A new study reveals the cerebellum as a source of generalized convulsive seizures

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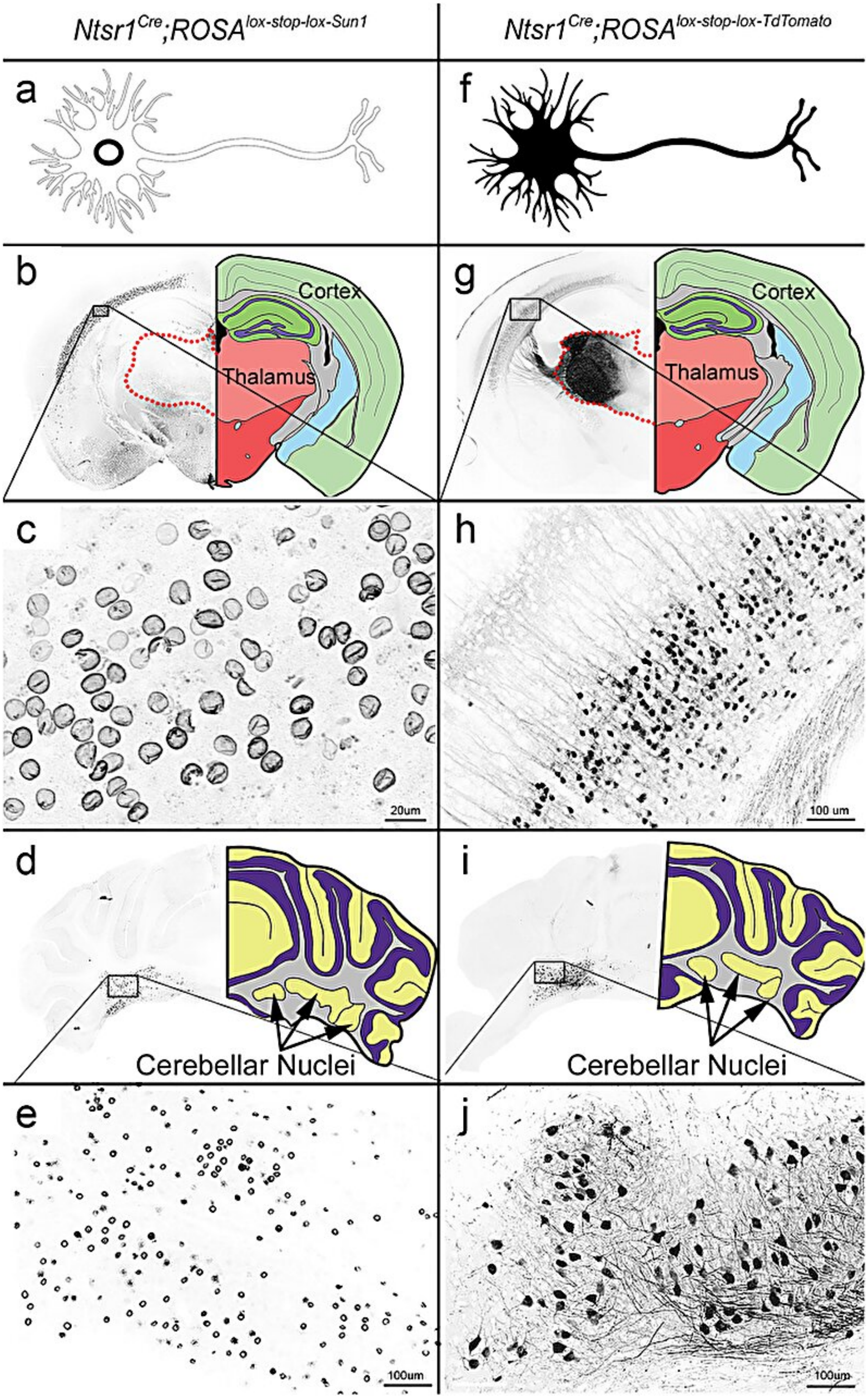

Ntsr1Cre;ROSAlox-stop-lox-Sun1
Ntsr1Cre;ROSAlox-stop-lox-TdTomato
a
f
b
Cortex
Thalamus
g
Cortex
Thalamus
c
20um
h
100 um
d
Cerebellar Nuclei
i
Cerebellar Nuclei
e
100um
j
100um

Ntsr1 Cre is expressed in corticothalamic layer 6, cerebellar nuclei, and the axons and fibers of passage within the thalamic nuclei. Credit: *Communications Biology* (2023). DOI: 10.1038/s42003-023-05100-w

Recurrent seizures are debilitating and can sometimes be fatal. The onset and presentation of seizures vary significantly among epilepsy patients. Of more than 25 categories of seizure presentations within epilepsy, those with motor convulsions are perhaps the most disruptive and generally most feared among patients and caregivers. Unfortunately, convulsive seizures are also the most commonly occurring type of generalized seizures. However, little is known about the source or the precise mechanism by which these seizures originate, making it difficult to optimize therapies and develop targeted treatments for these patients.

A study led by Dr. Roy Sillitoe, professor at Baylor College of Medicine and investigator at the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas Children's Hospital, has discovered the cerebellum as a source of generalized convulsive seizures. The researchers found that the cerebellum, which is a part of the hindbrain and responsible for motor coordination, alters the activity of a specific group of neurons in the midbrain that then initiates generalized convulsive seizures. The study was published in *Communications Biology*.

"To our knowledge, this is the first study to implicate the cerebellum in a pathway that alters the activity of a specific group of neurons in an area called the ventral posteromedial nucleus (VPM) in the thalamus to cause generalized seizures," Dr. Sillitoe said. "These findings not only deepen our understanding of how seizures originate, but are expected to have a wider impact on several neurological diseases. Moreover, it opens up the tantalizing possibility of using cerebellar circuits as a versatile target for therapeutic interventions to treat generalized epilepsies and other neurological disorders."

A reciprocal cortico-thalamic loop is central to generalized convulsive seizures

While each brain region is known to perform discrete functions, it is important to remember that the regions do not act in isolation. In fact, many regions are in constant communication with one another through a multitude of interconnected neural networks. The reciprocal cortico-thalamic loop is part of one such network that links neurons in the forebrain—namely the cerebral cortex—which controls cognition, memory, language, and emotion processing with the thalamus, an-egg-shaped midbrain structure that acts as a relay center for motor and sensory information.

This neural circuit is important for several critical brain functions such as sleep and learning, and plays an unequivocal role in different diseased states (e.g., certain types of generalized seizures and tremors). Thalamic neurons, a critical part of this circuit, are also the locus of seizure activity. However, exactly how these thalamic neurons generate or propagate generalized seizures was unclear.

Facial twitching is often among the first behavioral readouts in generalized convulsive seizures in patients and so, the authors chose to study the VPM thalamic circuits, which are tightly interconnected to the facial somatosensory cortex and have been previously suspected to play an important role in various types of epilepsies.

The majority of thalamic VPM neurons are active and contribute to seizures

Using optogenetics (i.e., using light stimulation to control genetically manipulated neurons) and drug injection techniques, the researchers found that activation of neuronal inputs specifically to the VPM, but not to other surrounding thalamic nuclei, caused severe convulsive seizures in mice. Despite the canonical view of homogenous, synchronous activity of thalamic neurons during seizures, recent studies indicate the presence of heterogenous activity among neuronal populations both at seizure onset as well as throughout the seizure period.

Furthermore, studies in animal models have established that a proportion of cells within the epileptic brain remain largely normal during seizure episodes. Here, the team found that a higher proportion—as many as 80%—of VPM neurons may change their activity and actively contribute to initiating or sustaining seizures. Within this population, the activity of the affected neurons can take on different forms, altogether suggesting a high level of heterogeneity in neural responses as well as the identity of neurons that respond versus those that remain unchanged.

The cerebellum is a major source of inputs to VPM neurons during seizures

To the team's greater surprise, in their model, cerebellar neurons showed the greatest ability to drive seizures among the possible contributing brain regions. Viral tracing experiments revealed specific inputs from the cerebral cortex and cerebellar regions to VPM neurons that were activated during seizures. Interestingly, when they inhibited the activity of the cerebellar output pathway with lidocaine, VPM neurons stopped inducing seizures.

"Identifying a new critical neural circuit from the cerebellum to the VPM neurons in the thalamus as the source of seizures is indeed exciting. It provides fundamental insights into how major brain nodes are interconnected and regulated for optimal function and behavior," commented first author Dr. Jaclyn Beckinghausen.

"It is becoming increasingly apparent that the cerebellum, Latin for 'little brain,' may not be so little in its ability to drive distinct behaviors under normal and diseased states," Dr. Sillitoe added. "Given its increasingly diverse and complex roles in motor and non-motor functions and accordingly, its contributions to diseases ranging from ataxia, dystonia and tremor to autism, schizophrenia, and seizures, one wonders what other big mysteries this powerful 'little brain' might be hiding."

Others involved in the study were Joshua Ortiz-Guzman, Tao Lin, Benjamin Bachman, Luis E. Salazar Leon, Yu Liu, Detlef H. Heck, and Benjamin R. Arenkiel. They are affiliated with one or more of the following institutions: Baylor College of Medicine, Texas Children's Hospital, and University of Minnesota Medical School.

More information: Jaclyn Beckinghausen et al, The cerebellum contributes to generalized seizures by altering activity in the ventral posteromedial nucleus, *Communications Biology* (2023). DOI: 10.1038/s42003-023-05100-w

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