Advancements in invasive and non-invasive neuromodulation for Parkinson's disease: current findings and future directions [Editorial]

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Editorial

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Neuromodulation techniques are undoubtedly a crucial component of today's Parkinson's disease (PD) treatment, offering a valuable complement to conventional pharmacological therapies such as dopamine replacement therapy, which provides symptomatic relief but has limitations, including motor fluctuations and long-term side effects. Invasive therapies targeting specific brain regions have paved the way for the precise modulation of neural networks, with Deep Brain Stimulation (DBS) being a well-established intervention. Additionally, non-invasive approaches like focused ultrasound stimulation (FUS), transcranial magnetic stimulation (TMS), and transcranial direct current stimulation (tDCS) are currently in experimental or early clinical stages (Fig. 1). This special issue compiles articles that synthesize recent research on these interventions and highlight potential future directions.

Several studies including reviews in this issue highlight recent advancements in DBS. One study explored the potential of using electrophysiological markers as feedback signals for a closed-loop system and demonstrated that subthalamic beta oscillations (13–35 Hz) are key correlates of motor symptom severity, exhibiting distinct response to medication and DBS[1]. Similarly, another study investigating power gradients in the subthalamic nucleus (STN) observed elevated power in the sub-beta range (8–12 Hz) toward the ventral STN and found that a reduced power was associated with apathetic symptoms[2]. These findings underscore the significance of spectral dynamics within the STN and reinforce their potential as biomarkers in guiding the development of integrative closed-loop or adaptive DBS systems.

Another line of research focused on understanding DBS effects on certain nonmotor features of PD. One study addressed motor-related sleep disturbances in PD, showing that GPi-DBS specifically targets fiber tracts associated with sleep improvement[3]. Another STN DBS study examined the modulation of central opioid pathways, influencing sensory complaints and pain perception in PD by an increase in central beta-endorphin levels, highlighting the need of considering neurochemical mediators involved in stimulation for the individualized treatment paradigm[4]. Similarly, while personalized DBS targeting specific anatomical regions can be effective for alleviating particular symptoms, it poses challenges such as higher costs, excessive dedicate time, and the need for extensive pre-surgical imaging and individualized monitoring. Moreover, the therapeutic gains may not always justify these efforts, especially when improvements in motor symptoms are accompanied by unintended trade-offs, such as worsening of non-motor symptoms like sleep disturbances[5].

From the non-invasive side, vagus nerve stimulation (VNS), specifically transcutaneous auricular VNS (taVNS), might improve cortical functional topological properties and intracortical facilitation, ultimately leading to motor symptom alleviation[6,7]. Scholtz et al. demonstrate that transcranial direct current stimulation (tDCS) has site-specific enhancements in motor and cognitive function, particularly through stimulation of the primary motor cortex and dorsolateral prefrontal cortex[8], with additional potential for improving speech and executive dysfunction through Broca's area stimulation[9]. Repetitive transcranial magnetic stimulation (rTMS) has been identified as an effective intervention for dysphagia in a PD mouse model, reducing neuroinflammation through inhibition of the NLRP3 inflammasome pathway[10]. Furthermore, Wang et al. found that dual-site stimulation, which combines rTMS to bilateral primary motor cortex and transcutaneous magnetic spinal cord stimulation at lumbar level as a promising strategy to address freezing of gait in levodopa-unresponsive PD patients[11]. Thus, integrating multiple modalities to target different regions with various modes of action could leverage the strengths of each approach and unlock their synergistic potential.

Many new neuromodulation strategies are evolving rapidly, with many already investigated in preclinical or early clinical trials (see[12] for a comprehensive review). Temporal interference stimulation, for example, is a non-invasive technique that can reach deep brain structures by leveraging the summation of two high-frequency electric fields to create a lower-frequency envelope. Without relying on surgical procedures and with the ability to target multiple regions, temporal interference stimulation presents a potential noninvasive alternative to DBS for modulating deep brain structures. Nanoparticles have been engineered to facilitate drug delivery across the blood-brain barrier, a major challenge when treating neurological disorders such as PD. These nanoparticles enable targeted delivery of therapeutic agents directly to the brain, enhancing treatment efficacy while minimizing systemic side effects. Similarly, low-intensity FUS has been shown to transiently open the blood–brain barrier, allowing targeted delivery of therapeutic agents to specific brain regions and thus providing another non-invasive means to enhance drug delivery and neuromodulation. Gene therapy is another emerging approach aimed at restoring dopamine production or protecting dopaminergic neurons from degeneration. Similarly, designer receptors exclusively activated by designer drugs provide a means of precisely controlling neuronal activity via synthetic ligands. Collectively, these emerging technologies that will require multiple clinical trials to establish safety and efficacy further expand the landscape of PD treatment, with ongoing research focused on translating these innovations into clinical practice.

These techniques, discussed in detail in this special issue, highlight the potential of integrating and making an informed decision on selecting invasive and non-invasive neuromodulation techniques for PD management, with the future heading toward a more precise personalized neuromodulation. Utilizing advancements in neurophysiological mapping for enabling patient-specific stimulation protocols and adaptive closed-loop stimulation combined with multi-technique application of invasive and non-invasive interventions will surely offer synergistic benefits, particularly in addressing both motor and non-motor symptoms in combination.

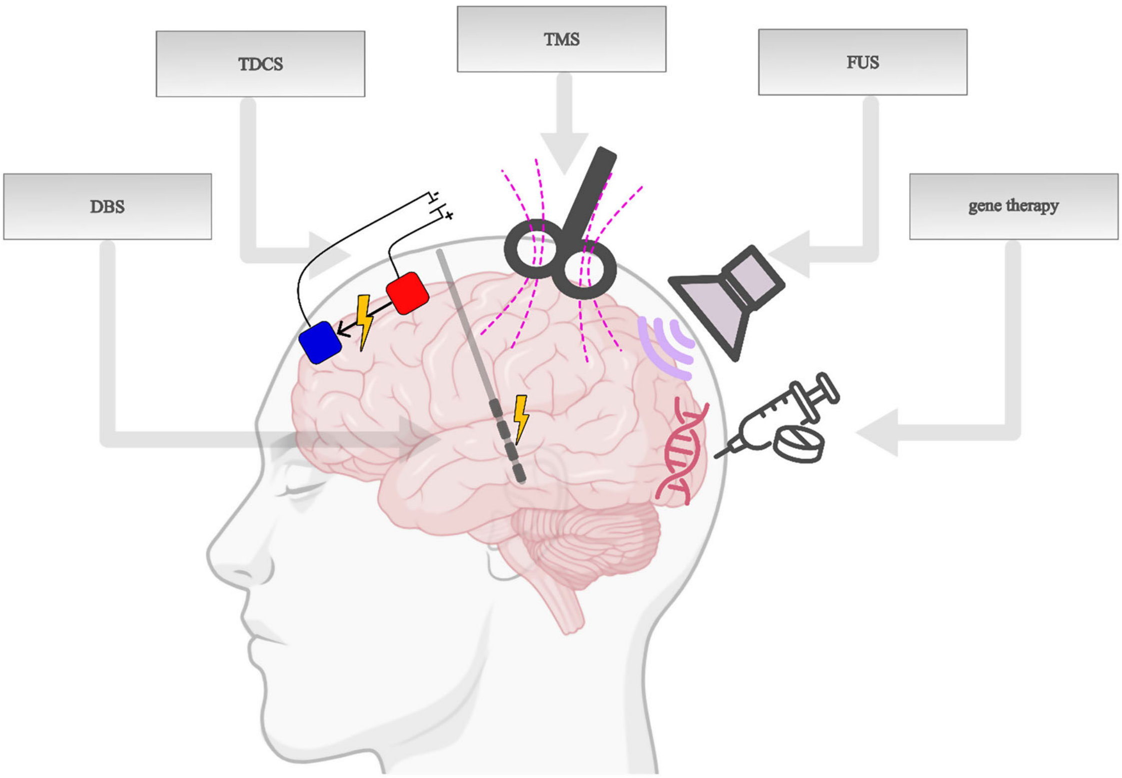

Fig. 1 | Toy illustration of invasive and non-invasive neuromodulation techniques used for the treatment of Parkinson's disease. Image was generated with biorender (https://app.biorender.com/) and the Noun Project ("gene therapy" by Hendrik Hermawan, (CCBY3.0); https://thenounproject.com/icon/gene-therapy-7322106/).

However, long-term efficacy research remains crucial for clinical adoption, as continued evaluation of neuromodulation durability and patient outcomes will be essential in determining its widespread use. By refining these technologies and addressing current limitations, the future of neuromodulation for PD will undoubtedly be shaped by increasingly personalized and adaptive therapeutic strategies.

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Competing interests

The authors declare no competing interests.