Brain plasticity promotes worsening of epileptic seizures

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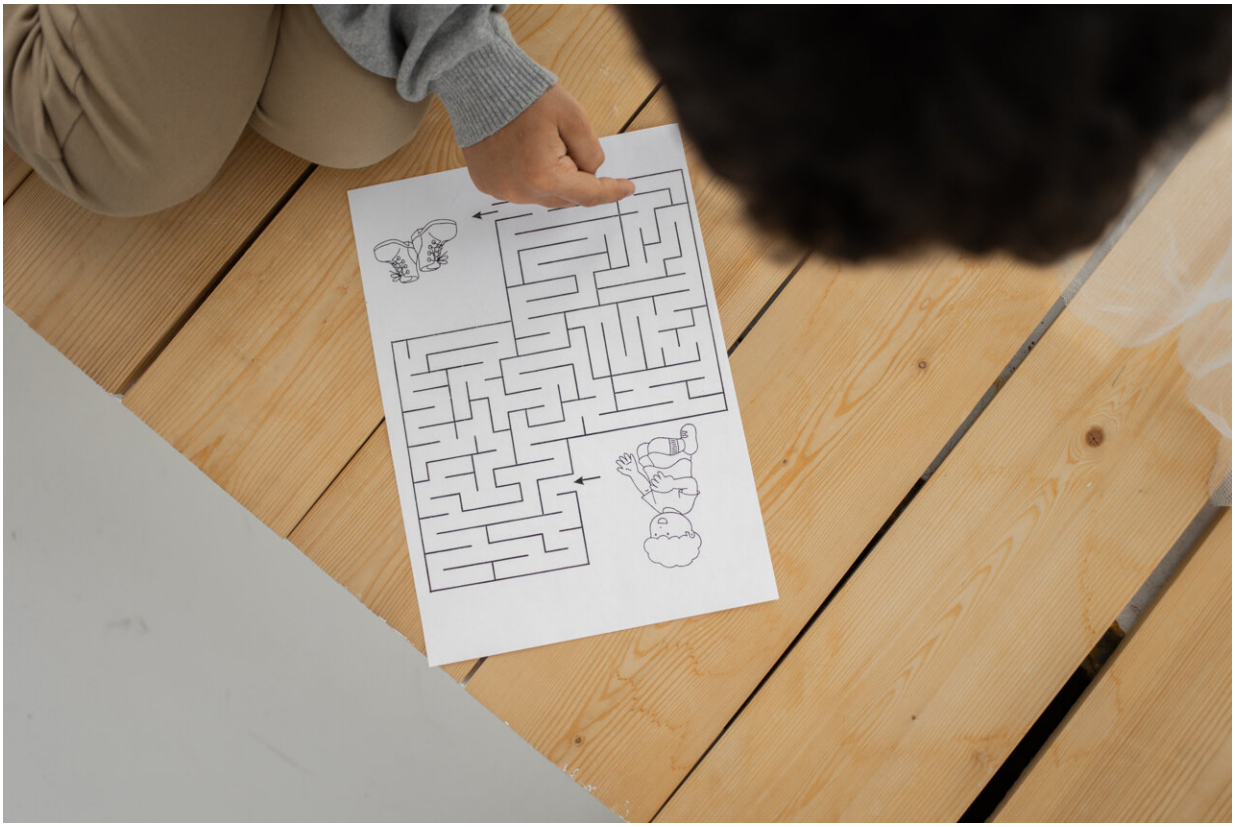

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Epileptic seizures worsen via the same mechanism by which practice makes perfect, a new study from the Stanford University School of Medicine has found.

The research, conducted on rodents with epilepsy, provides a major new insight into the mechanics of how seizures worsen: Seizures drive better insulation of the nerve fibers involved in seizing, allowing the brain to have seizures more efficiently. The findings explain why seizures generally become more frequent and severe in epilepsy patients who don't take medication or whose epilepsy doesn't respond to medication.

The study was published May 2 in *Nature Neuroscience*.

The research findings represent the first known example of a type of brain plasticity, called activity-dependent myelination, contributing to a disease. The study also suggests new drug targets to interrupt the process and prevent seizures from escalating.

"I was surprised by what we saw. Initially, I thought that because this is a disease process, we would see deficient myelination somehow," said the study's lead author, Juliet Knowles, MD, Ph.D., assistant professor of neurology and neurological sciences and of pediatrics. "What we're seeing is myelination in a pattern that favors seizure progression."

The study's senior authors are Michelle Monje, MD, Ph.D., professor of neurology and neurological sciences, and John Huguenard, Ph.D., professor of neurology and neurological sciences.

The learning process

Myelin is the fatty substance that insulates nerves. In adaptive myelination, which Monje's group discovered, the brain increases the number of myelinated fibers and the thickness of the coating around the nerve fibers that fire more often. This insulation helps cement things we learn in the physical structure of our brains.

Myelin plasticity contributes to many brain functions, including

attention, learning and memory. Normally, when someone practices a new skill, such as riding a bike or playing the piano, nerve firing triggers adaptive myelination. The busiest nerves become coated in thicker layers of insulating myelin, improving the speed and synchronization of nerve networks used in the skill and making the person a better cyclist or more accomplished musician.

But the research shows, for the first time, that myelination can also make the nerves more efficient at unwanted actions.

In a seizure, neurons fire with abnormal synchrony. Depending on the seizure type, the neural circuits involved may be localized to a small brain region, or they may extend across a large swath of the brain—but it's the same circuits every time.

Just as plenty of piano practice can cause a thick layer of myelination to increase the efficiency of the specific circuits needed to play a Beethoven sonata, lots of seizures can increase the myelination of—and therefore the efficiency of—the circuits that seize. This makes it easier for the brain to have seizures, similar to the way it's easier to play Beethoven on the 50th run-through than on the fifth.

"We think the onset of seizures begins with neuronal mechanisms, but the rearrangements in myelin really compound pathological changes in brain networks," Knowles said. The process appears to be one reason epilepsy patients who aren't taking medication or don't respond to medication may experience more frequent and/or more intense seizures as the disease progresses.

"This is the first demonstration of maladaptive myelination in a disease context, and I think this is the tip of the iceberg," Knowles said. "We have to explore how it plays out in different types of epilepsy and maybe in other neurological and neuropsychiatric diseases."

Focus on 'absence seizures'

In some seizures, the abnormal neuronal activity causes convulsions; in others, people lose muscle tone, causing them to collapse.

The researchers focused on a common type called absence seizures, in which all behavior stops, usually for less than a minute. People having such seizures look like they are staring or daydreaming. They also experience brief loss of consciousness; afterward, they don't know what happened. These seizures, though less dramatic than those that cause convulsions or collapse, still interfere with the lives of epileptic patients and can be dangerous if, for instance, someone has an absence seizure while crossing a street.

Children and adults with certain types of epilepsy can experience hundreds of absence seizures daily. Although medication can treat it, about 30% of patients with childhood absence epilepsy still have seizures even though they're taking medication.

"For most forms of epilepsy, we don't have disease-modifying treatment," Knowles said. "We can give medications that temporarily stop seizures, but this does not address what's happening structurally in the brain."

To understand how seizures change the brain, the researchers studied rodents with absence seizures. As in some types of human epilepsy involving absence seizures, the animals develop seizures in early life that gradually ramp up over time.

In the brains of rats with absence epilepsy, the researchers looked at changes to myelin-forming cells called oligodendrocytes. Compared with the time before seizures began, by the end of the period of seizure onset—4.5 months later—the animals had more and a greater density of

new or dividing oligodendrocyte precursor cells, and more mature oligodendrocytes.

This finding corresponded with the presence of thicker myelin coating on the nerve fibers—and more nerve fibers with myelin—in the brain region where seizures occur. However, there was no change in myelination in brain regions where seizures are uncommon. In addition, control animals without seizures did not show these changes.

To find out if interrupting the seizure-induced myelination could block the development of seizures, the researchers genetically engineered mice to further their understanding of absence epilepsy. The scientists changed an important receptor in mice oligodendrocyte precursor cells that is needed for adaptive myelination. Because of the genetic engineering, the researchers could selectively delete the receptor, TrkB, from the oligodendrocyte precursor cells in these mice beginning when the seizures were expected to start. When TrkB was deleted, the mice still had some seizures, but the number of seizures was lower, and they did not become more frequent.

The researchers also used a drug that blocks aspects of the maturation of oligodendrocyte precursor cells, administering the drug starting one week after the mice began having seizures. The findings were similar to those in genetically engineered mice: Seizures still occurred, but they did not become worse or more frequent.

The class of drugs used in the study, HDAC inhibitors, includes some FDA-approved medications. The scientists hope to study whether such drugs could improve outcomes, particularly in children newly diagnosed with severe forms of epilepsy.

"There's a lot more that needs to be done to explore the molecular mechanisms that link pathological patterns of neuronal activity to

maladaptive myelination and explore the potential of HDAC inhibition for severe and refractory epilepsy," Knowles said.

More information: Maladaptive myelination promotes seizure progression in generalized epilepsy, *Nature Neuroscience* (2022). DOI: 10.1038/s41593-022-01053-1

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