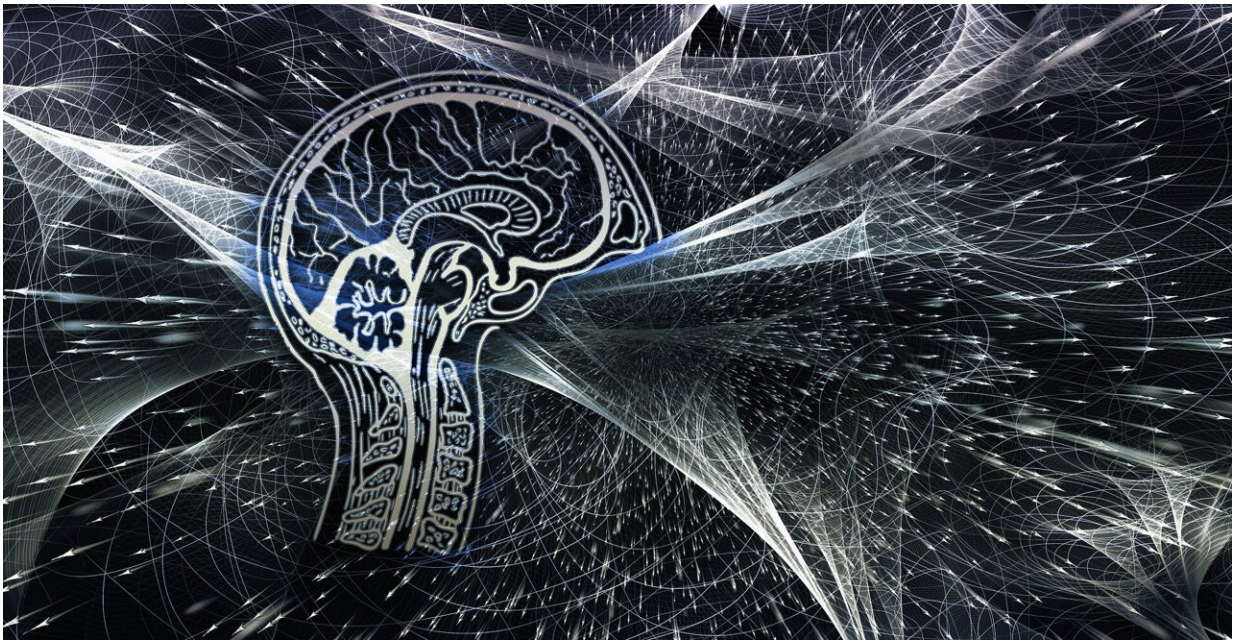


Organ transplant drug may slow Alzheimer's disease progression

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Protein imbalances that increase brain cell excitability may explain why individuals with Alzheimer's disease (AD) who also experience seizures demonstrate more rapid cognitive decline than those who do not experience seizures. These imbalances may be present in the brains of individuals before the onset of AD symptoms.

The new findings, from a research team at the University of

Pennsylvania's Perelman School of Medicine, are [published](#) this week in *Brain*.

The team found that an existing drug called rapamycin, initially developed as an immunosuppressant for [organ transplant patients](#) that suppresses signaling between neurons, was able to regulate the over-excited neurons in mouse models of AD and seizures, and preserve cognitive function, like memory and the ability to learn new things.

Previous [research](#) has shown similar [brain activity](#) in individuals with AD who experience epilepsy. Additionally, many individuals with AD have also experienced at least one seizure, and previous research has shown that these seizures cause a more rapid progression of the disease, and worsen [cognitive impairment](#), like trouble with memory or learning. However, researchers have not been able to identify the underlying connections between AD and seizures.

"Experts used to believe that seizures were an unfortunate byproduct of the neurodegeneration that causes Alzheimer's disease, but now we see that seizures are actually advancing the disease itself," said the study's co-senior author, Frances E. Jensen, MD, chair of Penn's Department of Neurology.

"Now that we have identified the mechanisms that cause neurons to get over-excited and lead to seizures that accelerate AD, we can explore therapies, like rapamycin, that can reverse the imbalance, and slow AD progression."

In a healthy brain, two neurotransmitters work together to manage the messaging between neurons. Glutamate is responsible for excitatory signaling from one cell to the next, telling neurons when to send a message. GABA manages inhibitory signaling that makes the cell less likely to fire, telling the cell when to stop signaling.

In this study, researchers evaluated post-mortem tissue from people with AD who also experienced at least one seizure and found that certain forms of these neurotransmitters were dysregulated. These neurons in these individuals exhibited increased excitability and suppressed inhibition, which result in the brain sending more signals between neurons than it needs to, a state that researchers refer to as a "hyperactive brain." Medical histories of these patients also confirmed worse cognitive evaluation scores than peers with AD but no seizures.

To determine at what stage of AD this dysregulation starts, researchers monitored the brain activity in mouse models of AD with [seizures](#). They found increased excitability and decreased inhibition in [neurons](#) even in preliminary stages of the disease, before cognitive symptoms presented.

"By the time many individuals are diagnosed with Alzheimer's disease and start receiving treatments, their disease is advanced, and they have lost significant cognitive function," said Aaron Barbour, Ph.D., a postdoctoral researcher in the department of Neurology, and co-senior author.

"Our research is an exciting step towards being able to intervene with a treatment before symptoms develop to slow the devastating effects of the disease."

More information: Aaron J Barbour et al, Seizures exacerbate excitatory: inhibitory imbalance in Alzheimer's disease and 5XFAD mice, *Brain* (2024). [DOI: 10.1093/brain/awae126](https://doi.org/10.1093/brain/awae126)

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