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Detection of Early BBB Dysfunction in Neuroinflammation Using Advanced Neuroimaging

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Abstract

Neuroinflammation and blood–brain barrier (BBB) dysfunction are two interconnected pathways that are involved in acute cerebrovascular injury, demyelinating disease, epilepsy, and neurodegeneration. One of the current obstacles is to identify the alteration of the barrier before it becomes evident by traditional imaging methods such as leakage, edema, or tissue injury. Dynamic contrast-enhanced MRI (DCE-MRI) measures BBB permeability to gadolinium-based agents; arterial spin labeling (ASL) and water exchange techniques assess BBB trans endothelial water transport; positron emission tomography (PET) maps inflammatory cell targets of the BBB or specific transport processes; and diffusion/perfusion measures provide contextual information on microvascular and tissue consequences. This narrative review aimed to present the provided references and methodological literature collecting them together with a focus on the biological interpretation, the strengths, and the limitations. These techniques are shown to be promising research biomarkers but are not universally validated as early diagnostic tests. For clinical translation, harmonized acquisition, modeling, longitudinal analysis and careful separation from the vascular confounding variables are prerequisites.

Keywords: blood brain barrier, neuroinflammation, DCE-MRI, arterial spin labeling, PET, neurovascular unit, early biomarkers.

Background

The BBB is not just a passive endothelial wall. A specialized and dynamic interface between brain microvascular endothelial cells, which expresses tight and adherents junctions and basement

membrane, pericytes, astrocytic end feet and the interaction with neurons, microglia, and circulating immune cells. These components, along with other components, are the components of the neurovascular unit (NVU), which coordinates selective transport, metabolic support, immune surveillance and cerebral homeostasis [5,6,9]. Disruption may result from a change in the organization of junctions, transcytosis of endothelial cells, dysfunction of the transporters, changes in the glycocalyx, basement membrane, injury of pericytes, and adhesion or migration of inflammatory cells, without causing the same imaging signal [5–7,15]. Damage-associated molecular patterns, reactive oxygen species, cytokines and chemokines can trigger endothelial signaling and gliosis. On the other hand, a dysfunction of barriers can allow entry of plasma proteins and peripheral immune signals, thus increasing neuroinflammation [9].

The bi-directional connection is particularly important for ischemic stroke multiple sclerosis, epilepsy, cerebral small-vessel disease and neurodegenerative disorders like Alzheimer's and Parkinson's disease [2,4,16,18,20]. The extent and duration of BBB changes depend upon the disease and stage and may be accompanied by changes in BBB transport and/or mild NVU dysfunction before leakage occurs.

The definition of “early BBB dysfunction” is thus operationalized. It can be a change in permeability, water exchange, transporter activity, vascular reactivity or recruitment of inflammatory cells that can be measured prior to the onset of conventional structural changes or clinical progression. None of these dimensions can be fully captured with one imaging method. Commonly, the leakage of extracellular gadolinium agents can be estimated using DCE-MRI, whereas ASL-based water-exchange measures are probing a different transport substrate. PET tracers that are targeted to translocator protein (TSPO) or other molecular targets are not direct measures of permeability but can provide information on cellular inflammatory activity [7,10,17,20].

Methodology

This article is written in narrative (as opposed to systematic) review format. The user-generated list of references (20 references in References.docx) was used as the primary source set. The list covers basic BBB morphology, neuroinflammatory mechanisms, in-vivo imaging techniques, disease-focused reviews and translational studies. Selected easily accessible source records were cross-checked online for methods and bibliographic information, especially with Harris et al. (2023), Candelario-Jalil et al. (2022), Kovbasyuk et al. (2025), and Sasannia et al. (2025).The synthesis was arranged around four themes, namely: (i) the biological substrates of early dysfunction; (ii) imaging methods and their measurable constructs; (iii) clinical and experimental application of the imaging methods; and (iv) technical limitations and translational priorities of the imaging methods. Narrative selection prioritized relevance to BBB function, neuroinflammation, in-vivo imaging, and methodological interpretation. There was no specific database search string, the duplicate screening, PRISMA flow or risk-of-bias tool was not used and no quantitative meta-analysis was completed. Thus, the review is not designed to be

a complete, systematic evidence map. No pooling of claims for sensitivity, diagnostic accuracy or clinical utility is done, nor is there quantification.

Discussion

DCE-MRI: established permeability imaging, with sensitivity constraints

DCE-MRI obtains serial images of the tissue after an injection of intravenous contrast material consisting of Gadolinium-based agents and fits the signal concentration curves with pharmacokinetic models. Volume transfer constant (Ktrans) is frequently reported as an index of transfer from plasma to tissue and related measures may include plasma volume, extracellular extravascular volume and leakage fraction. Low permeability and low leakage fractions present problems for reliable quantification at the BBB: errors in the arterial input function, T1 mapping, temporal resolution, motion correction, vascular input and model assumptions can all have a significant effect on estimation [7,10,17,18]. Ktrans is not a straightforward, universally comparable parameter of endothelial permeability. It is influenced by blood flow, surface area, delivery of the contrast agent and permeability depending on the regime and model. A negative or near zero estimate does not imply a fully intact barrier; it can be due to signal-to-noise and/or model limitations. Standardization of methods, clear model selection, pre-defined regions and reporting of uncertainty are key. DCE-MRI is especially applicable to the detection of contrast leakage from macromolecules and can have reduced ability to detect the earliest changes in smaller or naturally occurring substrates [7,17,19].

ASL and water-exchange MRI: probing a different aspect of barrier function

ASL labels the blood water in arteries magnetically and without using exogenous contrast, giving cerebral blood flow. Specific ASL models are able to calculate the water exchange of the BBB, usually expressed as kw or similar (K is a rate constant). Since water is much smaller than gadolinium chelates, if water exchange is altered, it may not be detectable by the amount of gadolinium leakage. This is a conceptual advantage in case of subtle dysfunction, but it is a reflection of several pathways such as passive permeability, transmembrane/channel mediated transport. Therefore, increases or decreases can be out of the ordinary, and the interpretation should consider the perfusion, the time being labeled, the time it takes for the transit, and the assumption of the model [7,18,19]. Water exchange using ASL cannot replace DCE Ktrans.

PET and molecular imaging: inflammation is not synonymous with leakage

Depending on the tracer and target expression, kinetics and quantification, PET can interrogate molecular processes with high sensitivity. TSPO-PET is an indicator of ‘glial-associated’ inflammatory activity and expression is not unique to any single cell type, and is influenced by genotype, tracer properties and disease context. There are more mechanistically targeted approaches using PET probes directed toward endothelial adhesion molecules, transporters or barrier associated targets, but they are still target and tracer specific. Thus, PET cannot be viewed as an index of BBB dysfunction, but rather

as evidence for a molecular context unless the tracer/model used in the study is explicitly shown to support this construct [7,10,20].

Perfusion, diffusion, and vascular-context imaging

Perfusion imaging (such as DSC-MRI, ASL and selected CT methods) provides the context for measurements of the BBB by detecting changes in flow, transit, or vascular delivery. Ischemia leads to both perfusion defects and barrier defects that develop concurrently and leakage estimates can also be affected by delayed arrival or tissue infarction [1,4,19]. Diffusion MRI can identify changes in tissue which are cytotoxic or vasogenic, whereas susceptibility and vessel-architecture techniques can identify the microvascular consequences. These techniques are clinically useful and are mostly indirect for BBB permeation. They have the best evidence to offer in cases of multimodal interpretation: in cases where there is an apparent signal of permeability, it should be assessed with the perfusion, diffusion, lesion and vascular anatomy.

Disease-specific patterns and implications

The BBB can be affected acutely, be regionally heterogeneous and may be accompanied by edema and hemorrhagic transformation and/or tissue remodeling following ischemic stroke, which makes temporal interpretation essential [4,19]. MRI techniques might provide complementary measures of subtle leakage and perivascular-space changes that may be occurring with chronic hypoperfusion and white-matter injury in cerebral small-vessel disease [18]. Barrier dysfunction in Alzheimer's disease and other neurodegenerative diseases can happen in a more subtle and spatially selective manner: there is evidence for associations, but the direction of causality and individual level diagnostic utility is not established [2,8,17,20]. Changes in the BBB may occur in both inflammatory demyelination and epilepsy along with inflammatory lesions, but generalization is not possible owing to the clinical state and the activity of lesions [10].

Another crucial difference is that the literature on focused ultrasound to open the BBB for therapeutic access does not apply to the ability to detect early BBB dysfunction. Targeted and controlled opening, as shown in the Parkinson's disease dementia study is feasible but the results should not be interpreted as evidence for the diagnostic capacity of a particular imaging biomarker for preclinical disease. Likewise, the BBB permeability markers that have been examined as prognostic factors of DCS after SAH or PSCD are context-specific, rather than broadly applicable, early detection test [11,12,13].

Strengths, limitations, and translation

Some advantages of MRI include the ability to rescan the brain repeatedly and in a non-invasive approach to do longitudinal mapping and assessment of changes on an individual basis. In the case of patients, DCE-MRI and ASL may be employed, while PET allows molecular specificity; in the preclinical context, intravital multiphoton microscopy is helpful in doing so [7]. Multimodal examination is better than the single sequence to distinguish between permeability, water transfer, perfusion, tissue injury and inflammation. The main drawbacks are low signal from subtle leakage in BBB, protocol variation, model dependence, scanner/vendor variability, motion, partial volume,

confounding with perfusion and tissue disease, and lack of universal acceptance of normative thresholds. The PET technique has exposure constraints and tracer availability, the gadolinium administration procedure is personalized, water-exchange MRI is methodologically complex, and microscopy is invasive and not applicable to routine care of humans. In addition, there is a biological specificity issue: BBB dysfunction can be mediated by unique molecular mechanisms which have varied therapeutic consequences [7,10,17].

Future studies should employ standardized acquisition and analysis pipelines, report raw parameters of the protocol and model assumptions, incorporate test–retest reliability and uncertainty, incorporate appropriate reference cohorts that are age-, vascular-risk-, and disease-stage-appropriate, and validate candidate markers with prospective validation against clinical outcomes or mechanistic measures. Of particular importance are designs utilizing longitudinal measurement and co-localization of permeability imaging with inflammatory PET, perfusion, diffusion and fluid biomarkers. Machine learning can be used to assist with segmentation and pattern detection, but external validation and interpretability must be achieved prior to clinical use [10,17,20].

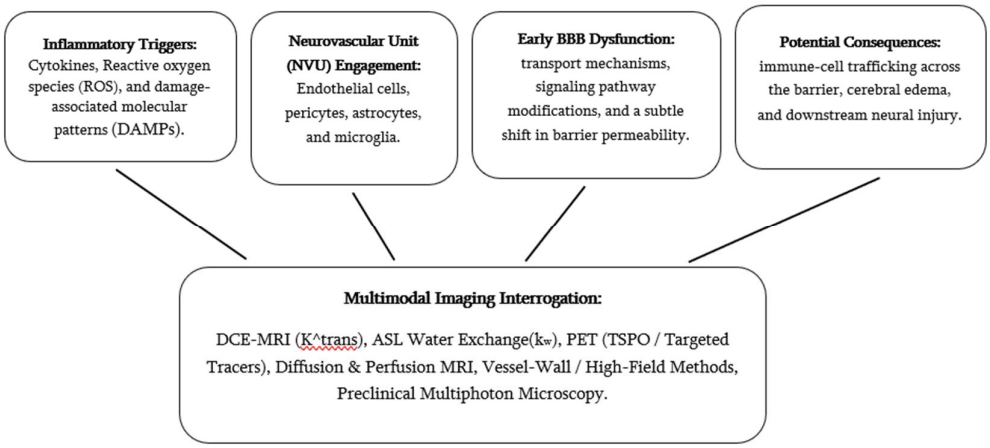


Figure 1. Conceptual framework linking inflammation, NVU alterations, and multimodal imaging.

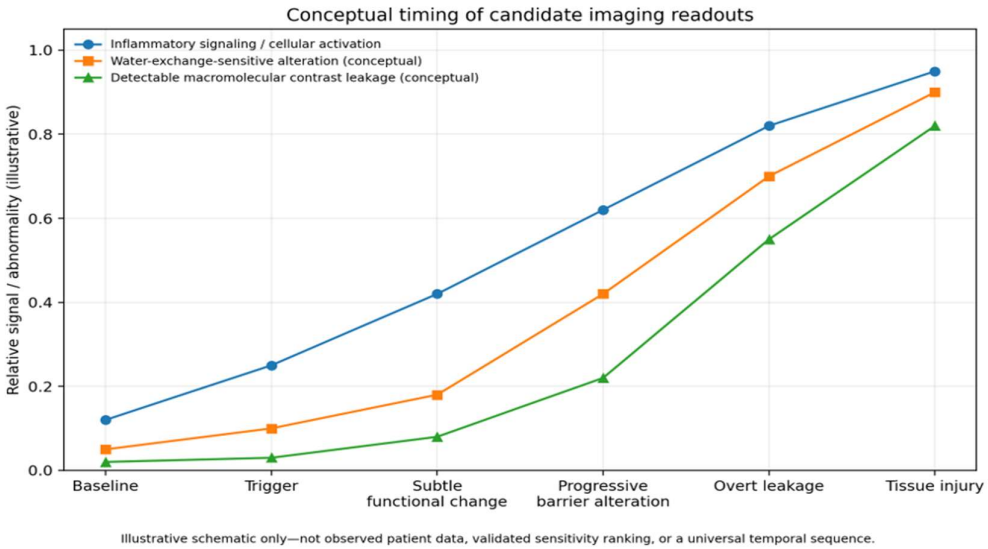


Figure 2. Conceptual timing of candidate imaging readouts.

Table 1. Advanced imaging modalities for BBB and neuroinflammation assessment.

Modality / approach	Primary construct	Strengths	Key limitations / interpretation
DCE-MRI (Ktrans, Ki, leakage fraction)	Extravasation of gadolinium-based extracellular agents	Clinically feasible; regional and longitudinal permeability-related estimates	Low-leak sensitivity; model/input-function dependence; Ktrans may be flow-influenced
ASL water-exchange MRI (kw-related)	Transendothelial exchange of labeled water	No exogenous contrast; potentially sensitive to subtle transport changes	Not specific to junctional leakage; perfusion/transit and model confounds
TSPO-PET	Molecular signal associated with glial/inflammatory activation	Molecular sensitivity; complements MRI permeability measures	Not a direct BBB leak measure; cell specificity, genotype, tracer and kinetics issues
Targeted PET/SPECT	Selected endothelial, adhesion, transporter, or barrier target	Potential mechanistic specificity	Target/tracer validation and availability are limiting
DSC/perfusion MRI; ASL CBF	Perfusion, blood delivery, vascular transit	Provides context and helps identify vascular confounding	Indirect BBB measure; signal affected by flow and timing
Diffusion / susceptibility / vessel architecture MRI	Tissue injury and microvascular consequences	Adds tissue and vascular context	Indirect, nonspecific for BBB mechanism
Intravital multiphoton microscopy (preclinical)	Cellular leakage, junctions, pericytes, immune-cell dynamics	High spatial and temporal resolution; mechanistic validation	Invasive, limited field/depth, preclinical translational gap

Table 2. Candidate imaging signatures across disease contexts.

Clinical context	BBB-related question	Potential imaging combination	Interpretive caveat
Acute ischemic stroke	Does barrier injury accompany ischemia and evolve toward edema/hemorrhagic risk?	DCE or perfusion leakage measures + DSC/ASL perfusion + diffusion	Infarct core, reperfusion, transit delay, and time-from-onset affect interpretation
Cerebral small-vessel disease	Is subtle leakage associated with chronic microvascular and white-matter injury?	DCE-MRI + ASL water exchange/CBF + FLAIR, diffusion and perivascular-space assessment	Low signal and age/vascular-risk confounding; disease heterogeneity
Alzheimer's / neurodegeneration	Are regionally subtle barrier or transport abnormalities associated with disease stage?	DCE-MRI + ASL water exchange + TSPO-PET or other molecular markers + structural MRI	Association does not establish causal direction; biomarkers are not validated stand-alone screening tools
Multiple sclerosis / neuroinflammatory lesions	Does focal and diffuse barrier alteration align with inflammatory activity?	DCE-MRI + conventional lesion MRI + selected PET research markers	Treatment status and lesion activity alter signal; focal enhancement may not represent diffuse dysfunction
Epilepsy	Are barrier changes present around seizure activity or in interictal tissue?	DCE-MRI + perfusion/diffusion; molecular PET in selected studies	Timing relative to seizures is essential; changes may be consequence as well as contributor
SAH / delayed cerebral ischemia	Can permeability-related imaging contribute to risk assessment?	Permeability imaging with perfusion and clinical/vascular assessment	Prognostic evidence is disease-specific and not broadly generalizable
Therapeutic focused ultrasound	Can controlled BBB opening be localized and monitored?	Targeted MRI monitoring with protocol-specific safety and delivery measures	Induced opening differs from spontaneous inflammatory dysfunction

Table 3. Sources of uncertainty and recommended reporting practices.

Challenge	Why it matters	Recommended practice
Low permeability / weak signal	Early leakage may be below reliable quantification	Report detectability, uncertainty, repeatability; avoid binary intact/broken labels
Model and arterial input function	Ktrans depends on model and input-function estimation	Specify model, input function method, T1 mapping, temporal resolution, and fitting constraints
Perfusion and transit effects	Flow/delivery can mimic or alter permeability estimates	Acquire or report perfusion and transit metrics; interpret in vascular context
Protocol heterogeneity	Cross-study values may not be comparable	Harmonize sequence, contrast dose/timing, field strength, segmentation, and QC
Construct confusion	Inflammatory PET, water exchange, and gadolinium leakage represent different biology	Name the construct measured; do not treat markers as interchangeable
Disease stage and confounders	Age, hypertension, diabetes, medication, lesion status and timing influence BBB measures	Prespecify covariates and stage; report cohort characteristics and stratified results
Translation / validation gap	Research biomarkers may lack normative thresholds or outcome validation	Conduct multicenter test–retest and prospective external validation; relate measures to outcomes

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References

1. Sasannia S, Leigh R, Bastani PB, Shin HG, van Zijl P, Knutsson L, et al. Blood-brain barrier breakdown in brain ischemia: insights from MRI perfusion imaging. Neurotherapeutics. 2025;22(1):e00516. doi:10.1016/j.neurot.2024.e00516.
2. Sweeney MD, Sagare AP, Zlokovic BV. Blood-brain barrier breakdown in Alzheimer disease and other neurodegenerative disorders. Nat Rev Neurol. 2018;14(3):133-50. doi:10.1038/nrneurol.2017.188.
3. Kovbasyuk Z, Tefera E, Li C, Baete SH, Steriade C. Imaging brain inflammation and blood-brain barrier permeability in neurological and psychiatric diseases: a review. J Neuroinflammation. 2025;22(1):275. doi:10.1186/s12974-025-03598-x.
4. Candelario-Jalil E, Dijkhuizen RM, Magnus T. Neuroinflammation, stroke, blood-brain barrier dysfunction, and imaging modalities. Stroke. 2022;53(5):1473-86. doi:10.1161/STROKEAHA.122.036946.
5. Liebner S, Dijkhuizen RM, Reiss Y, Plate KH, Agalliu D, Constantin G. Functional morphology of the blood-brain barrier in health and disease. Acta Neuropathol. 2018;135(3):311-36. doi:10.1007/s00401-018-1815-1.
6. Yu T, Wang Z, Chen Y, Xiang Y, Wu M, Zhang M, et al. Blood-brain barrier dysfunction in CNS diseases: paying attention to pericytes. CNS Neurosci Ther. 2025;31(5):e70422. doi:10.1111/cns.70422.
7. Harris WJ, Asselin MC, Hinz R, Parkes LM, Allan S, Schiessl I, et al. In vivo methods for imaging blood-brain barrier function and dysfunction. Eur J Nucl Med Mol Imaging. 2023;50(4):1051-83. doi:10.1007/s00259-022-05997-1
8. Ved A, Gajjar TB, Kakkad A, et al. Neurovascular uncoupling in Alzheimer's and Parkinson's diseases: mechanisms and therapeutic strategies. Brain Sci. 2026;16(5):434. doi:10.3390/brainsci16050434.
9. 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. doi:10.3389/fncel.2021.661838.
10. Gasca-Salas C, Fernández-Rodríguez B, Pineda-Pardo JA, Rodríguez-Rojas R, Obeso I, Hernández-Fernández F, et al. Blood-brain barrier opening with focused ultrasound in Parkinson's disease dementia. Nat Commun. 2021;12(1):779. doi:10.1038/s41467-021-21022-9.

11. Amoo M, Henry J, Pender N, Brennan P, Campbell M, Javadpour M. Blood-brain barrier permeability imaging as a predictor for delayed cerebral ischaemia following subarachnoid haemorrhage: a narrative review. Acta Neurochir (Wien). 2021. doi:10.1007/s00701-020-04670-6

12. Wang W, Zhang S, Yu L, Wang T, Wang G, Xu F, et al. Preoperative blood-brain barrier disruption increased risk of postoperative cognitive decline after coronary artery bypass grafting: a prospective cohort study. Int J Surg. 2025;111(11):7929-38. doi:10.1097/JS9.0000000000002902.

13. Zapata-Acevedo JF, García-Pérez V, Cabezas-Pérez R, Losada-Barragán M, Vargas-Sánchez K, González-Reyes RE. Laminin as a biomarker of blood-brain barrier disruption under neuroinflammation: a systematic review. Int J Mol Sci. 2022;23(12):6788. doi:10.3390/ijms23126788.

14. Blood-brain barrier breakdown in neuroinflammation: current in vitro models. Int J Mol Sci. 2023;24(16):12699. doi:10.3390/ijms241612699.

15. Botta D, Bernetti C, Hutuca I, Ojeda Esparza JF, Sveikata L, Lovblad KO, et al. Beyond the leak: advanced MRI assessment of the blood-brain barrier in neurodegeneration. Neurodegener Dis. 2026;26(3):197-212. doi:10.1159/000552173.

16. Voorter PHM, van Dinther M, Jansen WJJ, Postma AA, Staals J, Jansen JFA, et al. Blood-brain barrier disruption and perivascular spaces in small vessel disease and neurodegenerative diseases: a review on MRI methods and insights. J Magn Reson Imaging. 2024;59(2):397-411. doi:10.1002/jmri.28989

17. Chaudhary S, Chao HH, Agarwal K, Gupta S, Li CR. Imaging markers of neuroinflammation in aging and Alzheimer's disease and related dementia: a comprehensive review. Neurosci Biobehav Rev. 2025;176:106270. doi:10.1016/j.neubiorev.2025.106270

18. Moyaert J, Padrela E, Morgan T, Petr J, Versijpt J, Barkhof F, et al. Imaging blood-brain barrier dysfunction: a state-of-the-art review from a clinical perspective. Front Aging Neurosci. 2023;15:1132077. doi:10.3389/fnagi.2023.1132077

19. Montagne A, Nation DA, Pa J, Sweeney MD, Toga AW, Zlokovic BV. Imaging blood-brain barrier disruption in neuroinflammation and Alzheimer's disease. Neuron. 2023

20. Albrecht, D. S., Granziera, C., Hooker, J. M., & Loggia, M. L. (2016). In Vivo Imaging of Human Neuroinflammation. ACS chemical neuroscience, 7(4), 470–483. https://doi.org/10.1021/acschemneuro.6b00056.