Team locates absence epilepsy seizure 'choke point' in brain

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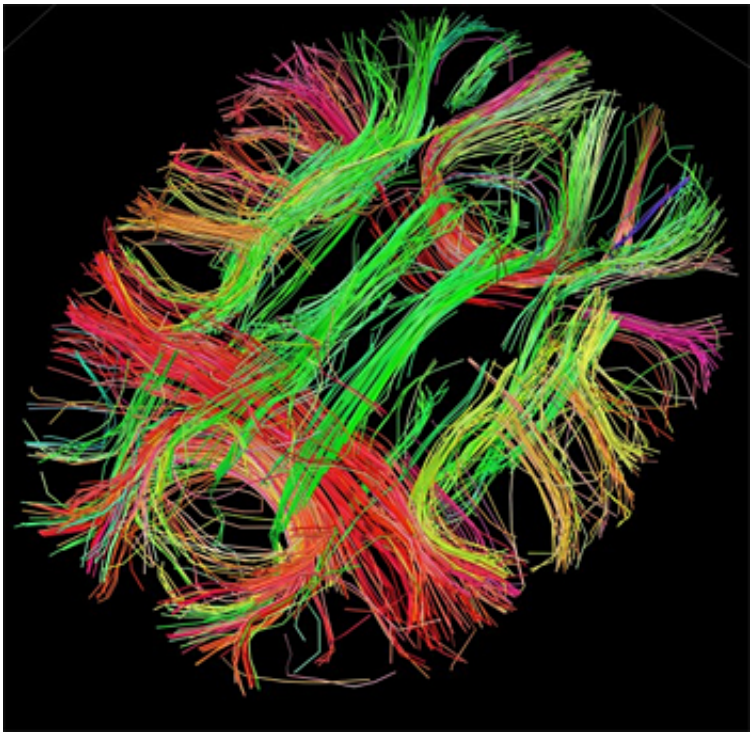

White matter fiber architecture of the brain. Credit: Human Connectome Project.

A particular structure in the brain is a "choke point" for a type of epileptic seizure that affects mostly children, Stanford University School of Medicine investigators have found.

The researchers used an advanced technology called optogenetics to

show, in rodent models of one of the most common forms of childhood epilepsy, that inducing synchronized, rhythmic activity in a specific nerve tract within this structure is sufficient to cause seizures, while disrupting that activity is sufficient to terminate them.

Epilepsy, a pattern of recurrent seizures, affects about 1 in 26 people over their lifetime, said John Huguenard, PhD, professor of neurology and neurological sciences and of molecular and cellular physiology. Absence, or petit-mal, seizures—a form of epilepsy most likely to occur among children ages 6-15—account for about 1 in 20 cases of epilepsy. They are characterized by a sudden loss of consciousness, accompanied by a behavioral and postural freezing in place, that persists for up to 15 seconds. A child experiencing an absence seizure usually has no recollection of it.

"These seizures can be so subtle that they go unnoticed or are mistaken for a lack of attention," Huguenard said.

The new findings, described in a study to be published online Dec. 15 in *Neuron*, point to the possibility of improved ways of reducing, halting or possibly even preventing absence seizures in susceptible children. There's reason to think these findings may also apply to a wider range of seizure types, including the more dramatic and better-known grand mal, characterized by involuntary jerking movements in addition to loss of consciousness.

Huguenard shares senior authorship of the study with Jeanne Paz, PhD, a former postdoctoral scholar in his group and now assistant professor of neurology at the University of California-San Francisco and assistant investigator at the Gladstone Institutes in San Francisco. After Paz, who initiated the study, departed for UCSF, the experiments were continued by Stanford graduate student Jordan Sorokin, the study's lead author, under Huguenard's direction.

Multiple, daily seizures

"Many people think of absence seizures as being mild because there's no shaking or falling on the floor," said Paz. "But some kids have more than 200 absence seizures a day, making it impossible for them to learn at school. And the drugs they take for their seizures may not work well."

Absence seizures are a type of so-called generalized seizures: patterns of rhythmic nerve-cell firing activity that, while originating in one or another brain region, propagate throughout the entire organ. Implicated in all generalized seizures is nerve circuitry in a deep-brain structure called the thalamus, whose normal functions include relaying sensory information to the cerebral cortex via a nerve projection called the thalamocortical tract.

Resorting to an increasingly widespread technology called optogenetics, pioneered in the lab of study co-author Karl Deisseroth, MD, PhD, a Stanford professor of bioengineering and of psychiatry and behavioral sciences, the researchers inserted the gene for a light-sensitive cell-surface protein called an opsin into a set of excitatory nerve cells in the thalamocortical tract of rats and mice bred to be prone to absence seizures.

As a result of this manipulation, the opsin appeared on the surfaces of those excitatory thalamocortical nerve cells. The particular opsin the scientists used for some of their experiments was inhibitory. Its presence on nerve cells meant that, whenever yellow light was delivered to them via an implanted fiber-optic cable, those cells would be prevented from firing.

The thalamocortical tract's excitatory nerve cells are somewhat like excitable second-graders. Imagine a classroom filled with children who share an inability to stay completely quiet for more than five seconds.

Imagine, further, a teacher who doesn't mind the occasional loud whisper or random outburst but who will not abide noise above a certain threshold. When the din exceeds that level, the teacher shouts a show-stopping, "Quiet!"

The inevitable result of this enforced silencing: Five seconds later, the room will erupt in a burst of noise, in turn inducing an authoritarian cease-and-desist command, followed by another eruption, and so forth. The very act of inhibition drives a pattern of rhythmic firing.

Disrupting the pattern

Similarly, back in the thalamus, inhibition (the "teacher" analog) is meted out to the thalamocortical tract's excitatory nerve cells by a different set of cells in the thalamus whose job it is to generate useful rhythms in this brain structure. A gentle, rhythmic firing pattern in the thalamocortical tract is typical during normal sleep. It makes sense, when an individual needs sleep, to tune out disruptive sensory inputs from the thalamus to the cortex.

But in absence epilepsy, this useful, rhythmic thalamocortical lullaby is hijacked and amplified into the distortion range. It appears that subtle defects within the circuitry can predispose the thalamocortical tract's firing to slip too easily into lockstep synchrony.

The researchers had observed that firing in the thalamocortical tract shifted from a chaotic to a rhythmic pattern during their test animals' naturally occurring seizures. Using optogenetics, the scientists were able to abruptly inhibit firing in excitatory thalamocortical cells—and, by so doing, to induce seizures at will in the animals—at the flick of a switch.

"A single pulse of yellow light was enough to generate rhythmic firing activity throughout the cortex, in both hemispheres of the brain,"

Huguenard said.

The insertion of a different kind of opsin, also developed in Deisseroth's lab, far from inhibiting excitatory thalamocortical cells made them more excitable in response to a blue-light pulse. This predisposition could be canceled by administering yellow light. Toggling from one to another color of delivered light, the investigators demonstrated that making the excitatory thalamocortical cells less susceptible to inhibition disrupted their collective firing synchrony and blocked seizure activity.

"Our study shows that the thalamus is a choke point whose involvement is essential to the maintenance of absence seizures," Paz said. Both Paz and Huguenard suggested that treatments capable of guiding excitatory thalamocortical nerve cells from a tightly synchronized to a more chaotic firing pattern may be able to halt absence seizures—and, maybe, other forms of generalized epilepsy, too.

Provided by Stanford University Medical Center

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