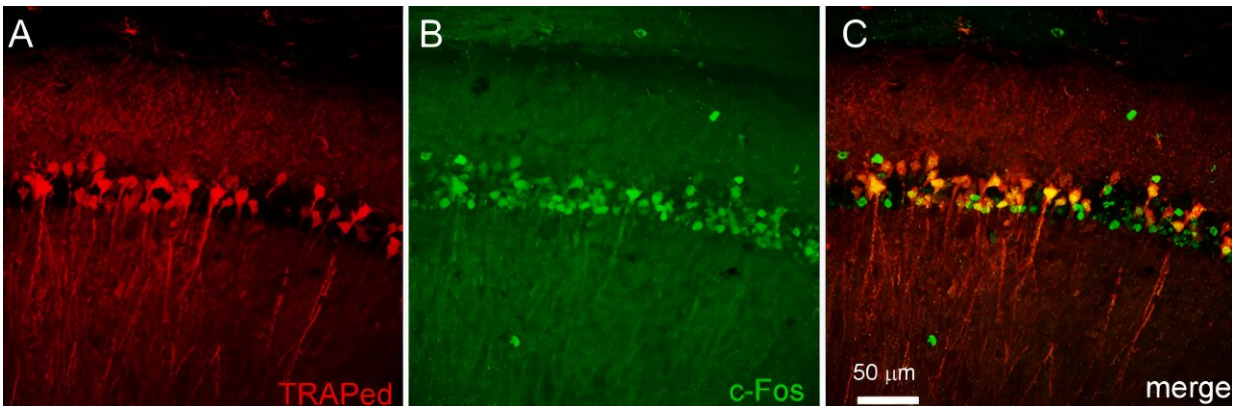


Intervention after first seizure may prevent long-term epilepsy

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Early-life seizure-associated neurons (A, red cells) are preferentially re-activated by later-life seizures (B, green cells; C, combined). Credit: *Journal of Clinical Investigation* (2024). DOI: 10.1172/JCI175167

Only a very small percentage of neurons show changes after an epileptic seizure in mice, but these alterations can be permanent and trigger future seizures that can affect the whole brain and lead to impaired cognition, like memory and learning, according to new research from the Perelman School of Medicine at the University of Pennsylvania.

The researchers identified an [experimental treatment](#) that, if provided within the first 48 hours after the first [seizure](#), can prevent these long-term changes.

The findings, which were [published](#) recently in the *Journal of Clinical Investigation*, suggest a promising target for developing treatments for epilepsy and preventing downstream effects of seizures.

Epilepsy is characterized by excessive activity of brain cells—[neurons](#)—which generate seizures. Research is increasingly showing that the development of epilepsy involves changes of synapses, which are structures that connect one neuron to another. While an estimated 3.4 million people in the United States live with some form of epilepsy, it is still unknown what causes it, and there is no cure.

Further, half of individuals with epilepsy experience [cognitive impairment](#), such as problems with memory or with emotional regulation, but it remains unclear why or how epilepsy changes brain cells to cause this. What's more, epilepsy is common in children with autism and individuals with dementia.

"It is clear that there is some connection between an epileptic brain, impaired memory, and trouble controlling emotions and how we act on those feelings, but we don't understand the underlying mechanisms," said Frances E. Jensen, MD, chair of the Department of Neurology, and senior author of the study. "Existing treatments for epilepsy only help manage seizures. This research gives us a promising starting point for developing therapies that prevent them from happening."

In this study, the researchers used a method that "tagged" neurons in the hippocampus—an area commonly affected by epilepsy and critical for memory—of mice that were activated by epileptic activity. The researchers were able to monitor those activated neurons over time and observe how they responded to subsequent seizures.

They found that only about twenty percent of neurons in the hippocampus were activated by seizures. Over time, the overactivity of

these neurons diminished their ability to make connections with other neurons, called synapses, which are necessary for learning.

"The overactive neurons lose their ability to build the strong synapses necessary for learning, which may explain why some people with epilepsy have trouble with learning and with [memory](#)," said Jensen. "If we can stop these neurons from undergoing changes after being activated by seizures, our hope is that we can also prevent not only the progression of epilepsy but also avoid these cognitive deficits individuals experience long-term."

To see if they could prevent neurons from becoming permanently epileptic, the researchers used an experimental glutamate receptor blocker called IEM-1460, which has been shown to reduce neuron hyperexcitability in models of mice with epilepsy.

They found when they treated mice with this blocker in the first 48 hours after their very first seizure the neurons did not become permanently activated, and the subjects did not experience future seizures or the associated effects, like impaired cognition and trouble learning.

"Now that we have identified the subgroup of neurons that are impacted by epilepsy, we can investigate what makes these cells vulnerable to becoming epileptic and whether that is something we can develop a therapy to stop," said Jensen. "We are also eager to determine whether there is a glutamate receptor-blocker that works similarly to IEM-1460 in humans, which could be given to people after their first seizure, and prevent the lifelong struggles associated with [epilepsy](#)."

More information: Bo Xing et al, Reversible synaptic adaptations in a

subpopulation of murine hippocampal neurons following early-life seizures, *Journal of Clinical Investigation* (2024). DOI: [10.1172/JCI175167](https://doi.org/10.1172/JCI175167)

Provided by Perelman School of Medicine at the University of Pennsylvania

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