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Newly discovered neural connections reveal that inhibitory neurons can also drive movement

Researchers at UC Santa Barbara are coming ever closer to uncovering the neural circuitry that translates stimulus to action, shining light on previously unseen neural connections and lesser-known functions of neurons that underlie behavior. Neuroscientists Durafshan Sakeena Syed, Primoz Ravbar and Julie H. Simpson have found that inhibitory neurons — nerve cells known to be responsible for suppressing movement — actively generate and coordinate the rhythmic limb movements required for grooming in fruit flies.

These findings, according to Syed, do not only demonstrate complexities of the animal nervous system that we are only beginning to learn; they also have potential implications for robotics and biomimetic design.

This work, supported by both the National Science Foundation and the National Institutes of Health, are published in the journal eLife.

Going by stopping

The release of the full fruit fly connectome in late 2024 represented a major milestone for neuroscientists, who can now use the complete map of all 139,000 neurons and roughly 50 million synapses in the adult *Drosophila* brain to find the structural underpinnings of the fly’s complex behaviors.

“We are at a very exciting time right now,” said Syed, an assistant project scientist in the Simpson Lab.

Among these behaviors is grooming — the “sweeping” of face, body and feet that rids them of debris. These movements are innate, rhythmic and require coordination between the extension and flexion of opposing muscles and limbs. The question for the researchers was: What happens along the circuit between the fly’s sensory neurons, which sense the dust, and the motor neurons, which tell the limbs to move?

“In between there is a ‘black box’ of neurons and we didn’t know how they receive the information, process it and send it to the motor neurons,” Syed said. Among these “pre-motor” neurons were a lineage of inhibitory neurons that caught the researchers’ attentions.

“The thing is, when you think about movement, traditionally you assume that the activated pre-motor neuron would excite the motor neuron,” Syed said, leading to movement. Instead, their optogenetic experiments, which use light to selectively control the activity of specific cells, revealed that these inhibitory pre-motor neurons, which function as a “stop” signal, are capable of driving movement without the need for excitatory signals.

“What they do is put the brakes on one muscle and then the same neuron can remove the brakes from the antagonistic muscle. Since these neuron groups are reciprocally connected, they can induce the alternation between extension and flexion so you can have these repetitive movements,” Syed explained.

While one neuron is busy braking one motion and releasing the brakes for the other, a complementary, connected neuron is doing the opposite on the same set of muscles, braking what was released, and releasing what had been stopped. That results in these alternating moments of extension and flexion. Coordination is one of the main functions of these neurons, preserving the sequence of braking and releasing, according to Syed, who added that If these inhibitory neurons were continuously activated, or if they were all silenced, in both cases grooming behavior would decrease. Excitatory neurons are likely still part of the broader motor pathway, she said, but their contribution in this context remains to be tested.

Additionally, the researchers found that there were multiple ways the fly nervous system could control each limb via “specialist” and “generalist” inhibitory neurons. The specialist cells control individual joints and fine movements, while the generalists can function like a switch controlling several movements across multiple joints, which is especially useful and efficient in cases of commonly repeated motions, such as those for grooming, flying, eating and walking. Generalists can be used to execute these common patterns of motion, while specialists can allow the organism to react to changes in the environment.

This work began before the full fruit fly connectome was completed, and is the result of years of painstaking effort by not just the researchers, but also cohorts of UCSB undergraduates who were trained to proofread the sets of electron microscopy data and trace the individual paths of these inhibitory neurons.

“The undergraduates who worked on this dataset have made important contributions in editing those neurons that laid the foundations for these discoveries,” Syed said. Manual tracing techniques turned into automated reconstructions over the years as the techniques evolved. In collaboration with Primoz Ravbar, also in the Simpson Lab, they built a computational model that enabled them to test these neural circuits.

Building on this research, future work may involve more interrogations of the neural basis of fruit fly behaviors, such as how the nervous system enables a switch from one complex task to another — investigations that could eventually set the stage for studying more complex organisms in the future.

“We know that flies don’t stop doing what they are doing and then start a new action; it’s continuous.” Syed said. “How does that transition happen? That’s what I’m interested in.”

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