

# Scientists uncover potential driver of age- and Alzheimer's-related memory loss

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Scientists from the Florida campus of The Scripps Research Institute (TSRI) have made an important discovery toward the development of drugs to treat age-related memory loss in diseases like Alzheimer's. They found that reduced levels of a protein called Rheb result in spontaneous symptoms of memory loss in animal models and are linked to increased levels of another protein known to be elevated in the brains of

Alzheimer's disease patients.

Their study, led by TSRI Associate Professor Srinivasa Subramaniam, was published recently online ahead of print in the journal *Neurobiology of Aging*.

## Link to Known Alzheimer's Trigger

In the new study, Subramaniam's group investigated the link between Rheb and an important enzyme called BACE1, which is elevated in older adults and people with Alzheimer's disease.

"We know that Rheb regulates BACE1, which is a major drug target in Alzheimer's disease," Subramaniam said. "Studies of the autopsied brains of Alzheimer's patients have found a significant reduction in Rheb, so it is possible that an increase in Rheb could reverse the buildup of amyloid plaque or help reduce or even reverse age-related [memory loss](#)."

To uncover the impact of eliminating Rheb, Subramaniam and his colleagues put genetically altered mice through a battery of behavior tests beginning at around six months of age.

While Rheb depletion did not affect the overall body weight or motor activity of the animals, it did have subtle and selective effects on certain memory tasks they performed, such as navigating a maze and memory recall. The researchers compared these symptoms to memory deficits that occur in humans with Alzheimer's disease and related dementia.

They also found that Rheb depletion increased BACE1 levels, which was consistent with previous research showing that higher BACE1 levels may be a contributing factor for memory deficits.

The fact that some research shows that Rheb messenger RNA is induced during protein starvation in fruit flies, led Subramaniam and his colleagues to theorize that a high-protein diet in humans might be a risk factor for decreasing Rheb levels with age, resulting in mild-to-severe cognitive deficits, as seen in animal models.

"This is an indication that nutrient signaling might regulate cognitive functions in mammals through alteration of Rheb–BACE1 pathway activity," Subramaniam said.

"Overall, our study demonstrates that forebrain Rheb depletion promotes aging-associated cognitive defects," said Neelam Shahani, the first author of the study. "Targeting the Rheb pathway may offer some therapeutic potential for aging- or Alzheimer's disease-associated [memory deficits](#)."

**More information:** Neelam Shahani et al. Forebrain Depletion of Rheb Elicits Spatial Memory Deficits in Mice, *Neurobiology of Aging* (2016). [DOI: 10.1016/j.neurobiolaging.2016.11.006](https://doi.org/10.1016/j.neurobiolaging.2016.11.006)

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