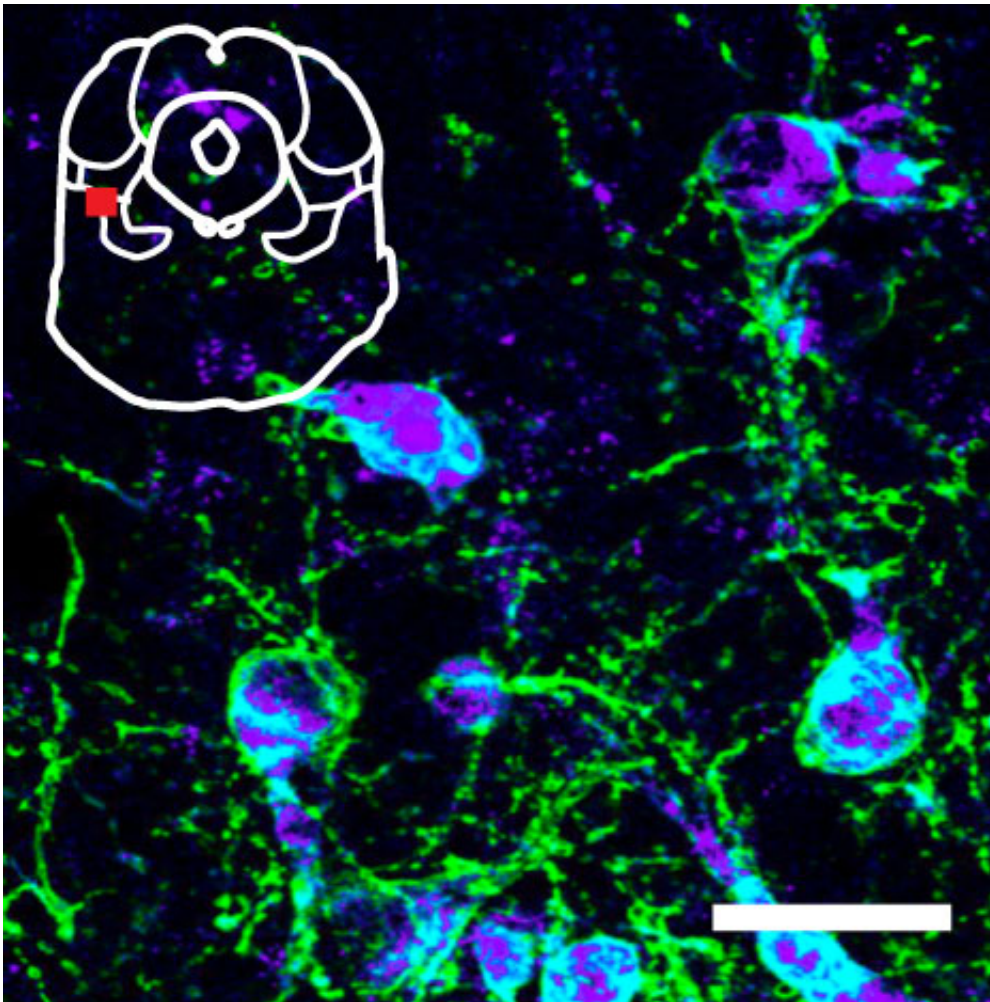


Treating Parkinson's disease by solving the mysteries of movement

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Neurons in the brainstem involved in walking are lit up using optogenetics.
[Roseberry et al., *Cell*] Credit: Tom Roseberry, Gladstone Institutes

Two secrets of one of the brain's most enigmatic regions have finally been revealed. In a pair of new studies, scientists from the Gladstone Institutes have discovered a specific neural circuit that controls walking, and they found that input to this circuit is disrupted in Parkinson's disease.

Walking becomes a major challenge for people afflicted by Parkinson's disease. Parkinson's is caused by a depletion of dopamine—an important neurochemical—in the basal ganglia (BG), a brain region involved in fundamental behaviors like movement, learning, reward, and motivation. In Parkinson's, an imbalance arises between two pathways in the BG: the direct or "go" pathway and the indirect or "stop" pathway. Ordinarily, these pathways work together seamlessly to control locomotion, but in Parkinson's the stop pathway overpowers the go pathway, making it difficult to initiate movement. How the imbalance between these two pathways developed remained a mystery—until now.

Correcting an Imbalance in the Brain

Published in *Neuron*, scientists led by Gladstone associate investigator Anatol Kreitzer, PhD, discovered that dopamine depletion causes a miscommunication between the BG and another region called the thalamus, an area thought to relay sensory information to the brain. This miscommunication results in a loss of input to the go pathway from the thalamus, which consequently disrupts movement. Blocking the connection between the two regions reversed the imbalance between the stop and go pathways and restored normal behavior in a mouse model of Parkinson's.

"This study provides strong evidence for a mechanism by which the stop pathway overcomes the go pathway in Parkinson's disease," says first author Philip Parker, PhD, a former [graduate student](#) in Dr. Kreitzer's lab at the Gladstone Institutes and the University of California, San

Francisco (UCSF). "Our findings implicate the thalamus in the development of the disease, an area of the brain that has received relatively little attention in Parkinson's research."

"Several studies have targeted the thalamus with [deep brain stimulation](#) to treat Parkinson's, but the region's role in the disease was not well established," adds Dr. Kreitzer, who is also an associate professor of physiology and neurology at UCSF. "Our findings finally provide a clear picture of how the thalamus can imbalance neural circuits and suppress movement in this condition."

Discovering How the Brain Controls Walking

In the second study, published in *Cell*, the scientists discovered that the go and stop pathways from the BG control locomotion by regulating a group of nerve cells in the brainstem that connects the brain to the spinal cord. The researchers revealed that the go pathway selectively activates a type of neuron in the brainstem that releases the neurochemical glutamate, and these neurons are responsible for triggering locomotion.

The scientists used optogenetics—an innovative research tool that uses light to activate or inhibit select cells in the [brain](#)—to stimulate either the go or the stop pathway in mice that were running on a tiny treadmill, while recording neural activity in the brainstem. They discovered that the go pathway selectively activated glutamate neurons, causing the mice to move, whereas the stop pathway inhibited these neurons and made the mice stop.

"This is the first time we have been able to demonstrate how the go and stop pathways regulate locomotion," says Tom Roseberry, a graduate student in the lab of Dr. Kreitzer. "We show a very precise connection from the [basal ganglia](#) to the brainstem that controls movement."

Remarkably, the researchers discovered that the brainstem neurons can overpower the signals from the BG—that is, if glutamate neurons were turned on, the animal moved even if the stop pathway is activated.

"In order to understand why walking is particularly disrupted in Parkinson's disease, we need to map out the circuitry that controls locomotion," says Dr. Kreitzer. "Our study shows that a specific set of neurons in the brainstem are both necessary and sufficient to initiate locomotion. This finding could open the door for new treatment targets to help Parkinson's patients walk more easily."

Provided by Gladstone Institutes

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