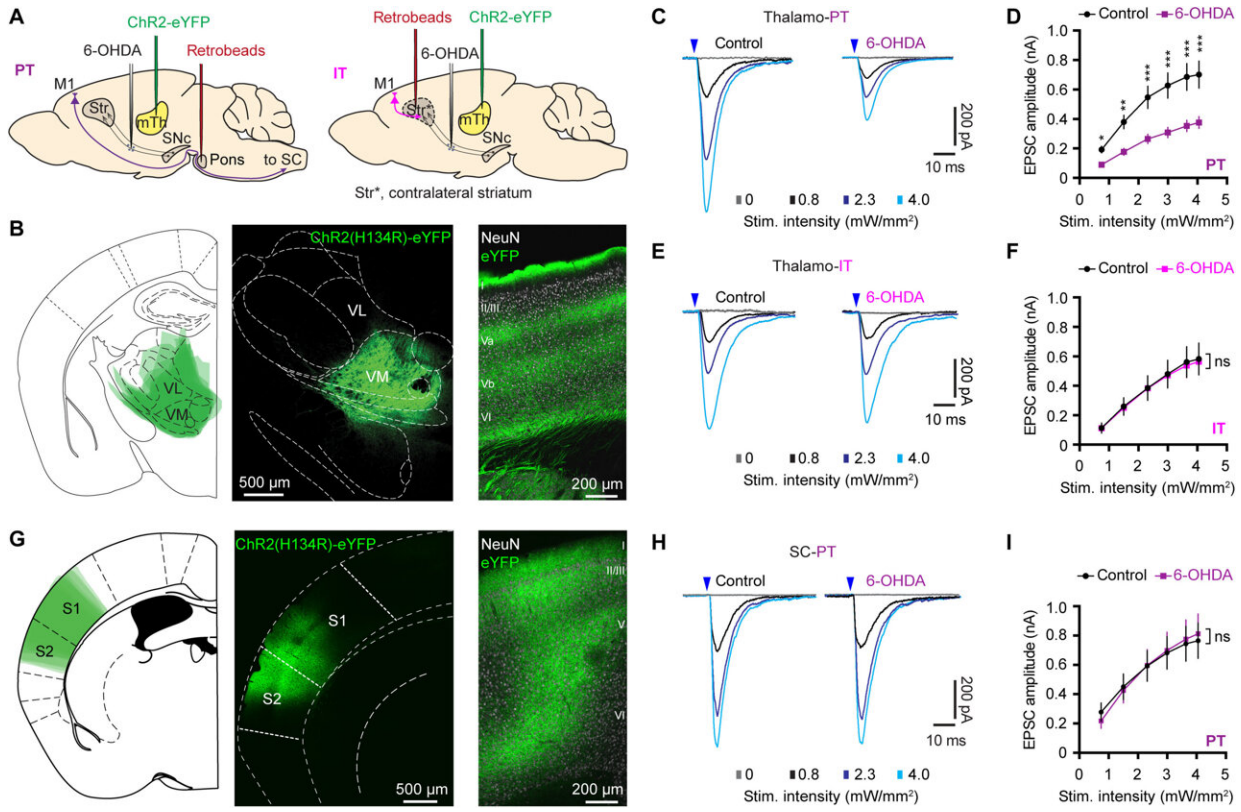
Repairing broken brain circuits may offer path to new Parkinson's treatments

August 24 2023



SNc DA degeneration induces cell subtype–and input-specific alterations in M1.(**A**) Overall strategies to label projection defined M1 pyramidal neurons and optogentically activate thalamocortical transmission arising from the mTh. (**B**) Overlaid image showing the averaged AAV injection sites in the motor thalamus (left), as well as representative confocal images showing an example of viral injection site in the motor thalamus (middle) and eYFP-expressing thalamic axon terminals in the M1 (right). eYFP-labeled terminals concentrate in the layers I and V and are consistent with the overall pattern of motor thalamic

innervation of M1 in rodents. (**C** and **D**) Representative traces of optogenetically evoked EPSCs across different stimulation intensities in PT neurons from controls and 6-OHDA mice (C) and the summarized results (D). *P* P P P E and **F**) Representative traces of optogenetically evoked EPSCs across different stimulation intensities in IT neurons from both controls and 6-OHDA mice (E) and the summarized results (F). ns, not significant between groups, mixed effects model. Twenty-six cells per three mice for each group. (**G**) AAV-infected cortical regions were overlaid to show the averaged AAV infection region across animals (left) and representative confocal images showing AAV9-ChR2(H134R)-eYFP infusion site in the sensory cortical (SC) areas (middle) and eYFP-expressing cortical axon terminals in the M1 (right). (**H** and **I**) Representative traces of optogenetically evoked EPSCs arising from the SC across different stimulation intensities in M1 PT neurons from both controls and 6-OHDA mice (H) and the summarized results (I). Control = 20 cells per three mice, 6-OHDA = 26 cells per three mice. Mixed effects model, not significant between groups. Arrowheads in (C), (E), and (H) indicate the timing of the optical stimulation. Credit: *Science Advances* (2023). DOI: 10.1126/sciadv.adg3038

Van Andel Institute scientists have identified a series of processes that help the brain adapt to damage caused by breakdowns in circuits that govern movement, cognition and sensory perception.

Because such breakdowns contribute to Parkinson's disease, the findings may one day help researchers optimize current treatments or develop new ones that repair or bypass the broken circuits.

A study describing the findings published this week in the journal *Science Advances*.

"Our work highlights the importance of brain circuits in Parkinson's and offers another path forward for new treatment strategies," said study senior author and VAI Assistant Professor Hong-yuan Chu, Ph.D. "We

are hopeful that this work will add to the scientific foundation for future therapies that better manage symptoms."

The findings center on the thalamus and the cerebral cortex, two regions of the brain that support movement and sensory perception. Despite their importance, relatively little is known about how exactly circuits in these vital areas impact and are impacted by Parkinson's.

Chu and colleagues found that certain broken circuits in the thalamus and cortex can be repaired using agents that suppress disease-related messages from the basal ganglia, another brain region implicated in Parkinson's disease.

Their findings also suggest circuits in the thalamus and cortex may be impacted by two current Parkinson's disease treatments: dopaminergic medications and deep brain stimulation, both of which help mitigate symptoms but do not slow disease progression. The effectiveness of both options can vary from person to person.

"The cortex has long been considered a potential target for noninvasive treatment but research to date has been stymied by a limited understanding of what goes wrong in cortical circuits," Chu said. "This study is a first step toward remedying that problem and offers a clearer picture of both circuitry dysfunction and potential therapeutic strategies."

More information: Liqiang Chen et al, Reduced thalamic excitation to motor cortical pyramidal tract neurons in parkinsonism, *Science Advances* (2023). DOI: 10.1126/sciadv.adg3038

Provided by Van Andel Research Institute