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Low- vs. high-frequency deep brain stimulation in Parkinson's disease: A two-center double-blind crossover trial

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Dear Editor,

High-frequency deep brain stimulation (HFS-DBS) of the subthalamic nucleus (STN) or internal segment of the globus pallidus (GPi) significantly alleviates motor complications in advanced Parkinson's disease (PD). However, axial symptoms—such as gait disturbances, postural instability, and freezing of gait (FOG)—often respond variably and may even worsen with standard HFS settings [1]. Low-frequency stimulation (LFS, ≤80 Hz) has been explored as an alternative strategy to improve axial symptoms in PD patients. However, its efficacy is heterogeneous, with some patients benefiting and others showing no improvement or even worsening of appendicular symptoms such as tremor [2]. This variability largely reflects methodological differences across studies, particularly in managing total electrical energy delivered (TEED), the limited use of objective gait and posture measures, and the reliance on small, single-center, single-blind crossover designs [3]. To address these limitations, we conducted a two-center, randomized, double-blind, crossover study in PD patients to compare the short-term effects of LFS (60 Hz) versus HFS (130 Hz) on gait, posture, and other axial symptoms, while adjusting stimulation parameters to maintain TEED constant across conditions.

Twenty patients who had received STN or GPi DBS implants at least one year earlier were evaluated in the OFF-medication state following a 12-h withdrawal of antiparkinsonian medications. They attended two visits one week apart, during which stimulation conditions were applied in randomized order, with parameters adjusted to maintain constant TEED calculated in constant-current mode as follows [4]:

$$TEED = \left(Current^2 * Impedance * Frequency * PulseWidth\right)$$

At each visit, patients were assessed in both OFF- and ON-DBS states by blinded neurologists using the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part III, the Berg Balance Scale (BBS), inertial-sensor-based Timed Up and Go (TUG) test, and static posturography, while stimulation was adjusted by a separate examiner. At baseline, the Freezing of Gait Questionnaire (FOGQ) and MDS-UPDRS part II were administered, and PD phenotypes were classified as described in Ref. [5] (Supplementary Materials).

Both LFS and HFS elicited significant improvements in MDS-UPDRS part III relative to baseline ($F_{(1, 19)} = 21.18$, $p < 0.001$), with estimated marginal means showing a reduction of 15.4 points (SE = 3.35; 95% CI: −22.1 to −8.73) (Fig. 1A). BBS scores also improved significantly ($F_{(1, 19)} = 29.35$, $p < 0.001$), with an estimated marginal mean increase of 6.57 points (SE = 1.21; 95% CI: 4.16 to 9.00). No significant differences were observed between LFS and HFS for either measure. The effects of LFS and HFS were also examined separately for each individual clinical feature of PD—FOG, tremor, postural instability and gait difficulty, bradykinesia, and rigidity—with significant improvements observed in all, but no differences between the two stimulation frequencies. TUG total duration also decreased significantly ($F_{(1, 19)} = 17.54$, $p < 0.001$), with estimated marginal means showing a reduction of 2.57 seconds (SE = 0.61; 95% CI: −3.81 to −1.34) across both stimulation conditions (Fig. 1B). Conversely, no pre-to-post changes in posturographic measures were observed for either HSF or LFS. Finally, stimulation target, PD phenotype, and FOG severity did not significantly affect any outcome measures when included as between-subject factors (Supplementary Materials).

Our findings suggest that, under TEED-matched conditions, LFS does not provide superior benefits over HFS in alleviating axial symptoms in the DBS-ON/medication-OFF state. Mechanistically, LFS may better engage mesencephalic structures implicated in locomotor control or modulate fiber pathways relevant to posture and gait. Among these, the pedunculopontine nucleus (PPN)—located in the caudal pontomesencephalic tegmentum approximately 5 mm from the STN—is particularly relevant for axial motor control, given its widespread projections to both the cortex and spinal cord [6]. LFS of the STN may affect PPN activity indirectly, either through passive current spread or via existing anatomical connections between the two structures [7]. Research in animal models found that only stimulation at 60 Hz—not at either 10 Hz or 130 Hz—was capable of synchronizing neuronal firing patterns within the PPN [8]. These observations raise the possibility that

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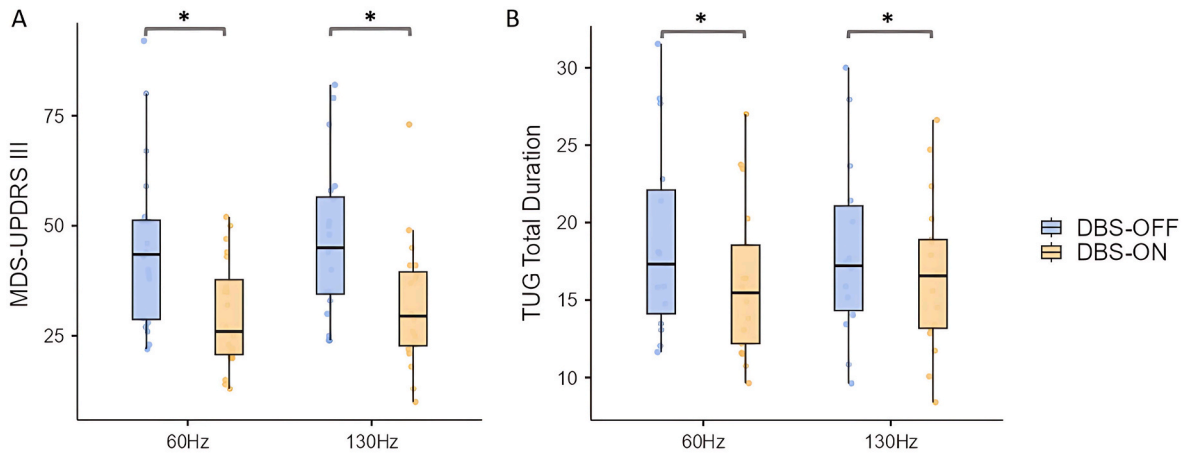

Fig. 1. Effects of Low- and High-Frequency Stimulation on Clinical and Kinematic Outcomes. (A) Pre- to post-stimulation reduction in MDS-UPDRS part III total scores following both low-frequency stimulation (LFS, 60 Hz) and high-frequency stimulation (HFS, 130 Hz). Both conditions led to significant improvements of motor symptoms relative to baseline (*$p < 0.05$).
(B) Pre- to post-stimulation reduction in Timed Up and Go (TUG) duration following LFS and HFS. Both conditions resulted in significant improvement in functional mobility (*$p < 0.05$). Error bars represent the standard error of the mean.

STN-LFS may facilitate PPN-related networks, thereby contributing to improvements in axial symptoms such as FOG. Nevertheless, evidence regarding LFS remains inconclusive, with some studies demonstrating improvements in axial symptoms, whereas others report minimal or no benefit [2]. A critical limitation of previous studies is that reducing frequency without a compensatory amplitude adjustment may result in subtherapeutic stimulation, potentially confounding the interpretation of frequency-dependent effects [3]. Our study directly addresses this issue by maintaining TEED constant across stimulation conditions, thereby enabling a more rigorous examination of frequency-specific outcomes.

The lack of a significant difference between HFS and LFS across clinical and biomechanical measures suggests that, when TEED is maintained, frequency alone does not differentially impact short-term motor performance in the OFF-medication state. Consistent with this, a recent meta-analysis reported benefits of LFS for axial symptoms in the ON- but not OFF-medication state, suggesting that frequency-dependent modulation of axial symptoms may require the synergistic effects of dopaminergic therapy [9]. This finding warrants further studies comparing ON- and OFF-medication states under TEED-controlled conditions. The absence of frequency-specific effects raises several important considerations for DBS programming. One interpretation is that TEED—not frequency—is the principal determinant of stimulation efficacy. Alternatively individual factors such as electrode placement, PD phenotype, and disease progression may influence responsiveness to frequency modulation. Notably, our additional analyses did not reveal significant moderation of stimulation effects by target, clinical phenotype, or FOG severity, although larger and more heterogeneous cohorts may be needed to detect such interactions. It is also possible that the efficacy of LFS is state-dependent, emerging only duringvoluntary movement. Indeed, neurophysiological studies suggest that pathological low-frequency oscillations in the STN are associated with gait disturbances, and modulating these rhythms may help engage brainstem locomotor networks [10]. This opens avenues for exploring adaptive DBS approaches, where stimulation parameters dynamically adjust in response to movement or neural biomarkers. Future research should investigate the interaction between stimulation frequency, medication state, and patient-specific factors, and consider adaptive or task-contingent DBS strategies to optimize treatment of axial symptoms in PD.

CRediT authorship contribution statement

Carmelo Luca Smeralda: Conceptualization, Data curation, Formal analysis, Visualization, Writing – original draft, Investigation, Methodology. **David De Monte:** Conceptualization, Investigation, Writing – review & editing. **Alice Cinesi:** Investigation, Writing – review & editing. **Alessandro Giannotta:** Investigation, Writing – review & editing. **Enrico Belgrado:** Investigation, Writing – review & editing. **Andrea Bernardini:** Investigation, Writing – review & editing. **Mariarosaria Valente:** Writing – review & editing. **Christian Lettieri:** Writing – review & editing. **Simone Rossi:** Conceptualization, Funding acquisition, Methodology, Project administration, Supervision.

Informed consent

Patients were required to provide informed consent to be included in the study. The study adhered to the guidelines of the Declaration of Helsinki and was approved by the research ethics committee of the University Hospital of Siena (protocol code: Brainsight 21/24).

Declaration of competing interest

All authors have nothing to declare.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.brs.2025.09.006.

References

[1] Fasano A, Aquino CC, Krauss JK, Honey CR, Bloem BR. Axial disability and deep brain stimulation in patients with Parkinson disease. Nat Rev Neurol 2015;11(2):98–110. https://doi.org/10.1038/nrneurol.2014.252.

[2] Phibbs FT, Arbogast PG, Davis TL. 60-Hz frequency effect on gait in Parkinson's disease with subthalamic nucleus deep brain stimulation. Neuromodulation J Int Neuromodulation Soc 2014;17(8):717–20. https://doi.org/10.1111/ner.12131. discussion 720.
[3] Conway ZJ, Silburn PA, Thevathasan W, Maley KO, Naughton GA, Cole MH. Alternate subthalamic nucleus deep brain stimulation parameters to manage motor symptoms of parkinson's disease: systematic review and meta-analysis. Mov Disord Clin Pract 2019;6(1):17–26. https://doi.org/10.1002/mdc3.12681.
[4] McAuley MD. Incorrect calculation of total electrical energy delivered by a deep brain stimulator. Brain Stimul Basic Transl Clin Res Neuromodulation 2020;13(5):1414–5. https://doi.org/10.1016/j.brs.2020.07.020.
[5] Stebbins GT, Goetz CG, Burn DJ, Jankovic J, Khoo TK, Tilley BC. How to identify tremor dominant and postural instability/gait difficulty groups with the movement disorder society unified Parkinson's disease rating scale: comparison with the unified Parkinson's disease rating scale. Mov Disord Off J Mov Disord Soc 2013;28(5):668–70. https://doi.org/10.1002/mds.25383.
[6] Elias GJB, Loh A, Gwun D, et al. Deep brain stimulation of the brainstem. Brain 2021;144(3):712–23. https://doi.org/10.1093/brain/awaa374.
[7] Weiss PH, Herzog J, Pötter-Nerger M, et al. Subthalamic nucleus stimulation improves Parkinsonian gait via brainstem locomotor centers. Mov Disord 2015;30(8):1121–5. https://doi.org/10.1002/mds.26229.
[8] Sitti I, Acar G, Zisakis AK, Özdemir M, Acar F, Burchiel KJ. Effect of subthalamic nucleus stimulation on Pedunculopontine nucleus neural activity. Stereotact Funct Neurosurg 2016;94(1):54–9. https://doi.org/10.1159/000442892.
[9] Tortato NCB, Ribas G, Frizon LA, Farah M, Teive HAG, Munhoz RP. Efficacy of subthalamic deep brain stimulation programming strategies for gait disorders in Parkinson's disease: a systematic review and meta-analysis. Neurosurg Rev 2024;47(1):525. https://doi.org/10.1007/s10143-024-02761-x.
[10] Chen CC, Yeh CH, Chan HL, et al. Subthalamic nucleus oscillations correlate with vulnerability to freezing of gait in patients with Parkinson's disease. Neurobiol Dis 2019;132:104605. https://doi.org/10.1016/j.nbd.2019.104605.

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