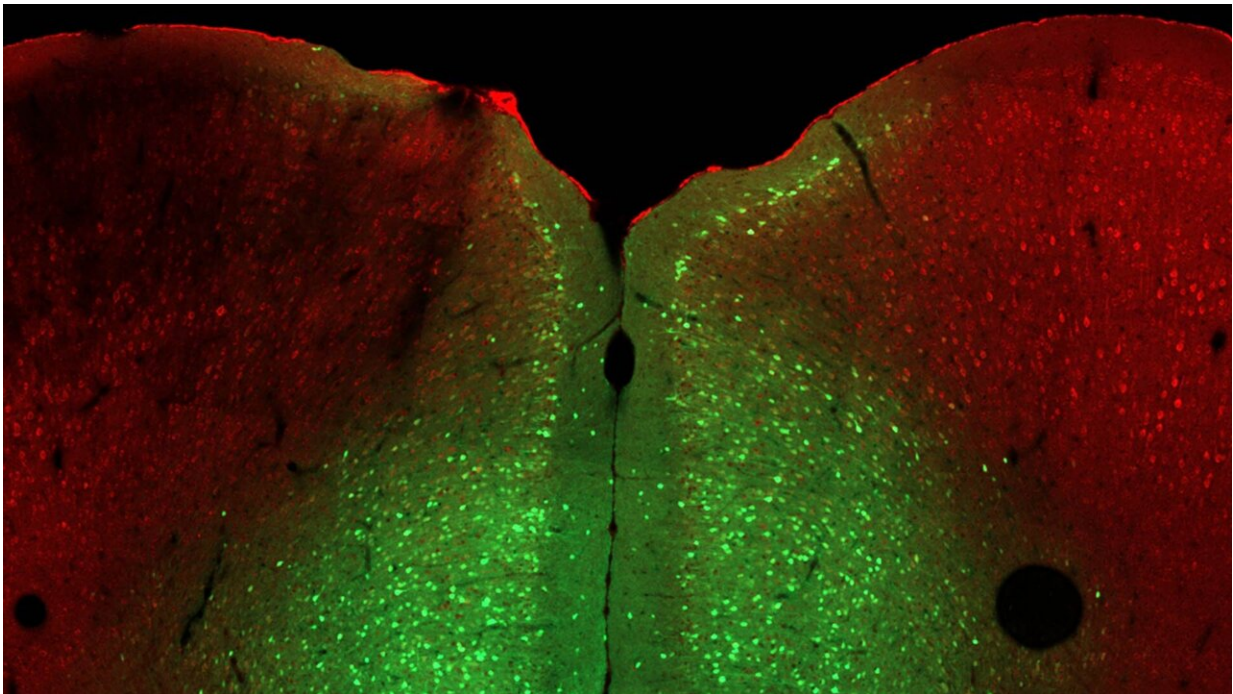


Reversing a genetic cause of poor stress responses in mice

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Deleting the *Ophn1* gene causes mice to respond to stressful situations with an inappropriate helpless behavior. CSHL Professor Linda Van Aelst and her lab wanted to know the exact location in the mouse brain affected by the lack of *Ophn1* that leads to this helpless/depressive behavior. In this image of a mouse brain, the green color shows the prelimbic region of the medial prefrontal cortex, where the researchers injected a virus to delete *Ophn1*. *Ophn1* (red) is still present in other parts of the brain. The researchers discovered that deleting the gene in only this part of the brain caused the observed failure in stress adaptation. Human brains are organized similarly, so their findings in mice may be applicable to helping human patients who experience an inability to deal with stressful situations. Credit: Minghui Wang/Van Aelst Lab, CSHL/2021

Everyone faces stress occasionally, whether in school, at work, or during a global pandemic. However, some cannot cope as well as others. In a few cases, the cause is genetic. In humans, mutations in the OPHN1 gene cause a rare X-linked disease that includes poor stress tolerance. Cold Spring Harbor Laboratory (CSHL) Professor Linda Van Aelst seeks to understand factors that cause specific individuals to respond poorly to stress. She and her lab studied the mouse gene *Ophn1*, an analog of the human gene, which plays a critical role in developing brain cell connections, memories, and stress tolerance. When *Ophn1* was removed in a specific part of the brain, mice expressed depression-like helpless behaviors. The researchers found three ways to reverse this effect.

To test for [stress](#), the researchers put mice into a two-room cage with a door in between. Normal mice escape from the room that gives them a light shock on their feet. But animals lacking *Ophn1* sit helplessly in that room without trying to leave. Van Aelst wanted to figure out why.

Her lab developed a way to delete the *Ophn1* gene in different brain regions. They found that removing *Ophn1* from the prelimbic region of the medial prefrontal cortex (mPFC), an area known to influence behavioral responses and emotion, induced the helpless phenotype. Then the team figured out which brain circuit was disrupted by deleting *Ophn1*, creating overactivity in the brain region and ultimately the helpless phenotype.

Understanding the circuit

Pyramidal [neurons](#) are central to this [brain](#) circuit. If they fire too much, the mouse becomes helpless.

Another cell, an interneuron, regulates the pyramidal neuron activity, making sure it does not fire too much.

These two cells feedback to each other, creating a loop.

Ophn1 controls a particular protein, RhoA kinase, within this [feedback loop](#) which helps regulate and balances activity.

Van Aelst found three agents that reversed the helpless phenotype. Fasudil, an inhibitor specific for RhoA kinase, mimicked the effect of the missing Ophn1. A second drug dampens excess pyramidal neuron activity. A third drug wakes up the interneurons to inhibit pyramidal neurons. Van Aelst says:

"So bottom line, if you can restore the proper activity in the medial prefrontal cortex, then you could rescue the phenotype. So that was actually very exciting. You should be open to anything. You never know. Everything is surprising."

Van Aelst hopes that understanding the complex feedback loop behind Ophn1-related stress responses will lead to better treatments for stress in humans.

The study is published in *Neuron*.

More information: *Neuron*, [DOI: 10.1016/j.neuron.2021.03.016](https://doi.org/10.1016/j.neuron.2021.03.016)

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