



Late-stage Parkinson's disease: Skilled walking with a neuroprosthesis

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Locomotor deficits are one of the main symptoms of Parkinson's disease (PD). These deficits manifest as gait impairments, balance problems, and freezing of gait (FOG) in the lower limbs. Approximately 90% of patients with advanced PD suffer from locomotor deficits, which seriously affect their quality of life. The current therapies available for treating locomotor deficits, such as dopamine replacement therapy and deep brain stimulation (DBS), are not highly effective. Therefore, there is an urgent need for treatments that can provide comprehensive and robust improvements in lower limb motor functions. A recent study published in *Nature Medicine* by Milekovic et al. proposed a novel method for alleviating locomotor deficits in advanced PD patients.¹ Their approach of targeting the lumbosacral motor neuron pools with a neuroprosthesis aims to reproduce the natural spatiotemporal activation of leg motor neurons to improve PD motor symptoms, including balance disorders and FOG, and restore skilled walking in PD patients (Figure 1).

Milekovic et al. developed a neuroprosthesis, an anatomy-specific spinal cord electrode array that can precisely induce muscle responses through

epidural electrical stimulation (EES), in macaques. The activity of leg motor neurons was recorded by electromyography to generate spatiotemporal maps of normal leg muscle movement, identifying hotspot events during natural walking. Cortical motor intentions were identified by matching neural signals from the cortical motor area with spatiotemporal maps of leg motor neuron activity and decoding the results via machine learning algorithm models. The authors developed a closed-loop system with a real-time implantable pulse generator to achieve real-time brain control of EES to the spinal cord. This novel therapeutic strategy targets the lumbar spinal cord in a way that is distinct from spinal cord stimulation (SCS). The latter uses open-loop stimulation of the thoracic spinal cord to induce changes in cortical–basal ganglia–thalamic neural circuits to improve motor impairments and FOG in PD patients.²

The neuroprosthesis significantly improved balance disturbances and gait impairments in macaques and exhibited a synergistic effect with DBS. Milekovic et al. subsequently verified this finding in PD patients. Two patients

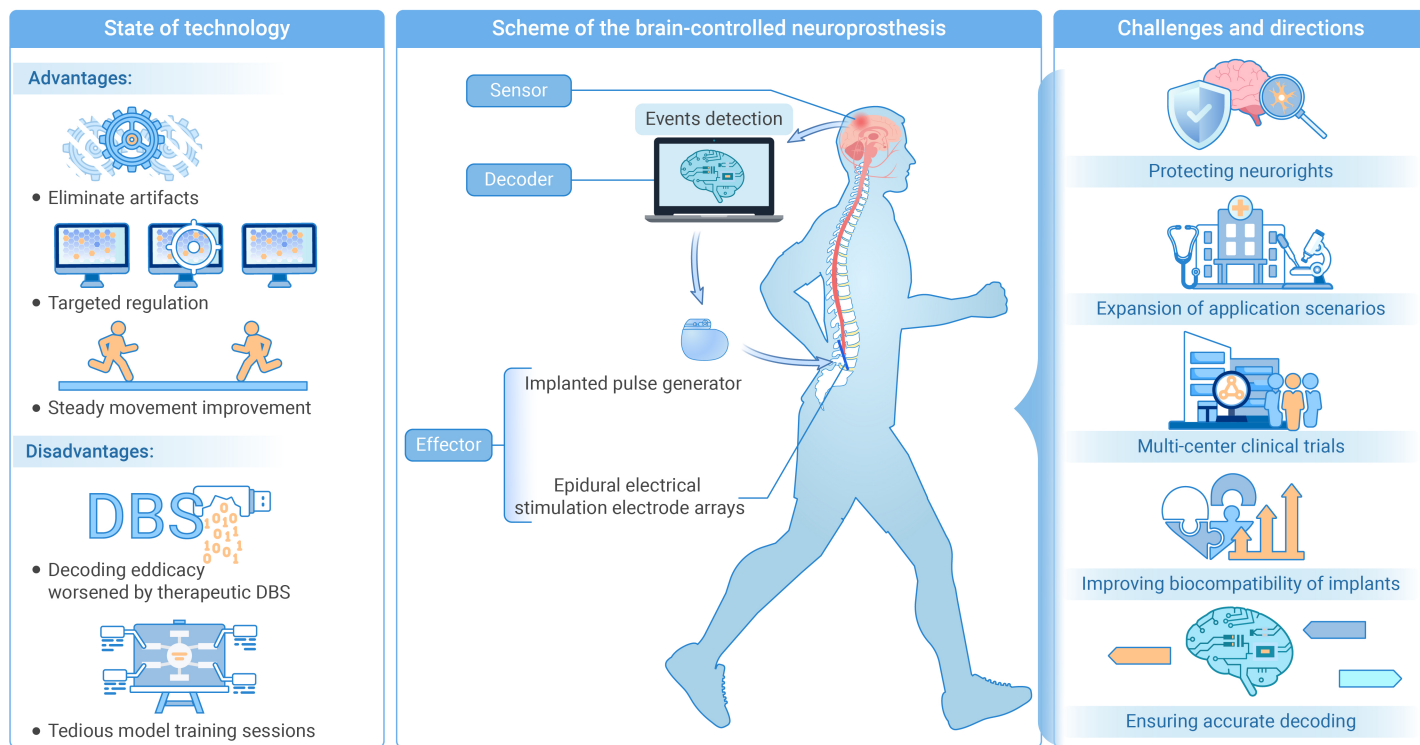


Figure 1. Closed-loop neuroprosthesis system for Parkinson's disease: current status and progress toward the future.

implanted with the closed-loop neuroprosthesis system demonstrated the feasibility of decoding motor intentions to activate EES in sync with PD patient movement. Subsequently, an advanced PD patient with a 30-year disease history and severe locomotor deficits underwent neuroprosthesis implantation, and the efficacy of the system was verified. After the neuroprosthesis was turned on, the patient's gait impairment, balance problems, and FOG were significantly alleviated, allowing him to produce a walking pattern similar to that of a healthy human. Remarkably, the neuroprosthesis independently improved FOG in PD patients, nearly eliminating FOG even in

narrow walking circuits with frequent turns and various obstacles. This outcome is significant because nonhuman primate models cannot replicate FOG. The frequent falls caused by FOG are a major reason for the decline in quality of life in PD patients, and current pharmacologic, surgical, and rehabilitative interventions are unable to meet the therapeutic needs of patients with FOG.

Interestingly, in the advanced PD patient, wearable sensors were used to collect cortex motor intention information rather than invasive cortical electrodes. This method reduces the risks of invasive treatments, although its

accuracy still requires comparison and verification. The EES electrodes used by PD patients had previously been clinically approved for treating neurogenic pain. In animal models of PD and in patients already treated with DBS, a neuroprosthesis has a synergistic therapeutic effect with DBS, leading to more effective improvement of locomotor deficits. This finding is fundamental and promising for the treatment of lower limb dyskinesias in PD patients, considering that EES restores walking function in paraplegic patients, as reported previously by this research team.³ We hope that the team will conduct a large cohort of randomized controlled trials to further determine the efficacy of the neuroprosthesis, which would be an exciting breakthrough for PD patients.

Closed-loop modulating systems, such as adaptive DBS (aDBS), have been widely used as therapeutic strategies in clinical practice to improve the precision of neuromodulation. However, because this method records and stimulates the same target, it is challenging to avoid contamination of the frequency spectrum by movement of the DBS electrode cables and stimulation artifacts, which hinders the recognition of feedback signals and the adjustment of control strategies.⁴ We are glad to see that the closed-loop neuroprosthesis system addresses this issue. Milekovic et al. trained a decoding algorithm model in the EES on and off states, eliminating the interference of stimulation artifacts and achieving accurate recognition of motor intentions and precise switching of control strategies. This algorithm enables the decoding of motor intentions and makes the operation of a closed-loop neuroprosthesis system feasible.

The principle of this system is to reestablish a natural pattern of connection between the brain's intentions and the effector organs that produce movement through artificial circuits. In contrast to neuromodulation methods of brain circuit activity, such as DBS and transcranial direct current stimulation (tDCS), neuroprostheses bypass brain lesions and use brain-computer interfaces to directly link cortical activity to electrical muscle stimulation for precise spatiotemporal neuromodulation. This therapeutic paradigm offers more accurate target modulation, addressing the shortcomings of neural modulation therapies in movement disorders, which lack specificity and fail to provide robust improvements.

Current research indicates that therapeutic electrical stimulation can significantly worsen decoding in some patients. This study did not explore whether the severity of neurodegeneration or therapeutic electrical stimulation with DBS interfered with the decoding of motor intention in patients with PD. To ensure the efficacy and safety of this treatment, neuroprosthesis treatments require training of the algorithmic models with DBS and EES data, each of which are turned on and off individually; this need for training places greater demands on medical professionals, device developers, and manufacturers.

The use of brain-computer interface technology in the treatment of disease is currently a rapidly growing field in personalized medicine and has spurred further research on neuroprosthesis therapy to enable clinical application. In the future, multicenter collaboration to recruit a group of patients with heterogeneous motor deficits at different stages of PD will be crucial to verify the safety and efficacy of neuroprostheses and advance this therapy. In addition, multiunit collaboration to establish a brain-computer interface platform to assist in the clinical customization of electrodes, selection of motor intention detection devices, and adjustment of stimulation parameters is essential for developing diagnostic and treatment pathways or operational protocols.⁵

In conclusion, the study by Milekovic et al. has made significant progress in alleviating severe locomotor deficits and FOG in advanced PD patients, revealing a promising therapy and robust improvement in motor function. While the safety of this treatment requires verification, further research is still possible, especially as brain-computer interface technology is widely approved for clinical trials and has demonstrated promising improvements in various diseases. The integration of multiple innovative approaches and the collaboration of patients, medical staff, rehabilitation therapists, and device technicians can facilitate the research and clinical application of closed-loop neuroprosthesis technology, meeting the challenges of precision therapy.

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DECLARATION OF INTERESTS

The authors declare no competing interests.