Brain noise found to nurture synapses

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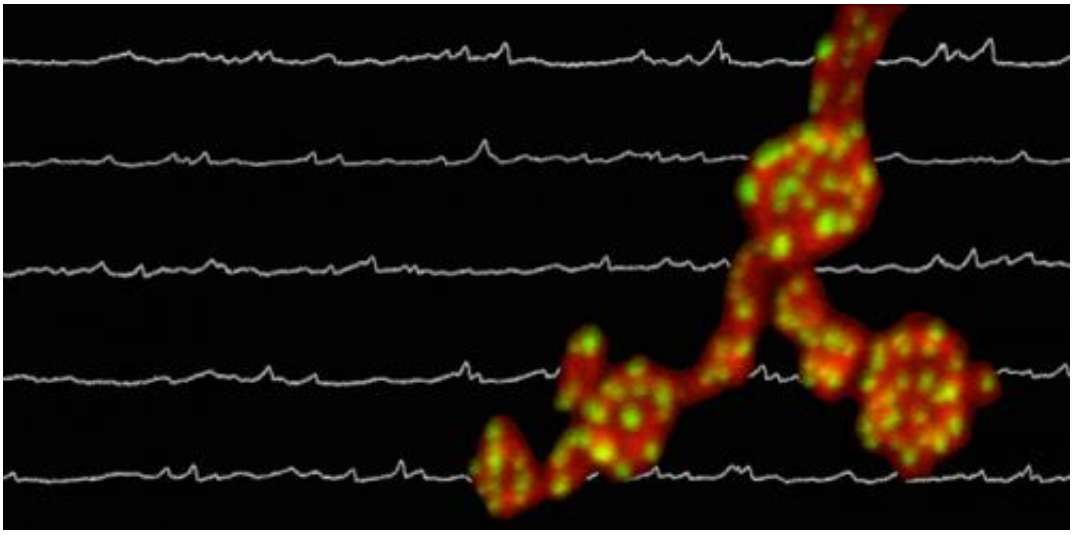

This is a developing *Drosophila* synapse superimposed over electrophysiology recordings of minis. Credit: Lab of Brian McCabe, PhD/ Columbia University Medical Center

A study has shown that a long-overlooked form of neuron-to-neuron communication called miniature neurotransmission plays an essential role in the development of synapses, the regions where nerve impulses are transmitted and received. The findings, made in fruit flies, raise the possibility that abnormalities in miniature neurotransmission may contribute to neurodevelopmental diseases. The findings, by researchers at Columbia University Medical Center (CUMC), were published today in the online edition of the journal *Neuron*.

The primary way in which neurons communicate with each another is through "evoked neurotransmission." This process begins when an electrical signal, or action potential, is transmitted along a long, cable-like extension of the neuron called an axon. Upon reaching the axon's terminus, the signal triggers the release of chemicals called neurotransmitters across the synapse. Finally, the neurotransmitters bind to and activate receptors of the neuron on the other side of the synapse. Neurotransmitters are packaged together into vesicles, which are released by the hundreds, if not thousands, with each action potential. Evoked neurotransmission was first characterized in the 1950s by Sir Bernard Katz and two other researchers, who were awarded the 1970 Nobel Prize in Physiology or Medicine for their efforts.

"Dr. Katz also found that even without action potentials, lone vesicles are released now and then at the synapse," said study leader Brian D. McCabe, PhD, assistant professor of pathology and cell biology and of neuroscience in the Motor Neuron Center. "These miniature events—or minis—have been found at every type of synapse that has been studied. However, since minis don't induce neurons to fire, people assumed they were inconsequential, just background noise."

Recent cell-culture studies, however, have suggested that minis do have some function and even their own regulatory mechanisms. "This led us to wonder why there would be such complicated mechanisms for regulating something that was just noise," said Dr. McCabe.

To learn more about minis, the CUMC team devised new genetic tools to selectively up- or down-regulate evoked and miniature neurotransmission in fruit flies (a commonly used model organism for neuronal function and development). This was the first study to identify a unique role for minis in an animal model.

The researchers found that when both types of neurotransmission were

blocked, synapse development was abnormal. However, inhibiting or stimulating evoked neurotransmission alone had no effect on synaptic development. "But when we blocked minis, synapses failed to develop," said Dr. McCabe, "and when we stimulated the release of more minis, synapses got bigger."

The study also showed that minis regulate synapse development by activating a signaling pathway in neurons involving Trio and Rac1 proteins in presynaptic neurons. These proteins are also found in humans.

It remains to be seen exactly how minis are exerting their effects. "Parallel communication occurs in computer networks," Dr. McCabe said. "Computers communicate primarily by sending bursts of data bundled into packets. But individual computers also send out pings, or tiny electronic queries, to determine if there is a connection to other computers. Similarly, neurons may be using minis to ping connected neurons, saying in effect, 'We are connected and I am ready to communicate.'"

The researchers are currently looking into whether minis have a functional role in the mature nervous system. If so, it's possible that defects in minis could contribute to neurodegenerative disease.

More information: The paper is titled, "Miniature Neurotransmission Regulates Drosophila Synaptic Structural Maturation."

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