Commentary

Neural circuits underlying motor and non-motor defects of Parkinson's disease

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AN OVERVIEW OF PARKINSON'S DISEASE

Parkinson's disease (PD) is a neurodegenerative disorder that causes unintended and uncontrollable movements, such as tremors, rigidity, and difficulty with balance and coordination. Neuronal degeneration in the basal ganglia network has been suggested as a likely cause for some PD symptoms. More specifically, such degeneration would lead to an imbalance between the direct pathway (from striatum to substantia nigra) and the indirect pathway (from striatum to pallidum), which subsequently drives movement deficits.[1] Current treatments for the motor dysfunction of PD include dopamine agonists, deep brain stimulation (DBS), and physical therapy. Aside from severe motor impairments, PD patients can also experience defects in cognitive processes such as memory and attention and suffer from depression or stress. However, the neural circuit basis for these different PD symptoms is not well understood. Improving our understanding of these non-motor PD symptoms could lead to the identification of novel therapeutic approaches for their treatment in the future.

A HINT FROM THE PARAFASCICULAR THALAMUS

The parafascicular thalamic nucleus (PF) is located in the caudal region of the intralaminar thalamic complex and projects to the subthalamic nucleus (STN), caudate putamen (CPu), and nucleus accumbens (NAc), among other regions. Based on the knowledge that both STN and CPu have been linked to PD defects, that NAc activity is correlated with reward/depression, and that DBS targeting PF alleviates some pathophysiological changes, Zhang and colleagues systematically investigated the function of these PF circuits in mice and published their findings in *Nature* recently.[2] In this study, the authors clarified the function of three different subpopulations of PF neurons in locomotion, motor learning, and depression-like states in PD mice, and they demonstrated that regulating specific nicotinic acetylcholine receptors (nAChRs) expressed in PF neurons and their projections was sufficient to rescue both motor and non-motor defects in PD mice (Figure 1).

FEATURES OF PF NEURAL CIRCUITRY

PF has extensive connectivity with the basal ganglia network. A recent study dissecting cortical-thalamic-striatal circuits suggests PF neurons are anatomically and transcriptionally organized.[3] The authors first investigated whether PF contains subpopulations based on their projections to three different brain regions. They found projections from PF thalamus to CPu, STN, and NAc, as expected. Retrogradely labeled PF neurons from CPu or STN (PF→CPu or PF→STN) were intermingled in lateral PF, whereas NAc-projecting PF neurons (PF→NAc) were restricted to medial PF. These three PF subpopulations showed minimal overlap, suggesting the existence of at least three distinct projection-specific circuits. Based on these anatomical data and additional electrophysiological differences, the authors hypothesized that the functions of these PF subpopulations might be different.

By manipulating individual PF subpopulations in wild-type mice, the authors found that CPu-projecting PF neurons contributed to general motor activity (i.e., locomotion), whereas the PF→STN circuit was critical for motor learning. These findings revealed differential functions of PF subpopulations located in the lateral region of this nucleus. In contrast, the PF→NAc circuit was found to be associated with a depression-like state but not locomotion or motor learning processes. Importantly, when the authors examined these three PF circuits in an acute PD model, they found that each circuit showed an alteration in its strength or plasticity, indicating that these circuits are not only critical for physiological functions but are also targeted in this disease model.

THERAPEUTIC POTENTIAL OF MODULATING PF IN PD

Although the above findings provided potential targets for developing DBS-based strategies, it is critical to find out if there was a molecular target-based alternative for treating motor and non-motor PD symptoms. The best-known treatment options for PD are levodopa and monoamine oxidase type B inhibitors, which mostly help with locomotion. Motor learning and non-motor symptoms, on the other hand, have fewer treating options. The authors identified an α7 nAChR agonist, PNU282987, which significantly improved motor learning through parvalbumin (PV^+) STN neurons. Further, an α6 nAChR antagonist targeting CPu-projecting PF neurons rescued locomotion deficits, and a β2 nAChR agonist acting on $D1^+$ NAc neurons alleviated depression-like behaviors in PD mice.

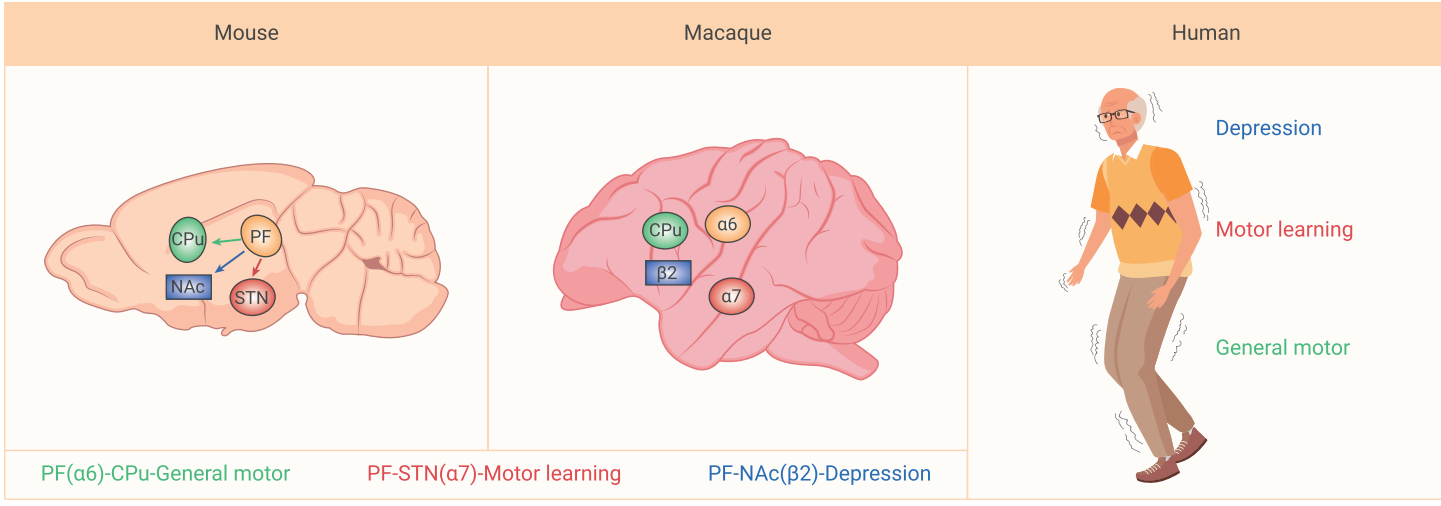

Figure 1. PF circuits underlying motor and mood defects of PD The specific nAChRs (α6 nAChR in PF; α7 nAChR in STN; β2 nAChR in NAc) that showed therapeutic potential in mouse experiments (left) exhibit a similar expression pattern in macaques (middle), thus showing promising potential for translational application (right).

Notably, the authors found that the identified molecular targets expressed in mouse PF can also be found in non-human primates (NHPs). They found that α7 nAChRs were highly expressed in PV^+ STN neurons, α6 nAChRs were expressed in PF cell bodies, and β2 nAChRs were highly expressed in $D1^+$ NAc neurons in NHPs. As NHPs are closely related to humans, these findings suggest that targeting different nAChRs in PF circuits may alleviate both motor and non-motor deficits in PD.

POTENTIAL FUTURE NEURAL CIRCUIT DIRECTIONS IN PARKINSON'S DISEASE

Another message from both Feng group and Sabatini group is that subpopulations and their projections play unique roles in PF circuitry.[2,3] Clinical research indicates that exercise can benefit PD patients through enhancing the neuroplasticity that targets motor and cognitive circuitry.[4] Combining single-cell sequencing technologies with neural tracing and electrophysiology recording to precisely dissect regional/subregional markers and their unique connectivity offers an exciting direction for future studies, which will not only strengthen our understanding of brain networks in health and disease conditions, but can also help identify cell type- and projection-specific therapeutic approaches.

Furthermore, given the PF-striatal projections were found to be topographically organized with unique molecular architecture and electrophysiological properties,[3] Zhang et al. indicated CPu projection was associated with general motor defects in PD. It is intriguing to explore whether heterogeneous populations in PF-striatal projections have distinct functions in PD. Another foreseeable challenge is the therapeutic method. Following the finding that regulating different nAChRs improves motor or non-motor symptoms in PD, it remains challenging to develop an all-in-one treatment. Given that the NHP model has a higher translational potential, the current study pointed out the importance of studying PF circuits and testing molecular target candidates using NHP PD models, which could speed up the clinical applications of this work.

HOW LONG BEFORE THESE FINDINGS CAN BE TRANSLATED TO HUMAN PATIENTS?

Realistically speaking there is a long way to go for the current study to directly benefit patients with PD. As a proof-of-concept study, the findings need to undergo verification in NHPs before an initial preclinical test,[5] which may take years before an official clinical trial gets approval. In addition to neural circuit-based strategies, other candidate therapeutic approaches are being developed in parallel with the hope of treating PD patients in the future. For instance, converting astrocytes to dopamine neurons using gene-editing technology has recently been reported in rodents. Therefore, there is reason to be hopeful that with the development of cutting-edge experimental techniques our understanding of PD mechanisms will improve and in this way lead to novel therapeutic approaches.

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DECLARATION OF INTERESTS

The author declares no competing interests.