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Rett Syndrome study finds mechanisms underlying its visual deficits

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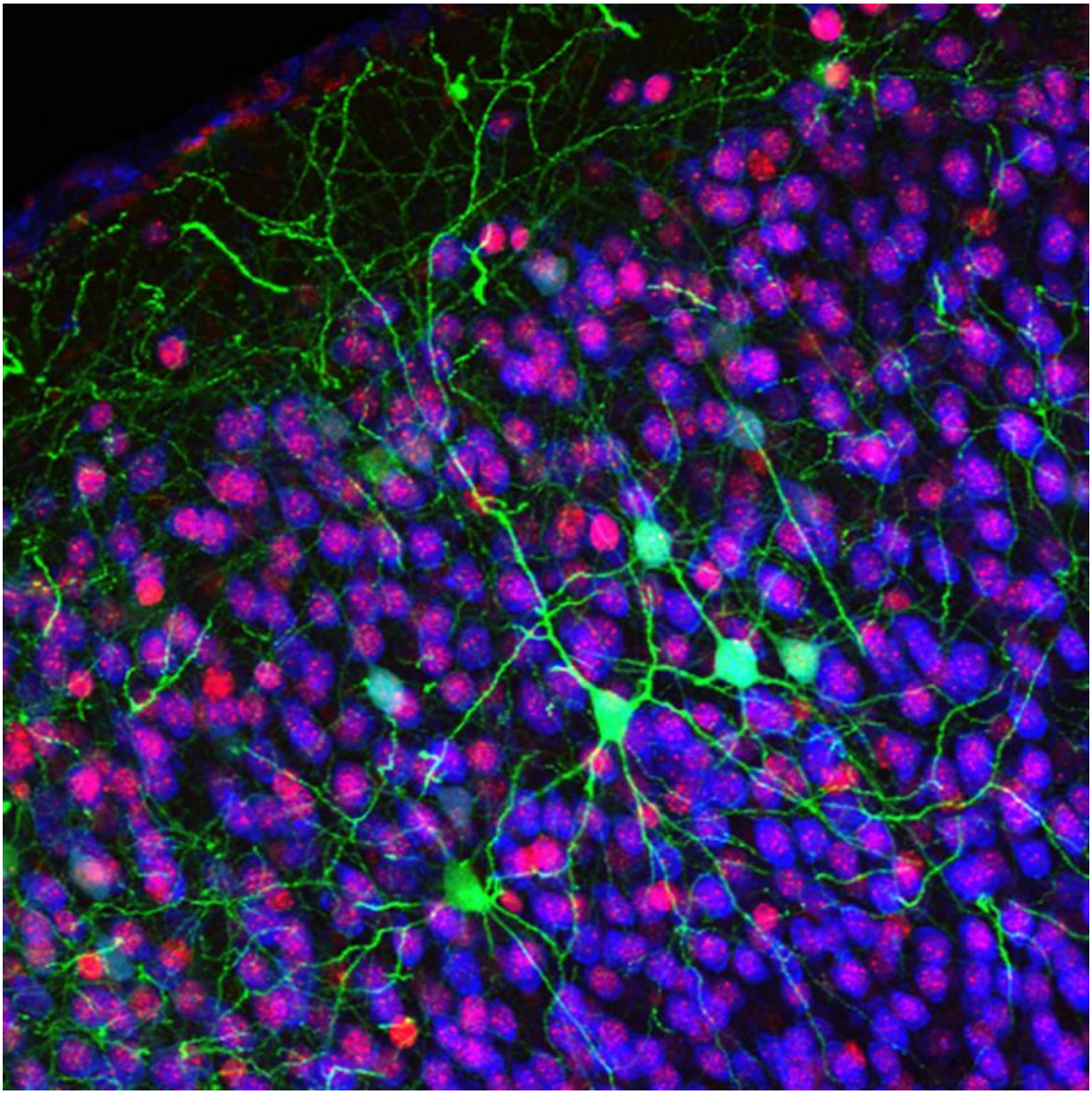

Callosal projection neurons (green) are shown in the cerebral cortex. Credit: Jessica MacDonald and Jeffrey Macklis

In research published this week in the *Proceedings of the National Academy of Sciences* (*PNAS*), researchers at the Whitehead Institute for Biomedical Research and the Picower Institute for Learning and Memory at Massachusetts Institute of Technology (MIT) have used precise genetic tools and sophisticated high-resolution electrophysiological measurements to track neurophysiological deficits resulting from the genetic mutation associated with Rett Syndrome (RTT). Further, they demonstrated the ability of recombinant human Insulin Like Growth Factor 1 (rhIGF1) and bumetanide to reverse such deficits in cell-type specific manner in RTT mice—and provided further mechanistic basis for observed clinical benefits of using rhIGF1 to treat RTT patients.

Understanding the physiological alterations in intact brain circuits in neurodevelopmental disorders is a fundamental challenge for neuroscience. It has been known that RTT arises from loss-of-function mutations in the gene Mecp2 in the brain. But MeCP2 protein is ubiquitously expressed in many cell-types and sub-regions of the brain; hence its role in cell-specific brain circuits has remained a mystery.

"When we try to understand the mechanisms by which the social brain is constructed, we start with a bottom-up view. Waves of gene expression (nature) and sequences of patterned network activity (nurture) interact to mold development of specific circuits in the brain. The interplay of these factors goes awry in neurodevelopmental disorders" says the paper's first lead author Abhishek Banerjee, who conducted the research while serving as a Simons Fellow and post-doctoral researcher at MIT's Picower Institute for Learning and Memory, and now a Marie Curie

Fellow and a NARSAD Young Investigator.

The authors in this study wanted to better understand how Mecp2 mutations affect specific neuronal subtypes that cumulatively result in RTT. To that end, they conducted technically challenging whole-cell recording of synaptic responses in vivo in the visual cortex of MeCP2-mutant mice, as well as recording dynamic neuronal population activity using two-photon microscopy. "This approach allowed us to conduct a series of in vivo studies in MeCP2-knockout mice, to see specific effects as they cascade, and to observe the relationship between neuronal subtypes and how they alter network dynamics," Banerjee says.

These recordings demonstrated that MeCP2 mutation affects cortical pyramidal neurons by reducing their excitatory and inhibitory function, and increasing their excitatory/ inhibitory ratio (E/I). "Previously, researchers have used brain slices to study synaptic E/I balance and simple alterations in neural circuits. We extended these observations to study how synaptic E/I deficits actually affect circuit-level computations within intact cortical circuits—deficits that subtly alter neural processing in patients," Banerjee notes.

"The dual effect that Mecp2 mutation exerts on excitatory and inhibitory function causes imbalances that interfere with normal processing of information through the neuronal circuit; and the resulting abnormal signaling appears to cause the visual impairment found in RTT," observes Xin Tang, a study co-author and post-doctoral researcher at Whitehead Institute.

Following the resulting cascade of effects through the pyramidal neurons, the researchers also observed that the polarity of GABAergic inhibition was altered and that a specific form of inhibitory interneurons named parvalbumin-expressing (PV+) inhibitory interneurons had reduced responses. That GABA polarity and PV+ responses were

ultimately affected by MeCP2 had previously not been recognized in an animal model of RTT.

Subsequently, the investigators treated MeCP2 mutant mice with rhIGF1, and found that it restored cortical population responses, GABA polarity, and normalized PV+ interneuronal responses. "Our previous work showed that rhIGF1 can benefit individual neurons affected by RTT. Now we've demonstrated that it can improve function for an entire circuit—and how it does so," explains senior author Mriganka Sur, the Paul E. and Lilah Newton Professor of Neuroscience, Director of the Simons Center for the Social Brain, and investigator in the Picower Institute for Learning and Memory at MIT.

"Initial clinical trials have already shown rhIGF1 has beneficial effects in treating RTT. This work helps to explain why there is therapeutic benefit, and lays the foundation for more targeted use of growth factors and other treatments," notes senior author Rudolf Jaenisch, Whitehead Institute Founding Member and professor of biology at MIT.

More information: Jointly reduced inhibition and excitation underlies circuit-wide changes in cortical processing in Rett syndrome, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1615330113

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