NEWS

Gut problems in autism may stem from neuronal connections

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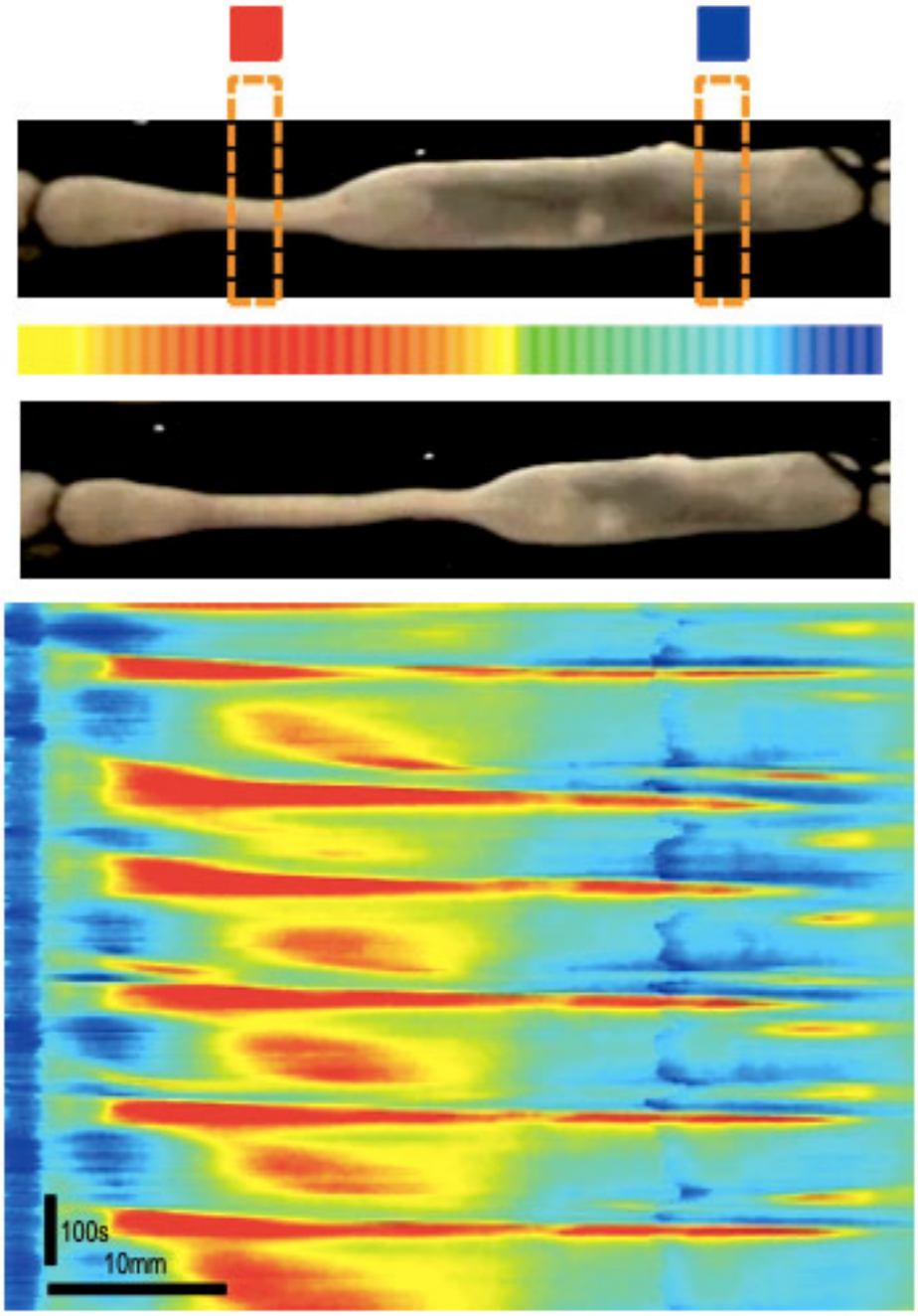
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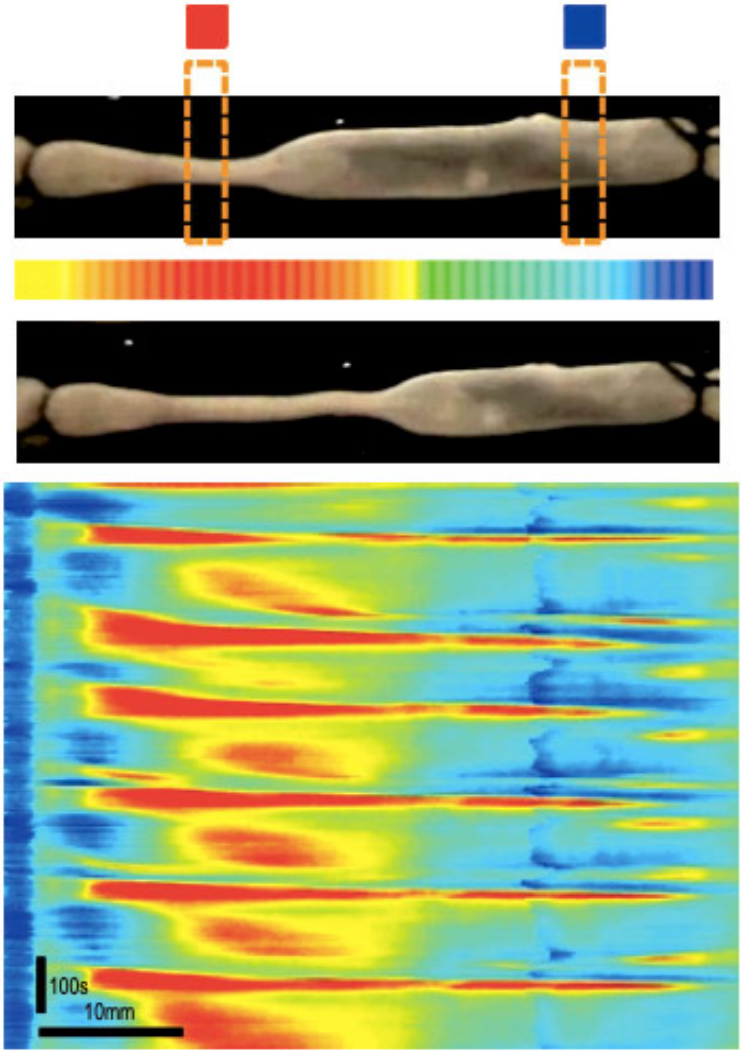

Beating gut: The researchers analyzed contractions (red) in short stretches of colon taken from a mouse model of autism.

Researchers have shown for the first time that glitches in a gene expressed at the junctions between neurons can cause gut problems in mice. The unpublished results were presented Tuesday at the **2013 Society for Neuroscience annual meeting** in San Diego.

The link between autism and the gut is **controversial**, but some studies estimate as many as 70 percent of children with the disorder **have gastrointestinal woes**. Researchers have proposed a wide range of explanations, from an **unbalanced composition of gut bacteria** to stress and **picky**

eating habits.

Elisa Hill-Yardin of the University of Melbourne and her colleagues investigated the gastrointestinal system in mice carrying a mutation in the neuroligin-3 (**NLGN3**) gene. These mutant animals, characterized by impaired social behaviors and enhanced spatial learning, debuted in 2007 as one of the **first mouse models of autism**[1].

In the brain, NLGN3 helps organize proteins at the **synapse**, the junction between neurons. It has turned out to be one of **many synaptic genes linked to autism** and related disorders. But no one had looked at whether these genes also affect the neurons in the gut.

The enteric nervous system — the mesh of neurons that lines the gastrointestinal tract — has many of the same types of synapses and molecules that are present in the brain and spinal cord. In the gut, these cells help with digestion by controlling secretions and contractions of the colon.

Hill-Yardin's team found that NLGN3 mutants weigh significantly less than controls. What's more, after a mild stressor, NLGN3 mutants produce more stool pellets — about 1.7 times more — than controls do. The mutant animals also have heavier pellets, but it's unclear why. It could be a change in the gut's absorption of water, for example, or a difference in motility, "where the gut is just pushing out more," says Hill-Yardin, who presented the work.

Her team also looked at 5-centimeter stretches of colon taken from adult NLGN3 mice and controls. "The nice thing about this system is, you cut out the gut and it keeps contracting — these beautiful, well-characterized contractions — for over three hours," she says. That presents a window of time for the researchers to apply chemicals to the gut cells and see what happens.

The researchers were interested in the gut's response to gamma-aminobutyric acid (GABA), a **chemical messenger** that keeps brain signals in check. The original NLGN3 mouse paper had reported that mutant animals have a much larger response to GABA than controls do.

Hill-Yardin's team found no difference in the baseline number of colonic contractions in tissue taken from NLGN3 mice and controls. But exposing the cells to gabazine — a drug that blocks a type of GABA receptor called GABA-A — caused a slight decrease in contractions in control cells, and "almost wiped them out in the mutant," Hill-Yardin says.

The researchers found no difference in the number of neurons in the colons of mutants and controls, meaning that couldn't account for the reported differences in GABA response. This suggests that the same synaptic defects occurring in the mutants' brains are responsible for the difference, Hill-Yardin says.

Her team plans to perform similar experiments on mice lacking **SHANK3**, another synaptic gene **linked to autism**.

“For this to be important, it has to be seen across models,” Hill-Yardin says. “And I think it will be.”

For more reports from the 2013 Society for Neuroscience annual meeting, please ***click here****.*

References:

1. Tabuchi K*. et al. Science* **318**, 71-76 (2007) **PubMed**