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EDITORIAL

BBB dynamics: the lifespan perspective

Xuefang Sophie Ren[1,2]✉

Recent advances have shifted our understanding of the blood–brain barrier (BBB) not as a static wall, but as a dynamic and evolving system whose property is variable across the lifespan: acquisitive in early development, heterogeneous in adulthood, and increasingly fragile in aging. This BBB dynamic has called for a conceptional shift in how we understand the physiological and pathological processes related to barrier functions, including CNS drug exposure and age-related neurological disorders (e.g., stroke, vascular dementia). This Editorial offers a lifespan-based perspective of the BBB dynamics, highlighting current knowledge on how the BBB evolves from development through adulthood and into aging. Overall, recognizing the developmental and dynamic nature of the BBB is essential for safer pediatric dosing, more predictable adult therapeutics, and effective vascular strategies for preserving cognitive health.

Previously, the BBB was largely viewed as a stationary wall. However, emerging molecular and proteomic advances have shifted this understanding, revealing that the BBB is a dynamic barrier, in which molecular composition, transport priorities, and cellular programs change across the human lifespan. A recent proteomic analysis, the Collection by Scientific Reports (https://www.nature.com/collections/ggegfehega), identified that BBB permeability may vary with age, reflecting developmental changes in basement membrane composition as well as age-dependent modifications in transporter expression[1]. Merging evidence from brain microvessel proteomics indicates that clinical pharmacology approaches increasingly view the BBB as a dynamic physiological interface rather than a static barrier, integrating transporter quantification with functional assessments of transcytosis.[1–3] Here, we offer a lifespan-based perspective on BBB dynamics, from infancy BBB developmental biology to aging BBB physiological remodeling, and highlight insights into age-dependent BBB-associated drug dosing and emerging concepts in BBB dysfunctions.

Infancy and childhood represent stages of rapid synaptogenesis, ongoing myelination, and refinement of neural circuits. Consistent with these metabolic demands, developmental profiling shows enrichment of key nutrient and carrier transporters, including SLC7A1 (CAT1), SLC1A4 (ASCT1), SLC16A1 (MCT1), and SLC52A2/3, facilitating efficient delivery of amino acids, monocarboxylates, and vitamins to the developing brain[1,4,5] Although tight-junction complexes are established early and limit paracellular permeability, the endocytic and transcytotic landscape in the developing brain differs markedly from that of adults. These properties support an interface specialized for importing substrates required for neurodevelopment, rather than representing an "immature" or leaky barrier[5]. These characteristics limit the applicability of simple weight-based extrapolation of adult dosing to pediatric populations, as central drug exposure in children differs fundamentally due to age-dependent differences in BBB transport biology[1,6]. These features of BBB transport biology have important practical consequences. Dose selection in pediatric populations should prioritize transporter ontogeny and developmental maturation of junctional complexes over traditional weight-based allometry. Moreover, pharmacokinetic variability in early life often stems from barrier level determinants rather than hepatic or renal function alone. Finally, clinical trials in infants and children are improved by integrating BBB-specific biomarkers, such as quantitative proteomic assays of critical SLC and ABC transporters, along with routine safety and pharmacokinetic endpoints.

In adults, the BBB is characterized by minimal paracellular permeability, sustained through mature tight-junction proteins (CLDN5, OCLN, TJP1) and a well-regulated complement of solute carriers and efflux transporters[1,7]. Despite this apparent stability, targeted absolute proteomic analyses of human microvessels demonstrate striking interindividual variability, approaching an order of magnitude, in ABCB1 (P-gp) and ABCG2 (BCRP) expression[1,8]. Such interindividual variation disrupts the assumed link between plasma levels and CNS exposure for narrow-therapeutic-index compounds[1,7]. Two patients with the same serum concentration may show different CNS effects because BBB transporter phenotype, more than plasma concentration, determines

[1]Department of Neurosurgery, McGovern School of Medicine, University of Texas Health Science Center at Houston, 6431 Fannin St., Houston, TX 77030, USA. [2]Novel Treatments for Acute Brain Injury Institute, Texas Medical Center, 6431 Fannin St., Houston, TX 77030, USA. ✉email: Xuefang.ren@uth.tmc.edu

effective brain delivery. In practice, dependence on serum monitoring alone can overestimate toxicity in some patients or fail to identify those whose restrictive barrier phenotype prevents adequate therapeutic exposure. Adult precision medicine benefits from a barrier centric strategy that integrates actionable transporter genotypes, direct phenotyping via probe substrates or imaging when feasible, and modifiers of transporter abundance such as inflammation or drug–drug interactions. For CNS drugs with tight therapeutic windows, exposure response models must explicitly represent BBB transport terms, rather than relegating these determinants to residual variability.

Aging drives several fundamental changes in BBB biology. Both functional assays and single-cell analyses reveal a transition from ligand-specific, receptor-mediated transport to non-specific caveolar transcytosis, coupled with diminished physiological protein trafficking and signatures of microvascular stress[5]. Human BMV proteomics demonstrate that aging reduces the abundance of critical nutrient transporters and endocytic machinery while promoting inflammatory signatures and altering basement-membrane composition, including shifts in collagens and laminins[1,2,5]. These cumulative changes compromise BBB integrity and mirror hallmark vulnerabilities of the aging brain: diminished metabolic flexibility, increased oxidative burden, and heightened sensitivity to neuroinflammatory damage. An additional clinically relevant finding is the wide interindividual variability that endures into aging. Although average transporter abundance changes, the spread remains substantial for ABCB1 and ABCG2 in human tissue, indicating that age alone does not define CNS exposure. Consequently, an aged adult with low efflux function may experience higher BBB permeability and greater susceptibility to adverse effects than younger adults despite receiving the same dose[1,8].

BBB dysfunction is a central feature of aging-related neurological disorders, such as ischemic stroke[9] and vascular dementia[10]. Acute ischemic injury generates a rapidly shifting barrier phenotype characterized by tight junction disruption[9,11–13], including increased caveolar transcytosis, and endothelial stress signaling. Efflux transporters may become transiently downregulated, while inflammatory signals reshape nutrient carrier function, creating unstable and unpredictable CNS exposure. These barrier level disturbances complicate pharmacotherapy and interact directly with blood replacement interventions[14] rapid exchange of peripheral blood alters circulating cytokines, coagulation proteins, and plasma protein binding, each capable of further modulating transporter activity and paracellular permeability. The result is a dynamically injured barrier in which plasma drug concentrations poorly reflect brain exposure, necessitating real time, BBB guided dosing strategies during acute stroke care.

BBB dysfunction also contributes to the onset and progression of vascular dementia. Vascular atlas studies show that multiple dementia associated genes are expressed in endothelial, mural, and perivascular cells, reinforcing a primary vascular contribution to susceptibility. Postmortem analyses in vascular cognitive impairment reveal reductions in tight junction proteins such as CLDN5 and OCLN within cortical microvessels, correlating with white matter injury and cognitive decline[15]. Consistent with these observations, human BMV proteomic studies identify age-linked alterations in vascular relevant proteins, induction of injury responsive repair pathways, and remodeling of basement membrane components[1]. Together, these findings position BBB degradation and microvascular dysfunction as early and actionable drivers of vascular dementia, rather than secondary byproducts of neural injury.

Clinical trials targeting CNS should incorporate transporter phenotyping, permeability measures, and vascular inflammatory markers, which predict brain exposure more accurately than age alone. These tools can include targeted proteomic panels from endothelial exosomes or image based permeability metrics. Pediatric dosing should be guided by BBB ontogeny, using developmental maps of SLC and ABC transporters and junctional maturation rather than scaling down adult doses. In neurodegeneration, targeting microvascular aging, by stabilizing junctions, restoring pericyte support, and normalizing transcytosis, offers a strategy to preserve neuronal integrity. Across all populations, precision medicine should extend to the BBB by integrating transporter genotype, phenotype, and functional measures so that dosing reflects the biology governing CNS exposure.

In short, the BBB does not stand still as we age; it changes with us. In early life, it is remarkably acquisitive, built to import the nutrients and signals needed for rapid brain growth. In adulthood, it becomes efficient yet strikingly heterogeneous, shaping how individuals respond to the same drug or insult. In later years, this once-resilient interface grows fragile, its defenses loosening just as vulnerability to age-related neurological disorders, such as ischemic stroke and vascular dementia, intensifies. Acknowledging this arc is not academic; it is central to safer medicines for children, more reliable therapeutics for adults, and credible strategies for preventing or mitigating cognitive decline. The BBB is not masonry but metabolism: an adaptive organ that continually edits the brain's chemical environment. Understanding its evolution is essential to understanding the diseases we confront and the therapies we aspire to build.

Published online: 18 May 2026

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Acknowledgements

This Editorial was supported by NINDS (1R01NS117606), NIA (4RF1AG073659), and new faculty start-up funds from the University of Texas Health Science Center at Houston.

Declarations

Competing interests

The author declares no competing interests.

Correspondence and requests for materials should be addressed to X.S.R.