NEWS

Mice reveal roots of sensory issues tied to top autism gene

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Mice with mutations in the autism-linked gene SYNGAP1 have trouble sensing touch, which may stem in part from brain-circuit alterations and dulled alertness. The findings could help explain the high pain threshold and other sensory-processing problems seen in people with mutations in the gene.

Researchers presented the unpublished work last Tuesday and Thursday at the **2020 International SYNGAP1 Scientific Conference**, which took place virtually because of the **coronavirus pandemic**.

The **SYNGAP1** protein is found mainly at **synapses**, the connections between neurons, where it helps brain cells pass along chemical signals. People with a mutated copy of SYNGAP1 often have autism, as well as intellectual disability, epilepsy and an impaired gait.

Mutations in the gene **hamper the ability** of neurons that process touch to transmit signals, according to a 2018 study. Of the 48 people with SYNGAP1 mutations in that study, 45 exhibited sensory-processing impairments and 17 had sensory-processing issues related to touch.

The new work in mice suggests the mutations alter sensory processing by dampening activity in the somatosensory cortex and blunting an animal's level of alertness, or arousal.

"If this arousal system is blunted and broken, it's going to result in a bunch of behaviors that are maladaptive," says one of the lead researchers, **Gavin Rumbaugh**, professor of neuroscience at Scripps Research in Jupiter, Florida. "My suspicion is that a lot of animal models for a lot of autism genes are going to have the same blunted arousal response."

Whisked away:

Mice use their whiskers to explore their environment, much as people might feel around with their hands to navigate in the dark. This process, called ‘active sensing,’ involves sensory and motor regions of the brain.

In one study, researchers monitored the activity of neurons in the somatosensory cortex, which receives and processes sensory information, as mice received light touches to their whiskers.

Mice missing a copy of SYNGAP1 showed significantly weaker brain activity in response to the touches than control mice did, which was surprising because neurons in other brain regions of the mutant mice are known to be hyperactive, says **Thomas Vaissière**, staff scientist at Scripps Research, who presented the findings.

He and his colleagues then used a virus to trace connections between the mice’s motor cortex — which is responsible for movements — and the somatosensory cortex. The SYNGAP1 mutant mice had significantly stronger connections in this circuit, which could potentially compensate for weaker neuronal activity, Vaissière says.

In an experiment that assessed both motor and sensory activity in the animals, Vaissière and his colleagues recorded videos of mice as they explored an object with their whiskers. The mutant mice tapped the object with their whiskers — a behavior called ‘whisking’ — less intently and for shorter periods of time than the wildtype mice did. Their whisker taps also elicited weaker activity in the somatosensory cortex.

Another experiment showed that mice missing a copy of SYNGAP1 could not distinguish between two objects with different textures by whisking, whereas the wildtype mice could.

The results suggest that SYNGAP1 mutations change the way the motor and sensory brain regions communicate with each other, the researchers say, which disrupts active sensing.

Arousal states:

In a separate study, Rumbaugh and his colleagues monitored pupil size — an indicator of a mouse’s level of arousal — in multiple situations. In one experiment, for example, they trained mice to lick a sensor in response to a whisker touch, receiving a little sip of water as a reward.

Mice with a mutated copy of SYNGAP1 had more trouble learning the task than the wildtype mice did, and their pupils expanded less than those of controls when they received their reward. The mice showed a similar lack of pupil dilation in response to an electric shock to the foot, suggesting that SYNGAP1 mutations lead to a dulled arousal response.

An impaired arousal response may contribute to sensory-processing issues in animals and people with mutated copies of SYNGAP1, says **Sheldon Michaelson**, a postdoctoral researcher in

Rumbaugh's lab who presented the findings.

Arousal levels affect sensory-processing ability: Being hyper-alert or hypo-alert results in poor sensory processing, he says. A disrupted arousal system could also hamper the ability to learn that a painful stimulus, such as touching a hot stove, is undesirable. Children with SYNGAP1 mutations often engage in behaviors that can hurt them, according to anecdotal reports from parents.

Recording pupil dilation in people with SYNGAP1 mutations could reveal whether they, too, have this dulled arousal response, Michaelson says.

*Read more reports from the **2020 International SYNGAP1 Scientific Conference**.*