coverage, tone	Preclinical	hu2023
Stem cell / exosome therapy	Endothelial and junctional repair	Preclinical	qi2024
Immune-directed therapy	Leukocyte trafficking, cytokines	Preclinical/early translational	wang2025
Anti-systemic-inflammation strategies	Peripheral inflammatory signalling	Early translational	simats2022
Imaging-guided patient selection	Trial enrichment for SVD	Methodological	pantoni2010

Conclusion

Across mechanistic, imaging and cohort studies, BBB disruption after ischaemic stroke emerges as more than a marker of acute injury: it is a dynamic, quantifiable and longitudinally consequential process that tracks with white matter injury, microbleeds and the cognitive trajectory of survivors. The convergence of DCE-MRI and PET methodology with standardised SVD imaging criteria now allows BBB status to be measured reproducibly across cohorts, while cell-based, immune-directed and pericyte-targeted therapies offer plausible, if still preclinical, routes to intervention. Incorporating BBB permeability into risk stratification and clinical trial design for PSCI represents a logical next step, and prospective studies powered specifically to test whether

stabilising the barrier improves cognitive outcome remain the most pressing unmet need in this field.

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