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Gene therapy in Alzheimer's disease mouse model preserves learning and memory

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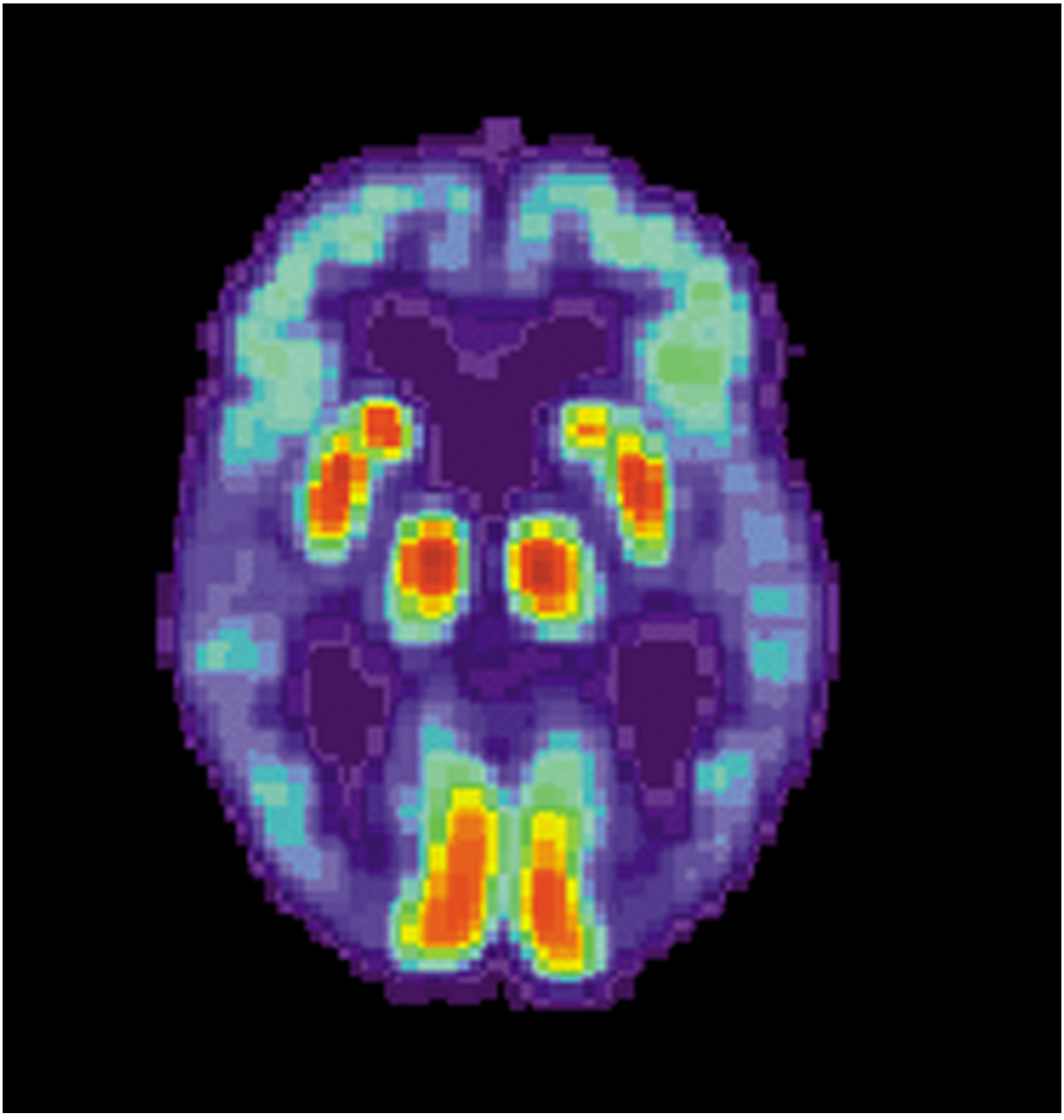

PET scan of a human brain with Alzheimer's disease. Credit: public domain

Researchers at University of California San Diego School of Medicine, with colleagues elsewhere, have used gene therapy to prevent learning and memory loss in a mouse model of Alzheimer's disease (AD), a key step toward eventually testing the approach in humans with the neurodegenerative disease.

The findings are published online in advance of the June 11, 2021 issue of *Molecular Therapy-Methods & Clinical Development*.

AD is characterized by the accumulation of clumps of misfolded proteins called amyloid plaques and neurofibrillary tau tangles, both of which impair cell signaling and promote neuronal death. Current AD treatments targeting plaques and tangles address only symptoms, which the study's authors say suggests a reversal and cure of AD will likely require a combination of interventional approaches that both decrease aggregating toxins and promote neuronal and synaptic plasticity.

Gene therapy is based on the premise that introducing a therapeutic compound to a precisely targeted region of the brain may restore or protect normal neural function and/or reverse neurodegenerative processes. In this case, researchers used a harmless adeno-associated viral vector to introduce synapsin-Caveolin-1 cDNA (AAV-SynCav1) into the hippocampus region of three-month-old transgenic AD mice.

The mice had been genetically modified to exhibit learning and memory deficits at 9 and 11 months, respectively. These deficits are associated with decreased expression of Caveolin-1, a scaffolding protein that

builds the membranes housing cellular signaling tools, such as neurotrophin receptors that receive the critical extracellular signals, which govern all cellular life and function. With decay and destruction of these membranes, cell dysfunction and neurodegeneration follow.

"Our goal was to test whether SynCav1 gene therapy in these AD mouse models might preserve neuronal and synaptic plasticity in targeted parts of the membrane, and improve higher brain function," said senior author Brian P. Head, Ph.D., adjunct professor in the Department of Anesthesiology at UC San Diego School of Medicine and research health scientist at the VA San Diego Healthcare System.

And, in fact, that's what happened after mice received a single injection of AAV-SynCav1 to their hippocampus, which is a complex region deep within the brain that plays a major role in learning and memory. In AD, the hippocampus is among the first areas of the brain to be impaired.

At 9- and 11-months, said Head, hippocampal learning and memory in the mice were preserved. Moreover, researchers found that critical membrane structures and associated neurotrophin receptors also remained intact. Furthermore, these neuroprotective effects from SynCav1 gene delivery occurred independent of reducing amyloid plaque depositions.

"These results suggest SynCav1 gene therapy is an attractive approach to restore brain plasticity and improve brain function in AD and potentially in other forms of neurodegeneration caused by unknown etiology," wrote the authors.

Head's laboratory is currently testing SynCav1 gene delivery in other AD models at symptomatic stages as well as in a mouse model of amyotrophic lateral sclerosis (Lou Gehrig's disease). He hopes to advance this work to human clinical trials soon.

More information: Shanshan Wang et al. Synapsin-caveolin-1 gene therapy preserves neuronal and synaptic morphology and prevents neurodegeneration in a mouse model of AD, *Molecular Therapy - Methods & Clinical Development* (2021). DOI: 10.1016/j.omtm.2021.03.021