Study reveals brain mechanisms behind speech impairment in Parkinson's

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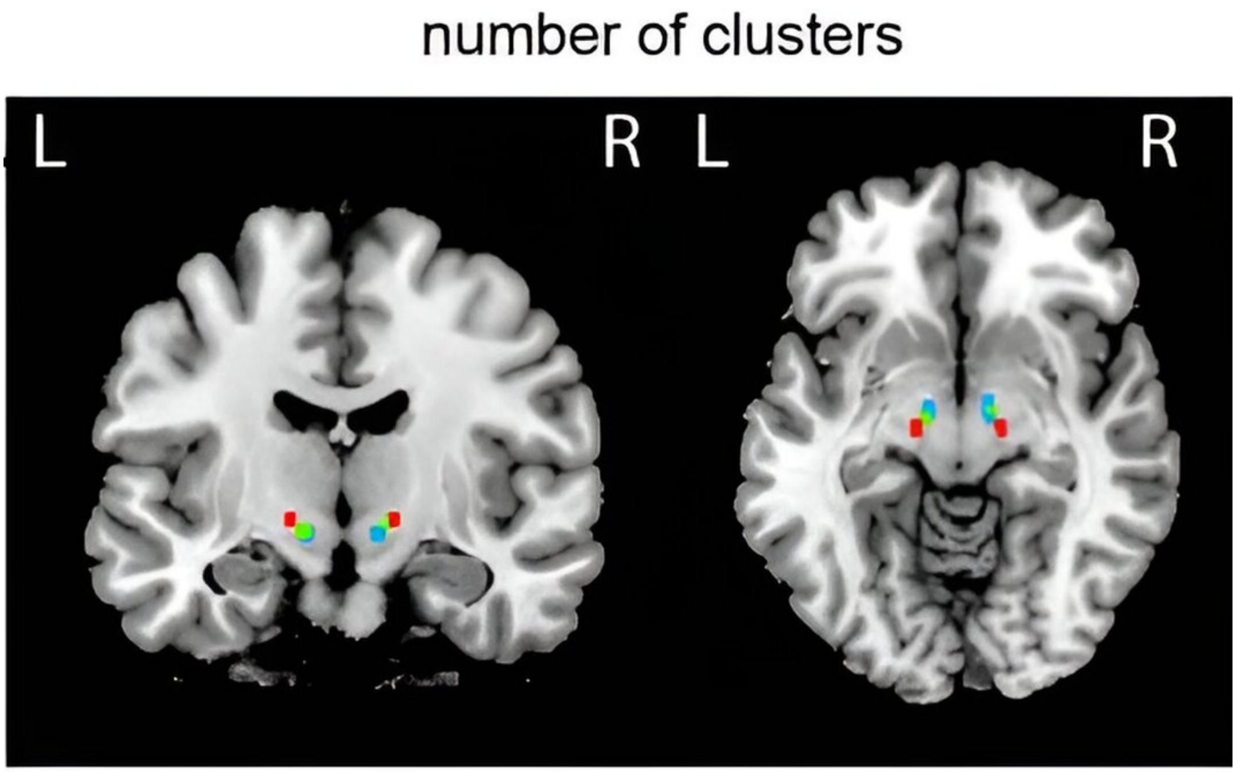

Functional parcellation of STN from Human Connectome Project resting-state fMRI data. (a) Consensus clustering produced the best parcellation solution with 3 clusters for both left and right STN. (b) Both the left and right STN ROIs were composed of dorsolateral (red), central (green) and ventromedial (blue) parts. (c) Stability of each voxel being assigned to dorsolateral, central and ventromedial parts of the STN was coded by the scale of red, green and blue colors in each RGB colored dot, respectively, which presents the voxel's color in a 3D space. Credit: *Proceedings of the National Academy of Sciences* (2024). DOI:

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Parkinson's disease is most well-known and well-studied for its motor impairments—tremors, stiffness and slowness of movement. But less visible symptoms such as trouble with memory, attention and language, which can also profoundly impact a person's quality of life, are less understood.

A new study by Stanford Medicine researchers reveals the brain mechanisms behind one of the most prevalent, yet often overlooked, symptoms of the disease—speech impairment. Based on brain imaging from Parkinson's patients, the researchers identified specific connections in the brain that may determine the extent of speech difficulties.

The findings, reported May 20 in the *Proceedings of the National Academy of Sciences*, could help explain why some treatments for Parkinson's—developed mainly to target motor symptoms—can improve speech impairments while other treatments make them worse.

More than a motor disorder

"Parkinson's disease is a very common neurological disorder, but it's mostly considered a motor disorder," said Weidong Cai, Ph.D., clinical associate professor of psychiatry and behavioral sciences and the lead author of the new study.

"There's been lots of research on how treatments such as medications and deep brain stimulation can help improve motor function in patients, but there was limited understanding about how these treatments affect cognitive function and speech."

More than 90% of people with Parkinson's experience difficulties with speech, an intricate neurological process that requires motor and cognitive control. Patients may struggle with a weak voice, slurring, mumbling and stuttering.

"Speech is a complex process that involves multiple cognitive functions, such as receiving auditory feedback, organizing thoughts and producing the final vocal output," Cai said.

The senior author of the study is Vinod Menon, Ph.D., professor of psychiatry and behavioral sciences and director of the Stanford Cognitive and Systems Neuroscience Laboratory.

The researchers set out to study how levodopa, a common Parkinson's drug that replaces the dopamine lost from the disease, affects overall cognitive function. They focused on the subthalamic nucleus, a small, pumpkin-seed-shaped region deep within the brain.

The subthalamic nucleus is known for its role in inhibiting motor activity, but there are clues to its involvement in other functions. For example, deep brain stimulation, which uses implanted electrodes to stimulate the subthalamic nucleus, has proven to be a powerful way to relieve motor symptoms for Parkinson's patients—but a common side effect is worsened speech impairment.

Same test, different scores

In the new study, 27 participants with Parkinson's disease and 43 healthy controls, all older than 60, took standard tests of motor and cognitive functioning. The participants with Parkinson's took the tests while on and off their medication.

As expected, the medication improved motor functioning in the patients, with those having the most severe symptoms improving the most.

The test for cognitive functioning offered a surprise. The test, known as the Symbol Digit Modalities Test, is given in two forms—oral and written. Patients are provided with nine symbols, each matched with a number—a plus sign for the number 7, for example. They are then asked to translate a string of symbols into numbers, either speaking or writing down their answers, depending on the version of the test.

As a group, the patients' performance on both versions of the cognitive test was little affected by medication. But taking a closer look, the researchers noticed that the subset of patients who performed particularly poorly on the spoken version of the test without medication improved their spoken performance on the medication. Their written test scores did not change significantly.

"It was quite interesting to find this dissociation between the written and oral version of the same test," Cai said.

The dissociation suggested that the medication was not enhancing general cognitive functions such as attention and working memory, but it was selectively improving speech.

"Our research unveiled a previously unrecognized impact of dopaminergic drugs on the speech function of Parkinson's patients," Menon said.

Uncovering connections

Next, the researchers analyzed fMRI brain scans of the participants, looking at how the subthalamic nucleus interacted with brain networks dedicated to various functions, including hearing, vision, language and executive control.

They found that different parts of the subthalamic nucleus interacted with different networks.

In particular, they discovered that improvements on the oral version of the test correlated with better functional connectivity between the right side of the subthalamic nucleus and the brain's language network.

Using a statistical model, they could even predict a patient's improvement on the oral test based on changes in their brain's functional connectivity.

"Here we're not talking about an anatomical connection," Cai explained. Rather, functional connectivity between brain regions means the activity in these regions is closely coordinated, as if they are talking to each other.

"We discovered that these medications influence speech by altering the functional connectivity between the subthalamic nucleus and crucial language networks," Menon said. "This insight opens new avenues for therapeutic interventions tailored specifically to improve speech without deteriorating other cognitive abilities."

This newly identified interaction between the subthalamic nucleus and the language network could serve as a biological indicator of speech behavior—in Parkinson's as well as other speech disorders like stuttering.

Such a biomarker could be used to monitor treatment outcomes and inspire new therapies. "Of course, you can directly observe the outcome of a medication by observing behavior, but I think to have a biomarker in the brain will provide more useful information for the future development of drugs," Cai said.

The findings also provide a detailed map of the subthalamic nucleus, which could guide neurosurgeons performing deep brain stimulation in avoiding damage to an area critical to speech function.

"By identifying key neural maps and connections that predict speech improvement, we can craft more effective treatment plans that are both precise and personalized for Parkinson's disease patients," Menon said.

More information: Weidong Cai et al, Subthalamic nucleus–language network connectivity predicts dopaminergic modulation of speech function in Parkinson's disease, *Proceedings of the National Academy of Sciences* (2024). DOI: 10.1073/pnas.2316149121

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