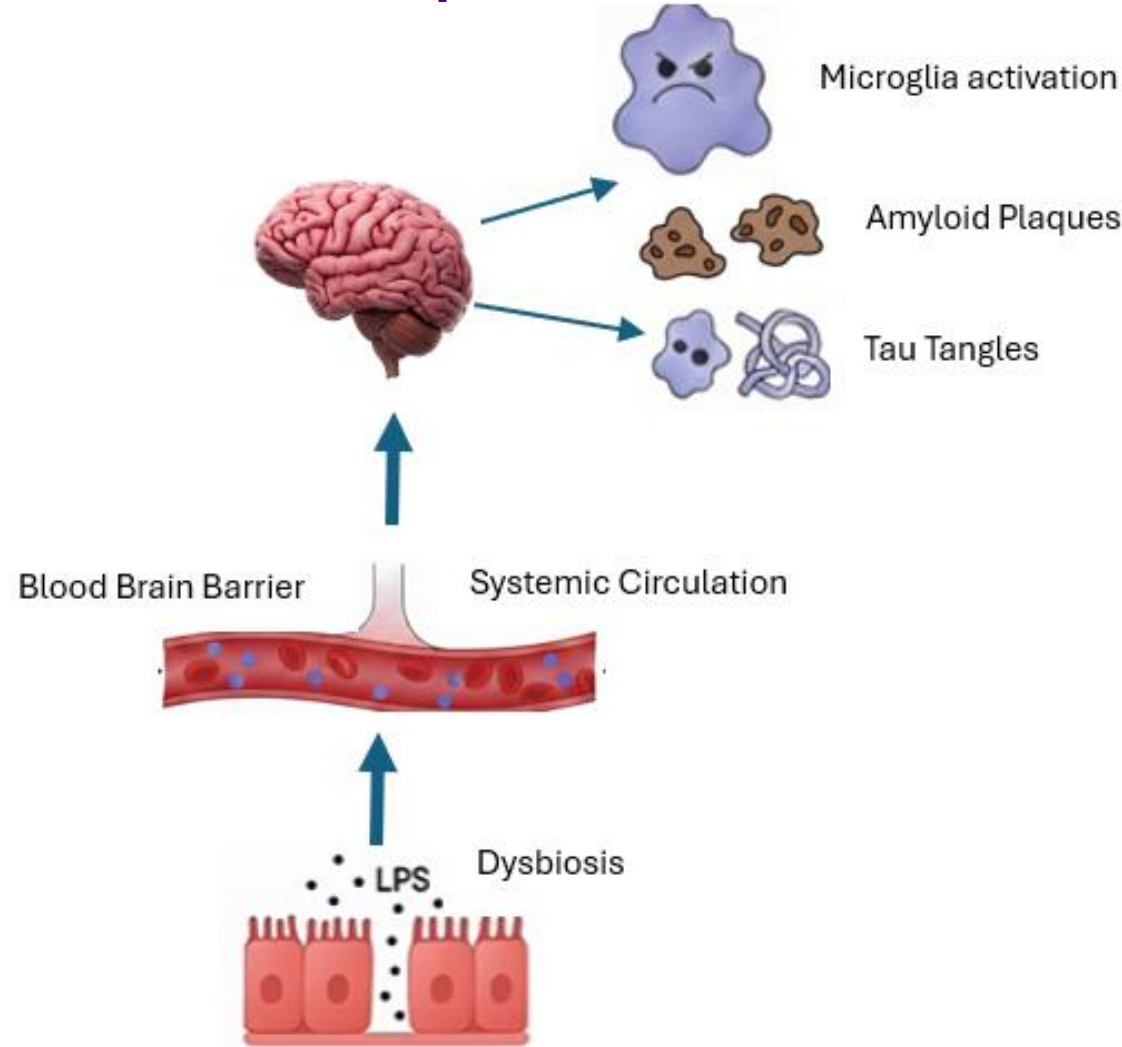


The Gut-brain Axis As A Driver Of Neuroinflammation: A Non-amyloid Pathogenesis Framework For Alzheimer's

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- ❖ Growing evidence supports the gut–brain axis as a key contributor to early Alzheimer's disease through LPS-mediated systemic inflammation.
- ❖ Blood-brain barrier dysfunction enables gut-derived inflammatory signals to activate microglia and sustain chronic neuroinflammation.
- ❖ Targeting neuroinflammation offers promising therapeutic opportunities beyond conventional amyloid-focused approaches.

INTRODUCTION	METHODS	RESULTS	CONCLUSIONS	REFERENCES
Even though the traditional Amyloid Cascade Hypothesis identifies the deposition of Amyloid-beta Aβ as the primary cause of Alzheimer's disease (AD), several clinical trials targeting amyloid therapies suggests that Aβ may signify a late-stage symptom rather than a key driver. Emerging research studies show that AD is not merely a central nervous system disorder, but a systemic multi-organ disorder. Precisely, the Microbiota-Gut-Brain Axis (MGBA) has grown as a compelling regulator of neuroinflammation, recognizing it as an important factor in the pathogenesis and early-stage progression of AD.	Using PRISMA 2020, a meta-synthetic methodology was followed. Through a systematic search, clinical data from high-impact literature (2022-2025) were evaluated. We selected 25 studies for synthesis and theoretical modeling of the gut-brain inflammatory axis. The focus of the review was on studies linking Dysbiosis to Microglial Activation, explicitly the role of microbial metabolites such as Lipopolysaccharides (LPS) and Short-Chain Fatty Acids (SCFAs) in lowering microglial phenotypes.	The neuroinflammatory pathways are activated by Dysbiosis through the gut-brain axis. This influence AD pathogenesis through inflammatory mediators. As a result, SCFA bacteria which normally protects the brain are reduced in AD patients. Also, the inflammatory theory of neurodegeneration is supported by the raised levels of biomarkers such as IL-1β, IL-6, and TNF-α, perceived in AD. Furthermore, consistent correlation between the increased microglial activation and LPS, the pro inflammatory toxic byproduct of bad gut bacteria which destroys healthy neurons exists. These toxins release pro-inflammatory cytokines which make microglia into a hyper-aggressive state and in turn this accelerates the formation of Amyloid plaques and Tau tangles.	The neuroinflammation can be reduced by targeting the gut microbiome to restore balance before cognitive decline happens. It is also necessary to study the role of significant factors such as genetic predispositions and environmental influences in the development of AD. 	1. Lei, W., Cheng, Y., Liu, X., Gao, J., Zhu, Z., Ding, W., ... & Chen, X. (2025). Gut Microbiota-Driven Neuroinflammation in Alzheimer's Disease: From Mechanisms to Therapeutic Opportunities. <i>Frontiers in Immunology</i>, 16, 1582119. 2. Wang, H., Yang, F., Gao, Z., Cheng, Z., & Liang, X. (2025). The Gut-Brain Axis in Alzheimer's Disease: How Gut Microbiota Modulate Microglial Function. <i>Frontiers in Aging</i>, 6, 1704047. 3. Al Noor, M. (2025). Alzheimer's and the Gut Microbiota: Impacts on Brain Health, Memory, and Inflammation. <i>Microbial Bioactives</i>, 8(1), 1-9.
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