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Commentary

Another Step Forward for Freezing of Gait in Parkinson's Disease

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Abstract. The study "A spinal cord neuroprosthesis for locomotor deficits due to Parkinson's disease" by Milekovic et al. introduces a novel neuroprosthesis for treating locomotor deficits in late-stage Parkinson's disease (PD). This approach employs an epidural spinal array targeting dorsal roots and electromyography to create a spatiotemporal map of muscle activation, aiming to restore natural gait patterns. Significant improvements in gait freezing and balance were observed in both non-human primate models and a human patient, resulting in improved mobility and quality of life. This innovative method, integrating real-time feedback and non-invasive motor intention decoding, marks a significant advancement in PD treatment.

Keywords: Spinal cord stimulation, deep brain stimulation, freezing of gait

The recent study "A spinal cord neuroprosthesis for locomotor deficits due to Parkinson's disease" by Milekovic et al. [1] published in *Nature Medicine*, presents another advance to address locomotor deficits in patients with late-stage Parkinson's disease (PD). The authors took advantage of convergent developments in neuroprosthetics and cortical physiological mapping to target a subset of PD symptoms such as balance impairment and freezing of gait, which are common in late-stage disease but often poorly responsive to existing therapies.

In a non-human primate (NHP) model of PD, Milekovic et al. developed a brain-controlled neuroprosthesis consisting of an epidural spinal array over the dorsal root entry zones innervating lumbosacral segments to deliver epidural electrical stimulation (EES). Leg muscle electromyography was used to define muscle activation during walking, and the associated lumbosacral segments known to produce this activation were identified as hotspots. The activation of these hotspots was mapped during walking, and together this data provided a spatiotemporal map of activation needed to reproduce normal gait. This concept of spatiotemporal activation provides a unique paradigm to address gait issues, to be distinguished from classic spinal cord stimulation (SCS), where a non-patterned stimulation over the posterior

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column of the spinal cord is delivered. Moreover, the stimulation hotspots are distal to the site of primary pathology in PD, further distinguishing the paradigm from classic SCS.

Given the limitations of the NHP model of PD, Milekovic et al. also acquired neural signals from the motor cortex from two participants with PD through bilateral subdural arrays over the primary motor cortex to determine motor intention. Interestingly, even with severe motor impairment in the participants, the authors were able to demonstrate the feasibility of recordings in this location.

Subsequently as proof of concept, the epidural spinal neuroprosthesis was successfully implanted in a single 62-year-old male with a 30-year history of PD, treated by previous subthalamic nucleus deep brain stimulation (STN DBS). His symptoms were characterized by severe locomotor deficits including gait freezing and frequent falls resistant to DBS and medication optimization. In contrast to the cortical recordings used in the NHP experiments, Milekovic et al. used inertial measurement units (IMUs) attached to the legs of the patient as a proxy for motor intention to drive EES. By integrating IMU data to spatiotemporal EES, this patient experienced significant improvements in balance, step length, and a reduction in gait freezing. In terms of overall improvement, this study showed a 55% reduction in the Unified Parkinson's Disease Rating scale (MDS-UPDRS III) with DBS turned on. A small but noticeable additional 8% reduction in MDS-UPDRS III was achieved with both SCS and DBS turned on, suggesting the potential for synergistic effect of brain and spine neuromodulation. The duration of this effect was observed up to 6 months postoperatively, though the authors note that the patient has continued to use the neuroprosthesis for two years hence. Interestingly, the authors used relatively low-frequency EES (60 Hz), which is typically associated with paresthesia, but it is unclear whether the patient perceived any sensation in the lower extremities associated with lumbosacral epidural stimulation.

The main strength of this study is its novel approach to addressing PD-related locomotor deficits. Unlike previous research employing SCS [2–5], this study's anatomical spatiotemporal specificity and proof of principle use of a closed-loop system represent an important milestone in the field. Furthermore, the potential to derive synergistic effects from brain and spinal neuromodulation enhances the overall therapeutic potential and presents a more integrated approach to managing PD symptoms. By mimicking the natural activation patterns of the spinal cord during walking, the researchers have potentially contributed to the effectiveness of the treatment in restoring more natural movement patterns in PD. Lastly, the group demonstrated the potential of non-invasive sensors mounted to the lower limbs as surrogates for motor intentions, thus serving as inputs to the closed-loop system, without the risks associated with invasive brain implants. This concept will also need further investigation to understand if it will be sufficient, superior and/or better tolerated compared to cortical recordings.

In comparison with previous work, this study moves the dial ahead with its specificity and integration of real-time feedback mechanisms, which allow for more precise and effective treatment of locomotor deficits in PD. Earlier studies, while also exploring SCS, often yielded mixed results due to potentially less targeted approaches. For instance, previous work showed some improvement in gait and balance with SCS but lacked the targeted, synergistic approach of the current study [4]. In our hands, the SCS subthreshold for paresthesia did not significantly improve freezing, suggesting a potentially placebo-related effect, a known problem in FOG [5]. Other work combining DBS and SCS showed a broad improvement in locomotion scores with 300 Hz epidural stimulation over the entire thoracic region, but the duration of this benefit has yet to be determined [2].

Looking ahead, prospective clinical trials involving a more heterogeneous set of PD patients are essential to validate these promising findings in this index patient, especially given the heterogeneous nature of freezing of gait. Assessing the long-term efficacy and safety of the treatment, along with potential side effects, will be crucial. Future research should harness the ability of the new generation of brain-sensing DBS systems which feature local field potential recordings at the site of stimulation to better understand the potential synergy of DBS with EES. In a similar manner to how cortical activity can decode gait and motor intention, the spectral signatures of DBS targets like the STN or globus pallidus may inform future generations of therapeutically synergistic neuroprostheses. In addition, clinicians involved in programming multi-modal therapy will likely face exponentially increased parameter complexity. As such, machine learning algorithms to automate, steer, and dose EES therapy will be useful to recruit the optimal combination of muscle groups for effective locomotion. Finally, EES leverages the myotatic

reflex of spinal cord via dorsal root stimulation. An alternative, though more invasive, approach might be direct stimulation of the ventral motor roots.

In conclusion, this work provides an important step forward in treating PD, particularly in managing locomotor deficits in late-stage patients. This innovative approach to integrate existing complementary therapies will be important to develop with care taken to maximize safety by identifying the least invasive but clinically sufficient biomarkers as well as including reduction in programming complexity for clinicians for this approach to be a viable therapeutic modality.

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