Cracking the code for cerebellar movement disorders

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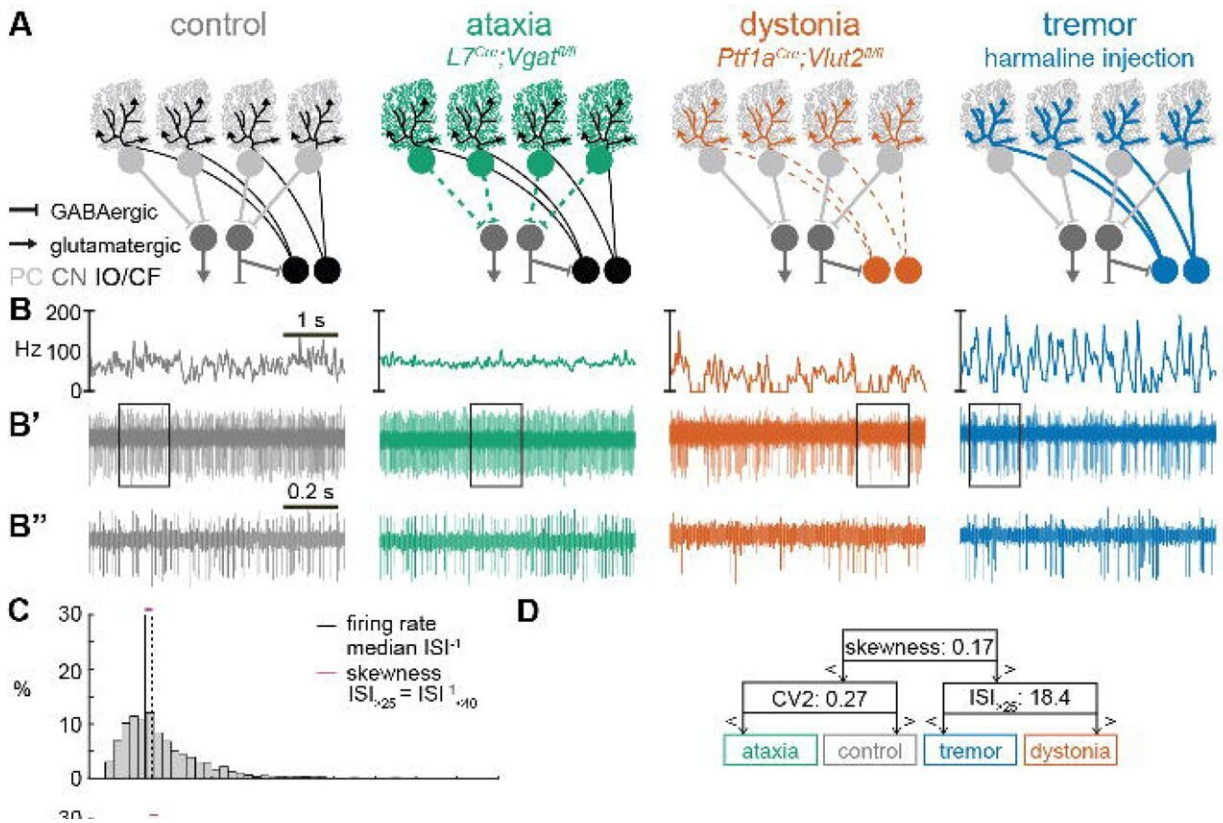

Supervised classifier model predicts mouse phenotype based on spike signatures. Credit: *eLife* (2024). DOI: 10.7554/eLife.91483.2

The cerebellum is a region of the brain that helps us refine our movements and learn new motor skills. Patients and mouse models

experience many kinds of abnormal movements when their cerebellum is damaged. They can have uncoordinated and unbalanced movements, called ataxia. They can have atypical positioning of body parts or uncontrolled movements because their muscles are working against each other, called dystonia. Or they can have disruptive shaky movements, called tremors. Understanding how changes in a single brain region can result in such a diverse range of motor defects has been a longstanding question in the field.

A recent study from the laboratory of Dr. Roy V. Sillitoe, a professor at Baylor College of Medicine, and the Chao Family Endowed Chair and a principal investigator at the Jan and Dan Duncan Neurological Research Institute (Duncan NRI) at Texas Children's Hospital, has found that the way cerebellar neurons communicate with other brain regions is different in various movement disorders. The team found unique cerebellar activity patterns responsible for different abnormal movements. This work provides a foundational framework for new treatment approaches to movement disorders.

The study was published in *eLife*.

"Brain cells communicate with each other through neural signals," said co-first and co-corresponding author Dr. Meike van der Heijden. "Those signals occur in specific patterns that represent a code for specific behaviors. Studying the code produced in the cerebellum gives us information about the animal's movements.

"We wondered whether we could crack the code for different movement disorders by comparing cerebellar neural activity patterns in healthy [mice] vs. mice with ataxia, dystonia, and tremors. To address this question, we built a computational model and revealed that cerebellar neurons fired differently in healthy [animals] compared to animals with disease-specific behaviors. Moreover, cerebellar neurons in each of the

disease mouse models showed a distinct and unique neural code."

"We performed further studies with other disease models to test whether different genetic or drug-induced origins of abnormal movements influenced the disease code. Importantly, we found that—irrespective of the disease origin—the abnormal features of the neural signals in mice with similar movement disorders were the same. However, those activity patterns were distinct in mice with different conditions," said co-first author of the paper and postdoctoral fellow in the Sillitoe lab, Dr. Amanda Brown. "This gave us the first hint that these unique neural codes may not just correlate with different abnormal movements but also cause them."

The researchers next mimicked the effects of these neural codes in healthy mice using optogenetics, an elegant approach that combines optical and genetic engineering techniques for precise regulation of biological functions in target cells. This technique allowed the researchers to shine a light on the cells in flashing patterns to alter the cells' activity pattern. They found that when they changed the light pattern, they could reliably switch the neural signal patterns of cerebellar neurons from a healthy code to the desired disease code.

The team then used these different light patterns to change the cerebellar neural code of healthy mice to test if they could create disease behaviors on demand as the mice freely moved around in a box.

"When we induced the activity patterns associated with ataxia, our healthy mice immediately exhibited ataxic movements. The same mice displayed dystonic movements with the dystonia-associated pattern and developed tremor when they were given the tremor-associated pattern." Dr. Brown added. "This means that each disease-associated neural pattern is alone sufficient to cause distinct dysfunctional behaviors, even in healthy brains."

"Together, our findings provide strong evidence for the important role of unique activity patterns of cerebellar neurons in generating different movement disorders." Dr. Sillitoe said. "Movements in the cerebellum of healthy animals are likely regulated by a range of activity patterns, and movement disorders occur when neurons shift within the range to a neural code that promotes one of the dysfunctional movements.

"Our study highlights the importance of studying cerebellar neural signals in health and disease. It points towards a potential new strategy of treating movement disorders by finely regulating the activity of cerebellar neurons."

More information: Meike E. van der Heijden et al, Cerebellar nuclei cells produce distinct pathogenic spike signatures in mouse models of ataxia, dystonia, and tremor, *eLife* (2024). DOI: 10.7554/eLife.91483.2

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