Study identifies two neuronal populations associated with symptoms of Parkinson's disease

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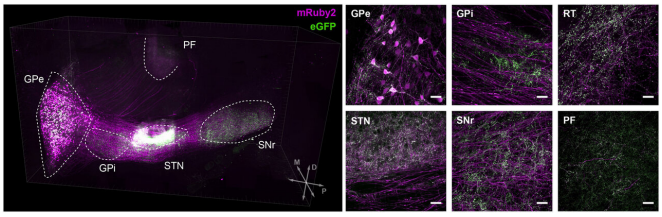

Credit: Lilascharoen et al.

Parkinson's disease is a progressive neurodegenerative disorder that manifests itself through a diverse range of motor and non-motor symptoms, including shaking and stiffness of the limbs, as well as difficulties in maintaining balance and coordination, walking and talking. As the disease progresses, these symptoms typically evolve and become increasingly severe.

Diagnosing Parkinson's disease in its early stages can be highly challenging, as the most evident symptoms, those affecting a patient's movements, generally start manifesting at a later stage of the disease. To devise new diagnostic tools and more effective treatment strategies, neuroscientists have been trying to gain more insight about the neural underpinnings of the disease's individual symptoms.

Past studies suggest that the impairments associated with Parkinson's disease could be linked to progressive changes in the basal ganglia, an area of the brain that regulates a number of motor and cognitive functions. However, the organization and functions of different basal ganglia circuits are still poorly understood.

Researchers at University of California in San Diego recently set out to investigate the functional roles of different parvalbumin-expressing neuronal populations in the external globus pallidus (GPe-PV), a small brain area that is part of the basal ganglia. Their paper, published in *Nature Neuroscience*, sheds light on the contributions of these neuronal populations to different behaviors associated with Parkinson's disease.

"Diagnosing Parkinson's disease early can be very difficult," Byung Kook Lim, one of the researchers who carried out the study, told Medical Xpress. "This is mainly because of the strong focus on the disease's motor symptoms, rather than on its non-motor symptoms, which usually occur at the earlier stage of Parkinson's disease. Our work identifies differential changes in different brain areas that are involved in motor and non-motor symptoms of Parkinson's disease exhibited throughout its progression."

To examine the neural basis of non-motor behaviors that resemble those observed in patients with Parkinson's disease, the researchers examined mice that were completing a reversal learning task. This type of task is designed specifically to assess and measure cognitive flexibility (i.e., the ability to switch between thinking about different things or to think about several concepts simultaneously).

"Poor cognitive flexibility is one of the major non-motor symptoms of Parkinson's disease," Lim explained. "Using cutting-edge fiber photometric measurement of the activity of specific projections and optogenetic/chemogenetic manipulation of this circuitry, we anatomically and functionally identified distinct parvalbumin-expressing neuronal populations in the external globus pallidus and observed their contributions to different behaviors associated with Parkison's disease."

Lim and his colleagues found that manipulating substantia nigra pars reticulata (SNr)-projecting neurons in the external globus pallidus alleviated the mice's locomotor deficits, while manipulating parafascicular thamalus (PF)-projecting neurons improved their performance on the reversal learning task. These findings highlight the crucial role that these two GPe-PV neuronal populations could play in the progressive development of motor and non-motor symptoms of Parkison's disease.

"Parkinson's disease is a progressive neurodegenerative disorder," Lim said. "However, how different brain areas are involved in the different symptoms exhibited at different stages of the disorder's development has not been fully elucidated yet. Our findings highlight a need to study circuit-specific adaptations at different stages of Parkinson's disease to unveil stage-specific and symptom-specific treatments that could delay its progression."

In the future, the results of this recent study could inform the development of more effective strategies to diagnose or treat different symptoms of Parkinson's disease at different stages of its progression. In their next studies, Lim and his colleagues plan to examine the role that other brain circuits play in the disorder's development over time, to gain a better understanding of its underlying neural mechanisms.

More information: Divergent pallidal pathways underlying distinct Parkinsonian behavioral deficits. *Nature Neuroscience*(2021). DOI: 10.1038/s41593-021-00810-y