Scientists reverse a sensory impairment in mice with autism

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“We’re trying to identify early brain processes that will impact behaviors in children when they are older,” said Anubhuti Goel, a postdoctoral researcher in neurology at UCLA and first author of the study. Credit: University of California, Los Angeles

Using a genetic technique that allows certain neurons in the brain to be

switched on or off, UCLA scientists reversed a sensory impairment in mice with symptoms of autism, enabling them to learn a sensory task as quickly as healthy mice.

The findings, which appear in the journal *Nature Neuroscience*, offer an intriguing glimpse of a potential strategy to help people with autism make sense of what their eyes see.

In humans, the ability to perceive visual information is critical to learning of all kinds, including the interpretation of social cues. In children with autism, avoiding eye contact and struggling to understand people's feelings may be rooted in how their brains process visual information.

"The focus in autism has been trying to tackle social impairment. But if there is a deficit in learning due to being unable to process certain kinds of sensory input, it affects your development," said Anubhuti Goel, a postdoctoral researcher in neurology at UCLA and the study's first author. "We're trying to identify early brain processes that will impact behaviors in children when they are older."

For this experiment, Goel and colleagues at UCLA used mice with a similar mutation in the FMR1 gene as humans with fragile X syndrome, a genetic condition that is the most commonly inherited cause of autism in humans. Mice with the mutation share a number of autism symptoms with people with fragile X syndrome, including anxiety, reduced social interaction and an overreaction to sensory stimuli such as texture and sound.

The researchers trained mice on a visual discrimination task, where the goal for the mice was to lick a drop of water in response to a specific visual cue on a screen. A pattern of parallel, black-and-white lines slanting a certain way signified the presence of a water drop; slanted a

different way, there was no water drop. If the mice took too long to decide, the water drop disappeared—vacuumed up by the scientists.

On average, normal control mice mastered the strategy for getting water in about three days, whereas the mice with autism typically required five to nine days.

By recording brain activity in the mice, researchers found that the visual cortex of the fragile X syndrome mice, or FXS mice, had fewer and less finely tuned neurons called pyramidal cells. These excitatory neurons—the "gas pedal" in the brain—found in rodents, monkeys and humans, are responsible for perceiving the orientation of visual information, for example, the angle of the lines in the experiment. In addition, researchers found reduced activity in parvalbumin neurons, which are inhibitory neurons—the "brake pedal"—that work in concert with pyramidal cells, kicking them into gear and "tuning" them to respond to specific, or more general, bits of visual information.

The researchers wondered if they could prod those parvalbumin cells into working harder, which would in turn stimulate the pyramidal cells.

They targeted the parvalbumin cells with a genetic technique called DREADD, which stands for Designer Receptors Exclusively Activated by Designer Drugs. They injected the fragile X syndrome mice with a virus carrying the genes for these special designer receptors; once inside the mouse's parvalbumin cells, the virus generates the DREADD receptors. Next, a drug administered intravenously reached those receptors and activated the parvalbumin cells.

Once the fragile X syndrome mice with the designer receptors received the drug, they could learn the visual discrimination task as quickly as their healthy counterparts did. The impact of the designer drug lasted for three to four hours.

"These experiments shed light on the brain circuit problems behind those difficulties in autism, and hint at directions we can pursue for treatment in the future," Goel said.

Goel's next step will be figuring out what happens in the visual discrimination task with sensory distractors, such as flashing lights or loud sounds. Many autistic children and adults are unable to tune out such distractors, which could contribute to poor performance in school and anxiety in social settings. Fragile X syndrome mice, too, have sensory over-reactivity, which could impede their learning.

More information: Anubhuti Goel et al. Impaired perceptual learning in a mouse model of Fragile X syndrome is mediated by parvalbumin neuron dysfunction and is reversible, *Nature Neuroscience* (2018). DOI: 10.1038/s41593-018-0231-0

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