Sensory signals are integrated differently, underrepresented by neurons in autism

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In fragile X syndrome (FXS), the most common cause of autism, sensory signals from the outside world are integrated differently, causing them to be underrepresented by cortical pyramidal neurons in the brain.

That's the conclusion of a new study by a team led by Université de Montréal neurosciences professor Roberto Araya, a biophysicist and researcher at the UdeM-affiliated CHU Sainte-Justine Research Centre.

The phenomenon the team observed could provide important clues to the underlying cause of the symptoms of FXS, and not only provides insight into the mechanism at the cellular level, but also opens the door to new targets for therapeutic strategies.

The study was published Jan. 3 in *Proceedings of the National Academy of Sciences*.

Autism is characterized by a wide range of symptoms that may stem from differences in brain development. With advanced imaging tools and the genetic manipulation of neurons, the team of researchers at CHU Sainte-Justine was able to observe the functioning of individual neurons—specifically, pyramidal neurons of cortical layer 5—one of the main information output neurons of the cortex, the thin layer of tissue found on the surface of the brain.

The researchers found a difference in how sensory signals are processed in these neurons.

"Previous work has suggested that FXS and autism spectrum disorders are characterized by a hyperexcitable cortex, which is considered to be the main contributor to the hypersensitivity to sensory stimuli observed in autistic individuals," said Araya.

"To our surprise, our experimental results challenge this generalized view that there is a global hypersensitivity in the neocortex associated with FXS," added his UdeM colleague Diana E. Michell, first co-author of the study. "They show that the integration of sensory signals in cortical neurons is underrepresented in a murine model of FXS."

The tree image helps to illustrate the morphology and function of pyramidal neurons in fragile X syndrome. These neurons are one of the main integrators of information in the cerebral cortex, with long "branches" and "roots" representing dendrites. The small "leaf-like" projections are the dendritic spines, where the excitatory synapses are located—connecting one neuron to another. The blurred sections of the image illustrate the altered integration and perception of sensory information from the outside world discovered by Diana E. Mitchell, Soledad Miranda-Rottmann and their colleagues.

An absent protein

A protein called FMRP that is absent in the brains of people with FXS modulates the activity of a type of potassium channel in the brain. According to the research group's work, it is the absence of this protein that alters the way sensory inputs are combined, causing them to be underrepresented by the signals coming out of the cortical pyramidal neurons in the brain.

Soledad Miranda-Rottmann, also first co-author of the study, attempted to rectify the situation with genetic and molecular biology techniques.

"Even in the absence of the FMRP protein, which has several functions in the brain, we were able to demonstrate how the representation of sensory signals can be restored in cortical neurons by reducing the expression of a single molecule," she said.

"This finding opens the door to new strategies to offer support to those with FXS and possibly other autism spectrum disorders to correctly perceive sensory signals from the outside world at the level of pyramidal neurons in the cortex," concluded Araya.

"Even if the over-representation of internal brain signals causing

hyperactivity is not addressed, the correct representation of sensory signals may be sufficient to allow better processing of signals from the outside world and of learning that is better suited to decision making and engagement in action."

"Altered integration of excitatory inputs onto the basal dendrites of layer 5 pyramidal neurons in a mouse model of fragile X syndrome," was published Jan. 3, 2023, in *Proceedings of the National Academy of Sciences*.

More information: Diana E. Mitchell et al, Altered integration of excitatory inputs onto the basal dendrites of layer 5 pyramidal neurons in a mouse model of Fragile X syndrome, *Proceedings of the National Academy of Sciences* (2023). DOI: 10.1073/pnas.2208963120

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