Lithium deficiency and the onset of Alzheimer's disease

Aron, L., Ngian, Z.K., Qiu, C. *et al*. *Nature* **645 :**712-721, 2025

Presenter: Jin-Syuan Huang **Date/Time:** 2025/11/27, 16:10 -17:00
Commentator: Dr. Chun-Hsien Chu **Location:** Room 601, Med College Building

Background: Alzheimer's disease involves cognitive decline driven by amyloid beta, tau, synaptic failure, and neuron inflammation. While dysregulation of several metal ions is known to influence AD pathology, the role of lithium, an essential ultra-trace element with strong neuroprotective properties, has been overlooked. Lithium regulates key neuronal pathways such as GSK3Beta signaling and synaptic maintenance. Recent population data also suggest that environmental lithium exposure may correlate with reduced dementia risk. Yet it remains unknown whether endogenous Li levels in the brain change during AD and whether lithium deficiency contributes directly to disease development.

Objective/Hypothesis: To investigate whether a reduction of endogenous Li levels in the brain, particularly in vulnerable regions such as the prefrontal cortex, contributes causally to cognitive impairment and the development of Alzheimer's disease pathology, rather than being a secondary effect of neurodegeneration.

Results: The study found that lithium levels are uniquely and significantly reduced in the prefrontal cortex of individuals with mild cognitive impairment and Alzheimer's disease, while other mental ions remain unchanged. To test causality, the authors generated lithium-deficient conditions in both 3xTg-AD and wild-type mice. Lithium deficiency resulted in significant impairments in learning and memory across multiple behavioral tests, without affecting locomotion or sensory function. In AD-model mice, lithium deficiency further exacerbated amyloid accumulation, tau phosphorylation, and loss of synaptic proteins. Transcriptomic analyses revealed the presence of lithium-deficient conditions in both 3xTg-AD and wild-type mice. Lithium deficiency resulted in significant impairments in learning and memory across multiple behavioral tests, without affecting locomotion or sensory function. In the AD model mice, lithium deficiency further exacerbated amyloid accumulation, tau phosphorylation, and loss of synaptic proteins. Transcriptomic analyses showed that lithium-deficient brains exhibit gene-expression changes that closely mirror the early Alzheimer's disease signatures, including synaptic dysfunction, metabolic stress, and neuroinflammatory pathways. Together, these findings demonstrate that endogenous lithium is essential for maintaining neuronal and cognitive function, and that lithium deficiency acts as an active driver of Alzheimer's pathology rather than a secondary consequence.

Conclusion: This study demonstrates that endogenous lithium is a previously overlooked but essential ultra-trace element required for maintaining neuronal health and cognitive function. Lithium levels are reduced explicitly in vulnerable brain regions of individuals with MCI and Alzheimer's disease, and experimentally induced lithium deficiency in mice is sufficient to trigger cognitive decline, exacerbate amyloid and tau pathology, and drive synaptic and transcriptional abnormalities that mirror early Alzheimer's disease changes. These findings indicate that lithium deficiency is not merely a byproduct of neurodegeneration but a causal and early contributor to Alzheimer's disease pathogenesis. Resorting to lithium homeostasis may therefore represent a prompting strategy for preventing or delaying the onset of AD-related cognitive impairment.