Neuroscientists engineer a protein that enhances memory to respond to anti-aging drug

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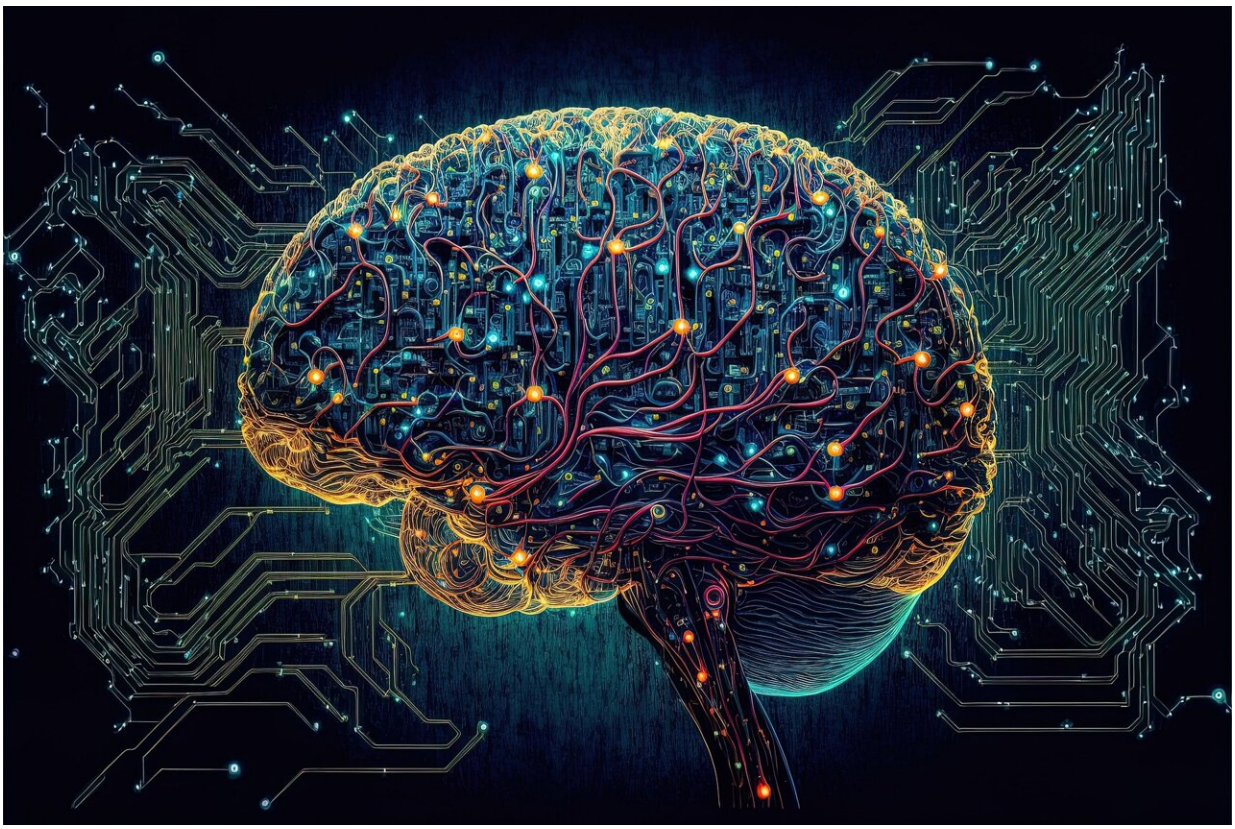

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Neuroscientists at the Faculty of Medicine and Surgery of the Catholic University, Rome, and the Fondazione Policlinico Universitario

Agostino Gemelli IRCCS have genetically modified a molecule, the protein LIMK1, which is normally active in the brain, with a key role in memory. They added a "molecular switch" that is activated by administering a drug, rapamycin, known for its several anti-aging effects on the brain.

This is the result of a study published in the journal *Science Advances*, which involves the Catholic University, Rome, and the Fondazione Policlinico Universitario Agostino Gemelli IRCCS. The study was coordinated by Claudio Grassi, Full Professor of Physiology and Director of the Department of Neuroscience.

The research has great potential applications, by improving our understanding of memory function and facilitating the identification of innovative solutions for neuropsychiatric diseases like dementia.

The LIMK1 protein plays a crucial role in determining structural changes in neurons, namely the formation of dendritic spines, which enhance information transmission in neural networks and are crucial in learning and memory processes.

Prof. Claudio Grassi, senior author of the study, explains, "Memory is a complex process that involves modifications in synapses, which are the connections between neurons, in specific brain areas such as the hippocampus, which is a neural structure playing a critical role in memory formation. This phenomenon, known as synaptic plasticity, involves changes in the structure and function of synapses that occur when a neural circuit is activated, for example, by sensory experiences. These experiences promote the activation of complex signaling pathways involving numerous proteins."

Prof. Grassi adds, "Some of these proteins are particularly important for memory, in fact reduced expression or modifications of these proteins

are associated with alterations in cognitive functions. One of these proteins is LIMK1. The goal of our study was to regulate the activity of this protein, as it plays a key role in the maturation of dendritic spines between neurons. Controlling LIMK1 with a drug means being able to promote synaptic plasticity and, therefore, the physiological processes that depend on it."

Cristian Ripoli, Associate Professor of Physiology at the Catholic University, and first author of the study, adds, "the key to this innovative 'chemogenetic' strategy, which combines genetics and chemistry, is precisely linked to the use of rapamycin," an immunosuppressive drug known to increase life expectancy and for its beneficial effects on the brain, in preclinical models.

"We have therefore modified the sequence of the LIMK1 protein by inserting a molecular switch that allowed us to activate it, on command, through the administration of rapamycin," Prof. Ripoli said.

"In animals with age-related cognitive decline, using this gene therapy to modify the LIMK1 protein and activate it with the drug resulted in a significant memory improvement. This approach allows us to manipulate synaptic plasticity processes and memory in physiological and pathological conditions. Furthermore, it paves the way for the development of further 'engineered' proteins that could revolutionize research and therapy in the field of neurology," the expert emphasizes.

"The next step will be to verify the effectiveness of this treatment in experimental models of neurodegenerative diseases exhibiting memory deficits, such as Alzheimer's disease. Further studies will also be necessary to validate the use of this technology in humans," Prof. Grassi concludes.

More information: Cristian Ripoli et al, Engineering memory with an

extrinsically disordered kinase, *Science Advances* (2023). DOI: 10.1126/sciadv.adh1110. www.science.org/doi/10.1126/sciadv.adh1110