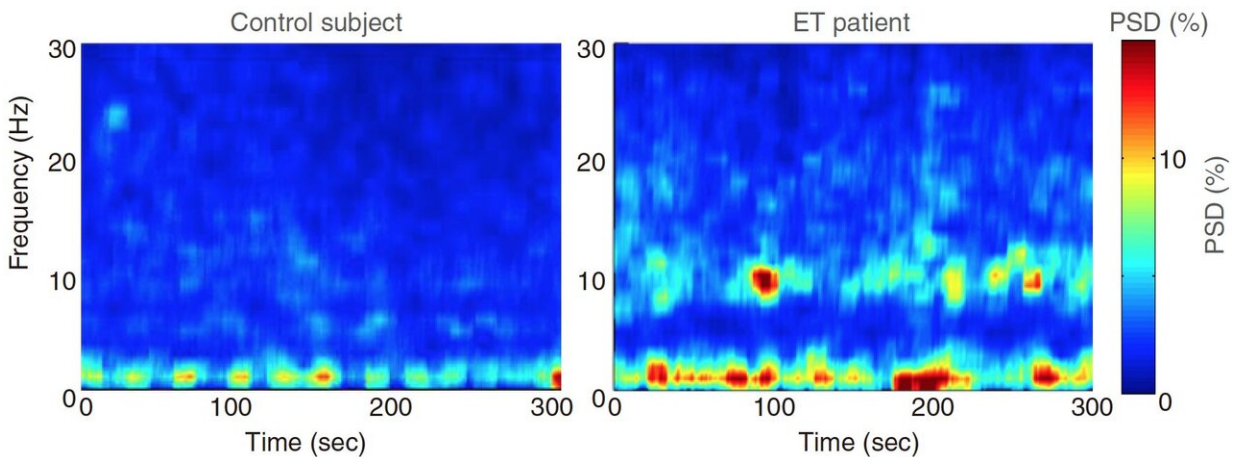


Overactive brain waves trigger essential tremor

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A new study suggests that patients with essential tremor have unusual brain waves in the cerebellum that cause the tremors (the same brain waves in mice produce tremor). The left image show a cerebellar electroencephalogram (EEG) in a control subject; the right image shows additional brain waves in a patient. Highest intensity is colored in red, lowest intensity in blue. Credit: Columbia University Irving Medical Center (Kuo lab)

The source of essential tremor—a movement disorder that causes involuntary trembling of the hands, arms, and head—has been enigmatic, impeding the development of effective treatments for a condition that affects 4% of people over 40.

Now a new study from Columbia University Irving Medical Center and

New York-Presbyterian suggests the tremors are caused by overactive [brain](#) waves at the base of the brain, raising the possibility of treating the disorder with neuromodulation to calm the oscillations.

"Past studies have identified changes in [brain structure](#) in people with [essential tremor](#), but we didn't know how those changes caused tremors," says Sheng-Han Kuo, MD, the study's senior author and assistant professor of neurology at Columbia University Vagelos College of Physicians and Surgeons.

"This study pins down how those structural changes affect brain activity to drive tremor."

The study was published online today in *Science Translational Medicine*.

About Essential Tremor

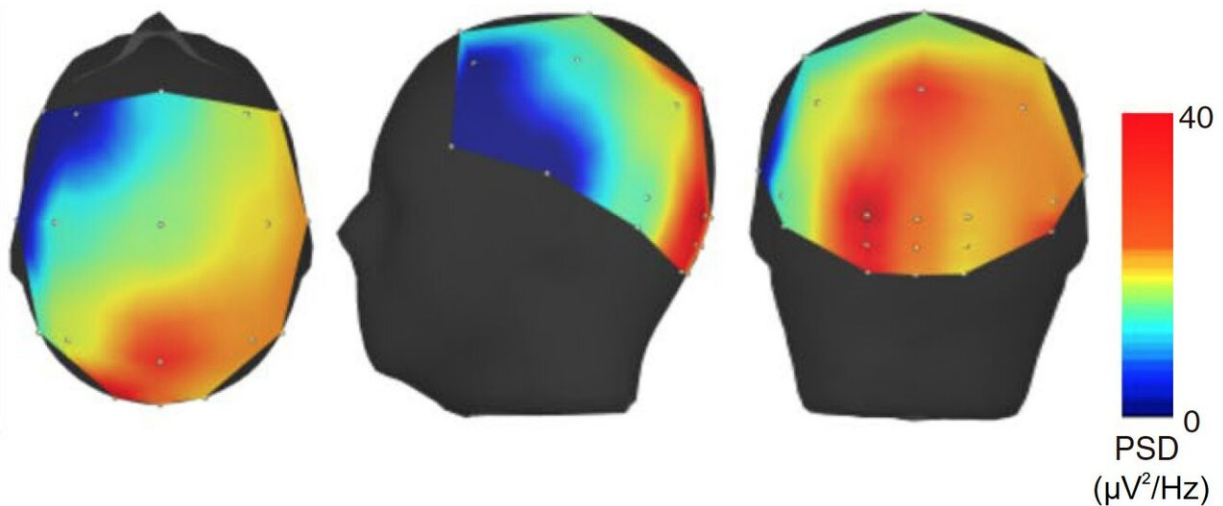
Essential tremor is the most common movement disorder in the United States, affecting about 10 million Americans (approximately eight times as many people as Parkinson's disease). The condition causes involuntary, rhythmic trembling, usually in the hands, and is exacerbated during such activities as buttoning a shirt or using utensils. Although essential tremor is not life-threatening, it can severely impact quality of life.

Some beta blockers and anti-epileptic drugs can reduce symptoms, but they carry side effects, such as fatigue and shortness of breath. They also don't work very well in essential tremor patients, which Kuo says isn't surprising since the cause of the condition hasn't been well understood.

Tremor Patients Have Excessive Brain Activity in the Cerebellum

The researchers have previously identified structural changes in the cerebellum of essential tremor patients and used a new cerebellar encephalogram (EEG) technique to search for unusual brain waves in this part of the brain.

Among 20 essential tremor patients examined with cerebellar EEG, most had strong oscillations (between 4 and 12 Hz) in the cerebellum that were not found in any of the 20 control subjects. Patients with more severe tremors had stronger oscillations.



Map of EEG intensity in patients with essential tremor. The highest intensity (red) is located in the cerebellar region of the brain. Credit: Columbia University Irving Medical Center (Kuo lab)

Oscillations First Found in Mice

The researchers first discovered the cerebellar oscillations in mice that had developed tremors closely resembling those seen in essential tremor

patients.

The tremors could be turned on and off by stimulating certain neurons in the mouse brain, alternately suppressing and unleashing the oscillations. "These results established a causal relationship between the brain oscillations and tremor, which cannot be directly tested in patients," says Kuo, who is also an assistant attending neurologist at New York-Presbyterian/Columbia University Irving Medical Center.

Excessive Oscillations Stem from Extra Synapses

In previous studies of postmortem brain tissue from essential tremor patients, the Columbia team discovered that patients with essential tremor had an abnormally high number of synapses, or connections, between two types of nerve cells in the brain's cerebellum—climbing fibers and Purkinje cells.

In the current study, again using postmortem brain tissue, the researchers found that the formation of these synapses appears to be influenced by a protein called glutamate receptor delta 2 (GluR δ 2). "When this protein is underexpressed, any excess synapses that form between climbing fibers and Purkinje cells are not eliminated, resulting in too many neuronal connections," says Kuo.

When the team reduced expression of GluR δ 2 in mice, the animals developed tremors similar to those seen in humans. Restoring GluR δ 2 function suppressed the tremors, proving that the protein plays a key role in essential tremor.

Potential for New Treatments

The study opens several new possibilities for treatment of essential

tremor, Kuo says.

"Using cerebellar EEG as a guide, we may be able to use neuromodulation techniques such as tDCS or TMS (transcranial direct-current stimulation or transcranial magnetic stimulation) to reduce tremor, or even drugs to reduce transmission between the climbing fibers and Purkinje cells."

Kuo is also working to develop medications that increase GluR2 expression in the brain, which may reduce tremor.

The study is titled "Cerebellar oscillations driven by synaptic pruning deficits of cerebellar climbing fibers contribute to tremor pathophysiology."

More information: M.-K. Pan et al., "Cerebellar oscillations driven by synaptic pruning deficits of cerebellar climbing fibers contribute to tremor pathophysiology," *Science Translational Medicine* (2019). stm.sciencemag.org/lookup/doi/10.1126/scitranslmed.aay1769

Provided by Columbia University Irving Medical Center

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