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Fragile X finding shows normal neurons that interact poorly

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Neurons in mice afflicted with the genetic defect that causes Fragile X syndrome (FXS) appear similar to those in healthy mice, but these neurons fail to interact normally, resulting in the long-known cognitive impairments, shows a new study by a team of neuroscientists.

The results point to a new approach to address FXS: targeting neuronal interactions rather than the immediate molecular abnormalities of genetic mutations.

"The genetic defect that causes the most widespread form of intellectual disability and autism is surprisingly characterized by normally functioning memory and cognition-encoding neurons," explains André Fenton, a professor in New York University's Center for Neural Science and the senior author of the paper, which appears in the journal *Neuron*. "But despite being individually normal, these neurons are abnormal in their interactions, which results in cognitive impairments.

"The good news, however, is we now have a better place to look for remedies: we can pursue a therapeutic strategy that targets neuronal interactions rather than the proximal molecular effects of a genetic mutation."

The study also included Dino Dvorak, a post-doctoral fellow in NYU's Center for Neural Science, Zoe Talbot, an NYU graduate student at the time of the study, Fraser Sparks, an NYU postdoctoral fellow at the time of the study and now at Columbia University, and researchers from

SUNY Downstate Medical Center.

It's long been known that FXS is caused by a mutation that shuts down a particular gene—FMR1—so the protein product it normally produces, FMRP, cannot be made. In their study, the scientists mimicked the genetic defect in FXS by mutating the FMR1 gene in mice so that it could not produce the protein FMRP, which is vital for learning and memory.

In a series of active place avoidance tests, the FXS mice could learn and remember a location they should avoid, but as expected, were unable to efficiently adapt to environmental changes that contradicted their prior experience; so, when the place to avoid was relocated, the FXS mice could not avoid the new location, unlike control mice that rapidly adapted to the new information.

When the researchers looked into what explained these cognitive flexibility deficits, they found that the neurons of the FXS mice appeared normal.

However, their examination also showed a lack of coordination among neurons—organized interaction that is crucial in processing information from contradictory sources. Specifically, the mutated FMR1 gene disrupted the functioning of the neurons in the hippocampus—a brain structure known to play a significant role in memory in general and for the place avoidance task in particular. The disruption prevented the neurons from appropriately forming and disbanding in groups—"neural coalitions" that work to perform cognitive tasks by transiently discharging together in time.

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