Gene linked to Alzheimer's disease impairs memory by disrupting brain's 'playback system'

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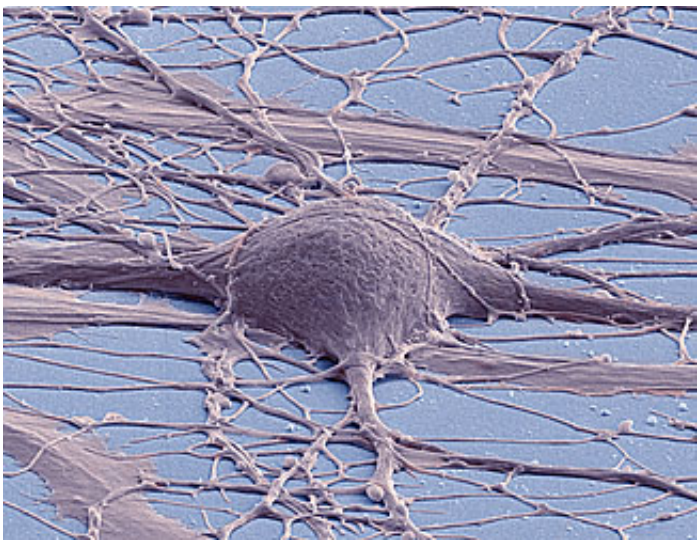

This is a scanning electron micrograph (false color) of a human induced pluripotent stem cell-derived neuron. Credit: Thomas Deerinck, UC San Diego

Scientists at the Gladstone Institutes have discovered how the major genetic risk factor for Alzheimer's disease causes memory impairment. A specific type of brain activity important for memory replay is disrupted in mice with the E4 version of the apolipoprotein E (apoE4) gene, which may interfere with memory formation.

The apoE4 gene creates a protein of the same name that markedly

increases a person's risk for Alzheimer's disease and occurs in 65%-80% of people with Alzheimer's disease. In the new research, published in *Neuron*, the scientists found that the apoE4 protein changes the activity of neurons in the hippocampus—an important memory center in the brain that is severely affected by Alzheimer's disease. In this region, apoE4 decreases two types of brain activity that are important for memory formation: sharp wave ripples (ripples) and coincident slow gamma activity. During the ripples, prior experiences are replayed numerous times to help preserve the memory of them, and the slow gamma activity that occurs during the ripples helps to ensure that the replay of those memories is accurate.

"When we experience something new, cells in the hippocampus fire in a particular order. Later, these same cells fire over and over again in the same order to replay the event, which helps consolidate the memory so we don't forget it," explained first author Anna Gillespie, PhD, a former graduate student in the Huang lab at Gladstone. "Slow gamma activity that occurs during the ripples organizes the firing of these cells. If this activity is disrupted, the playback will be disorganized, compromising the memory."

Mice with apoE4 had fewer ripples than mice with the normal apoE3 protein, and they had less slow gamma activity during the ripples. Based on these results, the scientists questioned whether these differences in activity affected the ability to form and replay memories.

To answer this, the researchers tested mice that expressed apoE4 in all cells except inhibitory neurons in the hippocampus. From earlier research, the scientists knew that these mice showed no signs of inhibitory neuron death in the hippocampus, and their ability to learn and form memories was not impaired. In the current study, the mice showed normal slow gamma activity despite having fewer ripples. Thus, slow gamma activity—the coordination of cell firing during

playback—appears to be a critical factor in memory consolidation, rather than the number of replay events from the ripples.

"Our research suggests that disrupted slow gamma activity during ripples is a major consequence of apoE4 expression that likely impairs memory consolidation," said senior author Yadong Huang, MD, PhD, a senior investigator at Gladstone. "With this knowledge, we can now work toward correcting or restoring slow gamma activity in the hippocampus to prevent or alleviate memory loss in Alzheimer's disease."

More information: Anna K. Gillespie et al, Apolipoprotein E4 Causes Age-Dependent Disruption of Slow Gamma Oscillations during Hippocampal Sharp-Wave Ripples, *Neuron* (2016). DOI: 10.1016/j.neuron.2016.04.009

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