Fluids and Barriers of the CNS

REVIEW

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Restoring brain barriers: an innovative approach for treating neurological disorders

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Abstract

The complex etiology of neurological disorders is a major challenge to the identification of therapeutic candidates. Tackling brain vascular dysfunction is gaining attention from the scientific community, neurologists and pharmaceutical companies, as a novel disease-modifying strategy. Here, we provide evidence that at least 41% of neurological diseases and related conditions/injuries display a co-pathology of blood-brain and blood-spinal cord barrier alterations and dysfunctions, and we discuss why this figure may represent only a fraction of a larger phenomenon. We further provide clinical evidence that barrier status may contribute to pathological and functional outcomes in patients. Finally, we discuss drug candidates under development to repair brain barriers.

Keywords BBB disruption, BSCB disruption, Tight junction, Claudin-5, Alzheimer's disease, Amyotrophic lateral sclerosis, Huntington's disease, Multiple sclerosis, Parkinson's disease, Therapeutic strategies

Introduction

According to the most recent Global Burden of Disease report published in 2024 in Lancet Neurology, 43% of the world's population suffers from a condition affecting the nervous system [1]. The most significant contributors to disability-adjusted life-years are stroke, neonatal encephalopathy, migraine, Alzheimer's disease (AD) and related dementias, diabetic neuropathy, meningitis, epilepsy, neurological complications due to pre-term birth, autism, and cancers of the nervous system [1]. Most neurological disorders significantly affect a person's quality of life, ability to perform daily activities, evolve in the workplace and, in doing so, redefine an individual's role in their own family and society at-large. Among the most disruptive consequences are the dependence on caregivers, and assistive technology may be required for mobility, communication, self-care, or domestic activities. Biotechnology and pharmaceutical companies have been leading efforts to identify, develop, and deploy therapeutic solutions to support and treat these patients. Among the most pressing unmet needs are therapeutic agents

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that halt or slow neurological disorders, but most clinical trials have been unsuccessful at developing safe and effective drugs for approval by regulatory agencies [2, 3]. In this context, conceptually novel approaches to drug design and unexplored target identification could benefit drug discovery efforts.

The blood-brain barrier (BBB) is a specialized interface between the blood and the brain. It is composed of microvascular endothelial cells, endothelial and parenchymal basement membranes that embed pericytes, and astrocyte endfeet that form the glia limitans and serve as a secondary layer to protect the brain parenchyma. The BBB controls brain homeostasis by selectively regulating the passage of ions, nutrients, molecules and cells from the systemic circulation [4, 5]. Brain microvascular endothelial cells are connected via adherens, tight, and gap junctions, which are essential elements forming a tightly and selectively regulated polarized barrier that restricts the paracellular diffusion of ions and small molecules. A functionally equivalent barrier exists between the blood and the spinal cord, called the blood-spinal cord barrier (BSCB), characterized by structural and molecular differences that may render the BSCB more permeable than the BBB [6]. The integrity of the BBB and BSCB is essential for proper brain and spinal cord function and by protecting the delicate tissues from potentially harmful agents, such as toxins, pathogens, and inflammatory mediators. Importantly, barrier properties of brain and spinal cord microvascular endothelial cells are not intrinsic, but rather rely on the cellular crosstalk with pericytes and astrocytes, which are in close contact with these endothelial cells. The cellular and acellular components contributing to barrier function of the central nervous system (CNS) microvascular endothelial cells are referred to as neurovascular unit (NVU) [7, 8]. The term NVU may encompass additional cells like neurons, microglia and even circulating cells, when referring to the role of the NVU in regulating blood flow in the CNS [9].

A growing body of evidence now indicates that structural alterations and dysfunctions of brain barriers are a hallmark of numerous severe neurological diseases or injuries associated with inflammation and neurodegeneration. They include AD [10], amyotrophic lateral sclerosis (ALS) [11–13], Huntington's disease (HD) [14–16], multiple sclerosis (MS) [17–19] and Parkinson's disease (PD) [20, 21] (Fig. 1). Numerous disturbances at the barrier interface have been reported to alter barrier functions. For example, altered caveolae-mediated transcytosis results in the trafficking of peripheral inflammatory factors and toxins into the brain [22], and the dysregulation of aquaporin-4 channels at astrocyte endfeet results in an abnormal entry of water into the brain [23]. Inflammation of the endothelium results in an uncontrolled trafficking of immune cells and loss of tight junction (TJ) integrity. More particularly, the loss of TJ integrity can be triggered by altered TJ recycling or changes to TJ phosphorylation/oligomerization, and their compromised functionality may lead to enhanced paracellular diffusion of ions and molecules into the brain parenchyma. Additionally, dysregulation of P-glycoprotein efflux transporters at the surface of endothelial cells promotes the accumulation of undesirable metabolites in the brain [24]. All of these disturbances at the barrier interface ultimately perturb homeostasis and lead to neuroinflammation and neurodegeneration, and eventually vasogenic edema such as in stroke and neurotraumas [25]. Among them, the loss of TJs and related proteins, and the presence of blood elements and cells within the CNS parenchyma represent the most investigated structural alterations and dysfunctions of brain barriers. They may therefore serve as common measures to evaluate barrier repair by therapeutic agents.

This comprehensive and systematic review of the literature provides clear evidence that compromised brain barriers are ubiquitous pathological features across brain disorders, and are not restricted to a subset of diseases. In fact, at least ~ 41% of brain disorders display dysfunctions and/or structural alterations of brain barriers, as evidenced by published literature covering over a hundred neurological diseases and injuries for potential BBB and BSCB dysfunctions in animal models and humans. Barrier dysfunctions documented in this study include abnormal leakage of blood-derived elements and red blood cells, and increased migration of immune cells into the CNS. In addition, we also examined articles reporting alterations of TJ structures and protein levels (e.g. claudin-5, occludin), along with changes to ubiquitous scaffolding proteins that anchor TJ proteins to the cytoskeleton (zonula occludens-1, ZO-1). We then compiled clinical evidence for the possible causal relationships between barrier damage and progression of neurological disorders. Finally, we provide an overview of the mechanisms of action and stage of development of drug candidates currently pursued by biotechnology and pharmaceutical companies to repair brain barriers. Based on the collected evidence, we propose that restoring BBB and/or BSCB integrity represents an innovative disease-modifying therapeutic approach to address pressing unmet medical needs associated to neurological disorders. In essence, this review focuses on brain barriers dysfunctions, structural alterations, and therapeutic treatments currently under development to treat symptomatic patients.

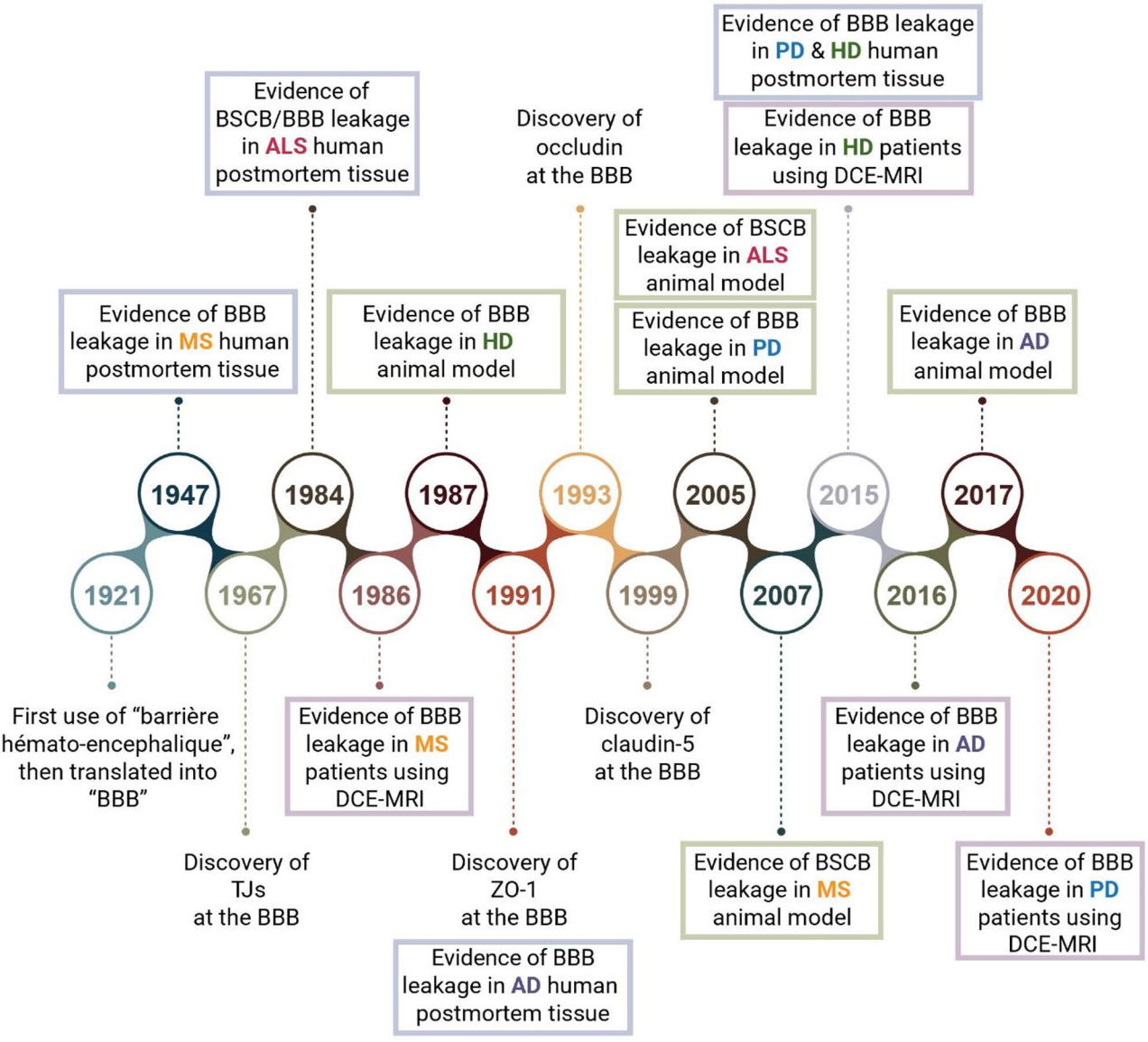

Fig. 1 Timeline of milestone discoveries in BBB and BSCB structural alterations and dysfunctions in neurological disorders. This figure depicts research milestones encompassing the first use of the French term "barrière hémato-encéphalique" by Lina Stern in 1921 [303], later translated into "BBB", the discovery of endothelial TJs in 1967 [304] and associated proteins (ZO-1 [305], occludin [306] and claudin-5 [307]) and the early use of DCE-MRI for diagnosis of MS lesions in patients [308] at the end of the 20th century. Rodent and human postmortem analyses of brain or spinal cord tissues to assess the extravasation of IgG, fibrin(ogen), albumin and/or hemoglobin provided the first demonstrations of BBB and BSCB leakage in neurological disorders, such as in AD [309, 310], ALS [119, 311], HD [16, 312], MS [313, 314] and PD [100, 101, 315]. In the last decade, advances in neuroimaging using DCE-MRI have paved the way for studying subtle BBB leakage in patients with neurological disorders, notably AD [96], HD [16] and PD [99], allowing earlier evidence/diagnosis of BBB dysfunction in the progression of neurological disorders than postmortem analyses

Evidence of BBB & BSCB dysfunctions and structural alterations in neurological disorders

Definition of key terms

In this review, pathological ***dysfunctions*** of brain barriers are defined as the increased permeability of barriers to blood components (such as fibrinogen, IgG or albumin) or an exacerbated immune cell trafficking into the brain and spinal cord parenchyma. These features are mostly measured in postmortem tissues but occasionally, as in epilepsy, diseased brain samples are collected for diagnostics and can be used for research purposes. Live imaging additionally enables the detection of brain barriers dysfunction. For example, dynamic contrast-enhanced MRI (DCE-MRI) is an imaging-based approach capable of identifying subtle abnormal enhancements of gadolinium (Gd) or Gd-derived contrast agents (such as gadobutrol or Dotarem) in the parenchyma, following injection of the molecule into the bloodstream. A common and similar technique consists in injecting exogenous tracers into the bloodstream that can reach the

parenchyma where brain barriers are impaired, but this methodological approach is restricted to animal studies. These tracers include Evans blue, fluorescent dextrans or sodium fluorescein, and can be observed and quantified in postmortem tissues.

The loss or discontinuity of TJs that seal brain barriers can lead to abnormal leakage of blood components into the parenchyma and further disease processes. For the purpose of this review, structural barrier ***alterations*** are restricted to defects in TJ formation and maintenance, as defined by electron microscopy-based ultrastructural analyses of postmortem tissues, or by quantification of TJ-associated protein levels using protein-based assays. Among the large number of TJ-associated proteins, the most expressed and studied at the barrier are claudin-5, occludin and ZO-1.

Terms related to BBB and BSCB dysfunctions and structural alterations were searched on the PubMed database and include a total of 132 neurological disorders (retrieval strategy provided as Supplementary Material). BBB alterations and dysfunctions reported in brain cancers [26] or after infection with viruses such as SARS-CoV-2 [27] fall outside the scope of this review. In addition, studies specifically investigating the blood-cerebrospinal fluid (CSF) barrier were not discussed in this review, but measures of CSF/serum albumin ratio (Qalb) were reported throughout the relevant sections. Over 350 articles were retrieved from this initial literature survey and encompass studies performed in both animal models and humans (Fig. 2), but exclude *in vitro* studies. The main findings for each of the 54 neurological disorders with compromised barriers are summarized in Supplementary Table 1. The 54 pathologies identified in this review encompass a large number of rare and incurable life-threatening diseases of sporadic or genetic etiology, and pediatric diseases. For a more exhaustive and detailed overview of BBB and BSCB alterations and dysfunctions in specific disorders, please refer to recent reviews on AD [10], ALS [11–13], cerebral small vessel disease [28], degenerative cervical myelopathy [29], epilepsy [30], hepatic encephalopathy [31], ischemic stroke [32, 33], MS [17–19], PD [20, 21], or psychiatric disorders [34–36].

Compromised brain barriers have been documented in most classes of neurological disorders

The heatmap presented in Fig. 3 highlights the occurrence of publications reporting barrier dysfunctions and alterations in 54 diseases/injuries affecting the CNS.

Brain barriers dysfunctions were reported in patients classified with **neurovascular** (cerebral small vessel disease [37–44], hemorrhagic stroke [45–49], ischemic stroke [50–55], cerebral cavernous malformation [56–58], Moyamoya disease [59]) and **autoimmune diseases** (MS [60–68], autoimmune encephalitis [69, 70], Susac syndrome [71]). Brain or spinal cord vascular dysfunctions are also evident in patients with **neurotraumas** (traumatic brain injury [72–81], chronic traumatic encephalopathy [82, 83], spinal cord injury [84, 85]) or **neurodegenerative diseases**. Besides AD [70, 86–98],

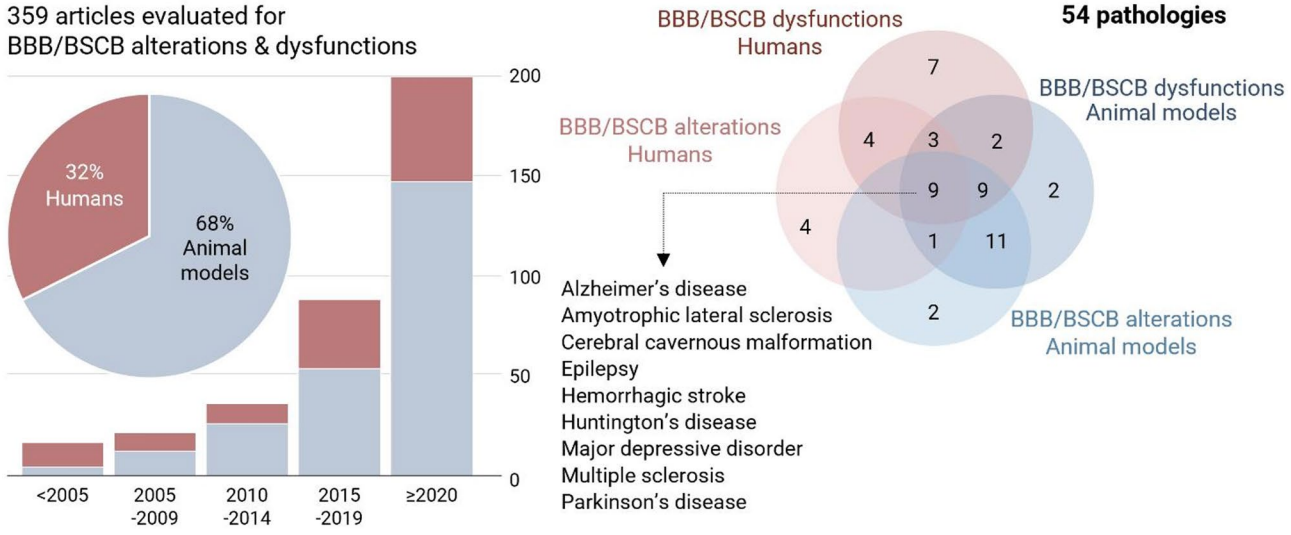

Fig. 2 Histogram and venn diagram analysis using publications reporting BBB and BSCB alterations and dysfunctions in neurological disorders. The histogram depicts the main characteristics of the 359 articles used for the survey of this review. About one third of these articles provided evidence in patients with neurological disorders, and the rest in animal models. The venn diagram highlights 54 neurological disorders for which BBB or BSCB alterations or dysfunctions were evidenced thus far in animal models and in humans. It shed light on 9 neurological disorders for which all the defects were reported: AD, ALS, cerebral cavernous malformation, epilepsy, HD, hemorrhagic stroke, major depressive disorder, MS and PD. Overall, this figure demonstrates the growing interest of the scientific and medical communities for barriers integrity, and the increasing number of pathologies for which BBB or BSCB alterations or dysfunctions are discovered over time

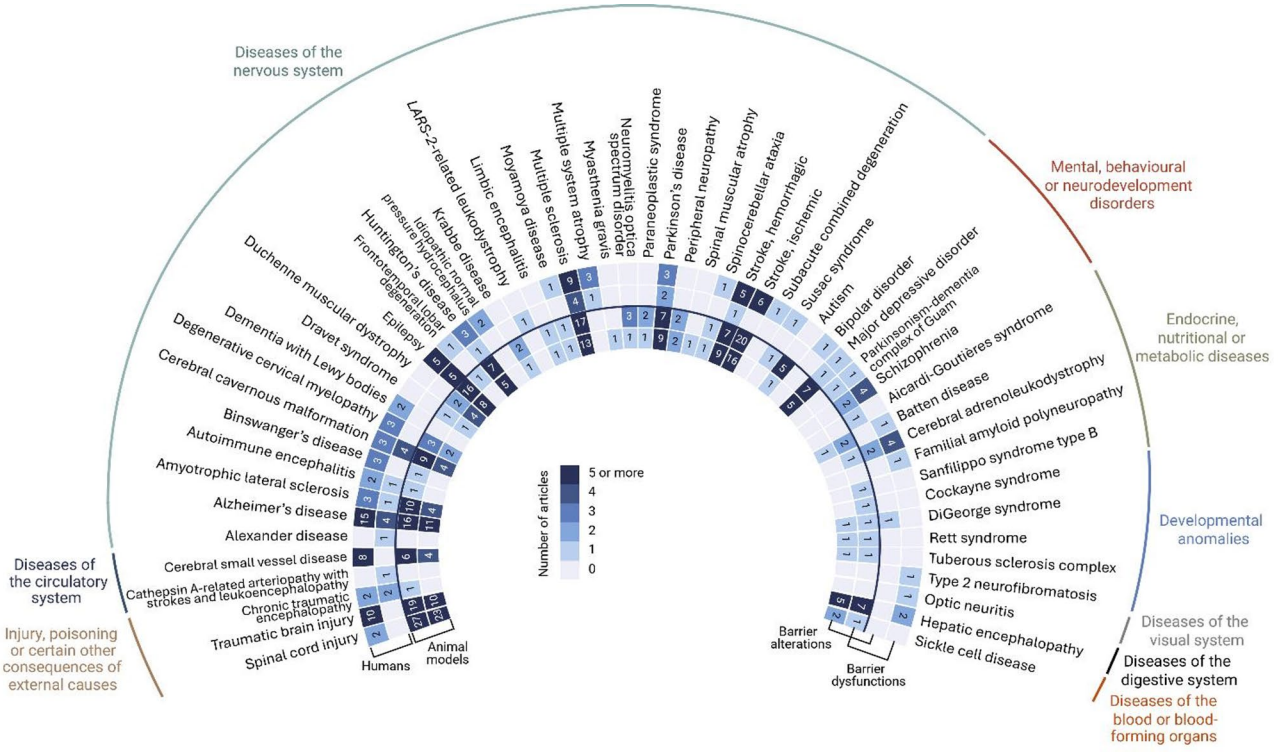

Fig. 3 BBB and BSCB alterations and dysfunctions in neurological disorders. Barriers between the blood and the parenchyma are essential to human health by maintaining brain and spinal cord homeostasis. When these barriers are readily interrupted (for example through a degradation of TJ proteins or increased vesicular activity), they leak circulating blood elements (such as fibrin(ogen) or IgG), and sometimes red blood cells in case of hemorrhagic transformation. The uncontrolled recruitment of immune cells into the parenchyma across the inflamed vascular wall (diapedesis) represents another major dysfunction of these barriers. Today, these BBB and BSCB alterations and dysfunctions, in particular, have been reported in ~41% of neurological diseases and injuries, suggesting that they may contribute to the pathogenesis of many neurological disorders. The heatmap highlights evidence found in animal models and in humans ranked from the most relevant to human patients' health to the less relevant (from the exterior to the interior of the circle: dysfunctions in humans, alterations in humans, dysfunctions in animal models and alterations in animal models). Features of barrier alterations included in this heatmap are a loss of TJs and/or decreased protein levels of TJ-associated proteins (claudin-5, occludin and/or ZO-1). Features of barrier dysfunctions are a leakage of circulating elements into the parenchyma and/or an increased/uncontrolled immune cell trafficking across the BBB. The numbers in the squares indicate the number of articles depicting these alterations and dysfunctions, and corresponding articles are reported in Supplementary Table 1

PD [99–101], epilepsy [102–106], Binswanger's disease [107–109], degenerative cervical myelopathy [110, 111], dementia with Lewy bodies [87, 88] and frontotemporal lobar degeneration [112], **rare neurodegenerative diseases** are also affected and include cerebral adrenoleukodystrophy [113–116], ALS [117–119], multiple system atrophy [120–122], HD [16, 123, 124], idiopathic normal pressure hydrocephalus [125, 126], Batten disease [127], spinocerebellar ataxia [128], parkinsonism-dementia complex of Guam [129], familial amyloid polyneuropathy [130] and type 2 neurofibromatosis [131]. Patients with **psychiatric disorders** (schizophrenia [132–135], major depressive disorder [136], bipolar disorder [137]), **hepatic encephalopathy** [138, 139] or **optic neuritis** [140] also displayed abnormal BBB leakage of blood components. Research performed in animal models supports barriers dysfunction in most of these pathologies (Fig. 3). Damage to TJs or TJ-associated proteins in both humans and animal models provide additional key evidence of structural barrier alterations (Fig. 3). Lastly, the following nine neurological disorders have been shown to display both barrier dysfunctions and structural alterations in animal models and humans: AD, ALS, cerebral cavernous malformation, epilepsy, HD, hemorrhagic stroke, major depressive disorder, MS and PD (Figs. 2 and 3).

Case studies also reported gadolinium extravasation into the spinal cord of patients with subacute combined degeneration [141], a rare neurodegenerative disease, and discontinuity of ZO-1 and/or claudin-5 was observed in the brain of patients with various leukodystrophies (Aicardi-Goutières syndrome, Alexander disease, cathepsin-A-related arteriopathy with strokes and leukoencephalopathy, *LARS-2*-related leukodystrophy) [142] and DiGeorge syndrome [143], a rare genetic disorder.

In addition to the pathologies discussed above, compromised brain barriers have also been documented in experimental animal models of neurodevelopmental disorders including autism [144–148], Krabbe disease

[149, 150], Rett syndrome [151], Cockayne syndrome [152], Dravet syndrome [153] and San Filippo syndrome type B [154]. Experimental animal models of autoimmune diseases (neuromyelitis optica spectrum disorder [155–157], limbic encephalitis [158]), neuromuscular diseases (Duchenne muscular dystrophy [159, 160]) and peripheral neuropathy [161, 162] also provided evidence of barriers dysfunction. Animals with neoplasms and related conditions (paraneoplastic syndrome [163, 164], tuberous sclerosis complex [165]) or Sickle cell disease [166] displayed reduced barrier integrity as well. Lastly, reduced levels of claudin-5 or its discontinuity in brain microvessels of animals with myasthenia gravis [167], a rare pediatric autoimmune disease, and in spinal muscular atrophy [168], a rare inherited pediatric neuromuscular disorder, further confirm that barrier pathology is a widespread feature across the plethora of brain disorders.

Altogether, several research groups have reported that BBB and BSCB alterations and dysfunctions occur early in the pathogenesis of neurological disorders, or even prior to the appearance of pathological hallmarks and symptoms in several genetic animal models of AD [91, 169, 170], ALS [171], Batten disease [127, 172], cerebral cavernous malformation [173], cerebral small vessel disease [174], Cockayne syndrome [152], Duchenne muscular dystrophy [160], HD [15], Sanfilippo syndrome type B [154], spinal muscular atrophy [168], spinocerebellar ataxia [128] and tuberous sclerosis complex [165] (Supplementary Table 1). These observations could support a possible causal relationship between BBB or BSCB damage and the onset and/or progression of several neurological disorders.

Genetic mutations of tight junction proteins are also associated with neurological disorders

Mutations in genes encoding claudin-5 and occludin have been reported in patients with extremely rare neurological disorders, further emphasizing that endothelial junction proteins are affected in a large range of neurological disorders. For example, a *de novo* mutation (G60R) on the coding sequence of claudin-5 was found in two children with alternative hemiplegia who developed heterogenous cerebral calcifications [175]. This mutation affects the extracellular loop of claudin-5 and converted TJs to anion-selective channels, thereby causing both a loss-of-function and a toxic gain-of-function in endothelial cell monolayers. Similarly, recessive mutations in occludin have been frequently identified in patients with band-like calcification with simplified gyration and polymicrogyria, characterized by cerebral calcifications, severe progressive microcephaly, early-onset seizures and developmental arrest [176–178]. Lower levels of claudin-5 proteins induced by one allele variant in claudin 5 (rs10314) relates to schizophrenia, a psychiatric disorder observed in 30% of individuals with the 22q11 deletion syndrome [179].

Compromised brain barriers: cause or co-pathology of neurological disorders?

Over the last decade, there has been a 5-fold increase in the number of publications reporting barrier *dysfunctions* or *alterations* in diverse populations of patients (Fig. 2), along with a surge of observational clinical trials aimed at evaluating BBB leakage using DCE-MRI or circulating biomarkers. Most of these trials will enable statistical analyses to correlate BBB integrity with disease severity and disability and, in doing so, indicate whether barriers may be envisioned as potential cause or co-pathology for the diseases under investigation. They include trials in patients with autism (NCT04321915), cerebral small vessel disease (NCT05902039, NCT05746221), epilepsy (NCT06057233), ischemic stroke (NCT05585255, NCT05556395), leukoaraiosis (NCT06181981), major depressive disorder (NCT06203015) or type 2 diabetes (NCT06322212), but also trials in healthy volunteers with cardiovascular risk factors (NCT06116630) or suicidal behavior (NCT06047613). It is reasonable to believe that the 54 pathologies presented in Fig. 3 represent only the tip of the iceberg and that brain vascular dysfunction may be a frequent and common pathophysiological component of neurological disorders.

Three main patterns of barrier disruption in humans seem to be at play. Barrier disruption may aggravate with disease progression, such as in people with multiple system atrophy [122], and this is consistent with observations from animal models of AD [91, 180], ALS [181, 182], HD [15], Batten disease [172] and Cockayne syndrome [152]. Barrier disruption peaks early after neurotraumas or stroke and then gradually attenuates overtime. In some instances, barrier integrity fully recovers as in spinal cord injury [84], or it may remain damaged as in traumatic brain injury [74]. Longitudinal studies are eagerly awaited to further evaluate how brain barriers disruption evolves over the course of each unique neurological disorder. Another pressing question is whether barrier disruption is a trigger or a significant contributor of specific neurological disorders, but not others. In this context, clinicopathological assessment and correlation analyses of BBB leakage rate, disease biomarkers, and patients' symptoms may yield new discoveries and lead the field of neurological diseases into new directions.

Barrier integrity status influences the clinical portrait of patients with neurological disorders

The most accurate method currently available to evaluate brain barriers integrity in patients is to measure the rate of Gd and Gd-based contrasts agents (i.e., transfer coefficient (K^{trans}) or influx constant (K_i)) using DCE-MRI.

This approach allows the detection of subtle and regional BBB/BSCB disruption. However, this technique is relatively recent and expensive, especially when considering measuring barrier leakage in large-scale clinical studies. As a consequence, the literature correlating brain barrier leakage using DCE-MRI to clinical deficits in patients is rather sparse. Therefore, this review also accounted for published literature linking clinical deficits to Qalb, or the release of claudin-5, occludin or ZO-1 into the bloodstream. Qalb may reflect changes at the blood-CSF barrier as well as at the BBB and BSCB. TJ-associated proteins are not expressed specifically in brain and spinal cord endothelium. These biomarkers are thus less precise and not entirely specific to brain barrier leakage compared to measures using DCE-MRI. However, they represent additional putative indicators of a loss of integrity of brain barriers, while they also provide more affordable alternative methods. As a result, biomarker-based associations of brain barriers integrity with clinical outcomes are emerging in the literature. Postmortem analyses further provide valuable evidence to define how the severity of brain barrier leakage/alterations influenced the clinical phenotypes of individuals with neurological disorders. The following sections present key studies conducted with the consent of human participants for 17 neurological diseases and injuries linking brain barriers dysfunctions/alterations and clinical outcome. For a more comprehensive overview of common barriers dysfunctions and alterations in human diseases and injuries, Table 1 is provided in the Supplementary Material. In addition, we also detail findings collected from DCE-MRI studies on healthy elderly volunteers and individuals with mild cognitive impairments.

Healthy aged volunteers & Individuals with mild cognitive impairments

Advanced age is a frequent risk factor in neurodegenerative diseases, and it is important to note that several groups have reported increased BBB leakage of Gd-based contrast agents into regions critical for cognitive functions using DCE-MRI, as well as correlations with cognitive decline, in cohorts of healthy elderly volunteers and people with mild cognitive impairments:

- age-dependent increase in K_i of gadobutrol into the white matter (WM) and grey matter (GM) of the cortex and hippocampus, and into higher-order cognition brain regions (orbitofrontal and cingulate cortex) in a sex-balanced cohort of 57 healthy volunteers (66 [47–91] ± 10 years old) [183].
- higher K_i of gadobutrol into the normal-appearing WM in a cohort of 39 healthy volunteers (69 ± 12 years old) was associated with lower scores on executive function using the Stroop color-word test interference score and information processing speed using the digit span forward test score [42]. No correlation was found in this study between the vascular volume or index and memory function using the Rey auditory verbal learning test score.
- higher BBB leakage rate of Gd-DTPA-BMA into the hippocampus of 11 individuals with mild cognitive impairments (74 ± 7 years old) compared to that of a age- and sex-matched cohort of 11 healthy volunteers [184]. Furthermore, the vascular rate was negatively correlated with naming ability using the Boston naming test score. Conversely, no correlation was found between the vascular volume or rate and cognitive function when using the mini-mental state examination (MMSE) score.

Neurodegenerative diseases

Alzheimer's disease

Several studies have reported increases in K_i of gadobutrol into the cortex and GM of patients with early AD [96] and in K^{trans} of Gd-DTPA into the hippocampus, cortex, occipital lobe and/or amygdala in AD patients with or without dementia [86–88], compared to age- and sex-matched healthy volunteers. Higher K^{trans} did not correlate with cognitive deficits, nor disease severity using plasma $A\beta_{1-42}/A\beta_{1-40}$ concentrations ratio [88]. However, when including healthy volunteers and patients with dementia with Lewy bodies, weak positive correlations were found between K^{trans} in various brain areas (occipital lobe, frontal lobe, parietal lobe, pallidum, hippocampus, amygdala) and clinical dementia rating score or cognitive deficits, and between K^{trans} in the cortex or parietal lobe and $A\beta_{1-42}/A\beta_{1-40}$ ratio [87, 88]. Higher BBB leakage rate of Gd-DTPA into the centrum semiovale was associated with high-grade enlarged perivascular spaces and reduced verbal fluency and attention [86]. Fibrinogen extravasation was evidenced in WM lesions and normal-appearing WM of postmortem brains of AD patients with small vessel disease, regardless of Braak staging of neurofibrillary tangles and Aβ pathology [93]. Fibrinogen burden was similar to that of non-cognitively impaired age- and sex-matched controls.

Claudin-5 and occludin protein levels, measured by ELISA, were specifically and strongly reduced in the cortex of postmortem brains of people with AD compared to healthy age-matched donors, particularly in patients characterized by advanced Braak staging of neurofibrillary tangles [185]. Interestingly, the loss of TJ proteins was not correlated to cerebrovascular pathology or cerebral amyloid angiopathy. Lower TJ protein levels were associated with higher levels of insoluble $A\beta_{1-40}$, $A\beta_{1-42}$, and Tau, and with lower levels of synaptophysin and postsynaptic density protein-95; this latter correlation was found to be independent of higher levels of insoluble

$A\beta_{1-40}$ and $A\beta_{1-42}$, and Tau. The authors suggested that loss of TJ proteins at the BBB "may contribute to AD pathogenesis in both synergistic and additive manners to typical Aβ and Tau pathologies".

Combined, these studies demonstrated that elevated BBB leakage rate or cerebral loss of TJ proteins, but not fibrinogen burden, relates to greater disease severity and disability in AD patients.

Parkinson's disease

A prospective clinical study has recently reported increases of at least 20% in K^{trans} of Dotarem into the *substantia nigra* and posterior cortex, in both normal-appearing WM and WM lesions of PD patients compared to age- and sex-matched controls [99]. Interestingly, no difference was found when comparing K^{trans} changes in these regions with age- and sex-matched controls who had a stroke or transient ischemic attack within 3 months to 2 years prior to the study. The authors suggest a similar burden of cerebral vascular disease in patients with a history of stroke and PD patients, despite lower cardiovascular risk factors. However, no correlations were found between K^{trans} and cognitive deficits, or disease severity using the unified PD rating scale. Importantly, levodopa equivalent daily dose was not associated with K^{trans} increases in PD patients, suggesting that BBB leakage was not triggered by medication.

Epilepsy

Large increases in Qalb were reported in patients with generalized tonic-clonic seizures or with post-encephalitic/encephalopathic epilepsy compared to controls [186, 187]. In subgroup analyses, Qalb was higher in patients with widespread lesions compared to those with focal lesions [186]. Furthermore, a weak positive correlation was found between Qalb and monthly seizure frequencies.

Occludin and ZO-1 protein levels were decreased in isolated microvessels from the temporal neocortex (resections) of drug-resistant patients presenting with temporal lobe epilepsy compared to control autopsy samples [188]. In contrast, claudin-5 protein levels were increased. No correlation between claudin-5, occludin or ZO-1 protein levels, and the age at onset, duration of epilepsy, or monthly frequency of seizures were found in these epileptic patients. It is important to note that there was a high inter- and intra-variability in the samples selected for these analyses in terms of age, sex, age at onset, disease duration, seizure frequency, and antiepileptic drug medication type.

Overall, these studies suggest that higher Qalb, but not changes in TJ protein cerebral levels, relates to greater disease severity in patients with epilepsy.

Dementia with lewy bodies

A recent prospective study reported increases in K^{trans} of Gd-DTPA into the cortex, parietal lobe and occipital lobe of patients with dementia with Lewy bodies compared to age- and sex-matched healthy volunteers [88]. Despite a trend towards a moderate negative correlation between K^{trans} in the occipital lobe and MMSE score, higher K^{trans} of any brain area did not relate to worse MMSE or cognitive scores. However, higher K^{trans} related to greater disease severity, as shown by moderate positive correlations between K^{trans} in the cerebral cortex or parietal lobe and plasma $A\beta_{1-42}/A\beta_{1-40}$ concentrations ratio. When including a higher number of participants (including healthy volunteers and patients with AD), weak positive correlations were found between K^{trans} in the parietal or occipital lobe and clinical dementia rating score. A strong increase in Qalb was also reported in patients diagnosed with dementia with Lewy bodies compared to healthy volunteers [88]. Interestingly, higher Qalb was associated with greater disease severity, as shown by a moderate negative correlation between Qalb and $A\beta_{1-42}$ concentration in the CSF, while no correlations were found between Qalb and Tau or phosphorylated Tau [189]. Overall, these studies suggest that increases in BBB leakage rate or Qalb relate to greater disease severity in patients with dementia with Lewy bodies.

Rare neurodegenerative diseases

Amyotrophic lateral sclerosis

Qalb and blood proteins in the CSF were reported to be increased in patients with ALS compared to age- and/or sex-matched controls [190–192]. Elevated Qalb was observed in 10–39% of patients with ALS [193–197]. Qalb was higher in males than in females [193, 195] and more frequently elevated in patients with limb onset [195, 197]. No further increase of Qalb was observed in patients with mutation in the *SOD1* gene or a pathological hexanucleotide expansion in the *C9orf72* gene compared to sporadic patients [194]. Several studies have shown that elevation in Qalb was related to an increased mortality risk in this patient population, using Cox regression analyses that allow to determine the influence of Qalb on survival time [191, 193, 194, 196]; two of them showed that this Qalb-associated increased mortality risk was mainly evident in males [193, 194]. Using the same type of analysis, elevated IgG levels in the CSF also related to an increased mortality risk [190, 191]. In addition, high levels of Qalb or CSF proteins were found to be poor prognostic indicators for patients with spinal pathology [196]. Weak positive correlations between Qalb and disease severity or clinical disability were also reported by several independent groups [193, 197]. Altogether, these prospective studies suggest that elevated

Qalb in patients with ALS relates to greater disease severity, disability, and poor prognosis.

Cerebral adrenoleukodystrophy

Adrenoleukodystrophy is a rare X-linked peroxisomal metabolic disorder caused by *ABCD1* mutation preventing the degradation of very long chain fatty acids that accumulate within tissues, and which causes a severe demyelination of the brain WM. Allogeneic hematopoietic stem cell transplantation represents the standard of care to halt disease progression and improve overall survival in patients with early-stage cerebral adrenoleukodystrophy [198].

In a cohort of 66 males (8.3 [4.4–47.1] years old), Gd extravasation into the brain was resolved by 30, 60, 100, 180 and 365 days after intravenous (i.v.) perfusion of allogeneic hematopoietic stem cell transplants for 43%, 77%, 90%, 94% and 98% of patients respectively [115]. To evaluate the status of the graft, the number of neutrophils was measured in the blood of these patients (i.e., a sustained drop in the number of neutrophils relates to graft failure). Interestingly, neutrophil recovery was accelerated in patients with Gd resolution compared to patients without Gd resolution. Furthermore, patients with faster neutrophil recovery were more likely to show Gd resolution into the brain than those engrafting more slowly. Higher CD3 or CD15 donor chimerism, another strong positive prognostic indicator of graft success, was associated with greater Gd resolution, independently of donor sources. In a separate cohort of 20 patients with cerebral adrenoleukodystrophy, primary or secondary engraftment failure was associated with a decreased number of patients presenting Gd resolution at 30 and 60 post-transplant compared to the cohort of patients mentioned above with successful engrafting (12.5% and 7.7% of patients versus 43% and 77% of patients, respectively) [115]. In a small cohort of 6 boys (9 [6–12] years old) with advanced cerebral adrenoleukodystrophy and not eligible for transplantation, i.v. administration of bevacizumab (an antibody targeting vascular endothelial growth factor) every two weeks also reduced Gd enhancement surrounding WM lesions, but did not halt disease progression [114]. Overall, these studies indicate that the resolution of BBB leakage may relate to hematopoietic stem cell transplantation halting disease progression and improving overall survival in patients with early-stage cerebral adrenoleukodystrophy.

Huntington's disease

In a small cohort of 7 HD patients (with heterogeneous disease duration and disabilities), a study suggested trends towards increases in K^{trans} of Gd-DTPA into the caudate and the putamen compared to sex-matched healthy volunteers, and corresponding positive correlations with mutant huntingtin burden score [16]. More particularly, a strong positive correlation was identified between K^{trans} in the right caudate and mutant huntingtin burden score, despite the low number of patients enrolled in this study. The increased BBB leakage rate found in these patients corroborate postmortem detections of fibrinogen deposits and decreased levels of TJ proteins in the putamen and spinal cord of individuals with HD (Supplementary Table 1) [16, 124].

Multiple system atrophy

A prospective clinical study recently reported a 29% increase in Qalb and a 69% increase in K^{trans} of gadobutrol into the periventricular WM of patients with multiple system atrophy (mainly composed of cerebellar C type, and some parkinsonian type) compared to age-matched healthy volunteers [122]. Subgroup analyses revealed that both parameters were higher at advanced disease stage (≥ 3 years) than at earlier stages. The authors of this study identified strong positive correlations between Qalb or K^{trans} and clinical disability, as defined by the unified multiple system atrophy rating scale. Furthermore, K^{trans} was strongly and positively correlated with the volume of WM hyperintensities in these patients.

Neurovascular diseases

Hemorrhagic stroke

Several studies have shown an increased BBB leakage rate of Gd-based contrast agents or permeability-surface area product of iodinated contrast agents (using computed tomographic perfusion) in the hematoma and perihematomal region in patients with hemorrhagic stroke compared to healthy volunteers [45–49]. An increased extravasation of Gd-DTPA into the brain was found in patients with aneurysmal subarachnoid hemorrhage compared to healthy controls as early as 24 h and for up to at least 6–12 months post-injury [47]. In this patient cohort, BBB disruption was greater in patients with progressive disease course (i.e., decreased healthy brain tissue between initial and last magnetic resonance scans). Interestingly, early and persistent BBB damage was associated with poor long-term clinical outcome. Similarly, K^{trans} of Dotarem was increased into the perihematomal region of the ipsilateral hemisphere of patients with acute supratentorial intracerebral hemorrhage compared to the contralateral hemisphere [45]. Higher K^{trans} in the contralateral hemisphere (but not in the perihematomal region) was associated with poor clinical outcome at 90 days post-injury assessed by the modified rankin scale (mRS) score. Higher K^{trans} of Gd-DTPA into the perihematomal region of the ipsilateral hemisphere of patients with acute intracerebral hemorrhage compared to the contralateral hemisphere was associated with larger edema volume at one-day and one-week post-injury [49]. Using a different

method to evaluate BBB disruption (i.e., computed tomographic perfusion), contradictory studies have reported either positive [46] or no [48] correlations between increases in perihematomal BBB disruption and larger edema volume. A two-fold increase in the peripheral levels of occludin was observed in patients with intracerebral hemorrhage compared to age- and sex-matched healthy volunteers, and correlated with larger perihematomal edema [199]. Overall, these studies imply that elevated BBB leakage rate, or increased peripheral levels of occludin, relate to greater disease severity and disability in patients with hemorrhagic stroke.

Ischemic stroke

A meta-analysis unveiled an increased BBB permeability using neuroimaging techniques in patients with ischemic stroke, from the hyperacute (≤ 6 h post-symptoms) to the chronic (≥ 30 days post-symptoms) phase [51]. Higher BBB leakage rate was associated with hemorrhagic transformation in the hyperacute phase and with greater functional outcome in the subacute phase. The authors acknowledged that most of the studies did not meet criteria to be included in the meta-analysis and that all of them separately reported that higher BBB permeability was associated with poor neurological outcome regardless of phase.

A 40% increase in occludin serum levels was associated with hemorrhagic transformation in patients with ischemic stroke [200]. This risk factor was independent of the poor neurological outcome in these patients, assessed by the NIH stroke scale. A two-fold increase in serum levels of occludin was also observed in patients with acute ischemic stroke enduring hemorrhagic transformations after recanalization compared to age- and sex-matched patients with ischemic stroke who did not [201]. Interestingly, combination of peripheral occludin levels and clinical risk factors improved the accuracy of predicting hemorrhagic transformation in patients with ischemic stroke after recanalization. Increases in serum levels of occludin and claudin-5/ZO-1 ratio were evidenced in patients with acute ischemic stroke who experienced clinical deterioration caused by hemorrhagic transformation compared to age- and sex-matched patients who did not [202]. Furthermore, higher serum levels of claudin-5 within 3 h following the onset of stroke symptoms were associated with clinical deterioration caused by hemorrhagic transformation. Blood levels of occludin within the first 24 h following the appearance of stroke symptoms were increased in patients with non-lacunar stroke (compared to those with lacunar stroke), a subtype of stroke related to worse functional outcome [203]. However, there were no associations between levels of TJ proteins in the blood (claudin-5 and occludin) and the neurological status assessed by NIH stroke scale and mRS scores at 24 h following the manifestation of symptoms. Evaluation of NIH stroke scale, combined to a measure of TJ-associated proteins in the serum, was also proposed to distinguish stroke patients from patients who exhibit functional neurological disorders, migraine or seizures that mimic stroke [204].

A recent study revealed that serum levels of occludin were significantly reduced in patients with ischemic stroke treated with thrombolysis and normobaric hyperoxia compared to patients treated with thrombolysis alone at 1 and 7 days after the appearance of stroke symptoms [50]. Accordingly, a reduction of the cerebral extravasation of an iodinated contrast agent was observed in patients who received normobaric hyperoxia compared to those who did not. Interestingly, patients who experienced BBB permeability resolution exhibited lower peripheral levels of occludin at one day post-symptoms. Furthermore, lower peripheral levels of occludin at 7 days after the manifestation of stroke symptoms were associated with a better prognosis assessed by the mRS score 83 days later.

Overall, these studies sustain that elevated BBB leakage rate, or increased peripheral levels of TJ proteins, relate to greater disease severity (hemorrhagic transformation) and disability in patients with ischemic stroke.

Cerebral small vessel disease

Patients with cerebral small vessel disease, whose cognitive function had declined over a 2-year period using the MMSE score, had a higher baseline BBB leakage volume and K_i of gadobutrol into the normal-appearing WM and cortical GM [41]. Increased decline in executive function in this cohort was also correlated with higher baseline leakage volume in the normal-appearing WM and cortical GM, and higher baseline K_i in the cortical GM. Another group has shown that higher BBB leakage volume and K_i of gadobutrol into WM hyperintensities were associated with larger WM hyperintensities volume in patients with cerebral small vessel disease, but not in healthy volunteers [42]. No correlation was found between the vascular volume or K_i and cognitive functions in this study. An increase in K^{trans} of gadoterate meglumine into the brain of at least 40% was also reported in patients with either sporadic or *HTRA1*-related cerebral small vessel disease compared to healthy volunteers, whereas it was unchanged for patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL) [37]. Furthermore, K^{trans} was increased in normal-appearing WM of sporadic patients. No correlation was found between K^{trans} and clinical disability using the mRS score. However, higher K^{trans} in the deep GM was correlated with poorer global cognition in sporadic and *HTRA1*-related cerebral small vessel disease. In patients with the

genetic form, higher K^{trans} was also positively correlated with an increased number of enlarged perivascular space in the basal ganglia and centrum semiovale. A prospective study has further assessed colocalization of BBB leakage of gadobutrol hotspots and lesions (MRI) in patients with cerebral small vessel disease including symptomatic sporadic patients or with a diagnosis of CADASIL [40]. They found that BBB disruption was particularly present at lacune edges (63%), WM hyperintensities core and edges (~50%), and microbleed edges (36%). A global decrease in cerebrovascular reactivity in WM hyperintensities core and edges was associated with the presence and number of hotspots at lacune edges which according to the authors, predicts tissue destruction and lacune formation. Overall, these studies demonstrate that elevated BBB leakage rate relates to greater lesion burden and disability in diverse subpopulations of patients with cerebral small vessel disease.

Neurotraumas

Traumatic brain injury

K^{trans} of gadobenate dimeglumine was increased into the lesional, perilesional and non-lesional regions in patients with traumatic brain injury during the subacute phase (23 days post-injury on average) compared to age- and sex-matched healthy controls [74]. No resolution of the contrast agent was observed between 23 and 204 days post-injury. Higher K^{trans} related to poor satisfaction with life scale scores during the subacute phase. The relevance of BBB disruption to long-term outcomes after traumatic brain injury is further supported by histological detection of blood elements (fibrinogen and IgG) into the brain parenchyma years to decades after the injury [80].

Serum levels of claudin-5 and occludin were increased in military personnel subjected to repetitive subconcussive blast overpressure exposure induced by heavy weapon training compared to age- and sex-matched healthy controls [205]. Experienced instructors showed even higher levels of peripheral TJ proteins than their trainees. A 16% increase in occludin was also observed in the plasma of patients with mild neurotraumas compared to age- and sex-matched healthy controls [206], whereas no changes in claudin-5 were found in patients or football players with mild traumas [206, 207]. However, higher serum levels of claudin-5 correlated with psychological symptoms in patients with traumatic brain injury [208].

Autoimmune diseases

Multiple sclerosis

Gadolinium enhancement is a standard criterion for diagnostic of MS, and is detected in acute inflammatory lesions of the WM and also in normal-appearing WM [60, 62, 68]. A prospective study evaluated if BBB leakage resolution was a predictor of a positive treatment response to alemtuzumab (an anti-CD42 monoclonal antibody; 1 course per year) in a cohort of patients with relapsing-remitting MS over a 2-year period [61]. Approximatively half of the patients in this study had a good treatment response, as defined by the absence of a disease activity-3 (NEDA-3) status, determined from T2-MRI lesion activity, expanded disability status scale (EDSS) score and the number of relapses, at 2 years after the initiation of treatment. The good treatment response group had a more prominent decrease in K_i of gadobutrol into the normal-appearing WM and GM between baseline and at 6- and 12-month follow-ups, than that of the poor treatment response group, despite similar EDSS scores among groups at baseline. Furthermore, ROC curve analysis of the K_i change in normal-appearing WM between baseline and 12 months post-treatment was a highly specific predictor of the loss of NEDA-3 status at 2 years post-treatment. Importantly, this study shows that BBB repair relates to clinical recovery. As suggested by the authors, the evolution of BBB leakage over the course of the disease, whether positive or negative, could be used as a surveillance readout to monitor treatment response. Such indicators could potentially guide neurologists in deciding whether to discontinue or continue a treatment.

Autoimmune encephalitis

An increase in K^{trans} of gadobutrol into several brain regions, particularly into the parahippocampal gyrus, was recently observed in patients with autoimmune encephalitis compared to healthy elderly volunteers [69]. This observation supports findings showing that Qalb is elevated in about one third of patients with autoimmune encephalitis [209–211]. A recent study also compared K^{trans} of gadobutrol in various brain areas in patients with autoimmune encephalitis at admission, with either a poor or a good response to their respective/individualized treatments at the last follow-up visit using the mRS score [69]. The poor treatment response group presented higher K^{trans} in the cerebellar cortex and the left postcentral gyrus than the good treatment response group.

Patients with neuronal surface antibody-mediated autoimmune encephalitis who presented an elevated Qalb were twice more likely to have brain lesions at admission, particularly in the basal ganglia, brainstem, frontal and parietal lobes, compared to those with a physiological Qalb [209]. At admission, the percentage of prodromal symptoms, the number of white blood cells in the CSF, as well as the concentrations of IgG and albumin in the CSF were significantly increased in patients presenting an elevated Qalb. Furthermore, elevated Qalb at admission was associated with greater disability at discharge or last follow-up visit in patients using mRS and EDSS scores. Patients with anti-N-methyl-D-aspartate

receptor (NMDAR) encephalitis whose Qalb was elevated were more prone to a decreased consciousness and admission to an intensive care unit than those with physiological Qalb [211]. The neutrophil-to-lymphocyte ratio in the blood and the intrathecal IgG synthesis were also significantly increased in these patients. Similarly, in a larger cohort of patients, elevated Qalb at admission was associated with greater disability using the mRS score and the clinical assessment scale for autoimmune encephalitis at the follow-up visit 30 days later [212]. The concentrations of IgG and the intrathecal IgG synthesis in the CSF were significantly increased in these patients. Conversely, no difference in MRI and electroencephalogram abnormalities or the neutrophil-to-lymphocyte ratio in the blood was found in this study.

Overall, these studies indicate that elevated BBB leakage rate or Qalb relates to greater disease severity, disability, and poor prognosis in patients with autoimmune encephalitis.

Neuromyelitis optica spectrum disorder

Qalb was found to be more elevated in patients with neuromyelitis optica compared to patients with MS [213], and increases in Qalb relates to greater disease severity and disability in these patients [78, 214, 215]. Indeed, patients with an elevated Qalb were twice more likely to have brain lesions [78]. Furthermore, positive correlations between higher Qalb and greater clinical disability using EDSS were found in patients with neuromyelitis optica [78, 214, 215].

Psychiatric disorders

Bipolar disorder

An extensive and diffuse BBB leakage of gadobenate dimeglumine into the brain was reported in 28% of patients with bipolar disorder [137]. These individuals developed more severe depression, anxiety, and socio-occupational functioning disability than patients with a preserved BBB integrity. Furthermore, BBB disruption aggravated the occurrence and severity of manic and depressive episodes in patients with bipolar disorder.

Strong positive correlations between age at onset and claudin-5 protein levels were found in the hippocampus (GM and WM) and orbitofrontal cortex (WM) of individuals with bipolar disorder [216]. In addition, a strong negative correlation was found between disease duration and claudin-5 levels in the orbitofrontal cortex (GM and WM). Conversely, no correlation was found between claudin-5 protein levels in the hippocampal GM and the age of onset or disease duration in patients with major depressive disorder.

Overall, these studies show that elevated BBB leakage rate or decreased cerebral claudin-5 levels relates to greater disease severity, disability and psychiatric morbidity in patients with bipolar disorder.

Schizophrenia

A higher K^{trans} to gadopentetate meglumine was observed into the thalamus bilaterally, notably the medial and lateral pulvinar nuclei, of patients with schizophrenia compared to age- and sex-matched healthy volunteers [133]. Higher K^{trans} was strongly correlated with reduced brain and thalamus volumes, longer disease duration and greater symptom severity using various scales assessing general psychopathology or negative and positive symptoms. Higher IgA responses to claudin-5 and occludin in blood sera were observed in patients with deficit schizophrenia, who exhibit psychosis, hostility, excitation, mannerism and negative symptoms, as well as impairments in semantic and episodic memory, compared to age-matched cohorts of healthy volunteers and patients with nondeficit schizophrenia [217].

Levels of ZO-1 were increased by three-fold in the serum of patients with schizophrenia compared to age- and sex-matched healthy volunteers without a medical psychiatric history [218]. A moderate positive correlation was established between ZO-1 levels and positive symptoms assessed by the positive and negative syndrome scale score. However, no correlations were found with disease duration, negative symptoms or general psychopathy.

Increases in K^{trans} into the brain and ZO-1 levels in the blood in schizophrenic patients reported above corroborate studies showing an elevation in Qalb in 17–34% of patients with first-episode psychosis [219, 220] and in 50% of patients with multiple-episode psychosis [219].

A moderate negative correlation between age at onset and claudin-5 protein levels in postmortem brain samples of people with schizophrenia was found in the GM of the orbitofrontal cortex, suggesting that loss of TJ proteins might influence disease severity [216]. Despite a decrease in claudin-5 protein levels in the hippocampal GM in postmortem samples from schizophrenic patients versus controls, no correlation was found with age of onset or disease duration.

Overall, these studies suggest that elevated BBB leakage rate, increased peripheral levels of ZO-1, or decreased cerebral levels of claudin-5, relate to greater disease severity, disability, and psychiatric morbidity in patients with schizophrenia.

Therapeutic agents to repair BBB/BSCB alterations and dysfunctions: mechanisms of action and stage of development

The causality dilemma: when and how to repair compromised brain barriers?

The exhaustive literature survey presented in this review provides valuable insights into how barrier integrity status (i.e., altered or repaired) influences pathological and functional outcomes in diverse diseases and injuries affecting the CNS. Loss of TJ integrity or elevated brain barrier leakage are associated with greater disease severity, worse clinical disability, and/or poor diagnosis in several neurological disorders. They include – so far – neurodegenerative diseases (AD, ALS, dementia with Lewy bodies, HD, multiple system atrophy), neurovascular diseases (cerebral small vessel disease, stroke), neuropsychiatric disorders (bipolar disorder, schizophrenia), neurotraumas (traumatic brain injury), autoimmune diseases (autoimmune encephalitis, MS, neuromyelitis optica spectrum disorder) and epilepsy. Furthermore, advanced age is a frequent risk factor in neurodegenerative diseases, and elevated BBB leakage rate of contrast agents into regions critical for cognitive functions, as well as correlations with cognitive decline, were reported in cohorts of healthy elderly volunteers [42, 183] and people with mild cognitive impairments [184]. Importantly, accumulating evidence indicate that measures of improved barrier function correlated with a favorable clinical outcome in patients with autoimmune encephalitis, cerebral adrenoleukodystrophy, ischemic stroke and MS. Furthermore, recovery of BBB integrity at early stages of cerebral adrenoleukodystrophy may contribute to the efficacy of successful hematopoietic stem cell transplantations that halt disease progression [115, 198]. Indeed, restoring BBB integrity with another therapeutic approach and at a more advanced disease stage did not alter disease course [114].

In this context, the central question of *when* and *how* to repair compromised brain barriers is of the essence. Longitudinal studies evaluating the evolution of brain barriers disruption across the spectrum of neurological disorders would thus provide critical directions for the design of clinical trials evaluating the efficacy of therapeutic agents in a disease-specific manner.

Overview of the therapeutic landscape

Targeting BBB and BSCB alterations/dysfunctions is an emerging therapeutic avenue with the potential to mitigate disease progression, and thus serve as a disease-modifying strategy to a wide range of neurological disorders. Most ongoing efforts by biotechnology and pharmaceutical companies can be categorized into three approaches (Fig. 4): **(1)** restoring normal levels of TJ proteins in order to mitigate the entry of circulating factors and blood cells, **(2)** exogenously supplying extracellular matrix-derived biopolymers to rescue gaps in the endothelium triggered by the loss of TJ, or **(3)** reducing immune cell trafficking across the BBB and BSCB. We will additionally discuss a drug candidate that blocks blood-derived fibrin present in the brain parenchyma to reduce neuroinflammatory processes.

Based on the retrieval strategy presented in the Supplementary information, a total of 11 therapeutic agents have been identified, and are currently being developed by 11 active biotechnology and pharmaceuticals companies to restore brain barriers integrity in neurodegenerative diseases and CNS injuries (Table 1; Figs. 4, 5 and 6). There are four candidates in phase 1 evaluation in healthy volunteers, and four companies have tested / are testing their drug candidates in diseased patients. More specifically, they include one phase 1 trial in human T-cell leukemia virus type 1-associated myelopathy (HAM), one phase 1/2 trial in AD, and four phase 2 clinical trials in ALS, HD, ischemic stroke and spinal cord injury.

The common features of therapeutic agents targeting BBB and BSCB alterations and dysfunctions, including drug modalities (mAb, small molecule, peptide or biopolymer) and development stages, administration routes, and number of patients with neurological disorders enrolled in clinical trials, are presented in Fig. 6. Notably, mAbs and small molecules represent 80% of the therapeutic candidates discussed here, and they include Pepinemab, MT3921, THN391, LYS241 and NVQXXX (mAbs), and OV888, SNP318, NRL1049 and Axitinib (small molecules). The most advanced drugs in the pipeline have reached clinical stages, either phase 1 (OV888, SNP318, NRL1049 and THN391), or phase 2 (Pepinemab, MT3921, NX210c and OTR4132). Among these, ~50% are delivered i.v., while the three small molecules currently in phase 1 are administered orally. For agents that have been launched in the clinical realm in patients with neurological disorders, the three trials with the highest number of expected participants include Pepinemab, NX210c, and MT3921. More specifically, Pepinemab enrolled 132 placebo- and 133 drug-treated patients with HD [221], NX210c is recruiting 20 placebo- and 60 drug-treated patients with ALS (NCT06365216), and MT3921 enrolled 24 placebo- and 48 drug-treated patients with spinal cord injury (NCT04683848).

Each of these therapeutic agents are presented in details in the sections below, and introduced in the order of development stage, from the most advanced clinical trials to the initial stages of preclinical testing. Key characteristics of these drug candidates and details on clinical trials are summarized in Tables 1 and 2, respectively.

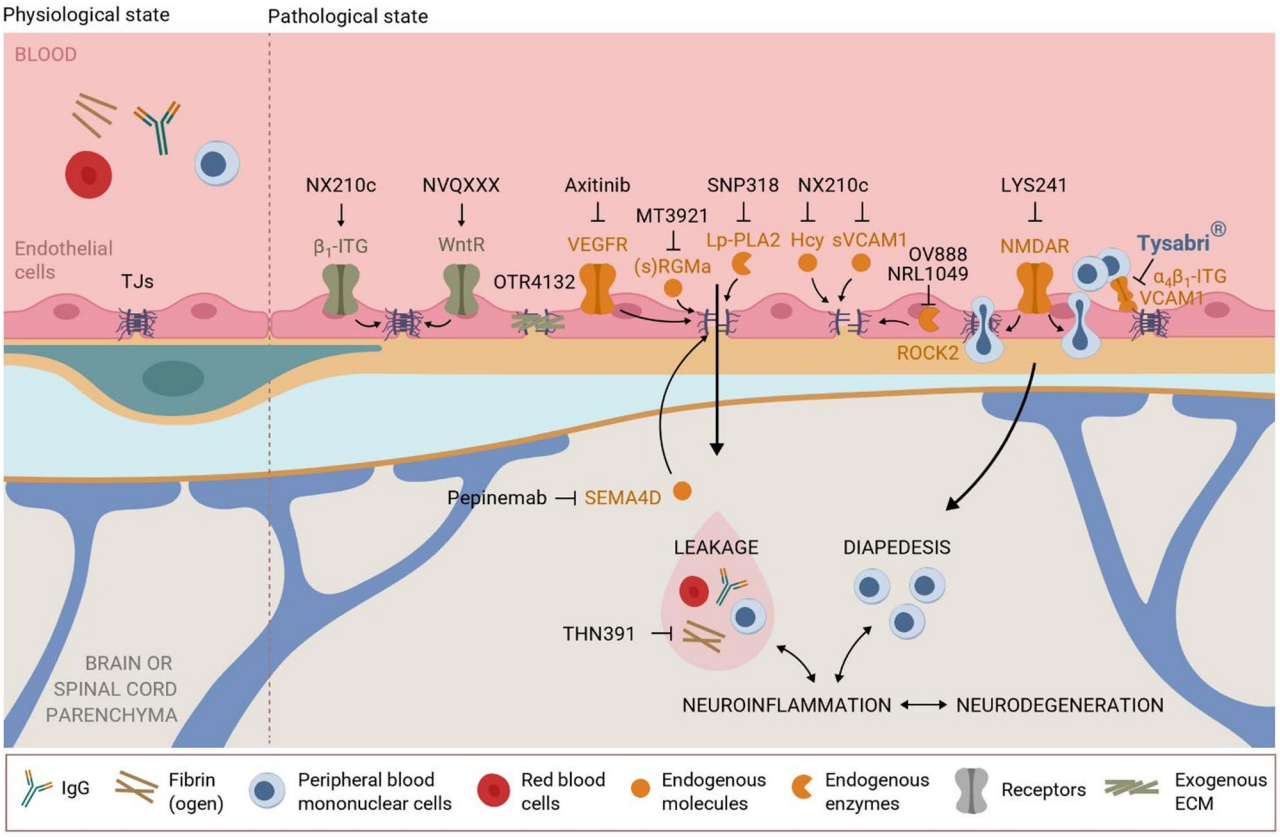

Fig. 4 High-level mechanism of action landscape of therapeutic agents targeting BBB and BSCB alterations and dysfunctions as a treatment for neurological disorders. The left panel represents the barrier interface in physiological condition, whereas the right panel represents the barrier interface in neurological disorders with barrier alterations. Several dysfunctions of brain barriers occur in neurological disorders; herein, we define dysfunctions by the leakage of blood elements and red blood cells into the parenchyma, and increased/uncontrolled trafficking of immune cells across the BBB or BSCB. Strategies to reduce blood-to-brain leakage consist in: **(1)** restoring normal levels of TJ proteins by promoting their expression through the activation of specific receptors (β_1-integrin or WntR; indicated in green), or by inhibiting/blocking receptors or intra/extracellular molecules or enzymes known to degrade TJs (VEGFR, SEMA4D, LpPLA2, ROCK2, sVCAM1, Hcy and (s)RGMa; indicated in orange), or **(2)** by adding an exogenous synthetic biopolymer to "replace" TJs. Strategies to reduce blood-to-brain immune cell entry consist in: **(3)** blocking the adhesion of immune cells to endothelial cells by blocking their interaction through $\alpha_4\beta_1$-integrin with VCAM1 present at the cell surface (indicated in orange), or **(4)** by blocking the interaction of circulating tPA with GluN1-NMDAR present at the surface of endothelial cells to reduce the extravasation of immune cells across the BBB (indicated in orange). An alternative or complementary strategy to BBB repair aims at blocking one blood element (fibrin) present in the parenchyma to reduce neuroinflammation and neurodegeneration. Tysabri® (i.e., Natalizumab) was added to this figure as the standard of care for reducing immune cell migration across the BBB in patients with RRMS. *ECM: extracellular matrix; GluN1-NMDAR: GluN1 subunit of NMDAR; Hcy: homocysteine; IgG: immunoglobulin G; ITG: integrin; Lp-PLA2: lipoprotein-associated phospholipase A2; NMDAR: N-methyl-D-aspartate receptor; (s)RGMa: (soluble) repulsive guidance molecule a; ROCK2: Rho-associated coiled-coil containing protein kinase 2; RRMS: relapsing-remitting multiple sclerosis; SEMA4D: semaphorin 4D; sVCAM1: soluble VCAM1; TJ: tight junction; tPA: tissue plasminogen activator; VCAM1: vascular cell adhesion molecule 1; VEGFR: vascular endothelial growth factor receptor; WntR: Wnt receptor; $\alpha_4\beta_1$-ITG: $\alpha_4\beta_1$ subunit of ITG; β_1-ITG: β_1 subunit of ITG*

Pepinemab

Pepinemab is a drug candidate developed by Vaccinex Inc (Rochester (NY), USA) for the treatment of AD and HD (https://www.vaccinex.com/). Pepinemab (formerly known as VX15/2503) is a humanized IgG4 monoclonal blocking antibody targeting semaphorin 4D. Semaphorin 4D binds to plexin-1 receptors to trigger collapse of the actin cytoskeleton in cells and leads to the loss of homeostatic functions of glial cells, particularly astrocytes, in the brain and of dendritic cells in the immune system [222]. Accordingly, Pepinemab [223] and its parental mouse antibody (MAb67-2) [223–225] were shown to promote remyelination and neuroprotection, reduce astrogliosis and microgliosis, and restore BBB integrity. Additional mechanistic investigations were carried out using a human 3D BBB-on-chip model consisting of endothelial cells and astrocytes. Pepinemab was found to alleviate recombinant semaphorin 4D-induced decrease in transendothelial electrical resistance (TEER), and partially rescue claudin-5 protein levels in chips exposed to TNF-α [223]. Furthermore, MAb67-2 reduced disease progression and promoted functional recovery in animal models of MS [223], HD [225] and Rett Syndrome [224]. MS-related investigations, carried out in an experimental

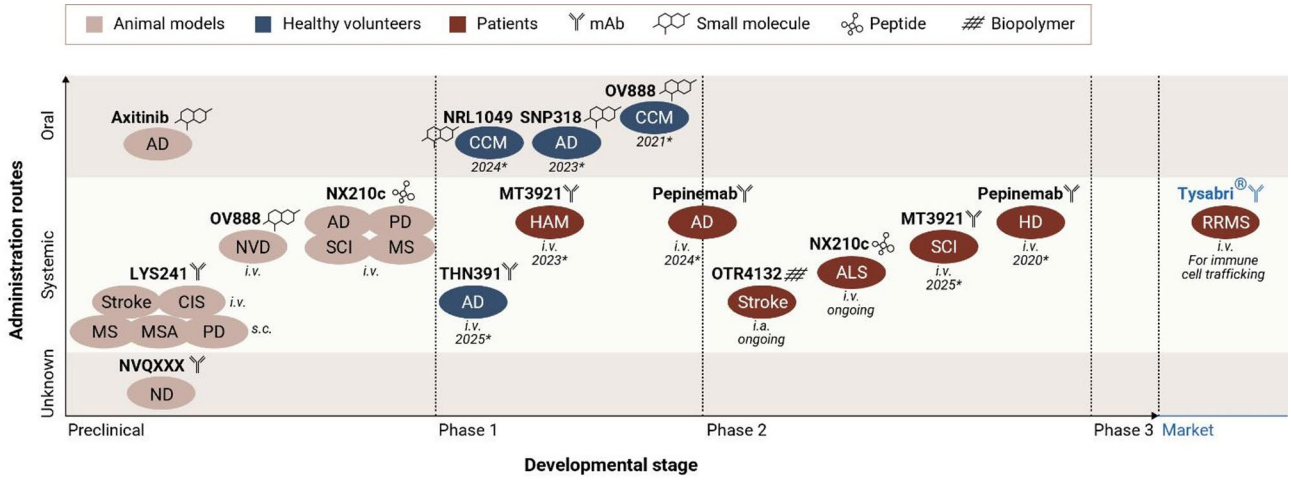

Fig. 5 Drug development pipeline of therapeutic agents targeting BBB and BSCB dysfunctions for the treatment of neurological disorders. This figure depicts drug candidates in preclinical and clinical drug development for the treatment of BBB and BSCB dysfunctions (from companies' pipeline online, and clinicaltrials.gov, accessed May 3rd, 2025). The administration route, the development stage, and the therapeutic modality are indicated whenever known for each drug candidate (name underlined in bold). Systemic administration routes include i.v., i.a., and s.c. For any agent at early developmental stage, we have reported the pathology and administration mode envisioned by the company for clinical trials in patients. Clinical trials are indicated as ongoing or completed (year of completion indicated). Tysabri® (i.e., Natalizumab) was added to this comprehensive SWOT analysis as the standard of care for reducing immune cell migration across the BBB in patients with RRMS. **clinical trial not disclosing brain barriers integrity biomarkers in the summary published on clinicaltrials.gov; CCM: cerebral cavernous malformation; CIS: clinically isolated syndrome; HAM: human T-cell leukemia virus type 1-associated myelopathy; i.a.: intraarterial; i.v.: intravenous; mAb: monoclonal antibody; MSA: multiple system atrophy; ND: neurological diseases; NVD: neurovascular diseases; RRMS: relapsing-remitting multiple sclerosis; s.c.: subcutaneous; SCI: spinal cord injury; SWOT: strengths, weaknesses, opportunities and threats*

autoimmune encephalomyelitis (EAE) mouse model, showed that MAb67-2 reduced fibrinogen extravasation into the spinal cord [223].

Pepinemab was well-tolerated with a favorable safety profile in clinical trials in different neurological conditions. A double-blind, randomized and placebo-controlled phase 1a (NCT01764737) evaluated the safety, tolerability and pharmacokinetics of single ascending dose of Pepinemab (i.v. at 1–20 mg/kg) in patients with MS in 2014 (enrollment of 20 patients) [226]. The maximum concentration (C_{max}) and plasmatic half-life were increased in a dose-dependent manner. The plasmatic half-life was 20 days when given at 20 mg/kg. Cellular saturation with the antibody persisted for more than 155 days. Most adverse events were mild to moderate, and included urinary tract infection, contusion, muscular weakness, insomnia and headache. One patient had a grade 3 event of increased Gd-positive lesions that were possibly related to the drug. A double-blind, randomized and placebo-controlled phase 2 (NCT02481674, "SIGNAL") evaluated the safety, tolerability, pharmacokinetic and efficacy of Pepinemab in early manifest and late prodromal HD patients in 2020 (enrollment of 265 patients) [221, 227]. Pepinemab was administered by i.v. infusions at 20 mg/kg every 4 weeks for up to 18 months of treatment [221]. A pharmacokinetic study demonstrated that Pepinemab was detected at 348 $ng.mL^{-1}$ in the CSF and that its average CSF/serum concentration ratio was of 0.38%. Most adverse events were mild to moderate, and serious adverse events slightly more frequent in Pepinemab-treated HD patients than vehicle-treated patients (19% and 15%, respectively). Common adverse events included headache, nasopharyngitis, fall, nausea and vomiting. Although the trial did not meet its co-primary efficacy endpoints, Pepinemab significantly improved motor functional outcome from baseline to 17 months after treatment initiation compared to the placebo group. A double-blind, randomized and placebo-controlled phase 1b/2 (NCT04381468, "SIGNAL-AD") further recently assessed the safety of Pepinemab and its effect on brain metabolic activity in AD patients for up to 8 months (enrollment of 50 patients; completed in June 2024).

MT3921

MT3921 is a drug candidate developed by Mitsubishi Tanabe Pharma (Osaka, Japan) for the treatment of HAM and spinal cord injury (https://www.mt-pharma.co.jp/e/). MT3921 (also known as unasnemab) is a humanized IgG1 monoclonal antibody targeting repulsive guidance molecule-a (RGMa). RGMa is a glycosylphosphatidylinositol-transmembrane protein that also exists in a soluble form, and both impede neurite growth by binding to neogenin receptors present at the surface of neurons [228]. In addition, when expressed by endothelial cells, RGMa impairs barrier integrity by reducing claudin-5 and ZO-1 protein levels [229]. The protein is also expressed by bone marrow-derived dendritic cells and

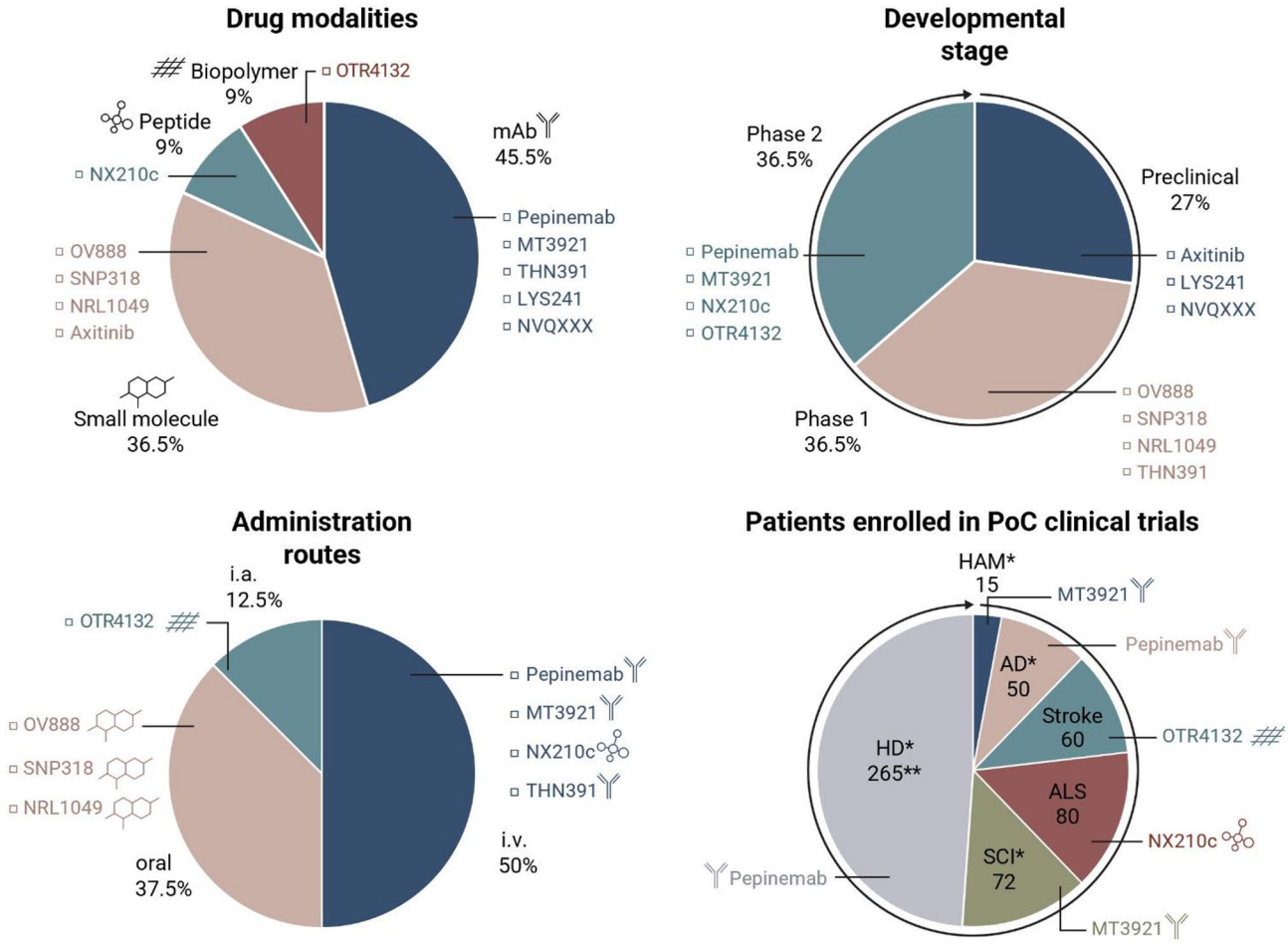

Fig. 6 Key features of therapeutic agents designed at repairing BBB and BSCB integrity. The upper panels depict two pie charts showing the respective proportions of each modality and development stage of all drug candidates currently being developed. On the lower panels, the two pie charts show the respective proportions of each administration route for agents at clinical stage in healthy volunteers or in patients, and of the number of patients with neurological disorders being /planned to be enrolled in clinical trials for evaluation of brain barriers therapeutic candidates. **clinical trial completed; **final number of patients enrolled; PoC: proof of concept*

binds to neogenin receptors at the surface CD4-positive T cells, which increases adhesion of T cells to intracellular adhesion molecule-1 at the surface of endothelial cells [230]. In this context, MT3921 [156, 231, 232] and its parental rat antibody [230, 232] were shown to promote neurogenesis, neurite growth, neuroregeneration and remyelination, and to restore BSCB integrity. Treatment with these anti-RGMa antibodies was associated with a reduction of disease progression and improved functional recovery in animal models of EAE [230, 232], neuromyelitis optica [156], spinal cord injury [233] and vascular dementia [231].

The effect of MT3921 on BSCB integrity was first evaluated in mice subjected to EAE, followed by an intraspinal injection of proinflammatory cytokines (TNF-α and IFN-γ) 3 weeks later [232]. Intravenous injections of MT3921 (10 mg/kg) twice a week reduced Gd extravasation into the spinal cord in 5 days, and reduced neurological deficits within 12 days. A microarray analysis of the spinal cord tissue collected 5 days after initiating the treatment showed that several genes, expressed at the BSCB interface and upregulated with EAE, were reduced after exposure to MT3921. These markers include genes that trigger: **(1)** BBB dysfunction such as *Selp*, *Timp1* and *Spp1*, **(2)** extracellular matrix production such as *Col4a1*, *Col6a1*, and *Hspg2*, and **(3)** endothelial-to-mesenchymal transition such as *Col1a1*, *Snai2* and *Acta2*.

The effect of MT3921 on BBB integrity was also evaluated in rats subjected to neuromyelitis optica [156]. Prophylactic i.v. injection of MT3921 prevented the entry of aquaporin-4 antibodies into the CSF and parenchyma. MT3921 restored a physiological Qalb and may have reduced the infiltration of neutrophils and monocytes into the thoracic spinal cord, as suggested by a decreased number of myeloperoxidase-positive cells and a decrease of CXCL1 and CXCL2 mRNA levels. This may have triggered the reduction of astrogliosis observed in the acute phase. A decrease in IL-17 A and neurofilament light

Table 1 Key characteristics of therapeutic agents designed at repairing BBB and BSCB integrity. All drug candidates are indicated by name, modality, target, approach, administration route(s), indication(s) in neurological disorders, stage of development and the name of sponsor companies developing these drugs. They are sorted out from the most advanced stage of development to the earliest stage of development. For drug candidates in phase 1 clinical trials in healthy volunteers, the pathologies are those envisioned by the companies, when they submitted investigational brochures for clinical trial approval by regulatory authorities, and reported on clinicaltrials.gov. For drug candidates at early stages of development (discovery, optimization, preclinical), the pathologies and administration modes are those envisioned for clinical trials in the development plan, reported on company websites. THN391 represents an alternative or complementary drug candidate to BBB repair that aims at blocking one blood element (fibrin) present in the parenchyma (brown color). Tysabri® (i.e., Natalizumab) was added to this table as the standard of care for reducing immune cell migration across the BBB in patients with RRMS (blue color). **: clinical trial completed; CCM: cerebral cavernous malformation; CIS: clinically isolated syndrome; GluN1-NMDAR: GluN1 subunit of NMDAR; HAM: human T-cell leukemia virus type 1-associated myelopathy; HV: healthy volunteers; i.a.: intraarterial; i.v.: intravenous; ITG: integrin; Lp-PLA2: lipoprotein-associated phospholipase A2; mAb: monoclonal antibody; MSA: multiple system atrophy; N/A: not applicable; ND: neurological diseases; NMDAR: N-methyl-D-aspartate receptor; NVD: neurovascular diseases; RGMa: repulsive guidance molecule a; ROCK2: Rho-associated coiled-coil containing protein kinase 2; RRMS: relapsing-remitting multiple sclerosis; s.c.: subcutaneous; SCI: spinal cord injury; SEMA4D: semaphorin 4D; VEGFR: vascular endothelial growth factor receptor; WntR: Wnt receptor; $\alpha_4\beta_1$-ITG: $\alpha_4\beta_1$subunit of ITG; β_1-ITG: $\beta_1$subunit of ITG*

Drug	Modality	Target	Approach	Route	Indication	Stage	Company
Pepinemab	mAb	SEMA4D	barrier sealing	i.v.	HD AD	phase 2* phase 1/2*	Vaccinex Inc
MT3921	mAb	RGMa	barrier sealing	i.v.	SCI HAM	phase 2* phase 1*	Mitsubishi Tanabe Pharma
NX210c	peptide	β_1-ITG	barrier sealing	i.v.	ALS AD, PD, SCI, MS	phase 2 preclinical	Axoltis Pharma
OTR4132	biopolymer	N/A	barrier sealing	i.a.	Stroke	phase 2	OTR3 Science for Regeneration
OV888	small molecule	ROCK2	barrier sealing	oral i.v.	CCM NVD	phase 1* (HV) preclinical	Ovid Therapeutics Graviton BioScience
SNP318	small molecule	Lp-PLA2	barrier sealing	oral	AD	phase 1* (HV)	SciNeuro Pharmaceuticals
NRL1049	small molecule	ROCK2	barrier sealing	oral	CCM	phase 1* (HV)	Neurelis
Axtinib	small molecule	VEGFR	barrier sealing	oral	AD	preclinical	CAVA Healthcare Inc
LYS241	mAb	GluN1-NMDAR	immune cell trafficking	i.v. s.c.	Stroke, CIS MS, PD, MSA	preclinical	Lys Therapeutics
NVQXXX	mAb	WntR	barrier sealing	unknown	ND	preclinical	Neuvasq Biotechnologies
THN391	mAb	fibrin	fibrin-induced inflammation	i.v.	AD	phase 1* (HV)	Therini Bio
Tysabri®	mAb	$\alpha_4\beta_1$-ITG	immune cell trafficking	i.v.	RRMS	market	Biogen

chain (NfL) levels was also noticed in the CSF, suggesting anti-inflammatory and neuroprotective effects of MT3921. As a result, the anti-RGMa mAb restored neurological scores back to the levels of control animals.

A quadruple-blind, randomized and placebo-controlled phase 1 clinical trial (NCT05240612) assessed the safety, tolerability and pharmacokinetics of MT3921 delivered by i.v. injections to Japanese patients diagnosed with HAM (enrollment of 15 patients; completed in December 2023). A phase 2 clinical trial (NCT04683848) also evaluated the safety and efficacy of MT3921 in patients with acute cervical spinal cord injury (enrollment of 72 patients). This quadruple-blind, randomized and placebo-controlled trial investigated the effect of MT3921 injected i.v., with a scheduled follow-up at 6-month post-treatment, on the upper extremity motor score as the primary endpoint. Secondary endpoints explored spinal cord independence measurement III score, grated redefined assessment of strength, sensibility and prehension score, spinal cord ability ruler, and proportion of responders (i.e., subjects with cutoff number or greater increase in the upper extremity motor score compared to baseline). Results may be expected shortly, since the study was completed in April 2025.

NX210c

NX210c is a drug candidate developed by Axoltis Pharma (Lyon, France) for the treatment of neurological diseases characterized by BBB/BSCB impairments. The product is currently at the clinical stage of evaluation in ALS patients (phase 2), and at preclinical stages for AD, PD and spinal cord injury (https://www.axoltis.com/). In

Table 2 List of clinical trials with therapeutic agents targeting brain barriers dysfunctions. This table reports key details of interventional clinical trials with barrier repair agents (to be) evaluated for safety, tolerability and/or efficacy in healthy volunteers or in patients with neurological disorders. THN391 represents an alternative or complementary drug candidate to BBB repair that aims at blocking one blood element (fibrin) present in the parenchyma (brown color). *HAM: human T-cell leukemia virus type 1-associated myelopathy; HV: healthy volunteers; SCI: spinal cord injury*

Drug (sponsor)	Clinicaltrials.gov identifier (trial name)	Phase	Status	Population	Start date	End date
Pepinemab (Vaccinex Inc)	NCT02481674 (SIGNAL-HD)	phase 2	completed	Late prodromal & Early manifest HD	07/2015	08/2020
MT3921 (Mitsubishi Tanabe Pharma America Inc)	NCT04683848	phase 2	completed	Acute cervical SCI	08/2021	04/2025
NX210c (Axoltis Pharma)	NCT06365216 (SEALS)	phase 2	recruiting	ALS	10/2024	02/2026
OTR4132 (OTR3 Science for Regeneration)	NCT06700824 (MATRISS-II)	phase 2	not yet recruiting	Acute ischemic stroke	02/2025	03/2026
Pepinemab (Vaccinex Inc)	NCT04381468 (SIGNAL-AD)	phase 1/2	completed	Early AD	07/2021	06/2024
MT3921 (Mitsubishi Tanabe Pharma Corporation)	NCT05240612	phase 1	completed	HAM	05/2022	12/2023
OV888 (=GV101) (Ovid Therapeutics, Graviton BioScience)	NCT05068947	phase 1	completed	HV	09/2021	10/2021
SNP318 (SciNeuro Pharmaceuticals)	NCT05792163	phase 1	completed	HV	03/2023	11/2023
NRL1049 (Neurelis)	Not registered	phase 1	completed	HV	03/2023	2024
THN391 (Therini Bio)	Not registered	phase 1	completed	HV	05/2023	2025

addition, the company used a Quantitative System Pharmacology in silico modelling to predict potential effects of NX210c in virtual MS patients. NX210c is a 12-amino acid peptide analogue of the most conserved sequence of type 1 thrombospondin repeats. It promotes neuroprotection against glutamate-induced excitotoxicity [234], improves synaptic transmission in basal and hypoxic conditions [235, 236], and restores BBB integrity [237]. NX210c mediates its neuroprotective effects via integrins containing the β_1 subunit [234], a class of receptors implicated in synaptic transmission [238, 239] and BBB integrity maintenance [240–242]. NX210c has been shown to attenuate disease progression and promote functional recovery in animal models of AD [243], ischemic stroke [244], schizophrenia [235] and spinal cord injury [245]. The BBB-protective properties of NX210c include increased levels of claudin-5 and occludin in bEnd3 endothelial cell monolayers, which improved TEER and reduced BBB permeability to a 40-kDa FITC-dextran [237]. Similarly, NX210c increased TEER in human brain microvascular endothelial cell (HBMVEC) monolayers and tricultures with human astrocytes and pericytes. Furthermore, NX210c increased TEER and barrier integrity by reducing permeability of a 4-kDa FITC dextran tracer in a microfluidic-based model of the BBB, consisting of HBMVECs, human astrocytes, and pericytes. Finally, few systemic injections of NX210c (10 mg/kg) increased claudin-5 and occludin levels in the cortex and hippocampus of old mice. In healthy elderly volunteers (69 [56–91] ± 8 years old), i.v. injections of NX210c at concentrations of 5 or 10 mg/kg, following a regimen of three injections per week for a total of 4 weeks, were shown to be safe and well-tolerated in a phase 1b multiple ascending dose study (NCT05827653) [246]. No serious adverse events were reported and those observed were mild, transient, and related to the CNS such as headache. NX210c pharmacokinetics showed a dose-dependent C_{max} reached within 6 to 8 min and with ~ 17 to 18 min half-life, with no accumulation following multiple doses. NX210c treatment decreased circulating claudin-5 in the plasma of healthy elderly volunteers. Furthermore, pharmacokinetic-pharmacodynamic relationships were observed for soluble vascular cell adhesion molecule 1, homocysteine, claudin-5 and NfL in the plasma of healthy aged participants treated with NX210c, denoting a beneficial effect of NX210c on BBB integrity and neuroprotection.

A phase 2 double-blind, randomized and placebo-controlled clinical trial (NCT06365216, "SEALS") has been recruiting patients with ALS since October 2024 to evaluate the safety, tolerability and efficacy of NX210c (enrollment goal of 80 patients). This trial will investigate the effects of 5 and 10 mg/kg NX210c, following a regimen of three 10-minutes i.v. injections per week for a total of 4 weeks, with a scheduled 3-month follow-up after the end of treatment. The primary endpoints of the trial are changes in serum NfL or in Qalb. Secondary endpoints will explore: **(1)** additional biomarkers related to the drug mechanism of action and ALS pathophysiology, in CSF, blood and urine, and **(2)** a comprehensive assessment of disease-related symptoms, including evaluations based

on the ALS functional rating scale-revised. Results of this study are expected in Q2 2026.

OTR4132

OTR4132 is a biological device developed by OTR3 Science for Regeneration (Paris, France) for the treatment of stroke (https://www.otr3.com/en/home/). OTR4132 (also known as HSm4131; 132 kDa) is composed of synthetic polysaccharides with a dextran backbone engineered to mimic heparan sulfate functions (extracellular matrix scaffold element, protection of extracellular matrix proteins and storage of peptides needed for cell-cell communication), while remaining more resistant to proteoglycanases than the physiological heparan sulfates. OTR4132 was neuroprotective in rats injected via the intracerebroventricular (i.c.v.) route with the cholinergic immunotoxin 192 IgG-saporin that triggers degeneration of the septohippocampal cholinergic pathway [247]. It was also shown that a fluorescein-labeled OTR4132, injected via the i.c.v. or intramuscular route immediately after injury, accumulated specifically at the lesion site. It also reduced the lesion volume and promoted functional recovery in a rat model of transient ischemic stroke [248]. A biodistribution study using [^{99m}Tc]-labeled OTR4132 demonstrated radioactivity in the brain, with a peak of the signal 3 h after i.v. injection in the lesioned hemisphere. The product's patent application described that an intravenous injection of OTR4132 1 h after ischemia in rats reduced the extravasation of a Gd-based contrast agent into the brain within 24–48 h, and of Evans blue 72 h post-injury in the ischemic hemisphere [249].

A phase 2 clinical trial (NCT06700824, "MATRISS-II") has been announced to evaluate the safety and efficacy of OTR4132 in patients with acute ischemic stroke (enrollment of 60 patients). This quadruple-blind, randomized and placebo-controlled trial will investigate the effect of OTR4132 on baseline-adjusted 24-hour NIH stroke scale as primary endpoint. Secondary endpoints will explore the rate of intracerebral hemorrhage at 24 h, and changes in mRS, lesion volume and Barthel index at 3-month follow-up. Completion of this study is expected by March 2026. This trial builds on an open-label and single ascending dose study which enrolled 19 patients with acute ischemic stroke to evaluate the safety and tolerability of a single intraarterial injection of OTR4132 (0.2–2.5 mg), that was completed in June 2024 (NCT04083001, "MATRISS").

OV888

OV888 is a drug candidate developed at preclinical and clinical stages by Ovid Therapeutics and Graviton BioScience (New-York (NY), USA) for the treatment of neurovascular diseases and cerebral cavernous malformation, respectively (https://ovidrx.com/; https://gravitoncorp.com/). OV888 (formerly known as GV101) is a highly selective and potent small molecule inhibitor of the serine/threonine Rho-associated coiled-coil containing kinase isoform 2 (ROCK2). This molecule's selectivity to inhibit ROCK2 is more than 1000-fold greater than that of ROCK1, with IC_{50} at 8 nM and >30 µM, respectively [250]. RhoA/ROCK2 is a critical signaling pathway for endothelial cell barrier function by acting on actin cytoskeletal processes, cellular to extracellular matrix adhesion and fibrosis. However, abnormal activation of this pathway causes endothelial cell barrier dysfunction by phosphorylating and inactivating myosin light chain phosphatase, subsequently leading to actin polymerization and formation of stress fibers. In turn, these processes increase endothelial cell contraction, detachment of TJ proteins and subsequently, paracellular permeability [251]. This ultimately leads to intracerebral hemorrhage [252], notably in cerebral cavernous malformation [252–254]. A less potent inhibitor of ROCK2, Fasudil, (IC_{50} = 1.9 µM), marketed in Japan and China for the treatment of cerebral vasospasm, was shown to preserve BBB integrity in various *in vitro* and *in vivo* models, including EAE [255, 256]. Fasudil was safe and well tolerated by patients with ALS in a phase 2 study (sponsor: University Medicine Göttingen, Germany) [257]. Furthermore, it significantly reduced the loss of muscle motor units in ALS patients. Overall, these results collected on Fasudil suggest a beneficial effect of inhibiting ROCK2 on BBB repair and neuroprotection.

Phase 1 single and multiple ascending dose studies (referenced in clinicaltrials.gov as NCT05068947 or in the company's website [258]; enrollment of 16 and 50 healthy volunteers, respectively) evaluated the safety, tolerability and pharmacokinetic of OV888 administered orally either as tablets (50–400 mg) or liquid suspension (400–1200 mg) once a day (o.d.) for up to 7 days. More recently, the company performed a double-blind, randomized and placebo-controlled phase 1 multiple ascending dose (100, 200, 400 and 600 mg) study (not registered on clinicaltrials.gov) launched in Q3 2023 to confirm the safety of OV888 given orally as tablets o.d. for 7 days and to establish the maximum dose tolerated [259]. No serious adverse events were recorded, all other adverse events were mild and resolved within 24 h (mainly headache). Blood levels of bilirubin and creatine phosphokinase were increased in 30% and 7% of the total number of participants, respectively; these increases had no clinical impacts (i.e., no jaundice, nor muscle pain or weakness). The C_{max} and total drug exposure over time were dose-dependent for up to the 400 mg dose, and the plasmatic half-life was ~12 h when a 400 mg dose of the molecule was ingested daily for a total of 7 days. Furthermore, a pharmacodynamic response on the reduction of the secretion of proinflammatory interleukins, IL-17 and

IL-21, by peripheral blood mononuclear cells, validated the target engagement of OV888 to selectively inhibit ROCK2. The company has recently obtained a phase 2 authorization for cerebral cavernous malformation, but has paused this program to evaluate clinical studies recently completed by other companies in the same therapeutic indication.

SNP318

SNP318 is a drug candidate developed by SciNeuro Pharmaceuticals (Rockville (MD), USA) for the treatment of AD (https://scineuro.com/). SNP318 is a small molecule that inhibits lipoprotein-associated phospholipase A2 (Lp-PLA2) enzyme which produces pro-inflammatory mediators and thereby damages BBB integrity. SNP318 is the second-generation of Rilapladib, a compound shown to be beneficial for improving executive function and working memory in patients with mild AD in a placebo-controlled phase 2a trial sponsored by GSK (62 placebo- and 62 drug-treated patients) (NCT01428453) [260]. Rilapladib (250 mg, o.d. for 24 weeks) did not impact the levels of $A\beta_{1-42}$ in the CSF, but this trial provided preliminary evidence for the reduction of Qalb, Tau/pTau and NfL with a Lp-PLA2 inhibitor ($p > 0.05$).

A placebo-controlled and randomized phase 1 single ascending dose (starting at 1 mg) and multiple ascending dose (starting at 30 mg) study (NCT05792163) was performed in 2023 to evaluate the safety, tolerability and pharmacokinetics of SNP318 given orally for up to 20 days to healthy volunteers (enrollment of 76 subjects), with the long-term objective to treat neurodegenerative diseases including AD. This trial revealed that SNP318 penetrated the brain and was more potent than first-generation Lp-PLA2 inhibitors, thereby achieving better target engagement and broader anti-inflammatory benefits [261].

NRL1049

NRL1049 is a drug candidate developed by Neurelis (San Diego (CA), USA) for the treatment of cerebral cavernous malformation (https://www.neurelis.com/). NRL1049 (formerly known as BA1049) is a selective and potent small molecule inhibitor of ROCK2. This molecule's selectivity to inhibit ROCK2 is more than 43-fold greater than that of ROCK1, with IC_{50} at 0.59 µM and 26 µM, respectively [262]. In different models of cerebral cavernous malformation and brain injury [253, 262], NRL1049's protective effects could be mediated by the maintenance of BBB integrity via a decrease in ROCK2 activation. A dose-dependent reduction in the lesion volume was observed in *CCM3*$^{+/-}$ mice after oral administration of NRL1049 for 90 days [253]. Iron deposits were also reduced regardless of NRL1049 concentration, and fewer large stage 2 lesions were reported in treated animals. In *CCM1*$^{+/-}$ mice that exhibit smaller lesions than *CCM3*$^{+/-}$ mice, only the higher dose of NRL1049 administered for 120 days reduced the lesion volume, and there was a dose-dependent decrease in the number of mice that had lesions [253]. In mice subjected to a cortical cryo-injury, intraperitoneal (i.p.) dosing with NRL1049 after the injury was associated with lower rates of brain edema and seizures [262]. A non-significant drop of Evans blue extravasation across the BBB was also observed in injured mice treated with NRL1049. In rats subjected to transient ischemic stroke, i.p. dosing with NRL1049 15 min after reperfusion reduced intracerebral hemorrhage and Evans blue extravasation into the ischemic hemisphere [262].

A double-blind, randomized and placebo-controlled phase 1 single ascending dose study (not registered on clinicaltrials.gov) assessed the safety, tolerability and pharmacokinetics of NRL1049 in healthy volunteers (completed in 2024) [263]. The maximum tolerated dose of a single oral dose of NRL1049 was established. Pharmacokinetics showed a dose-dependent C_{max} of NRL1049 and its metabolite (NRL2017) that is also active for ROCK2 over ROCK1; their half-life was short and both were rapidly eliminated. No significant safety issues were reported by the company.

THN391

THN391 is a drug candidate developed by Therini Bio (Sacramento (CA), USA) for the treatment of AD (https://www.therinibio.com/). THN391 is a first-in-cl ass humanized affinity-matured IgG1 monoclonal antibody targeting the P2 cryptic epitope of fibrin fragments, which prevents their binding to CD11b and CD11c on microglia, macrophages and dendritic cells, responsible for driving neuroinflammation and neurodegeneration. THN391 has a 100-fold greater affinity for fibrin P2 and improved development properties than its parental mouse antibody 5B8 targeting the cryptic fibrin epitope of $\gamma_{377-395}$ developed by the Akassoglou's team [264]. Both THN391 and 5B8 antibodies selectively inhibit fibrin-induced inflammation and oxidative stress without interfering with blood clotting [264, 265]. Indeed, 5B8 antibody was shown to suppress fibrin-induced nicotinamide adenine dinucleotide phosphate oxidase activation as well as the expression of pro-inflammatory genes [265]. The 5B8 antibody was also shown to cross the BBB/BSCB in rodent models of MS and AD and bind to fibrin present in the parenchyma, which reduced the activation of innate immunity and amyloid-induced neurodegeneration, respectively.

Phase 1 single ascending dose (0.3, 1.0, 3.0, and 10 mg/kg) and multiple ascending dose (3 mg/kg, every 2 weeks and every 4 weeks) studies (not registered in clinicaltrials.gov) were launched in May 2023 to evaluate the safety and tolerability of THN391 injected i.v. in healthy

volunteers. According to the Alzheimer's Drug Discovery Foundation, interim results presented at Clinical Trials in Alzheimer's Disease meeting in 2023 suggested that THN391 was well-tolerated and did not generate serious adverse events [266]. The half-life of THN391 in the plasma was ~50 days when given as single ascending doses at 0.3 and 1 mg/kg.

Axitinib

Axitinib is a drug candidate developed at preclinical stage by CAVA Healthcare Inc (Surrey, Canada) for the treatment of AD (https://www.cavahealthcare.ca/). Axitinib is a potent and selective small molecule tyrosine kinase inhibitor (386 kDa) that targets the phosphorylation of vascular endothelial growth factor receptors, reaching 50% inhibition with concentrations at a sub-nanomolar range [267]. This anti-angiogenic drug is approved as a second line treatment for advanced renal cell carcinoma and the recommended starting dose is set at 5 mg twice daily orally. Common adverse events of Axitinib include diarrhea, fatigue and hypertension. Axitinib is absorbed rapidly with a dose-dependent C_{max} reached within 4 h and a plasmatic half-life ranging from 2.5 to 6.1 h. Plasmatic levels attain a steady-state within 15 days, with no accumulation [268].

Preclinical evidence recently published in the Tg2576 mouse model of AD [269] and in a rat model of transient ischemic stroke [270] suggest the drug repurposing potential of Axitinib for the treatment of these neurological disorders. Pharmacokinetics studies of Axitinib given to mice by oral gavage have shown a total drug exposure over time of 55 nM×h in the plasma and 0.00885 pM×h in the brain [269]. In the same study, Axitinib attenuated neoangiogenesis and amyloidogenesis in aged Tg2576 mice. Furthermore, the drug restored normal protein levels of ZO-1 and occludin, reduced TJ disruption in mature blood vessels and thereby significantly attenuated BBB leakage of Evans blue into the brain. In line with these observations, Axitinib restored memory and cognitive functions in Tg2576 mice. In bEnd3 endothelial cell monolayers exposed to oxygen glucose deprivation, Axitinib partially restored claudin-5 and occludin protein levels and slightly improved TEER measures [270]. The BBB-protective effect of Axitinib was likely a consequence of a greater endothelial cell survival under treatment. Accordingly, in rats subjected to transient ischemic stroke, i.v. administration of Axitinib at the beginning of reperfusion reduced the lesion volume and edema in the acute phase. Anti-angiogenic and anti-inflammatory effects of Axitinib were accompanied by a restoration of normal protein levels of claudin-5 and occludin in the penumbra, and a reduced extravasation of Evans blue into the brain. In addition, Axitinib ameliorated neurological deficits triggered by ischemic stroke.

LYS241

LYS241 is an antibody developed by Lys Therapeutics (Caen, France) for the treatment of MS, PD, multiple system atrophy, stroke and clinically isolated syndrome (www.lystherapeutics.com). LYS241 is an IgG1 humanized monoclonal blocking antibody targeting the amino-terminal domain of the GluN1 subunit of NMDAR to prevent the binding of endogenous tissue plasminogen activator or its recombinant forms (alteplase and tenecteplase), which are the gold standard thrombolytic treatments for ischemic stroke [271]. Although tissue plasminogen activator plays essential roles in physiological conditions (notably synaptic transmission for learning and memory functions), it potentiates glutamate-induced excitotoxic neuronal death and loss of BBB integrity in pathological conditions [272]. A mouse monoclonal antibody targeting the N-terminal domain of the GluN1 (amino acids at position 169–192) (named Glunomab) was shown to reduce glutamate-induced neuronal death [273], immune cell migration across the BBB and BBB leakage [274–276]. Consequently, Glunomab reduced disease progression and promoted functional recovery in animal models of PD [274], ischemic stroke [275] and MS [277].

NVQXXX

NVQXXX is an antibody developed by Neuvasq Biotechnologies (Charleroi, Belgium) for the treatment of neurological diseases (https://neuvasq.com/). Little is known about this new drug candidate, given that it is at early stage of development, but it activates the Wnt signaling pathway as a barrier-repair strategy. Proof of concept studies support the relevance of the Wnt7a/b/β-catenin pathway in barrier repair mechanisms, notably in SARS-CoV-2-induced cognitive impairments, ischemic stroke, and glioblastoma expansion [278, 279]. The same company also developed NVQ401, another Wnt surrogate antibody, for the treatment of wet age-related macular degeneration and diabetic macular edema.

Conclusions & perspectives

In this review, we evaluated over 350 scientific publications reporting on BBB and/or BSCB alterations and dysfunctions in more than 130 neurological diseases (Supplementary Tables 1 and Figs. 2 and 3). This extensive survey indicates that 54 pathologies display BBB and/or BSCB dysfunction, which represent over 40% of neurological disorders being associated with barrier impairments. Among the remaining 60%, barriers dysfunction and structural alterations were not systematically reported or investigated and additional studies are necessary to conclude on this potential aspect of disease pathology.

The field of brain barriers is emerging as an important contributor to the understanding of the causes and consequences of neurological disorders. The clinical studies discussed in this review have shed light on several factors critical to data interpretation and that need to be considered when designing future studies. For example, increased cardiovascular risk factors, or concomitant cerebrovascular or inflammatory diseases, represent major cofounding factors to barrier disruption in neurological disorders. Barrier integrity is also compromised during normal aging and may vary in a sex-dependent manner. For example, in ALS, elevated levels of biomarkers of barrier disruption are more frequent in males than in females, and relate to poor prognosis in males. This observation emphasizes the need to design adequate pairing of sex- and age-balanced cohorts to enable sex- and age-based analyses, and identify subpopulations at-risk of developing brain barriers pathologies. Such information would allow more accurate evaluations of how barrier disruption influences the clinical portrait of patients respective to their own pathology. Importantly, barrier damage is also not observed in all patients suffering from the same pathology. For example, extravasation of gadolinium-based contrast agents was observed in 28% and 38% of patients with bipolar disorder [137] and spinal cord injury [85], respectively. Similarly, elevation of Qalb was observed in 17–29%, 27–29%, and 10–39% of patients with schizophrenia [219, 220], anti-NMDAR encephalitis [210, 211] and ALS [193–197], respectively.

Established biomarkers to evaluate and measure the evolution of barrier disruption in humans are currently limited as of today. They mainly consist in measuring Qalb or the kinetics of penetration of contrast agents into the brain or spinal cord. The levels of TJ-related proteins in the blood have been measured, thus far, in psychiatric disorders (bipolar disorder [280], obsessive-compulsive disorder [281–283], schizophrenia [218]), autism [284], stroke [199–202, 204], Moyamoya disease [285], traumatic brain injury [205], MS [286] and AD [287]. While these proteins are ubiquitously expressed in several organs and therefore their presence in the bloodstream may not be specific to neurological disorders, these biomarkers correlate with disease progression and clinical outcome in AD [287], autism [284], schizophrenia [218] and stroke [50, 199, 201–204]. Whether these proteins can serve as biomarkers to evaluate barrier integrity across the diversity of neurological disorders, or whether they are disease-specific remains to be determined. They may possibly provide a window into the stage of disease progression, severity, and clinical outcomes. However, challenges remain to determine what should be considered "physiological" levels of TJ-related proteins in the bloodstream, and if changes accurately reflect various states of brain barriers integrity. Indeed, barriers are dynamic structures that undergo continuous remodeling and recycling of TJs under physiological conditions. Furthermore, it should be considered that TJ-associated proteins assemble into multiprotein complexes and hence following only the blood level of a given monomer of a TJ protein may be misleading.

In our opinion, there is an urgent need to establish standardized protocols for the detection of barriers disruption in patients. As a first step, it would be advisable to establish a list of circulating biomarkers for systematic inclusion in clinical protocols. If biomarkers are measured concomitantly with the detection of BBB leakage using appropriate neuroimaging techniques, studies may unravel peripheral markers indicative of barrier damage and severity. Biomarkers of barrier damage, in conjunction with other disease-specific biomarkers, could guide diagnostic and help determine disease onset, progression, and prognosis in patient populations. Lessons learnt from past clinical studies and efforts to identify putative biomarkers of brain barriers disruption may also provide precious insights for drug development. Companies developing therapeutic agents targeted to repair brain barriers could leverage these blood biomarkers to refine study protocols for clinical trials. They may include stratifying patients using barrier disruption biomarkers, or defining appropriate inclusion/exclusion criteria. Altogether, it would allow a more precise targeting of patient subpopulations that may best respond to specific treatments. In this sense, personalized medicine may also benefit patients or individuals at risk of barrier disruption. To develop such approaches, establishing dedicated platforms specialized in modeling patient-derived brain barriers would be key to determining *if* and *how* barriers are altered, what signaling pathways are specifically implicated, and which therapeutic agents may best support each patient's needs. The relevance of such platforms is supported by a recent study by Wasielewska and colleagues, who demonstrated that induced pluripotent stem cells-derived BBB models developed from asymptomatic carriers of *C9ORF72* mutations exhibited evidence of a compromised barrier in vitro, and these individuals eventually developed ALS later in life [288]. In fact, while this review focused primarily on human- and animal-based *in vivo* studies, the recent development of *in vitro* BBB models using patient-derived induced pluripotent stem cells also provided evidence of brain barriers dysfunctions and alterations in neurological disorders. They include ALS [288–290], cerebral adrenoleukodystrophy [291], cerebral cavernous malformation [292], DiGeorge syndrome [143, 293–295], HD [296], Friedreich's ataxia [297], MS [298], PD [299], psychiatric disorders [300, 301] and tuberous sclerosis complex [302].

Most existing therapeutic approaches do not stop or slow the progression of neurological disorders, leaving patients and their families suffering the burden of debilitating motor and/or cognitive deficits. In this context, it can be argued that therapeutic avenues aimed at safeguarding the integrity of brain barriers will offer a novel strategy for treating neurological disorders, and could be a game changer for patients and their caregivers.

Strengths & weaknesses

This article offers a comprehensive and systematic review of over one hundred neurological disorders that have been evaluated for possible brain barriers alterations and leakage. In doing so, this manuscript provides readers with a global overview of the extent of barrier dysfunction in individuals affected by neurological disorders, and suggests that brain barriers may be leveraged as drug targets. Using the classification of diseases from the World Health Organization, we have attempted to cover a large number of diseases of the nervous system, as well as diseases classified in other categories but associated with the nervous system. For a subset of illnesses and injuries where brain barriers alterations and dysfunctions have been extensively investigated in animal models, such as AD, MS, spinal cord injury, stroke, and traumatic brain injury, we focused our efforts on presenting results in well-known models for each pathology. Lastly, the molecular mechanisms underlying barrier dysfunction are complex and they implicate a large range of transporters as well as the activation of signaling pathways. This article focused primarily on surveying the scientific literature that reported alterations of TJs and associated proteins, and extravasation of blood-borne factors; we did not review additional indicators such as changes in the phosphorylation and oligomerization of TJ proteins, dysfunctions of efflux transporters (such as P-glycoprotein) or ion/water channels. Furthermore, perturbations in the dynamic crosstalk between endothelial cells, glial cells and neurons are important contributors of NVU dysfunctions to be considered.

Abbreviations

3D	Three dimensional
Aβ	Amyloid beta
AD	Alzheimer's disease
ALS	Amyotrophic lateral sclerosis
BBB	Blood-brain barrier
BSCB	Blood-spinal cord barrier
CADASIL	Cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy
CD	Cluster of differentiation
C_{max}	Maximum concentration
CNS	Central nervous system
CSF	Cerebrospinal fluid
CXCL	Chemokine (C-X-C motif) ligand
DCE-MRI	Dynamic contrast enhanced-MRI
DTPA	Diethylenetriamine penta-acetic acid
EAE	Experimental autoimmune encephalomyelitis
EDSS	Expanded disability status scale
ELISA	Enzyme-linked immunosorbent assay
FITC	Fluorescein isothiocyanate
Gd	Gadolinium
GM	Grey matter
HAM	Human T-cell leukemia virus type 1-associated myelopathy
HBMVEC	Human brain microvascular endothelial cell
HD	Huntington's disease
i.c.v.	Intracerebroventricular
i.p.	Intraperitoneal
i.v.	Intravenous(ly)
IC_{50}	Half-maximal inhibitory concentration
IFN-γ	Interferon-γ
IgA	Immunoglobulin A
IgG	Immunoglobulin G
IL	Interleukin
K_i	Influx constant
K^{trans}	Transfer coefficient
Lp-PLA2	Lipoprotein-associated phospholipase A2
mAb	Monoclonal antibody
MMSE	Mini-mental state examination
MRI	Magnetic resonance imaging
mRNA	Messenger ribonucleic acid
mRS	Modified rankin scale
MS	Multiple sclerosis
NEDA-3	No evidence of disease activity-3
NfL	Neurofilament light chain
NIH	National institutes of health
NMDA	N-methyl-D-aspartate receptor
NVU	Neurovascular unit
o.d.	Once a day
PD	Parkinson's disease
Q	Quarter
Qalb	CSF/serum albumin ratio
RGMa	Repulsive guidance molecule-a
ROC	Receiver operating characteristic
ROCK	Rho-associated coiled-coil containing kinase isoform
SAB	Scientific advisory board
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TEER	Transendothelial electrical resistance
TJ	Tight junction
TNF-α	Tumor necrosis factor-α
WM	White matter
ZO-1	Zonula occludens-1

Supplementary Information

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Supplementary Material 1

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Author contributions

SL drafted the manuscript and the figures. AdRJ corrected and commented on the first draft of the manuscript and figures. BE, FC, GB, AJ, YG, HB, MC and

AdRJ provided corrections, additions and critical comments on the second draft of the manuscript with a focus on their own expertise in neurology (AJ), medicine (GB), drug development (YG), and BBB/BSCB alterations and dysfunctions in ALS (HB, BE), epilepsy (MC), HD (FC), MS (BE), PD (AdRJ, FC), schizophrenia (MC), stroke (GB) and TBI (MC). All the authors read and approved the final version of the manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Competing interests
SL and AJ are employed by Axoltis Pharma and are respectively chief scientific officer and chief medical officer of the company. YG is chief executive officer and a shareholder of Axoltis Pharma. BE, GB, FC and MC are members of the scientific advisory board (SAB) of Axoltis Pharma. BE and MC are members of the SAB of Neuvasq Biotechnologies. As employees, chief executive officer, or SAB members of companies working on drug candidates for barrier repair in neurological disorders, we have deliberately chosen to stay neutral on the third part of this review by just reporting factual elements without interpretation and comparison of the mechanisms of action of the drug candidates being developed, to avoid any conflict of interest.

Ethics approval
Not applicable.

Consent to publication
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References

1. Collaborators GBDNSD. Global, regional, and National burden of disorders affecting the nervous system, 1990–2021: a systematic analysis for the global burden of disease study 2021. Lancet Neurol. 2024;23(4):344–81.
2. Kim CK, Lee YR, Ong L, Gold M, Kalali A, Sarkar J. Alzheimer's disease: key insights from two decades of clinical trial failures. J Alzheimers Dis. 2022;87(1):83–100.
3. Faden AI, Stoica B. Neuroprotection: challenges and opportunities. Arch Neurol. 2007;64(6):794–800.
4. Lacoste B, Prat A, Freitas-Andrade M, Gu C. The blood-brain barrier: composition, properties, and roles in brain health. Cold Spring Harb Perspect Biol. 2025;17(5):a041422.
5. Greene C, Hanley N, Campbell M. Claudin-5: gatekeeper of neurological function. Fluids Barriers CNS. 2019;16(1):3.
6. Prockop LD, Naidu KA, Binard JE, Ransohoff J. Selective permeability of [3H]-D-mannitol and [14 C]-carboxyl-inulin across the blood-brain barrier and blood-spinal cord barrier in the rabbit. J Spinal Cord Med. 1995;18(4):221–6.
7. Sa-Pereira I, Brites D, Brito MA. Neurovascular unit: a focus on pericytes. Mol Neurobiol. 2012;45(2):327–47.
8. Abbott NJ, Ronnback L, Hansson E. Astrocyte-endothelial interactions at the blood-brain barrier. Nat Rev Neurosci. 2006;7(1):41–53.
9. Iadecola C. The neurovascular unit coming of age: a journey through neurovascular coupling in health and disease. Neuron. 2017;96(1):17–42.
10. Yue Q, Leng X, Xie N, Zhang Z, Yang D, Hoi MPM. Endothelial dysfunctions in blood-brain barrier breakdown in alzheimer's disease: from mechanisms to potential therapies. CNS Neurosci Ther. 2024;30(11):e70079.
11. Manora L, Borlongan CV, Garbuzova-Davis S. Cellular and noncellular approaches for repairing the damaged blood-CNS-barrier in amyotrophic lateral sclerosis. Cells. 2024;13(5):435.
12. 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.
13. Alarcan H, Al Ojaimi Y, Lanznaster D, Escoffre JM, Corcia P, Vourc'h P, et al. Taking advantages of blood-brain or spinal cord barrier alterations or restoring them to optimize therapy in ALS? J Pers Med. 2022;12(7):1071.
14. Wei Z, Liu H, Lin Z, Yao M, Li R, Liu C, et al. Non-contrast assessment of blood-brain barrier permeability to water in mice: an arterial spin labeling study at cerebral veins. NeuroImage. 2023;268:119870.
15. Di Pardo A, Amico E, Scalabri F, Pepe G, Castaldo S, Elifani F, et al. Impairment of blood-brain barrier is an early event in R6/2 mouse model of huntington disease. Sci Rep. 2017;7:41316.
16. Drouin-Ouellet J, Sawiak SJ, Cisbani G, Lagace M, Kuan WL, Saint-Pierre M, et al. Cerebrovascular and blood-brain barrier impairments in huntington's disease: potential implications for its pathophysiology. Ann Neurol. 2015;78(2):160–77.
17. Zierfuss B, Larochelle C, Prat A. Blood-brain barrier dysfunction in multiple sclerosis: causes, consequences, and potential effects of therapies. Lancet Neurol. 2024;23(1):95–109.
18. Schreiner TG, Romanescu C, Popescu BO. The blood-brain barrier-a key player in multiple sclerosis disease mechanisms. Biomolecules. 2022;12(4):538.
19. 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;22(16):8370.
20. Lau K, Kotzur R, Richter F. Blood-brain barrier alterations and their impact on parkinson's disease pathogenesis and therapy. Transl Neurodegener. 2024;13(1):37.
21. Khor SLQ, Ng KY, Koh RY, Chye SM. Blood-brain barrier and neurovascular unit dysfunction in parkinson's disease: from clinical insights to pathogenic mechanisms and novel therapeutic approaches. CNS Neurol Disord Drug Targets. 2024;23(3):315–30.
22. Yang K, Li Q, Ruan Y, Xia Y, Fang Z. Caveolae-mediated transcytosis and its role in neurological disorders. Biomolecules. 2025;15(4):456.
23. Mader S, Brimberg L. Aquaporin-4 water channel in the brain and its implication for health and disease. Cells. 2019;8(2):90.
24. Bartels AL, Willemsen AT, Kortekaas R, de Jong BM, de Vries R, de Klerk O, et al. Decreased blood-brain barrier P-glycoprotein function in the progression of parkinson's disease, PSP and MSA. J Neural Transm (Vienna). 2008;115(7):1001–9.
25. Lemarchant S, Badaut J. In: Badaut J, Plesnila N, editors. Brain edema formation in traumatic brain injury. Brain Edema: Academic; 2017. pp. 235–59.
26. Wu J, Wu H, Zhou F, Wang Y, Wang C, Ji J. Blood-brain barrier alterations as an initiator of brain metastasis from lung cancer: a new take on an old story. Cancer Gene Ther. 2025. https://doi.org/10.1038/s41417-025-00916-6
27. Greene C, Connolly R, Brennan D, Laffan A, O'Keeffe E, Zaporojan L, et al. Blood-brain barrier disruption and sustained systemic inflammation in individuals with long COVID-associated cognitive impairment. Nat Neurosci. 2024;27(3):421–32.
28. Kremer R, Williams A, Wardlaw J. Endothelial cells as key players in cerebral small vessel disease. Nat Rev Neurosci. 2025;26(3):179–88.
29. Kim HW, Yong H, Shea GKH. Blood-spinal cord barrier disruption in degenerative cervical myelopathy. Fluids Barriers CNS. 2023;20(1):68.
30. Ogaki A, Ikegaya Y, Koyama R. Vascular abnormalities and the role of vascular endothelial growth factor in the epileptic brain. Front Pharmacol. 2020;11:20.
31. Le Guennec L, Mouri S, Thabut D, Weiss N. Blood-brain barrier dysfunction in hepatic encephalopathy: pathophysiology, diagnostic assessment and therapeutic perspectives. Metab Brain Dis. 2025;40(5):223.
32. Qi L, Wang F, Sun X, Li H, Zhang K, Li J. Recent advances in tissue repair of the blood-brain barrier after stroke. J Tissue Eng. 2024;15:20417314241226551.
33. Candelario-Jalil E, Dijkhuizen RM, Magnus T. Neuroinflammation, stroke, blood-brain barrier dysfunction, and imaging modalities. Stroke. 2022;53(5):1473–86.
34. Maridaki Z, Syrros G, Gianna Delichatsiou S, Warsh J, Konstantinou GN. Claudin-5 and occludin levels in patients with psychiatric disorders - a systematic review. Brain Behav Immun. 2025;123:865–75.
35. Zhang F, Zhang J, Wang X, Han M, Fei Y, Wang J. Blood-brain barrier disruption in schizophrenia: insights, mechanisms, and future directions. Int J Mol Sci. 2025;26(3):873.

36. Millett CE, Monir F, Sanelli P. The role of blood-brain barrier dysfunction in cognitive impairments in bipolar disorder-a narrative review. Front Hum Neurosci. 2025;19:1504575.
37. Ying Y, Li Y, Yao T, Shao X, Tang W, Montagne A, et al. Heterogeneous blood-brain barrier dysfunction in cerebral small vessel diseases. Alzheimers Dement. 2024;20(7):4527–39.
38. Deshpande T, Hannocks MJ, Kapupara K, Samawar SKR, Wachsmuth L, Faber C, et al. Microglial activation without peripheral immune cell infiltration characterises mouse and human cerebral small vessel disease. Neuropathol Appl Neurobiol. 2024;50(6):e13015.
39. Elschot EP, Backes WH, de Jong JJA, Drenthen GS, Wong SM, Staals J, et al. Assessment of the clinical feasibility of detecting subtle blood-brain barrier leakage in cerebral small vessel disease using dynamic susceptibility contrast MRI. Magn Reson Imaging. 2023;102:55–61.
40. Rudilosso S, Stringer MS, Thrippleton M, Chappell F, Blair GW, Jaime Garcia D, et al. Blood-brain barrier leakage hotspots collocating with brain lesions due to sporadic and Monogenic small vessel disease. J Cereb Blood Flow Metab. 2023;43(9):1490–502.
41. Kerkhofs D, Wong SM, Zhang E, Uiterwijk R, Hoff EI, Jansen JFA, et al. Blood-brain barrier leakage at baseline and cognitive decline in cerebral small vessel disease: a 2-year follow-up study. Geroscience. 2021;43(4):1643–52.
42. Zhang CE, Wong SM, Uiterwijk R, Backes WH, Jansen JFA, Jeukens C, et al. Blood-brain barrier leakage in relation to white matter hyperintensity volume and cognition in small vessel disease and normal aging. Brain Imaging Behav. 2019;13(2):389–95.
43. Rajani RM, Ratelade J, Domenga-Denier V, Hase Y, Kalimo H, Kalaria RN, et al. Blood brain barrier leakage is not a consistent feature of white matter lesions in CADASIL. Acta Neuropathol Commun. 2019;7(1):187.
44. Zhang CE, Wong SM, van de Haar HJ, Staals J, Jansen JF, Jeukens CR, et al. Blood-brain barrier leakage is more widespread in patients with cerebral small vessel disease. Neurology. 2017;88(5):426–32.
45. Jones OA, Mohamed S, Hinz R, Paterson A, Sobowale OA, Dickie BR, et al. Neuroinflammation and blood-brain barrier breakdown in acute, clinical intracerebral hemorrhage. J Cereb Blood Flow Metab. 2025;45(2):233–43.
46. Yang D, Wang X, Zhang X, Zhu H, Sun S, Mane R, et al. Temporal evolution of perihematomal blood-brain barrier compromise and edema growth after intracerebral hemorrhage. Clin Neuroradiol. 2023;33(3):813–24.
47. Lublinsky S, Major S, Kola V, Horst V, Santos E, Platz J, et al. Early blood-brain barrier dysfunction predicts neurological outcome following aneurysmal subarachnoid hemorrhage. EBioMedicine. 2019;43:460–72.
48. McCourt R, Gould B, Kate M, Asdaghi N, Kosior JC, Coutts S, et al. Blood-brain barrier compromise does not predict Perihematoma edema growth in intracerebral hemorrhage. Stroke. 2015;46(4):954–60.
49. Aksoy D, Bammer R, Mlynash M, Venkatasubramanian C, Eyngorn I, Snider RW, et al. Magnetic resonance imaging profile of blood-brain barrier injury in patients with acute intracerebral hemorrhage. J Am Heart Assoc. 2013;2(3):e000161.
50. Li W, Hu W, Yuan S, Chen J, Wang Q, Ding J, et al. Enhancing blood-brain barrier integrity in patients with acute ischemic stroke via Normobaric hyperoxia. J Am Heart Assoc. 2024;13(21):e036474.
51. Bernardo-Castro S, Sousa JA, Martins E, Donato H, Nunes C, d'Almeida OC, et al. The evolution of blood-brain barrier permeability changes after stroke and its implications on clinical outcome: a systematic review and meta-analysis. Int J Stroke. 2023;18(7):783–94.
52. Li Y, Xia Y, Chen H, Liu N, Jackson A, Wintermark M, et al. Focal low and global high permeability predict the possibility, risk, and location of hemorrhagic transformation following intra-arterial thrombolysis therapy in acute stroke. AJNR Am J Neuroradiol. 2017;38(9):1730–6.
53. Merali Z, Huang K, Mikulis D, Silver F, Kassner A. Evolution of blood-brain-barrier permeability after acute ischemic stroke. PLoS ONE. 2017;12(2):e0171558.
54. Villringer K, Sanz Cuesta BE, Ostwaldt AC, Grittner U, Brunecker P, Khalil AA, et al. DCE-MRI blood-brain barrier assessment in acute ischemic stroke. Neurology. 2017;88(5):433–40.
55. Liu HS, Chung HW, Chou MC, Liou M, Wang CY, Kao HW, et al. Effects of microvascular permeability changes on contrast-enhanced T1 and Pharmacokinetic MR imagings after ischemia. Stroke. 2013;44(7):1872–7.
56. Yau ACY, Globisch MA, Onyeogaziri FC, Conze LL, Smith R, Jauhiainen S, et al. Inflammation and neutrophil extracellular traps in cerebral cavernous malformation. Cell Mol Life Sci. 2022;79(4):206.
57. Clatterbuck RE, Eberhart CG, Crain BJ, Rigamonti D. Ultrastructural and immunocytochemical evidence that an incompetent blood-brain barrier is related to the pathophysiology of cavernous malformations. J Neurol Neurosurg Psychiatry. 2001;71(2):188–92.
58. Wong JH, Awad IA, Kim JH. Ultrastructural pathological features of cerebrovascular malformations: a preliminary report. Neurosurgery. 2000;46(6):1454–9.
59. Narducci A, Yasuyuki K, Onken J, Blecharz K, Vajkoczy P. In vivo demonstration of blood-brain barrier impairment in Moyamoya disease. Acta Neurochir (Wien). 2019;161(2):371–8.
60. Oghabian MA, Fatemidokht A, Haririchian MH. Quantification of blood-brain-barrier permeability dysregulation and inflammatory activity in MS lesions by dynamic-contrast enhanced MR imaging. Basic Clin Neurosci. 2022;13(1):117–28.
61. Knudsen MH, Lindberg U, Frederiksen JL, Vestergaard MB, Simonsen HJ, Varatharaj A, et al. Blood-brain barrier permeability changes in the first year after alemtuzumab treatment predict 2-year outcomes in relapsing-remitting multiple sclerosis. Mult Scler Relat Disord. 2022;63:103891.
62. Varatharaj A, Liljeroth M, Darekar A, Larsson HBW, Galea I, Cramer SP. Blood-brain barrier permeability measured using dynamic contrast-enhanced magnetic resonance imaging: a validation study. J Physiol. 2019;597(3):699–709.
63. 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.
64. Leech S, Kirk J, Plumb J, McQuaid S. Persistent endothelial abnormalities and blood-brain barrier leak in primary and secondary progressive multiple sclerosis. Neuropathol Appl Neurobiol. 2007;33(1):86–98.
65. van Horssen J, Brink BP, de Vries HE, van der Valk P, Bo L. The blood-brain barrier in cortical multiple sclerosis lesions. J Neuropathol Exp Neurol. 2007;66(4):321–8.
66. Kirk J, Plumb J, Mirakhur M, McQuaid S. Tight junctional abnormality in multiple sclerosis white matter affects all calibres of vessel and is associated with blood-brain barrier leakage and active demyelination. J Pathol. 2003;201(2):319–27.
67. Plumb J, McQuaid S, Mirakhur M, Kirk J. Abnormal endothelial tight junctions in active lesions and normal-appearing white matter in multiple sclerosis. Brain Pathol. 2002;12(2):154–69.
68. Kermode AG, Thompson AJ, Tofts P, MacManus DG, Kendall BE, Kingsley DP, et al. Breakdown of the blood-brain barrier precedes symptoms and other MRI signs of new lesions in multiple sclerosis. Pathogenetic and clinical implications. Brain. 1990;113:1477–89.
69. Ji SH, Yoo RE, Choi SH, Lee WJ, Lee ST, Jeon YH, et al. Dynamic contrast-enhanced MRI quantification of altered vascular permeability in autoimmune encephalitis. Radiology. 2024;310(3):e230701.
70. Fiala M, Liu QN, Sayre J, Pop V, Brahmandam V, Graves MC, et al. Cyclooxygenase-2-positive macrophages infiltrate the alzheimer's disease brain and damage the blood-brain barrier. Eur J Clin Invest. 2002;32(5):360–71.
71. Gross CC, Meyer C, Bhatia U, Yshii L, Kleffner I, Bauer J, et al. CD8(+) T cell-mediated endotheliopathy is a targetable mechanism of neuro-inflammation in Susac syndrome. Nat Commun. 2019;10(1):5779.
72. Dean T, Mendiola AS, Yan Z, Meza-Acevedo R, Cabriga B, Akassoglou K, et al. Fibrin promotes oxidative stress and neuronal loss in traumatic brain injury via innate immune activation. J Neuroinflammation. 2024;21(1):94.
73. Fullerton JL, Hay J, Bryant-Craig C, Atkinson J, Smith DH, Stewart W. Pediatric traumatic brain injury and microvascular blood-brain barrier pathology. JAMA Netw Open. 2024;7(11):e2446767.
74. Ware JB, Sinha S, Morrison J, Walter AE, Gugger JJ, Schneider ALC, et al. Dynamic contrast enhanced MRI for characterization of blood-brain-barrier dysfunction after traumatic brain injury. Neuroimage Clin. 2022;36:103236.
75. Yoen H, Yoo RE, Choi SH, Kim E, Oh BM, Yang D, et al. Blood-brain barrier disruption in mild traumatic brain injury patients with post-concussion syndrome: evaluation with region-based quantification of dynamic contrast-enhanced MR imaging parameters using automatic whole-brain segmentation. Korean J Radiol. 2021;22(1):118–30.
76. Veksler R, Vazana U, Serlin Y, Prager O, Ofer J, Shemen N, et al. Slow blood-to-brain transport underlies enduring barrier dysfunction in American football players. Brain. 2020;143(6):1826–42.
77. 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.
78. You X, Yan L, Li X, Pang Y, Guo X, Ye J, et al. Disruption of blood-brain barrier integrity associated with brain lesions in Chinese neuromyelitis Optica spectrum disorder patients. Mult Scler Relat Disord. 2019;27:254–9.

79. Johnson VE, Weber MT, Xiao R, Cullen DK, Meaney DF, Stewart W, et al. Mechanical disruption of the blood-brain barrier following experimental concussion. Acta Neuropathol. 2018;135(5):711–26.
80. Hay JR, Johnson VE, Young AM, Smith DH, Stewart W. Blood-brain barrier disruption is an early event that May persist for many years after traumatic brain injury in humans. J Neuropathol Exp Neurol. 2015;74(12):1147–57.
81. Liu HM, Sturner WQ. Extravasation of plasma proteins in brain trauma. Forensic Sci Int. 1988;38(3–4):285–95.
82. Farrell M, Aherne S, O'Riordan S, O'Keeffe E, Greene C, Campbell M. Blood-brain barrier dysfunction in a boxer with chronic traumatic encephalopathy and schizophrenia. Clin Neuropathol. 2019;38(2):51–8.
83. Doherty CP, O'Keefe E, Wallace E, Loftus T, Keaney J, Kealy J, et al. Blood-brain barrier dysfunction as a hallmark pathology in chronic traumatic encephalopathy. J Neuropathol Exp Neurol. 2016;75(7):656–62.
84. Kleiser R, Rademacher GU, Niedeggen A, Muller HW, Seitz RJ. Assessment of gadolinium leakage into traumatic spinal cord lesion using magnet resonance imaging. Spine (Phila Pa 1976). 2010;35(26):E1604–9.
85. Terae S, Takahashi C, Abe S, Kikuchi Y, Miyasaka K. Gd-DTPA-enhanced MR imaging of injured spinal cord. Clin Imaging. 1997;21(2):82–9.
86. Wen C, Gan JH, Liu S, Lu H, Wang LC, Wu H, et al. Enlarged perivascular spaces correlate with blood-brain barrier leakage and cognitive impairment in alzheimer's disease. J Alzheimers Dis. 2025;104(2):382–92.
87. Xu Z, Ji Y, Wen C, Gan J, Chen Z, Li R, et al. Tracer kinetic model detecting heterogeneous blood-brain barrier permeability to water and contrast agent in alzheimer's disease and dementia with lewy bodies. Alzheimers Dement. 2025;21(2):e14529.
88. Gan J, Xu Z, Chen Z, Liu S, Lu H, Wang Y, et al. Blood-brain barrier breakdown in dementia with lewy bodies. Fluids Barriers CNS. 2024;21(1):73.
89. Preis L, Villringer K, Brosseron F, Duzel E, Jessen F, Petzold GC, et al. Assessing blood-brain barrier dysfunction and its association with alzheimer's pathology, cognitive impairment and neuroinflammation. Alzheimers Res Ther. 2024;16(1):172.
90. Merlini M, Sozmen EG, Subramanian KS, Nana AL, Seeley WW, Akassoglou K. Three-dimensional imaging of fibrinogen and neurovascular alterations in alzheimer's disease. Methods Mol Biol. 2023;2561:87–101.
91. Wang Q, Huang X, Su Y, Yin G, Wang S, Yu B, et al. Activation of Wnt/beta-catenin pathway mitigates blood-brain barrier dysfunction in alzheimer's disease. Brain. 2022;145(12):4474–88.
92. Tayler H, Miners JS, Guzel O, MacLachlan R, Love S. Mediators of cerebral hypoperfusion and blood-brain barrier leakiness in alzheimer's disease, vascular dementia and mixed dementia. Brain Pathol. 2021;31(4):e12935.
93. McAleese KE, Graham S, Dey M, Walker L, Erskine D, Johnson M, et al. Extravascular fibrinogen in the white matter of alzheimer's disease and normal aged brains: implications for fibrinogen as a biomarker for alzheimer's disease. Brain Pathol. 2019;29(3):414–24.
94. Miners JS, Schulz I, Love S. Differing associations between Abeta accumulation, hypoperfusion, blood-brain barrier dysfunction and loss of PDGFRB pericyte marker in the precuneus and parietal white matter in alzheimer's disease. J Cereb Blood Flow Metab. 2018;38(1):103–15.
95. van de Haar HJ, Jansen JFA, Jeukens C, Burgmans S, van Buchem MA, Muller M, et al. Subtle blood-brain barrier leakage rate and Spatial extent: considerations for dynamic contrast-enhanced MRI. Med Phys. 2017;44(8):4112–25.
96. 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.
97. Ryu JK, McLarnon JG. A leaky blood-brain barrier, fibrinogen infiltration and microglial reactivity in inflamed alzheimer's disease brain. J Cell Mol Med. 2009;13(9A):2911–25.
98. Alafuzoff I, Adolfsson R, Grundke-Iqbal I, Winblad B. Blood-brain barrier in alzheimer dementia and in non-demented elderly. An immunocytochemical study. Acta Neuropathol. 1987;73(2):160–6.
99. Al-Bachari S, Naish JH, Parker GJM, Emsley HCA, Parkes LM. Blood-brain barrier leakage is increased in parkinson's disease. Front Physiol. 2020;11:593026.
100. Pienaar IS, Lee CH, Elson JL, McGuinness L, Gentleman SM, Kalaria RN, et al. Deep-brain stimulation associates with improved microvascular integrity in the subthalamic nucleus in parkinson's disease. Neurobiol Dis. 2015;74:392–405.
101. Gray MT, Woulfe JM. Striatal blood-brain barrier permeability in parkinson's disease. J Cereb Blood Flow Metab. 2015;35(5):747–50.
102. Behan C, Greene C, Hanley N, Salla CV, Brennan D, Connolly R, et al. Restoration of blood brain barrier integrity post neurosurgical resection in drug resistant epilepsy. Epilepsy Behav. 2025;168:110425.
103. Cafri N, Mirloo S, Zarhin D, Kamintsky L, Serlin Y, Alhadeed L, et al. Imaging blood-brain barrier dysfunction in drug-resistant epilepsy: a multi-center feasibility study. Epilepsia. 2025;66(1):195–206.
104. 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.
105. Li H, Liu X, Wang R, Lu A, Ma Z, Wu S, et al. Blood-brain barrier damage and new onset refractory status epilepticus: an exploratory study using dynamic contrast-enhanced magnetic resonance imaging. Epilepsia. 2023;64(6):1594–604.
106. 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.
107. Akiguchi I, Tomimoto H, Suenaga T, Wakita H, Budka H. Blood-brain barrier dysfunction in binswanger's disease; an immunohistochemical study. Acta Neuropathol. 1998;95(1):78–84.
108. Huisa BN, Caprihan A, Thompson J, Prestopnik J, Qualls CR, Rosenberg GA. Long-term blood-brain barrier permeability changes in Binswanger disease. Stroke. 2015;46(9):2413–8.
109. Rosenberg GA, Prestopnik J, Adair JC, Huisa BN, Knoefel J, Caprihan A, et al. Validation of biomarkers in subcortical ischaemic vascular disease of the Binswanger type: approach to targeted treatment trials. J Neurol Neurosurg Psychiatry. 2015;86(12):1324–30.
110. Sasamori T, Hida K, Yano S, Takeshi A, Iwasaki Y. Spinal cord swelling with abnormal gadolinium-enhancement mimicking intramedullary tumors in cervical spondylosis patients: three case reports and review of the literature. Asian J Neurosurg. 2010;5(2):1–9.
111. Ozawa H, Sato T, Hyodo H, Ishii Y, Morozumi N, Koizumi Y, et al. Clinical significance of intramedullary Gd-DTPA enhancement in cervical myelopathy. Spinal Cord. 2010;48(5):415–22.
112. De Reuck J, Deramecourt V, Cordonnier C, Auger F, Durieux N, Bordet R, et al. Detection of microbleeds in post-mortem brains of patients with frontotemporal Lobar degeneration: a 7.0-Tesla magnetic resonance imaging study with neuropathological correlates. Eur J Neurol. 2012;19(10):1355–60.
113. Hashemi E, Srivastava IN, Aguirre A, Yoseph ET, Kaushal E, Awani A, et al. A novel mouse model for cerebral inflammatory demyelination in X-linked adrenoleukodystrophy: insights into pathogenesis and potential therapeutic targets. Ann Neurol. 2025;97(2):296–312.
114. Gupta AO, Furcich JW, Nascene DR, Kemp S, King CJ, Nolan EE, et al. Targeting VEGF-mediated blood-brain barrier disruption in advanced cerebral leukodystrophy. J Neuroimmunol. 2024;393:578395.
115. Orchard PJ, Nascene DR, Miller WP, Gupta A, Kenney-Jung D, Lund TC. Successful donor engraftment and repair of the blood-brain barrier in cerebral adrenoleukodystrophy. Blood. 2019;133(12):1378–81.
116. Musolino PL, Gong Y, Snyder JM, Jimenez S, Lok J, Lo EH, et al. Brain endothelial dysfunction in cerebral adrenoleukodystrophy. Brain. 2015;138(Pt 11):3206–20.
117. Waters S, Swanson MEV, Dieriks BV, Zhang YB, Grimsey NL, Murray HC, et al. Blood-spinal cord barrier leakage is independent of motor neuron pathology in ALS. Acta Neuropathol Commun. 2021;9(1):144.
118. Garbuzova-Davis S, Hernandez-Ontiveros DG, Rodrigues MC, Haller E, Frisina-Deyo A, Mirtyl S, et al. Impaired blood-brain/spinal cord barrier in ALS patients. Brain Res. 2012;1469:114–28.
119. Donnenfeld H, Kascsak RJ, Bartfeld H. Deposits of IgG and C3 in the spinal cord and motor cortex of ALS patients. J Neuroimmunol. 1984;6(1):51–7.
120. Gabdulkhaev R, Shimizu H, Kanazawa M, Kuroha Y, Hasegawa A, Idezuka J, et al. Blood-brain barrier dysfunction in multiple system atrophy: a human postmortem study. Neuropathology. 2025;45(3):210–22.
121. Shibata M, Makioka K, Nakamura T, Kasahara H, Yamazaki T, Takatama M, et al. Role of complement activation and disruption of the blood-brain barrier in the pathogenesis of multiple system atrophy. Neurosci Lett. 2024;822:137642.
122. Song SK, Lee SK, Lee JJ, Lee JE, Choi HS, Sohn YH, et al. Blood-brain barrier impairment is functionally correlated with clinical severity in patients of multiple system atrophy. Neurobiol Aging. 2011;32(12):2183–9.
123. Tan AYS, Martinez L, Murray HC, Mehrabi NF, Tippett LJ, Turner CP, et al. Elucidating cortical neurovascular involvement in huntington's disease using human brain tissue microarrays. Neurobiol Dis. 2025;206:106829.
124. Sciacca G, Cicchetti F. Mutant Huntingtin protein expression and blood-spinal cord barrier dysfunction in huntington disease. Ann Neurol. 2017;82(6):981–94.
125. Eide PK. Cellular changes at the glia-neuro-vascular interface in definite idiopathic normal pressure hydrocephalus. Front Cell Neurosci. 2022;16:981399.

126. Eide PK, Hansson HA. Blood-brain barrier leakage of blood proteins in idiopathic normal pressure hydrocephalus. Brain Res. 2020;1727:146547.
127. Lim MJ, Alexander N, Benedict JW, Chattopadhyay S, Shemilt SJ, Guerin CJ, et al. IgG entry and deposition are components of the neuroimmune response in Batten disease. Neurobiol Dis. 2007;25(2):239–51.
128. Duarte Lobo D, Nobre RJ, Oliveira Miranda C, Pereira D, Castelhano J, Sereno J, et al. The blood-brain barrier is disrupted in Machado-Joseph disease/spinocerebellar ataxia type 3: evidence from Transgenic mice and human post-mortem samples. Acta Neuropathol Commun. 2020;8(1):152.
129. Majerova P, Garruto RM, Kovac A. Cerebrovascular inflammation is associated with Tau pathology in Guam parkinsonism dementia. J Neural Transm (Vienna). 2018;125(7):1013–25.
130. Nakamura M, Yamashita T, Ueda M, Obayashi K, Sato T, Ikeda T, et al. Neuroradiologic and clinicopathologic features of oculoleptomeningeal type amyloidosis. Neurology. 2005;65(7):1051–6.
131. Li KL, Zhu X, Zhao S, Jackson A. Blood-brain barrier permeability of normal-appearing white matter in patients with vestibular schwannoma: a new hybrid approach for analysis of T(1) -W DCE-MRI. J Magn Reson Imaging. 2017;46(1):79–93.
132. Moussiopoulou J, Yakimov V, Roell L, Rauchmann BS, Toth H, Melcher J, et al. Higher blood-brain barrier leakage in schizophrenia-spectrum disorders: a comparative dynamic contrast-enhanced magnetic resonance imaging study with healthy controls. Brain Behav Immun. 2025;128:256–65.
133. Cheng Y, Wang T, Zhang T, Yi S, Zhao S, Li N, et al. Increased blood-brain barrier permeability of the thalamus correlated with symptom severity and brain volume alterations in patients with schizophrenia. Biol Psychiatry Cogn Neurosci Neuroimaging. 2022;7(10):1025–34.
134. Goldwaser EL, Swanson RL 2nd, Arroyo EJ, Venkataraman V, Kosciuk MC, Nagele RG, et al. A preliminary report: the hippocampus and surrounding Temporal cortex of patients with schizophrenia have impaired blood-brain barrier. Front Hum Neurosci. 2022;16:836980.
135. Cai HQ, Catts VS, Webster MJ, Galletly C, Liu D, O'Donnell M, et al. Increased macrophages and changed brain endothelial cell gene expression in the frontal cortex of people with schizophrenia displaying inflammation. Mol Psychiatry. 2020;25(4):761–75.
136. Shang B, Wang T, Zhao S, Yi S, Zhang T, Yang Y, et al. Higher blood-brain barrier permeability in patients with major depressive disorder identified by DCE-MRI imaging. Psychiatry Res Neuroimaging. 2024;337:111761.
137. Kamintsky L, Cairns KA, Veksler R, Bowen C, Beyea SD, Friedman A, et al. Blood-brain barrier imaging as a potential biomarker for bipolar disorder progression. Neuroimage Clin. 2020;26:102049.
138. Chaganti J, Zeng G, Patil A, Lockart I, Dellalana M, Montagnese S et al. Altered blood-brain barrier permeability is associated with abnormal distant connectivity and regional homogeneity in Covert hepatic encephalopathy - a cross sectional study. Hepatology. 2025. https://doi.org/10.1097/HEP.0000000000001343
139. Chaganti J, Zeng G, Tun N, Lockart I, Abdelshaheed C, Cysique L, et al. Novel magnetic resonance KTRANS measurement of blood-brain barrier permeability correlated with Covert HE. Hepatol Commun. 2023;7(4):e0079.
140. Cramer SP, Modvig S, Simonsen HJ, Frederiksen JL, Larsson HB. Permeability of the blood-brain barrier predicts conversion from optic neuritis to multiple sclerosis. Brain. 2015;138(Pt 9):2571–83.
141. Küker W, Hesselmann V, Thron A, de Simone A. MRI demonstration of reversible impairment of the blood-CNS barrier function in subacute combined degeneration of the spinal cord. J Neurol Neurosurg Psychiatry. 1997;62(3):298–9.
142. Zarekiani P, Breur M, Wolf NI, de Vries HE, van der Knaap MS, Bugiani M. Pathology of the neurovascular unit in leukodystrophies. Acta Neuropathol Commun. 2021;9(1):103.
143. Crockett AM, Ryan SK, Vasquez AH, Canning C, Kanyuch N, Kebir H, et al. Disruption of the blood-brain barrier in 22q11.2 deletion syndrome. Brain. 2021;144(5):1351–60.
144. Kim YE, Kim M, Kim S, Lee R, Ujihara Y, Marquez-Wilkins EM, et al. Endothelial SHANK3 regulates tight junctions in the neonatal mouse blood-brain barrier through beta-catenin signaling. Nat Commun. 2025;16(1):1407.
145. Mehra S, Ahsan AU, Sharma M, Budhwar M, Chopra M. Gestational Fisetin exerts neuroprotection by regulating mitochondria-directed canonical Wnt signaling, BBB integrity, and apoptosis in prenatal VPA-induced rodent model of autism. Mol Neurobiol. 2024;61(7):4001–20.
146. Kumar H, Kulkarni GT, Diwan V, Sharma B. Shielding effect of Ryanodine receptor modulator in rat model of autism. Basic Clin Neurosci. 2023;14(2):247–61.
147. Jagadapillai R, Qiu X, Ojha K, Li Z, El-Baz A, Zou S, et al. Potential cross talk between autism risk genes and neurovascular molecules: a pilot study on impact of blood brain barrier integrity. Cells. 2022;11(14):2211.
148. Kumar H, Diwan V, Sharma B. Protective effect of nimodipine against valproic-acid induced biochemical and behavioral phenotypes of autism. Clin Psychopharmacol Neurosci. 2022;20(4):725–36.
149. Heller GJ, Marshall MS, Issa Y, Marshall JN, Nguyen D, Rue E, et al. Waning efficacy in a long-term AAV-mediated gene therapy study in the murine model of Krabbe disease. Mol Ther. 2021;29(5):1883–902.
150. Kondo A, Nakano T, Suzuki K. Blood-brain barrier permeability to horseradish peroxidase in twitcher and cuprizone-intoxicated mice. Brain Res. 1987;425(1):186–90.
151. Pepe G, Fioriniello S, Marracino F, Capocci L, Maglione V, D'Esposito M, et al. Blood-brain barrier integrity is perturbed in a Mecp2-null mouse model of Rett syndrome. Biomolecules. 2023;13(4):606.
152. Kajitani GS, Brace L, Trevino-Villarreal JH, Trocha K, MacArthur MR, Vose S, et al. Neurovascular dysfunction and neuroinflammation in a Cockayne syndrome mouse model. Aging. 2021;13(19):22710–31.
153. Alonso C, Garcia-Culebras A, Satta V, Hernandez-Fisac I, Sierra A, Guimare JA, et al. Investigation in blood-brain barrier integrity and susceptibility to immune cell penetration in a mouse model of Dravet syndrome. Brain Behav Immun Health. 2025;44:100955.
154. Garbuzova-Davis S, Louis MK, Haller EM, Derasari HM, Rawls AE, Sanberg PR. Blood-brain barrier impairment in an animal model of MPS III B. PLoS ONE. 2011;6(3):e16601.
155. Fu C, Huang L, Lian C, Yue J, Lin P, Xu L, et al. Effects of long-term magnesium L-threonate supplementation on neuroinflammation, demyelination and blood-brain barrier integrity in mice with neuromyelitis Optica spectrum disorder. Brain Res. 2025;1846:149234.
156. Katsu M, Sekine-Tanaka M, Tanaka M, Horai Y, Akatsuka A, Suga M, et al. Inhibition of repulsive guidance molecule-a ameliorates compromised blood-spinal cord barrier integrity associated with neuromyelitis Optica in rats. J Neuroimmunol. 2024;388:578297.
157. Shimizu F, Schaller KL, Owens GP, Cotleur AC, Kellner D, Takeshita Y, et al. Glucose-regulated protein 78 autoantibody associates with blood-brain barrier disruption in neuromyelitis Optica. Sci Transl Med. 2017;9(397):eaai9111.
158. Tröscher AR, Klang A, French M, Quemada-Garrido L, Kneissl SM, Bien CG, et al. Selective limbic blood-brain barrier breakdown in a feline model of limbic encephalitis with LGI1 antibodies. Front Immunol. 2017;8:1364.
159. Tamma R, Annese T, Capogrosso RF, Cozzoli A, Benagiano V, Sblendorio V, et al. Effects of prednisolone on the dystrophin-associated proteins in the blood-brain barrier and skeletal muscle of dystrophic Mdx mice. Lab Invest. 2013;93(5):592–610.
160. Nico B, Paola Nicchia G, Frigeri A, Corsi P, Mangieri D, Ribatti D, et al. Altered blood-brain barrier development in dystrophic MDX mice. Neuroscience. 2004;125(4):921–35.
161. Wei X, Zhou Y, Ma L, Li W, Shan C, Zhang S, et al. Inhibition of the Notch pathway alleviates nab-paclitaxel-induced peripheral neuropathic pain in rats by suppressing HMGB1/caveolin-1 signaling in the spinal cord. Mediators Inflamm. 2025;2025:4638804.
162. Sauer RS, Kirchner J, Yang S, Hu L, Leinders M, Sommer C, et al. Blood-spinal cord barrier breakdown and pericyte deficiency in peripheral neuropathy. Ann N Y Acad Sci. 2017;1405(1):71–88.
163. Kim J, Chuang HC, Wolf NK, Nicolai CJ, Raulet DH, Saijo K, et al. Tumor-induced disruption of the blood-brain barrier promotes host death. Dev Cell. 2021;56(19):2712–e214.
164. Michalak S, Wender M, Michalowska-Wender G, Kozubski W. Blood-brain barrier breakdown and cerebellar degeneration in the course of experimental neoplastic disease. Are Circulating cytokine-induced neutrophil chemoattractant-1 (CINC-1) and– 2alpha(CINC-2alpha) the involved mediators? Folia Neuropathol. 2010;48(2):93–103.
165. Guo D, Zhang B, Han L, Rensing NR, Wong M. Cerebral vascular and blood brain-barrier abnormalities in a mouse model of epilepsy and tuberous sclerosis complex. Epilepsia. 2024;65(2):483–96.
166. Tran H, Mittal A, Sagi V, Luk K, Nguyen A, Gupta M, et al. Mast cells induce blood brain barrier damage in SCD by causing Endoplasmic reticulum stress in the endothelium. Front Cell Neurosci. 2019;13:56.
167. Hao Y, Su Y, He Y, Zhang W, Liu Y, Guo Y, et al. Impaired cerebral microvascular endothelial cells integrity due to elevated dopamine in myasthenic model. J Neuroinflammation. 2024;21(1):10.

168. Somers E, Lees RD, Hoban K, Sleigh JN, Zhou H, Muntoni F, et al. Vascular defects and spinal cord hypoxia in spinal muscular atrophy. Ann Neurol. 2016;79(2):217–30.
169. Ting KK, Coleman P, Kim HJ, Zhao Y, Mulangala J, Cheng NC, et al. Vascular senescence and leak are features of the early breakdown of the blood-brain barrier in alzheimer's disease models. Geroscience. 2023;45(6):3307–31.
170. Shibly AZ, Sheikh AM, Michikawa M, Tabassum S, Azad AK, Zhou X, et al. Analysis of cerebral small vessel changes in AD model mice. Biomedicines. 2022;11(1):50.
171. Yoshikawa M, Aizawa S, Oppenheim RW, Milligan C. Neurovascular unit pathology is observed very early in disease progression in the mutant SOD1(G93A) mouse model of amyotrophic lateral sclerosis. Exp Neurol. 2022;353:114084.
172. Saha A, Sarkar C, Singh SP, Zhang Z, Munasinghe J, Peng S, et al. The blood-brain barrier is disrupted in a mouse model of infantile neuronal ceroid lipofuscinosis: amelioration by Resveratrol. Hum Mol Genet. 2012;21(10):2233–44.
173. Phillips CM, Johnson AM, Stamatovic SM, Keep RF, Andjelkovic AV. 20 kDa isoform of connexin-43 augments Spatial reorganization of the brain endothelial junctional complex and lesion leakage in cerebral cavernous malformation type-3. Neurobiol Dis. 2023;186:106277.
174. Wei W, Ma D, Gu L, Li Y, Zhang L, Li L, et al. Epimedium flavonoids improve cerebral white matter lesions by inhibiting neuroinflammation and activating neurotrophic factor signal pathways in spontaneously hypertensive rats. Int Immunopharmacol. 2024;139:112683.
175. Hashimoto Y, Poirier K, Boddaert N, Hubert L, Aubart M, Kaminska A, et al. Recurrent de Novo mutations in CLDN5 induce an anion-selective blood-brain barrier and alternating hemiplegia. Brain. 2022;145(10):3374–82.
176. Oner TO, Unalp A, Hiz S, Bayram E, Kaytan I, Cingoz S. OCLN gene variants identified in three patients with severe neurodevelopmental disorder associated with epilepsy, intellectual disability and malformation of cortical development. Epileptic Disord. 2021;23(6):843–53.
177. Jenkinson EM, Livingston JH, O'Driscoll MC, Desguerre I, Nabbout R, Boddaert N, et al. Comprehensive molecular screening strategy of OCLN in band-like calcification with simplified gyration and polymicrogyria. Clin Genet. 2018;93(2):228–34.
178. Abdel-Hamid MS, Abdel-Salam GMH, Issa MY, Emam BA, Zaki MS. Band-like calcification with simplified gyration and polymicrogyria: report of 10 new families and identification of five novel OCLN mutations. J Hum Genet. 2017;62(5):553–9.
179. Greene C, Kealy J, Humphries MM, Gong Y, Hou J, Hudson N, et al. Dose-dependent expression of claudin-5 is a modifying factor in schizophrenia. Mol Psychiatry. 2018;23(11):2156–66.
180. Jana A, Wang X, Leasure JW, Magana L, Wang L, Kim YM, et al. Increased type I interferon signaling and brain endothelial barrier dysfunction in an experimental model of alzheimer's disease. Sci Rep. 2022;12(1):16488.
181. Nicaise C, Mitrecic D, Demetter P, De Decker R, Authelet M, Boom A, et al. Impaired blood-brain and blood-spinal cord barriers in mutant SOD1-linked ALS rat. Brain Res. 2009;1301:152–62.
182. Garbuzova-Davis S, Saporta S, Haller E, Kolomey I, Bennett SP, Potter H, et al. Evidence of compromised blood-spinal cord barrier in early and late symptomatic SOD1 mice modeling ALS. PLoS ONE. 2007;2(11):e1205.
183. Verheggen ICM, de Jong JJA, van Boxtel MPJ, Gronenschild E, Palm WM, Postma AA, et al. Increase in blood-brain barrier leakage in healthy, older adults. Geroscience. 2020;42(4):1183–93.
184. Wang H, Golob EJ, Su MY. Vascular volume and blood-brain barrier permeability measured by dynamic contrast enhanced MRI in hippocampus and cerebellum of patients with MCI and normal controls. J Magn Reson Imaging. 2006;24(3):695–700.
185. Yamazaki Y, Shinohara M, Shinohara M, Yamazaki A, Murray ME, Liesinger AM, et al. Selective loss of cortical endothelial tight junction proteins during alzheimer's disease progression. Brain. 2019;142(4):1077–92.
186. Kimizu T, Takahashi Y, Oboshi T, Horino A, Omatsu H, Koike T, et al. Chronic dysfunction of blood-brain barrier in patients with post-encephalitic/encephalopathic epilepsy. Seizure. 2018;63:85–90.
187. Li YJ, Wang ZH, Zhang B, Zhe X, Wang MJ, Shi ST, et al. Disruption of the blood-brain barrier after generalized tonic-clonic seizures correlates with cerebrospinal fluid MMP-9 levels. J Neuroinflammation. 2013;10:80.
188. Castañeda-Cabral JL, Colunga-Duran A, Urena-Guerrero ME, Beas-Zarate C, Nunez-Lumbreras MLA, Orozco-Suarez S, et al. Expression of VEGF- and tight junction-related proteins in the neocortical microvasculature of patients with drug-resistant Temporal lobe epilepsy. Microvasc Res. 2020;132:104059.
189. Llorens F, Schmitz M, Gloeckner SF, Kaerst L, Hermann P, Schmidt C, et al. Increased albumin csf/serum ratio in dementia with lewy bodies. J Neurol Sci. 2015;358(1–2):398–403.
190. Fu J, Lai X, Wei Q, Chen X, Shang H. Associations of cerebrospinal fluid profiles with severity and mortality risk of amyotrophic lateral sclerosis. Front Neurosci. 2024;18:1375892.
191. Li JY, Cai ZY, Sun XH, Shen DC, Yang XZ, Liu MS, et al. Blood-brain barrier dysfunction and Myelin basic protein in survival of amyotrophic lateral sclerosis with or without frontotemporal dementia. Neurol Sci. 2022;43(5):3201–10.
192. Wu Y, Yang X, Li X, Wang H, Wang T. Elevated cerebrospinal fluid homocysteine is associated with blood-brain barrier disruption in amyotrophic lateral sclerosis patients. Neurol Sci. 2020;41(7):1865–72.
193. Klose V, Jesse S, Lewerenz J, Kassubek J, Dorst J, Rosenbohm A, et al. Blood-CSF barrier integrity in amyotrophic lateral sclerosis. Brain. 2024;147(12):4254–64.
194. Alarcan H, Vourc'h P, Berton L, Benz-De Bretagne I, Piver E, Andres CR, et al. Implication of central nervous system barrier impairment in amyotrophic lateral sclerosis: gender-related difference in patients. Int J Mol Sci. 2023;24(13):11196.
195. Verde F, Ferrari I, Maranzano A, Ciusani E, Torre S, Milone I, et al. Relationship between cerebrospinal fluid/serum albumin quotient and phenotype in amyotrophic lateral sclerosis: a retrospective study on 328 patients. Neurol Sci. 2023;44(5):1679–85.
196. Assialioui A, Domínguez R, Ferrer I, Andrés-Benito P, Povedano M. Elevated cerebrospinal fluid proteins and albumin determine a poor prognosis for spinal amyotrophic lateral sclerosis. Int J Mol Sci. 2022;23(19):11063.
197. Prell T, Vlad B, Gaur N, Stubendorff B, Grosskreutz J. Blood-brain barrier disruption is not associated with disease aggressiveness in amyotrophic lateral sclerosis. Front Neurosci. 2021;15:656456.
198. Miller WP, Rothman SM, Nascene D, Kivisto T, DeFor TE, Ziegler RS, et al. Outcomes after allogeneic hematopoietic cell transplantation for childhood cerebral adrenoleukodystrophy: the largest single-institution cohort report. Blood. 2011;118(7):1971–8.
199. Yuan S, Ma Q, Hou C, Zhao Y, Liu KJ, Ji X, et al. Association of serum occludin levels and perihematomal edema volumes in intracranial hemorrhage patients. CNS Neurosci Ther. 2024;30(3):e14450.
200. Yuan S, Li W, Hou C, Kang H, Ma Q, Ji X, et al. Serum occludin level combined with NIHSS score predicts hemorrhage transformation in ischemic stroke patients with reperfusion. Front Cell Neurosci. 2021;15:714171.
201. Yuan S, Ma Q, Hou C, Li W, Liu KJ, Ji X, et al. The combination model of serum occludin and clinical risk factors improved the efficacy for predicting hemorrhagic transformation in stroke patients with recanalization. Heliyon. 2024;10(2):e25052.
202. Kazmierski R, Michalak S, Wencel-Warot A, Nowinski WL. Serum tight-junction proteins predict hemorrhagic transformation in ischemic stroke patients. Neurology. 2012;79(16):1677–85.
203. Lasek-Bal A, Kokot A, Gendosz de Carrillo D, Student S, Pawletko K, Krzan A, et al. Plasma levels of occludin and claudin-5 in acute stroke are correlated with the type and location of stroke but not with the neurological state of patients-preliminary data. Brain Sci. 2020;10(11):831.
204. Kakkar P, Almusined M, Kakkar T, Munyombwe T, Makawa L, Kain K, et al. Circulating blood-brain barrier proteins for differentiating ischaemic stroke patients from stroke mimics. Biomolecules. 2024;14(11):1344.
205. Agoston DV, McCullough J, Aniceto R, Lin IH, Kamnaksh A, Eklund M, et al. Blood-based biomarkers of repetitive, subconcussive blast overpressure exposure in the training environment: a pilot study. Neurotrauma Rep. 2022;3(1):479–90.
206. Robinson BD, Tharakan B, Lomas A, Wiggins-Dohlvik K, Alluri H, Shaji CA, et al. Exploring blood-brain barrier hyperpermeability and potential biomarkers in traumatic brain injury. Proc (Bayl Univ Med Cent). 2020;33(2):199–204.
207. Sun M, Symons GF, O'Brien WT, McCullough J, Aniceto R, Lin IH, et al. Serum protein biomarkers of inflammation, oxidative stress, and cerebrovascular and glial injury in concussed Australian football players. J Neurotrauma. 2022;39(11–12):800–8.
208. Eagle SR, Svirsky SE, Puccio AM, Borrasso A, Edelman K, Beers S, et al. Predictive blood biomarkers of targeted intervention for chronic mental health symptoms following traumatic brain injury. J Neurotrauma. 2024;42(5–6):e454–60.
209. Lai QL, Cai MT, Zheng Y, Fang GL, Du BQ, Shen CH, et al. Evaluation of CSF albumin quotient in neuronal surface antibody-associated autoimmune encephalitis. Fluids Barriers CNS. 2022;19(1):93.

210. Yu Y, Wu Y, Cao X, Li J, Liao X, Wei J, et al. The clinical features and prognosis of anti-NMDAR encephalitis depends on blood brain barrier integrity. Mult Scler Relat Disord. 2021;47:102604.
211. Wang R, Guan HZ, Ren HT, Wang W, Hong Z, Zhou D. CSF findings in patients with anti-N-methyl-D-aspartate receptor-encephalitis. Seizure. 2015;29:137–42.
212. Cheng X, Li Y, Wang Y, Sun Y, Lian Y. Impact of blood-brain barrier disruption on clinical features and treatment response in patients with newly diagnosed autoimmune encephalitis. J Neuroimmunol. 2023;383:578203.
213. Hosokawa T, Nakajima H, Doi Y, Sugino M, Kimura F, Hanafusa T, et al. Increased serum matrix metalloproteinase-9 in neuromyelitis optica: implication of disruption of blood-brain barrier. J Neuroimmunol. 2011;236(1–2):81–6.
214. Zheng X, Yan H, Yin H, Shi J, Liu Y, Zhao H, et al. Acute neuromyelitis Optica spectrum disorder patients' clinical analysis of disability-related biomarkers. BMC Neurol. 2025;25(1):119.
215. Tomizawa Y, Yokoyama K, Saiki S, Takahashi T, Matsuoka J, Hattori N. Blood-brain barrier disruption is more severe in neuromyelitis Optica than in multiple sclerosis and correlates with clinical disability. J Int Med Res. 2012;40(4):1483–91.
216. Greene C, Hanley N, Campbell M. Blood-brain barrier associated tight junction disruption is a hallmark feature of major psychiatric disorders. Transl Psychiatry. 2020;10(1):373.
217. Maes M, Sirivichayakul S, Kanchanatawan B, Vodjani A. Breakdown of the paracellular tight and adherens junctions in the gut and blood brain barrier and damage to the vascular barrier in patients with deficit schizophrenia. Neurotox Res. 2019;36(2):306–22.
218. Aydogan Avşar P, Akkuş M. ZO-1 serum levels as a potential biomarker for psychotic disorder. Clin Neuropharmacol. 2024;47(3):67–71.
219. Campana M, Lohrs L, Strauss J, Munz S, Oviedo-Salcedo T, Fernando P, et al. Blood-brain barrier dysfunction and folate and vitamin B12 levels in first-episode schizophrenia-spectrum psychosis: a retrospective chart review. Eur Arch Psychiatry Clin Neurosci. 2023;273(8):1693–701.
220. Oviedo-Salcedo T, Wagner E, Campana M, Gagsteiger A, Strube W, Eichhorn P, et al. Cerebrospinal fluid abnormalities in first- and multi-episode schizophrenia-spectrum disorders: impact of clinical and demographical variables. Transl Psychiatry. 2021;11(1):621.
221. Feigin A, Evans EE, Fisher TL, Leonard JE, Smith ES, Reader A, et al. Pepinemab antibody Blockade of SEMA4D in early huntington's disease: a randomized, placebo-controlled, phase 2 trial. Nat Med. 2022;28(10):2183–93.
222. Feigin A, Evans EE, Fisher TL, Zauderer M. Pepinemab: a SEMA4D antagonist for treatment of huntington's and other neurodegenerative diseases. Expert Opin Investig Drugs. 2025;34(3):109–19.
223. Smith ES, Jonason A, Reilly C, Veeraraghavan J, Fisher T, Doherty M, et al. SEMA4D compromises blood-brain barrier, activates microglia, and inhibits remyelination in neurodegenerative disease. Neurobiol Dis. 2015;73:254–68.
224. Mao Y, Evans EE, Mishra V, Balch L, Eberhardt A, Zauderer M, et al. Anti-semaphorin 4D rescues motor, cognitive, and respiratory phenotypes in a Rett syndrome mouse model. Int J Mol Sci. 2021;22(17):9465.
225. Southwell AL, Franciosi S, Villanueva EB, Xie Y, Winter LA, Veeraraghavan J, et al. Anti-semaphorin 4D immunotherapy ameliorates neuropathology and some cognitive impairment in the YAC128 mouse model of huntington disease. Neurobiol Dis. 2015;76:46–56.
226. LaGanke C, Samkoff L, Edwards K, Jung Henson L, Repovic P, Lynch S, et al. Safety/tolerability of the anti-semaphorin 4D antibody VX15/2503 in a randomized phase 1 trial. Neurol Neuroimmunol Neuroinflamm. 2017;4(4):e367.
227. Zauderer M, Evans EE. Conclusions of the SIGNAL study in huntington and implications for treatment of other slowly progressive neurodegenerative diseases. Clin Transl Med. 2023;13(2):e1169.
228. Tseriotis VS, Liampas A, Lazaridou IZ, Karachrysafi S, Vavougios GD, Hadjigeorgiou GM, et al. Repulsive guidance molecule-A as a therapeutic target across neurological disorders: an update. Int J Mol Sci. 2025;26(7):3221.
229. Zhang L, Tang S, Ma Y, Liu J, Monnier P, Li H, et al. RGMa participates in the blood-brain barrier dysfunction through BMP/BMPR/YAP signaling in multiple sclerosis. Front Immunol. 2022;13:861486.
230. Muramatsu R, Kubo T, Mori M, Nakamura Y, Fujita Y, Akutsu T, et al. RGMa modulates T cell responses and is involved in autoimmune encephalomyelitis. Nat Med. 2011;17(4):488–94.
231. Yamamoto M, Itokazu T, Uno H, Maki T, Shibuya N, Yamashita T. Anti-RGMa neutralizing antibody ameliorates vascular cognitive impairment in mice. Neurotherapeutics. 2025;22(2):e00500.
232. Hirata T, Itokazu T, Sasaki A, Sugihara F, Yamashita T. Humanized anti-RGMa antibody treatment promotes repair of blood-spinal cord barrier under autoimmune encephalomyelitis in mice. Front Immunol. 2022;13:870126.
233. Hata K, Fujitani M, Yasuda Y, Doya H, Saito T, Yamagishi S, et al. RGMa Inhibition promotes axonal growth and recovery after spinal cord injury. J Cell Biol. 2006;173(1):47–58.
234. Delétage N, Le Douce J, Callizot N, Godfrin Y, Lemarchant S. SCO-spondin-derived peptide protects neurons from glutamate-induced excitotoxicity. Neuroscience. 2021;463:317–36.
235. Lemarchant S, Sourioux M, Le Douce J, Henriques A, Callizot N, Hugues S, et al. NX210c peptide promotes glutamatergic receptor-mediated synaptic transmission and signaling in the mouse central nervous system. Int J Mol Sci. 2022;23(16):8867.
236. Sourioux M, Lemarchant S, Le Douce J, Hugues S, Farinelli M, Godfrin Y. A subcommissural organ-spondin-derived peptide (NX210c) improves the recovery of synaptic transmission after in vitro ischemia. BRAIN and BRAIN-PET 2022 abstracts. J Cereb Blood Flow Metab. 2022;42(1):108–273.
237. Greene C, Rebergue N, Fewell G, Janigro D, Godfrin Y, Campbell M, et al. NX210c drug candidate peptide strengthens mouse and human blood-brain barriers. Fluids Barriers CNS. 2024;21(1):76.
238. Kramar EA, Lin B, Rex CS, Gall CM, Lynch G. Integrin-driven actin polymerization consolidates long-term potentiation. Proc Natl Acad Sci USA. 2006;103(14):5579–84.
239. Huang Z, Shimazu K, Woo NH, Zang K, Muller U, Lu B, et al. Distinct roles of the beta 1-class integrins at the developing and the mature hippocampal excitatory synapse. J Neurosci. 2006;26(43):11208–19.
240. Halder SK, Sapkota A, Milner R. beta1 integrins play a critical role maintaining vascular integrity in the hypoxic spinal cord, particularly in white matter. Acta Neuropathol Commun. 2024;12(1):45.
241. Halder SK, Delorme-Walker VD, Milner R. beta1 integrin is essential for blood-brain barrier integrity under stable and vascular remodelling conditions; effects differ with age. Fluids Barriers CNS. 2023;20(1):52.
242. Osada T, Gu YH, Kanazawa M, Tsubota Y, Hawkins BT, Spatz M, et al. Interendothelial claudin-5 expression depends on cerebral endothelial cell-matrix adhesion by beta(1)-integrins. J Cereb Blood Flow Metab. 2011;31(10):1972–85.
243. Le Douce J, Delétage N, Bourdès V, Lemarchant S, Godfrin Y. Subcommissural organ-spondin-derived peptide restores memory in a mouse model of alzheimer's disease. Front Neurosci. 2021;15:651094.
244. Yang L, Zhu J, Yang L, Gan Y, Hu D, Zhao J, et al. SCO-spondin-derived peptide NX210 rescues neurons from cerebral ischemia/reperfusion injury through modulating the integrin-beta1 mediated PI3K/Akt pathway. Int Immunopharmacol. 2022;111:109079.
245. Sakka L, Delétage N, Lalloue F, Duval A, Chazal J, Lemaire JJ, et al. SCO-spondin derived peptide NX210 induces neuroprotection in vitro and promotes fiber regrowth and functional recovery after spinal cord injury. PLoS ONE. 2014;9(3):e93179.
246. Janus A, Dumas D, Le Douce J, Marie S, Pasculli G, Bambury P, et al. Safety, tolerability and pharmacokinetic-pharmacodynamic relationship of NX210c peptide in healthy elderly volunteers: randomized, placebo-controlled, double-blind, multiple ascending dose study. Neurol Ther. 2025;14(1):357–77.
247. Pereira PM, Papy-Garcia D, Barritault D, Chiappini F, Jackisch R, Schimchowitsch S, et al. Protective effects of a synthetic glycosaminoglycan mimetic (OTR4132) in a rat immunotoxic lesion model of septohippocampal cholinergic degeneration. Glycoconj J. 2022;39(1):107–30.
248. Khelif Y, Toutain J, Quittet MS, Chantepie S, Laffray X, Valable S, et al. A Heparan sulfate-based matrix therapy reduces brain damage and enhances functional recovery following stroke. Theranostics. 2018;8(21):5814–27.
249. Barritault D, Bernaudin M, Touzani O, Toutain J, Khelif Y. inventors; organes Tissus regeneration reparation remplacement, assignee. Composition for the protection and repair of the blood brain barrier. France patent WO2020/239356. 2019;30 Apr 2020. https://worldwide.espacenet.com/patent/search/family/068138337/publication/WO2020239356A1?q=WO2020%2F239356
250. Zanin-Zhorov A, Chen W, Moretti J, Nyuydzefe MS, Zhorov I, Munshi R, et al. Selectivity matters: selective ROCK2 inhibitor ameliorates established liver fibrosis via targeting inflammation, fibrosis, and metabolism. Commun Biol. 2023;6(1):1176.
251. Cerutti C, Ridley AJ. Endothelial cell-cell adhesion and signaling. Exp Cell Res. 2017;358(1):31–8.
252. Fu Z, Chen Y, Qin F, Yang S, Deng X, Ding R, et al. Increased activity of Rho kinase contributes to hemoglobin-induced early disruption of the

blood-brain barrier in vivo after the occurrence of intracerebral hemorrhage. Int J Clin Exp Pathol. 2014;7(11):7844–53.
253. McKerracher L, Shenkar R, Abbinanti M, Cao Y, Peiper A, Liao JK, et al. A brain-targeted orally available ROCK2 inhibitor benefits mild and aggressive cavernous Angioma disease. Transl Stroke Res. 2020;11(3):365–76.
254. Borikova AL, Dibble CF, Sciaky N, Welch CM, Abell AN, Bencharit S, et al. Rho kinase Inhibition rescues the endothelial cell cerebral cavernous malformation phenotype. J Biol Chem. 2010;285(16):11760–4.
255. Sato K, Nakagawa S, Morofuji Y, Matsunaga Y, Fujimoto T, Watanabe D, et al. Effects of fasudil on blood-brain barrier integrity. Fluids Barriers CNS. 2022;19(1):43.
256. Huang XN, Fu J, Wang WZ. The effects of fasudil on the permeability of the rat blood-brain barrier and blood-spinal cord barrier following experimental autoimmune encephalomyelitis. J Neuroimmunol. 2011;239(1–2):61–7.
257. Koch JC, Leha A, Bidner H, Cordts I, Dorst J, Gunther R, et al. Safety, tolerability, and efficacy of fasudil in amyotrophic lateral sclerosis (ROCK-ALS): a phase 2, randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2024;23(11):1133–46.
258. Ovid Therapeutics. Ovid R&D Day. 2023. Available from: https://investors.ovidrx.com/events-and-presentations/events/event-details/2023/Ovid-RD-Day/default.aspx
259. Ovid Therapeutics. Ovid Therapeutics and Graviton Bioscience announce topline data from a phase 1 clinical trial studying OV888/GV101 capsule, a potential first-in-class therapy for cerebral cavernous malformations. 2024. Available from: https://investors.ovidrx.com/news/news-details/2024/Ovid-Therapeutics-and-Graviton-Bioscience-Announce-Topline-Data-from-a-Phase-1-Clinical-Trial-Studying-OV888GV101-Capsule-a-Potential-First-In-Class-Therapy-for-Cerebral-Cavernous-Malformations/default.aspx?_ga=2.2298613.499700970.1739355008-880086808.1736179630.
260. Maher-Edwards G, De'Ath J, Barnett C, Lavrov A, Lockhart A. A 24-week study to evaluate the effect of Rilapladib on cognition and cerebrospinal fluid biomarkers of alzheimer's disease. Alzheimers Dement (N Y). 2015;1(2):131–40.
261. SciNeuro Pharmaceuticals. Deciphering the enigma of brain disease. 2023. Available from: https://www.nature.com/articles/d43747-023-00121-0
262. Mulder IA, Abbinanti M, Woller SA, Ruschel J, Coutinho JM, de Vries HE, et al. The novel ROCK2 selective inhibitor NRL-1049 preserves the blood-brain barrier after acute injury. J Cereb Blood Flow Metab. 2024;44(11):1238–52.
263. Neurelis. Neurelis pipeline update - Advancements to address unmet needs in neuroscience 3.7.24. 2024. Available from: https://vimeo.com/1017961143/b99041b328?share=copy
264. Kantor AB, Akassoglou K, Stavenhagen JB. Fibrin-targeting immunotherapy for dementia. J Prev Alzheimers Dis. 2023;10(4):647–60.
265. Ryu JK, Rafalski VA, Meyer-Franke A, Adams RA, Poda SB, Rios Coronado PE, et al. Fibrin-targeting immunotherapy protects against neuroinflammation and neurodegeneration. Nat Immunol. 2018;19(11):1212–23.
266. Alzheimer's Drug Discovery Foundation. THN391. 2024. Available from: https://www.alzdiscovery.org/cognitive-vitality/researchers
267. Chen Y, Suzuki A, Tortorici MA, Garrett M, LaBadie RR, Umeyama Y, et al. Axitinib plasma pharmacokinetics and ethnic differences. Invest New Drugs. 2015;33(2):521–32.
268. Rugo HS, Herbst RS, Liu G, Park JW, Kies MS, Steinfeldt HM, et al. Phase I trial of the oral antiangiogenesis agent AG-013736 in patients with advanced solid tumors: Pharmacokinetic and clinical results. J Clin Oncol. 2005;23(24):5474–83.
269. Singh CSB, Choi KB, Munro L, Wang HY, Pfeifer CG, Jefferies WA. Reversing pathology in a preclinical model of alzheimer's disease by hacking cerebrovascular neoangiogenesis with advanced cancer therapeutics. EBioMedicine. 2021;71:103503.
270. Wang K, Zhou W, Wen L, Jin X, Meng T, Li S, et al. The protective effects of axitinib on blood-brain barrier dysfunction and ischemia-reperfusion injury in acute ischemic stroke. Exp Neurol. 2024;379:114870.
271. Wang Y, Li S, Pan Y, Li H, Parsons MW, Campbell BCV, et al. Tenecteplase versus Alteplase in acute ischaemic cerebrovascular events (TRACE-2): a phase 3, multicentre, open-label, randomised controlled, non-inferiority trial. Lancet. 2023;401(10377):645–54.
272. Lemarchant S, Docagne F, Emery E, Vivien D, Ali C, Rubio M. tPA in the injured central nervous system: different scenarios starring the same actor? Neuropharmacology. 2012;62(2):749–56.
273. Lesept F, Chevilley A, Jezequel J, Ladepeche L, Macrez R, Aimable M, et al. Tissue-type plasminogen activator controls neuronal death by Raising surface dynamics of extrasynaptic NMDA receptors. Cell Death Dis. 2016;7(11):e2466.
274. Torrente D, Su EJ, Citalan-Madrid AF, Schielke GP, Magaoay D, Warnock M, et al. The interaction of tPA with NMDAR1 drives neuroinflammation and neurodegeneration in alpha-synuclein-mediated neurotoxicity. J Neuroinflammation. 2025;22(1):8.
275. Lebrun F, Levard D, Lemarchand E, Yetim M, Furon J, Potzeha F, et al. Improving stroke outcomes in hyperglycemic mice by modulating tPA/NMDAR signaling to reduce inflammation and hemorrhages. Blood Adv. 2024;8(5):1330–44.
276. Mehra A, Guerit S, Macrez R, Gosselet F, Sevin E, Lebas H, et al. Nonionotropic action of dndothelial NMDA receptors on blood-brain barrier permeability via Rho/ROCK-mediated phosphorylation of myosin. J Neurosci. 2020;40(8):1778–87.
277. Macrez R, Ortega MC, Bardou I, Mehra A, Fournier A, Van der Pol SM, et al. Neuroendothelial NMDA receptors as therapeutic targets in experimental autoimmune encephalomyelitis. Brain. 2016;139(Pt 9):2406–19.
278. Trevino TN, Fogel AB, Otkiran G, Niladhuri SB, Sanborn MA, Class J, et al. Engineered Wnt7a ligands rescue blood-brain barrier and cognitive deficits in a COVID-19 mouse model. Brain. 2024;147(5):1636–43.
279. Martin M, Vermeiren S, Bostaille N, Eubelen M, Spitzer D, Vermeersch M, et al. Engineered Wnt ligands enable blood-brain barrier repair in neurological disorders. Science. 2022;375(6582):eabm4459.
280. Kılıç F, Işık Ü, Demirdaş A, Doğuç DK, Bozkurt M. Serum Zonulin and claudin-5 levels in patients with bipolar disorder. J Affect Disord. 2020;266:37–42.
281. Kılıç F, Işık Ü, Kumbul Doğuç D. Serum claudin-5, but not zonulin, May be associated with obsessive-compulsive disorder. Psychiatr Danub. 2022;34(2):273–8.
282. Işık Ü, Aydoğan Avşar P, Aktepe E, Doğuç DK, Kılıç F, Büyükbayram Hİ. Serum Zonulin and claudin-5 levels in children with obsessive-compulsive disorder. Nord J Psychiatry. 2020;74(5):346–51.
283. Akın-Kınay F, Uzun N, Kılınç İ, Kılıç AO. Tight junction proteins and blood-brain barrier integrity in pediatric obsessive-compulsive disorder: a study on claudin-5, claudin-12, occludin, tricellulin, and angulin-1. Clin Psychopharmacol Neurosci. 2025. https://doi.org/10.9758/cpn.25.1293
284. Bilgiç A, Ferahkaya H, Karagöz H, Kılınç İ, Energin VM. Serum claudin-5, claudin-11, occludin, vinculin, paxillin, and beta-catenin levels in preschool children with autism spectrum disorder. Nord J Psychiatry. 2023;77(5):506–11.
285. Lu J, Wang J, Lin Z, Shi G, Wang R, Zhao Y, et al. MMP-9 as a biomarker for predicting hemorrhagic strokes in Moyamoya disease. Front Neurol. 2021;12:721118.
286. Olsson A, Gustavsen S, Langkilde AR, Hansen TH, Sellebjerg F, Bach Sondergaard H, et al. Circulating levels of tight junction proteins in multiple sclerosis: association with inflammation and disease activity before and after disease modifying therapy. Mult Scler Relat Disord. 2021;54:103136.
287. Tachibana K, Hirayama R, Sato N, Hattori K, Kato T, Takeda H, et al. Association of plasma claudin-5 with age and alzheimer disease. Int J Mol Sci. 2024;25(3):1419.
288. Wasielewska JM, Chaves JCS, Cabral-da-Silva MC, Pecoraro M, Viljoen SJ, Nguyen TH, et al. A patient-derived amyotrophic lateral sclerosis blood-brain barrier model for focused ultrasound-mediated anti-TDP-43 antibody delivery. Fluids Barriers CNS. 2024;21(1):65.
289. Aragón-González A, Shaw AC, Kok JR, Roussel FS, Santos Souza CD, Granger SM, et al. C9ORF72 patient-derived endothelial cells drive blood-brain barrier disruption and contribute to neurotoxicity. Fluids Barriers CNS. 2024;21(1):34.
290. Matsuo K, Nagamatsu J, Nagata K, Umeda R, Shiota T, Morimoto S, et al. Establishment of a novel amyotrophic lateral sclerosis patient (TARDBP (N345K/+))-derived brain microvascular endothelial cell model reveals defective Wnt/beta-catenin signaling: investigating diffusion barrier dysfunction and immune cell interaction. Front Cell Dev Biol. 2024;12:1357204.
291. Lee CAA, Seo HS, Armien AG, Bates FS, Tolar J, Azarin SM. Modeling and rescue of defective blood-brain barrier function of induced brain microvascular endothelial cells from childhood cerebral adrenoleukodystrophy patients. Fluids Barriers CNS. 2018;15(1):9.
292. Dao L, You Z, Lu L, Xu T, Sarkar AK, Zhu H, et al. Modeling blood-brain barrier formation and cerebral cavernous malformations in human PSC-derived organoids. Cell Stem Cell. 2024;31(6):818–e3311.
293. Crockett AM, Kebir H, Anderson SA, Jyonouchi S, Romberg N, Alvarez JI. 22q11.2 deletion-associated blood-brain barrier permeability potentiates systemic capillary leak syndrome neurologic features. J Clin Immunol. 2024;44(4):87.
294. Li Y, Sun Z, Zhu H, Sun Y, Shteyman DB, Markx S, et al. Inhibition of Abl kinase by Imatinib can rescue the compromised barrier function of 22q11.2DS patient-iPSC-derived blood-brain barriers. Cells. 2023;12(3):422.

295. Li Y, Xia Y, Zhu H, Luu E, Huang G, Sun Y, et al. Investigation of neurodevelopmental deficits of 22 q11.2 deletion syndrome with a patient-iPSC-derived blood-brain barrier model. Cells. 2021;10(10):2576.
296. Vignone D, Gonzalez Paz O, Fini I, Cellucci A, Auciello G, Battista MR, et al. Modelling the human blood-brain barrier in huntington disease. Int J Mol Sci. 2022;23(14):7813.
297. Smith FM, Kosman DJ. Brain microvascular endothelial cells differentiated from a friedreich's Ataxia patient iPSC are deficient in tight junction protein expression and paracellularly permeable. Front Mol Neurosci. 2025;18:1511388.
298. Nishihara H, Perriot S, Gastfriend BD, Steinfort M, Cibien C, Soldati S, et al. Intrinsic blood-brain barrier dysfunction contributes to multiple sclerosis pathogenesis. Brain. 2022;145(12):4334–48.
299. de Rus Jacquet A, Alpaugh M, Denis HL, Tancredi JL, Boutin M, Decaestecker J, et al. The contribution of inflammatory astrocytes to BBB impairments in a brain-chip model of parkinson's disease. Nat Commun. 2023;14(1):3651.
300. Stankovic I, Notaras M, Wolujewicz P, Lu T, Lis R, Ross ME, et al. Schizophrenia endothelial cells exhibit higher permeability and altered angiogenesis patterns in patient-derived organoids. Transl Psychiatry. 2024;14(1):53.
301. Lizano P, Pong S, Santarriaga S, Bannai D, Karmacharya R. Brain microvascular endothelial cells and blood-brain barrier dysfunction in psychotic disorders. Mol Psychiatry. 2023;28(9):3698–708.
302. Brown JA, Faley SL, Judge M, Ward P, Ihrie RA, Carson R, et al. Rescue of impaired blood-brain barrier in tuberous sclerosis complex patient derived neurovascular unit. J Neurodev Disord. 2024;16(1):27.
303. Stern L, Gautier R. Recherches Sur Le Liquide Céphalorachidien. I. Les rapports entre Le Liquide Céphalorachidien et La circulation sanguine. Arch Int Physiol. 1921;17:138–92.
304. Reese TS, Karnovsky MJ. Fine structural localization of a blood-brain barrier to exogenous peroxidase. J Cell Biol. 1967;34(1):207–17.
305. Watson PM, Anderson JM, Vanltallie CM, Doctrow SR. The tight-junction-specific protein ZO-1 is a component of the human and rat blood-brain barriers. Neurosci Lett. 1991;129(1):6–10.
306. Furuse M, Hirase T, Itoh M, Nagafuchi A, Yonemura S, Tsukita S, et al. Occludin: a novel integral membrane protein localizing at tight junctions. J Cell Biol. 1993;123(6 Pt 2):1777–88.
307. Morita K, Sasaki H, Furuse M, Tsukita S. Endothelial claudin: claudin-5/TMVCF constitutes tight junction strands in endothelial cells. J Cell Biol. 1999;147(1):185–94.
308. Grossman RI, Gonzalez-Scarano F, Atlas SW, Galetta S, Silberberg DH. Multiple sclerosis: gadolinium enhancement in MR imaging. Radiology. 1986;161(3):721–5.
309. Park JC, Baik SH, Han SH, Cho HJ, Choi H, Kim HJ, et al. Annexin A1 restores Abeta(1–42) -induced blood-brain barrier disruption through the Inhibition of RhoA-ROCK signaling pathway. Aging Cell. 2017;16(1):149–61.
310. Kalaria RN, Golde TE, Cohen ML, Younkin SG. Serum amyloid P in alzheimer's disease. Implications for dysfunction of the blood-brain barrier. Ann N Y Acad Sci. 1991;640:145–8.
311. Engelhardt JI, Soós J, Obál I, Vigh L, Siklós L. Subcellular localization of IgG from the Sera of ALS patients in the nervous system. Acta Neurol Scand. 2005;112(2):126–33.
312. Hamilton BF, Gould DH. Correlation of morphologic brain lesions with physiologic alterations and blood-brain barrier impairment in 3-nitropropionic acid toxicity in rats. Acta Neuropathol. 1987;74(1):67–74.
313. Morgan L, Shah B, Rivers LE, Barden L, Groom AJ, Chung R, et al. Inflammation and dephosphorylation of the tight junction protein occludin in an experimental model of multiple sclerosis. Neuroscience. 2007;147(3):664–73.
314. Broman T. Supravital analysis of disorders in the cerebral vascular permeability II. Two cases of multiple sclerosis. Acta Psychiatr Scand. 1947;22:58–71.
315. Carvey PM, Zhao CH, Hendey B, Lum H, Trachtenberg J, Desai BS, et al. 6-hydroxydopamine-induced alterations in blood-brain barrier permeability. Eur J Neurosci. 2005;22(5):1158–68.

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