Timing may be key to understanding cognitive problems in Parkinson's disease

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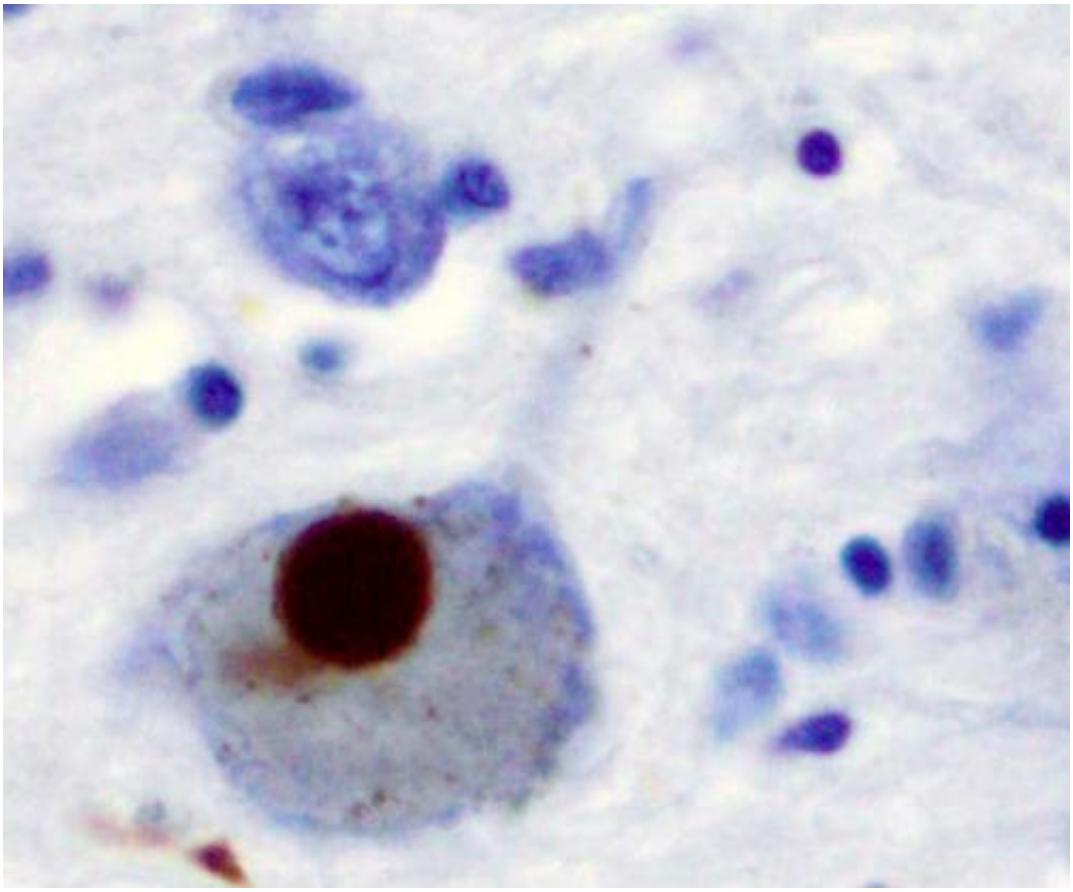

Immunohistochemistry for alpha-synuclein showing positive staining (brown) of an intraneural Lewy-body in the Substantia nigra in Parkinson's disease. Credit: Wikipedia

When a cheetah chases a gazelle, it's not raw speed that predicts the

outcome of the contest. Instead, it's the animal that times its movements better that has the advantage. That ability to consciously guide movements over a timeframe of a few seconds is a simple but universal thinking skill in mammals. It also is an ability that is consistently impaired in patients with Parkinson's disease (PD), and for University of Iowa neurologist Nandakumar Narayanan that makes "timing" an ideal tool to study cognitive problems in PD.

Parkinson's disease is caused by loss of the brain signaling chemical dopamine and affects about 1 million people in the United States. It is most commonly thought of as a disease that causes movement problems, but neurologists now know that PD can significantly affect patients' thinking, or cognitive abilities, too.

"The cognitive problems associated with PD are very debilitating," says Narayanan, MD, PhD, UI assistant professor of neurology. "They affect quality of life by causing loss of the ability to work, nursing home placement, falls, and increased health care costs. We have a lot of great treatments for the motor symptoms of Parkinson's disease, but there is very little I can do to treat the cognitive symptoms, and that is very frustrating for me."

Working in the lab and the clinic, Narayanan and his team record brain activity in mice and humans as they do simple timing tasks. The scientists also use various genetic technologies to manipulate and study brain activity in the mice. These experiments help to reveal the neurocircuitry that controls timing ability, and explain how this simple cognitive process is disrupted by a lack of dopamine.

In a new study, published online Dec. 15 in the journal *Current Biology*, the researchers show for the first time that brain stimulation of specific neurons at a specific frequency can improve timing in mice that are missing dopamine. The findings imply that, at least in theory, it might be

possible to use brain stimulation to improve cognitive problems caused by PD, and possibly other cognitive disorders, too.

The team studied 12 patients with PD and showed that their ability to judge a period of time (12 seconds) was much poorer than people without PD. Measurements of brain activity from the frontal cortex using EEG (electroencephalography) showed that PD patients were also missing a specific brain wave known as the delta wave, which cycles at a frequency of about 1-4 times per second (1-4 Hertz), while they were doing the timing task.

As expected, mice that lacked dopamine in their frontal cortex also performed poorly on a timing task. However, the team was excited to discover that the animals were also missing the delta rhythm, suggesting that this specific, dopamine-dependent neural signal might be important for timing abilities.

In the frontal cortex, dopamine normally activates neurons with D1 dopamine receptors. The UI team, including Young-Cho Kim, PhD, first author on the study and a postdoctoral fellow in Narayanan's lab, genetically altered the mice so that the D1 neurons could be artificially activated using pulses of light. When the researchers pulsed the light at the same frequency as the missing delta wave signal—2 Hertz—the mice recovered their ability to perform the timing task.

"This was jaw-dropping," Narayanan says. "For the first time we are able to deliver brain stimulation to improve a cognitive behavior.

"When we stimulated D1 neurons in normal mice, we did not improve their timing'" he adds. "But in mice that have cognitive (timing) impairment due to loss of dopamine, we can make those mice better. The results suggest that, theoretically, delivering targeted, selective, and specific brain stimulation might improve some of the cognitive aspects

of losing dopamine in Parkinson's disease."

Brain stimulation is already used to treat some patients with PD, but the therapy targets specific areas of the brain that are important for motor control (not the frontal cortex) and only improves movement problems of PD. The new findings suggest precise stimulation of specific neural networks in the cortex might also form the basis of new therapies that improve cognitive processes that depend on dopamine.

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