Changing behavior through synaptic engineering

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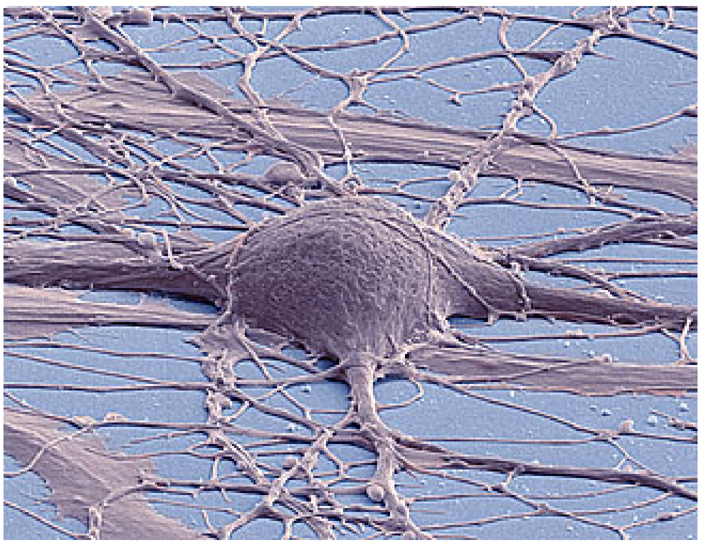

This is a scanning electron micrograph (false color) of a human induced pluripotent stem cell-derived neuron. Credit: Thomas Deerinck, UC San Diego

Researchers at the University of Massachusetts Medical School are the first to show that it's possible to reverse the behavior of an animal by flipping a switch in neuronal communication. The research, published in *PLOS Biology*, provides a new approach for studying the neural circuits that govern behavior and has important implications for how scientists think about neural connectomes.

New technologies have fueled the quest to map all the neural connections in the brain to understand how these networks processes information and control behavior. The human brain consists of 1011 neurons that make 1015 connections. The total length of neuronal processes in the human brain is approximately 4 million miles long, similar in length to the total number of roads in the U.S. Along these networks neurons communicate with each other through excitatory and inhibitory synapses that turn neurons on or off.

The neuronal roadmap, or connectome, however, doesn't include information about the activity of neurons or the signals they transmit. How stable are these neural circuits in the brain? Does their wiring constrain the flow of information or the behaviors they control? The complexity of the human brain makes it almost impossible to address these questions.

Mark Alkema, PhD, associate professor of neurobiology at UMass Medical School turned to the nematode C. elegans to find answers. A tiny worm with only 302 neurons, it is the only animal for which its neural road map has been completely defined.

In this study, Alkema and colleagues sought to determine if flipping the sign of a synapse from inhibitory to excitatory in the worm's brain was enough to reverse a behavior. To do this, they analyzed nematode touch response which C. elegans employ to escape from carnivorous fungi that use hyphal nooses to catch nematodes. During this response neurotransmitters are released that activate an inhibitory ion channel. This causes the worm to relax its head and quickly reverse direction away from the predator.

Jenn Pirri, a doctoral student in the Alkema lab and Diego Rayes, PhD, a former post-doctoral fellow now at the Instituto de Investigaciones Bioquímicas de Bahía Blanca in Argentina, replaced the inhibitory ion channel with an excitatory version of the channel in a live nematode.

"Surprisingly, the engineered channel does not affect development of and is properly incorporated into the neural circuits of the worm brain," said Dr. Alkema. "Cells that are normally inhibited in the brain now get activated.

"What was most striking is that we were able to completely reverse behavior by simply switching the sign of a synapse in the neural network," explained Alkema. "Now the animal contracts its head and tends to move forward in response to touch. This suggests that the neural wiring diagram is remarkably stable and allows these types of changes.

"Our studies indicate that switching the sign of a synapse not only provides a novel synthetic mechanism to flip behavioral output but could even be an evolutionary mechanism to change behavior," said Alkema. "As we start to unravel the complexity and design of the neural network, it holds great promise as a novel mechanism to test circuit function or even design new neural circuits in vivo."

Provided by University of Massachusetts Medical School

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