

A hippocampal vascular–glymphatic model of brain maintenance and cognitive resilience in Alzheimer’s disease and post-stroke dementia

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Abstract

Individuals with comparable burdens of brain pathology often follow markedly different cognitive trajectories. This heterogeneity is captured by three partly dissociable constructs—brain reserve, cognitive reserve, and brain maintenance—here grouped under the superordinate term cognitive resilience. Cognitive reserve has traditionally been indexed by education, occupational complexity, and lifelong cognitive engagement, yet its biological substrates remain incompletely defined. We propose that hippocampal vascular supply and perivascular (glymphatic) and meningeal lymphatic clearance, modulated by blood–brain barrier integrity and neuroinflammatory tone, constitute one biological substrate of resilience. We make its conceptual placement explicit: these processes operate predominantly as substrates of brain maintenance (efficient clearance limiting amyloid- β and tau accumulation) and brain reserve (a redundant hippocampal arterial supply buffering partial vascular compromise), rather than of cognitive reserve *sensu stricto*. We hypothesize, as an inference requiring direct testing rather than an established mechanism, that vascular architecture and clearance capacity are mechanistically coupled through perfusion and arterial pulsatility, rather than acting as independent parallel contributors. Preserved blood–brain barrier integrity and a regulated neuroinflammatory tone are proposed to sustain this axis, whereas their disruption, through astrocytic aquaporin-4 mislocalization, microglial activation, and barrier breakdown, accelerates cognitive decline. We additionally outline one speculative pathway by which cerebral perfusion may contribute directly to cognitive reserve. Consistent with a Hypothesis article, the model is framed as a small set of constrained, falsifiable predictions—distinguishing established, inferred, and speculative links—and as a research roadmap for Alzheimer’s disease and post-stroke dementia, identifying modifiable targets (cerebral perfusion, sleep, vascular risk control) and reframing cognitive resilience as biologically grounded and potentially actionable.

Keywords

Alzheimer’s disease, blood–brain barrier, brain maintenance, cognitive resilience, glymphatic clearance, hippocampal vascularization, neuroinflammation, post-stroke dementia

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Introduction

A central question in the neurobiology of aging is why individuals with comparable burdens of age- and disease-related brain pathology show markedly different cognitive trajectories. Three partly dissociable constructs have been formalized to account for this heterogeneity.¹ Brain reserve denotes the passive, quantitative neurobiological capital—broadly, the amount of available structural substrate—such that a larger reserve permits more pathology to accrue before a clinical threshold is crossed. Cognitive reserve denotes the active, functional capacity to sustain performance at a given level of pathology through more efficient, flexible, or compensatory

engagement of neural networks, and has traditionally been indexed by proxies such as educational attainment, occupational complexity, premorbid intelligence, and sustained cognitive and social engagement.^{2,3} Brain maintenance denotes

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