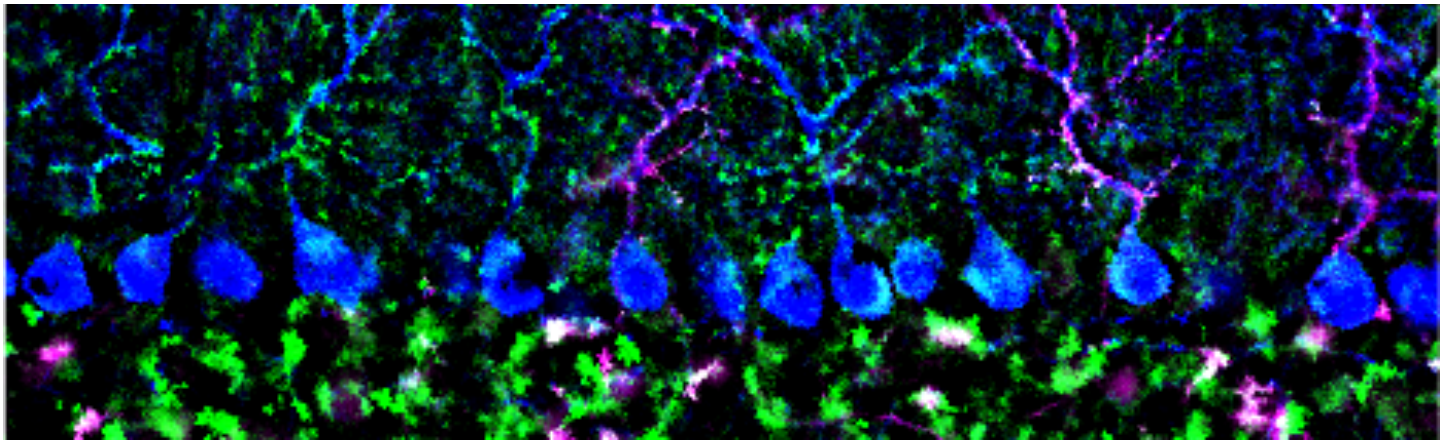

Same same but different

ME van der Heijden

A mole, a cat, a dog, a turkey, a swallow, a sparrow, a barn owl, a very large duck, and a dormouse.

No, this is not the start of a children's book, but the experimental subjects in a pioneering publication on the cerebellum. For his 1841 book on the nervous system function, Pierre Flourens studied the cerebellum by damaging it in the aforementioned animals.(*1*)

Flourens observed uncoordinated movements during locomotion in all animals, but noted that breathing, memory, and vision were unaltered. Flourens concluded his chapter on the cerebellum: "Je n'ajouterai pas ici de nouvelles expériences; l'exacte conformité de celles qu'on vient de voir rend tout répétition inutile." (I will not add any new experiments here; the consistency of those we have just seen makes any repetition unnecessary.)(*1*)

The cerebellum kept its reputation as relatively boring brain region solely important for motor coordination for over a century after Flourens' pioneering studies. But currently it is experiencing a renaissance based on renewed appreciation for its functional complexity and clinical importance.(*2*) Work from my colleagues and I shows how different types of cerebellar dysfunction can cause diverse motor disorders(*3*) and even impair complex non-motor behaviors, like social interactions.(*4*)

The cerebellum's neuroanatomical simplicity often masked its functional complexity. Santiago Ramón y Cajal leveraged the cerebellum's uniform circuitry to support his 1906 Nobel Prize winning theory that the brain is comprised of individual cells rather than a continuous mass (the neuron doctrine).(*5*) Cajal presciently noted how the cerebellum's neurons are arranged in a strikingly consistent architecture across different regions and in different species. This uniform architecture aligns with Flourens' uniform observations but more detailed experiments revealed a more complex story.

Most cerebellar manipulations — whether genetic, anatomical, or pharmacological — result in motor disturbances, but close observation shows various types of motor impairments. In mice, cerebellar dysfunction can result in uncoordinated movements as described by Flourens, now called "ataxia." Other mice predominantly express involuntary muscle over-contractions, like the motor disorder "dystonia," or rhythmic shaky movements, like "tremor." In three archetypal mouse models, manipulations to the same cerebellar neurons in the same cerebellar regions resulted in ataxia, dystonia, or tremor.

My colleagues and I wondered why.(*6*)

We hypothesized that the expression of motor disturbances is not determined by which neurons are affected but by the changes in their neural communications. Neurons communicate with each other using brief electric signals, commonly called "spikes." Their language is encoded in the signal patterns, or how fast and how regular the signals occur. We set out to decode the neural language for cerebellar movement disorders.

We focused our analyses on the signal patterns in cerebellar nuclei cells, which form the highway between the cerebellar cortex and other brain regions

involved in motor control. We found that spikes patterns were different between the ataxia, dystonia, and tremor models.

But the signal patterns were similar across mouse models with similar behaviors caused by different experimental manipulations. These findings suggest that signal patterns correlate with the expression of cerebellar movement disorders. But could these signal patterns also cause different behaviors?

To answer this question, we turned to optogenetics – a powerful tool that uses light pulses to playback disease-associated signal patterns in healthy mice's cerebellums. Remarkably, stimulating the same neurons in the same animals produced different behaviors depending on whether we activated ataxia-, dystonia-, or tremor-like signal patterns.

These findings confirm that disease-specific signal patterns in the cerebellum produce different motor phenotypes.(*6*) And while looking at cerebellum may not immediately reveal its functional diversity, eavesdropping onto its neural communication does. Much like the words in a picture book tell a more detailed story than its pictures.

There is even more to the story. Initially reported in patients with damaged cerebella, controlled experiments in mice confirmed that the cerebellum also contributes to higher cognitive behaviors, including social interactions between individuals.

The cerebellum's uniform architecture suggests it may optimize diverse behaviors using similar molecular and genetic pathways. However, an extensive literature review shows that the same genetic manipulation to the same neuron type often has different effects on social and motor behaviors in mice (15/36 varieties of cerebellar mutants exhibited abnormal social interactions without changes in motor behaviors, or vice versa).(*4*)

Thus, the cerebellum may employ some similar and some different molecular pathways for social versus motor behaviors. Similar to books about farm animals or kings and queens using some similar and some different words to tell different stories.

A final plot twist lays in how the cerebellum communicates with other brain regions for diverse behaviors. Cerebellar nuclei consist of intermingled neuron types. One type, glutamatergic neurons, are unique for their dense connections to the thalamus, through which they can indirectly modulate the cerebral cortical neurons usually associated with cognitive functions, like social behaviors.(*7*)

Based on these anatomical connections my colleagues and I hypothesized that the glutamatergic neurons may be the neural pathway through which the cerebellum mediates social behaviors.(*8*) To test this, we selectively eliminated neurotransmission from glutamatergic nuclei neurons in mice but, surprisingly, these mice exhibited abnormal movements but normal social interactions. A different group found that other manipulations to glutamatergic neurons also cause in motor but not social impairments.(*9*)

Together, these results suggest that diverse cerebellar output pathways may differentially contribute to diverse cerebellar-mediated behaviors but not always in a way that can be predicted based on neuroanatomical connections alone.

For over a century, the cerebellum's simple anatomy masked its functional complexity. Rather than employing different cell types and circuits, the cerebellum uses the same neurons in the same neuroanatomical circuits but generates different spike patterns, relies on different molecular pathways, and communicates through different output pathways to modulate a variety of behaviors.

These findings show that biology has found various ways to achieve functional complexity in neural circuits. And had this story been a children's book, its moral would be to not judge a book by its cover or a brain region by its neuroanatomical architecture.

Citations

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