Neuroscientists identify mechanism for long-term memory storage

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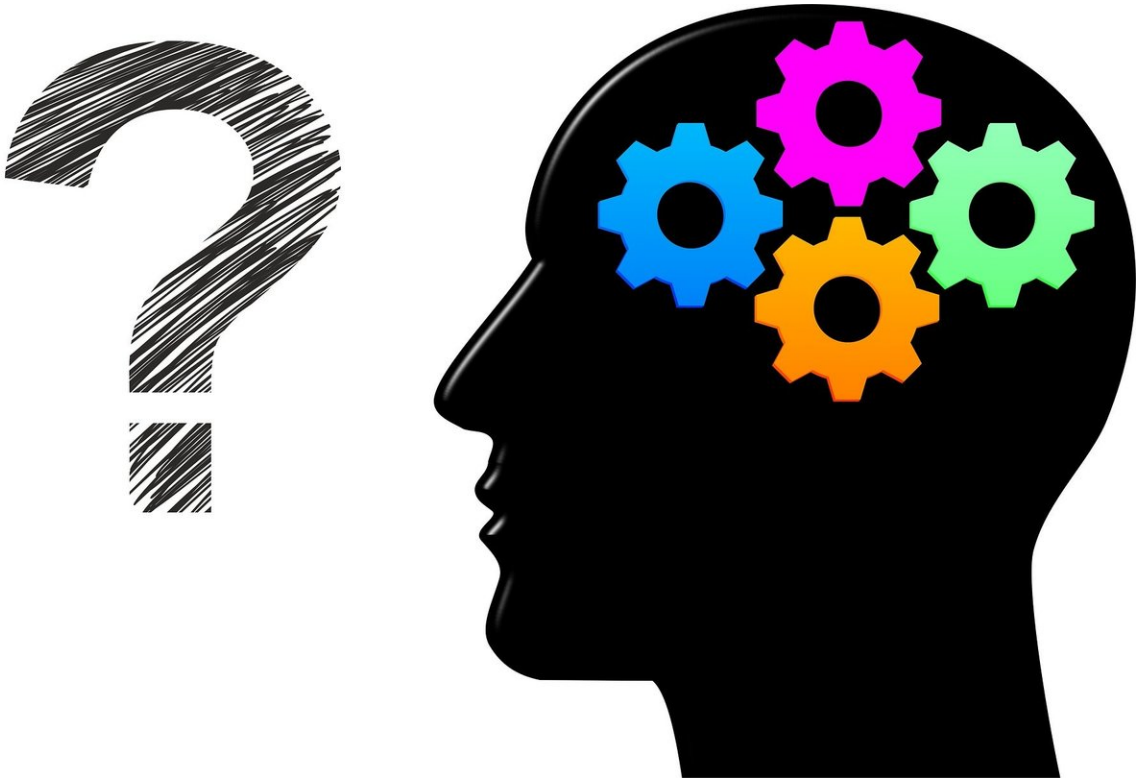

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A University of Iowa neuroscience research team has identified a fundamental biochemical mechanism underlying memory storage and has linked this mechanism to cognitive deficits in mouse models of Alzheimer's disease and related dementias.

While working to understand how memories are formed and stored in the brain, the team identified a novel protein folding mechanism in the endoplasmic reticulum that is essential for long-term memory storage. They further demonstrated that this mechanism is impaired in a tau-based mouse model of Alzheimer's disease and that restoring this protein folding mechanism reverses memory impairment in this mouse model for the study of dementia. The findings are published in the March 23 issue of the journal *Science Advances*.

The team was led by Snehajyoti Chatterjee, Ph.D., a research associate in the lab of Ted Abel, Ph.D., Director of the Iowa Neuroscience Institute and chair and DEO of the UI Department of Neuroscience and Pharmacology. The Abel lab has previously shown that the Nr4a family of transcription factors is essential for long-term memory consolidation. This study identified chaperone proteins in the endoplasmic reticulum, which are regulated by Nr4a.

"The role of protein folding machinery in long-term memory has been overlooked for decades," Chatterjee says. "We know that gene expression and protein synthesis are essential for long-term memory consolidation, and following learning a large number of proteins are synthesized. For proteins to be functionally active they need to be folded correctly. Our work demonstrates the conceptual idea that these chaperone proteins are the ones that actually fold the proteins to impact synaptic function and plasticity."

The team also used gene therapy to reactivate the chaperone protein in a mouse model and found that the memory deficit was reversed, confirming that the protein folding machinery acts as a molecular switch for memory.

"Identifying this protein folding mechanism is a crucial step toward understanding how memories are stored and what goes wrong in diseases

associated with memory impairment," Abel says. "Even though we are not yet at a point of translating this to patient care, understanding this pathway is essential to one day being able to prevent and treat neurodegenerative disease."

More information: Snehajyoti Chatterjee et al, Endoplasmic reticulum chaperone genes encode effectors of long-term memory, *Science Advances* (2022). DOI: 10.1126/sciadv.abm6063

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