Schizophrenia signs in mice linked to uncoordinated firing of brain cells

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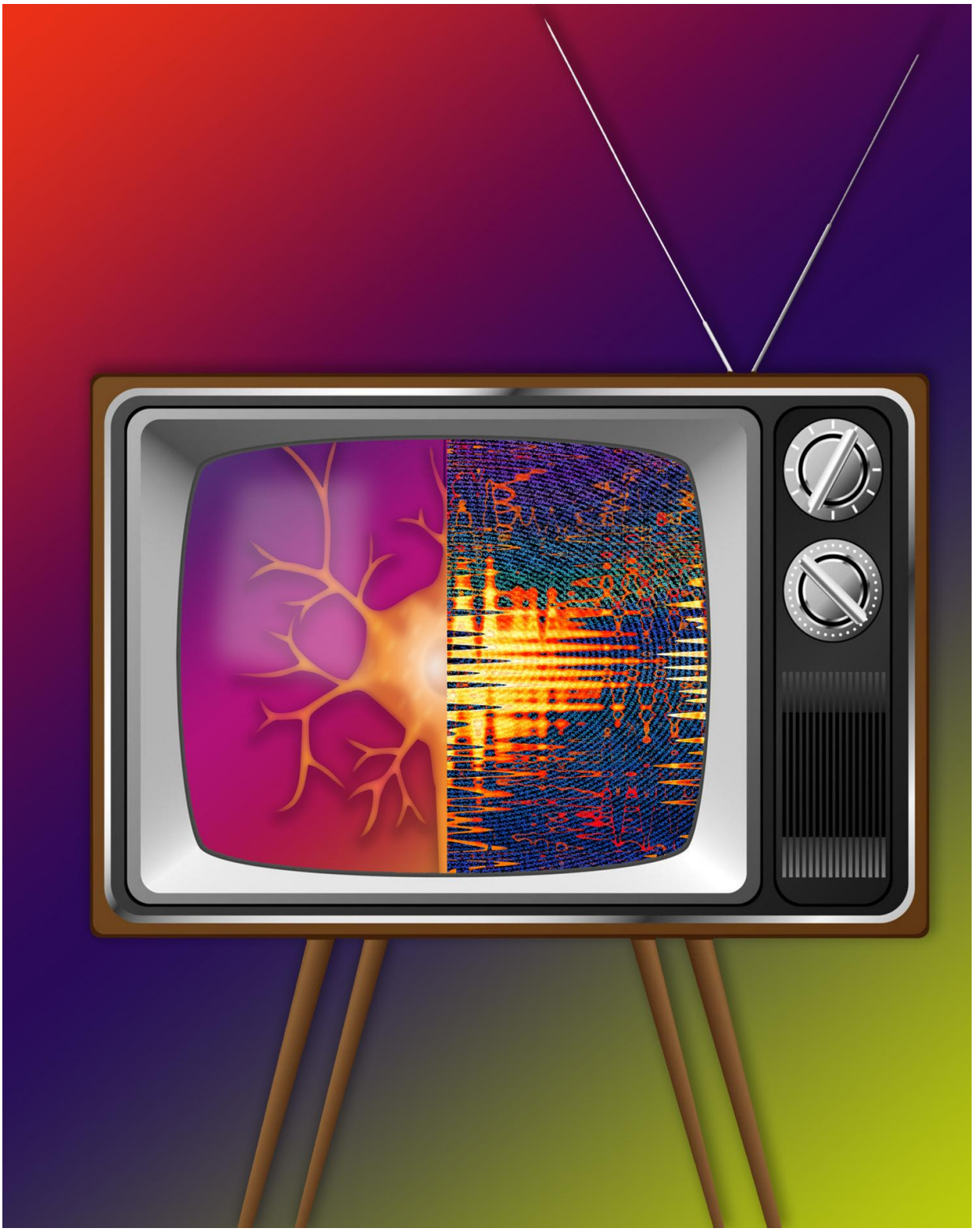

Columbia researchers have linked schizophrenia signs in mice to the haphazard firing of small networks of neurons. Credit: Nicoletta Barolini/Columbia

Researchers at Columbia University have discovered that a small group of neurons fired haphazardly in mice with signs of schizophrenia. The findings suggest that a breakdown in the synchronized behavior of these brain cells could produce the classic disordered thinking and perceptions associated with the disease.

The study, which may be the first to test the idea that schizophrenia arises from disruptions in small networks of neurons, was published today in *Neuron*.

Affecting about one percent of the population, schizophrenia is marked by a range of distinct symptoms, from hallucinations and delusions, to memory problems and social withdrawal. It also comes in a variety of forms, which has hindered researchers in finding a unifying explanation for the disease that could improve diagnosis and treatment.

"If you think of the neurons in the schizophrenic mice as pixels on a TV screen, it's as if most of the pixels have been scrambled," said the study's lead author, Jordan Hamm, a postdoctoral researcher at Columbia University. "Each pixel no longer relates to its neighbor to form a coherent, stable picture."

The researchers chose to focus on the visual cortex because impaired visual processing is one of schizophrenia's defining traits. Using calcium-imaging techniques, they recorded flashes of light emitted by individual neurons as each fired off an electric signal. In healthy mice, they found that groups of 60 to 120 neurons flashed in a consistent pattern, as if following a choreographed arrangement. The neurons in the mice with signs of schizophrenia, by contrast, fired more randomly as if working in

isolation.

The researchers tested two mouse models of the disease, genetic and chemical, and found similar results. Mice given regular doses of ketamine, an anesthetic that acts on glutamate receptors and can produce psychotic behavior, showed erratic neural activity, as did mice bred with a genetic mutation associated with a high risk of developing schizophrenia in humans.

"The pattern emerging from this analysis is one of profound disorganization, as though neurons were acting on their own rather than as a coherent group," said study coauthor Dr. Joseph Gogos, a neuroscientist at Columbia University Medical Center and Columbia's Zuckerman Institute who studies underlying mechanisms of schizophrenia in genetic models of the disorder.

In a related study published in *Science* last year, the researchers showed that repeatedly stimulating a small group of neurons in the same region of the mouse brain, the visual cortex, caused the neurons to fire together, as if their respective connections had been strengthened by use. Dr. Rafael Yuste, the study's senior author and a neuroscientist at Columbia, has suggested that this process could explain how memories and thoughts form, and how neural circuits might be reprogrammed through artificial manipulation.

Both studies suggest new avenues for treating schizophrenia, the researchers say, through the manipulation of genes, genetic pathways, and even individual neurons, to restore disrupted neural units to their normal functioning.

"I've experienced deep frustration in trying to treat schizophrenic patients without understanding how this disease works," said Yuste. "I'm excited by the possibility of reversing some of schizophrenia's symptoms

by reprogramming neurons to fire in a more coordinated fashion."

More information: "Altered Cortical ensembles in mouse models of schizophrenia." *Neuron* (2017). DOI: 10.1016/j.neuron.2017.03.019

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