

Effects of Trans-Spinal Magnetic Stimulation on DBS' Induced Freezing of Gait in a Patient with Generalized Dystonia

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Internal globus pallidus deep brain stimulation (GPi DBS) is an effective treatment for relieving refractory isolated dystonia,¹ however a rare stimulation-side effect is Parkinsonism and freezing of gait (FoG)² which can greatly reduce treatment benefit^{3,4} and often requires partial or complete reduction of stimulation. Recently, trans-spinal magnetic stimulation (TsMS) has been proposed as a possible strategy for relieving Parkinson's disease (PD) FoG⁵ and parkinsonian symptoms in general.⁶ In this study, we report a patient with GPi DBS for dystonia who presented with pallidal stimulation induced FoG and was subjected to TsMS.

Epidural spinal cord stimulation has been demonstrated in small, mostly open-label studies as possibly effective for FoG and PD gait disorders⁷; however, due to its invasive nature alternative spinal cord stimulation techniques are currently under exploration. TsMS is a noninvasive alternative that appears to be capable of modulating spinal circuitry, and has superior availability, cost, and safety profile.⁸ Using magnetic stimulation alongside DBS warrants caution as interference can be produced with coil to device proximity under 10 cm, harmful under 2 cm.⁹ Stimulation over implanted leads can induce currents but again this is distance dependent, and some reports of safe transcranial stimulation with DBS exist.¹⁰ Thoracic TsMS however exceeds all discussed safe distances by wide margins.

A 61-year-old man with generalized dystonia since he was 9 years old underwent bilateral GPi DBS in 2015 with 45% to motor improvement (motor Burke–Fahn–Marsden 60 to 33). Genetic testing was not performed. Despite the motor improvement, 18 months after DBS, he progressively developed bilateral parkinsonism and FoG, reversible by interrupting stimulation. Several alternative DBS programs were attempted including unilateral stimulation, reduction of stimulation amplitude or pulse width, and several bipolar configurations, all resulting in either improvement of FoG coupled with intolerable worsening of dystonic symptoms or no improvement.

To ameliorate FoG, the patient underwent TsMS in a double-blind crossover design. The study was approved by the local ethics committee and the patient provided written informed consent. Two sessions of either sham or active stimulation were performed 8 weeks apart, in random order. An intermittent theta burst stimulation protocol of 1200 pulses as described⁵ was applied at T2–T3 thoracic level, with 1 hr interval between sessions. A Magventure® MagPro® R20 device was used with a circular coil. Stimulation intensity was determined at 100% of the sufficient to produce abdominal muscle contractions. For blinding in the sham phase, an inactive coil was pressed at the same thoracic level while another active coil 15 cm behind provided a similar sound experience. Paraspinal and abdominal muscle contraction were not replicated. The Timed Get Up and Go (TUG) test, Unified Parkinson's Disease Rating Scale (UPDRS) parts 2.12 and 2.13, and the New Freezing of Gait Questionnaire (nFoG) were assessed 1 hr before stimulation, 1 week after and 4 weeks after the stimulation in each of the phases. In addition, the UPDRS part 3 and FoG score were assessed 1 hr before and immediately after stimulation.

One week after the intervention, TUG time improved by an average of 47% in the active phase while 26% in sham, measured with turns to the right (clockwise) and left (counterclockwise) sides separately (Fig. 1A), and nFOG improved by 48% in the active group versus 8% in the sham group (Fig. 1B) (sham, 23/28; active, 14/28). Patient gait recording in all conditions is available in Video 1. UPDRS part 2, items 12 and 13, showed complete improvement from 4 and 3 to zero, respectively, whereas sham led to mixed results (Fig. 1C). After 4 weeks TUG time was similar between sham and active, as UPDRS part 2 items 12 and 13 improved, but nFOG questionnaires still suggested improvement with scores 37% lower than baseline with active stimulation versus 16% with sham (sham 21/28; active: 17/28) (Fig. 1D). FoG score presented 9.10% improvement

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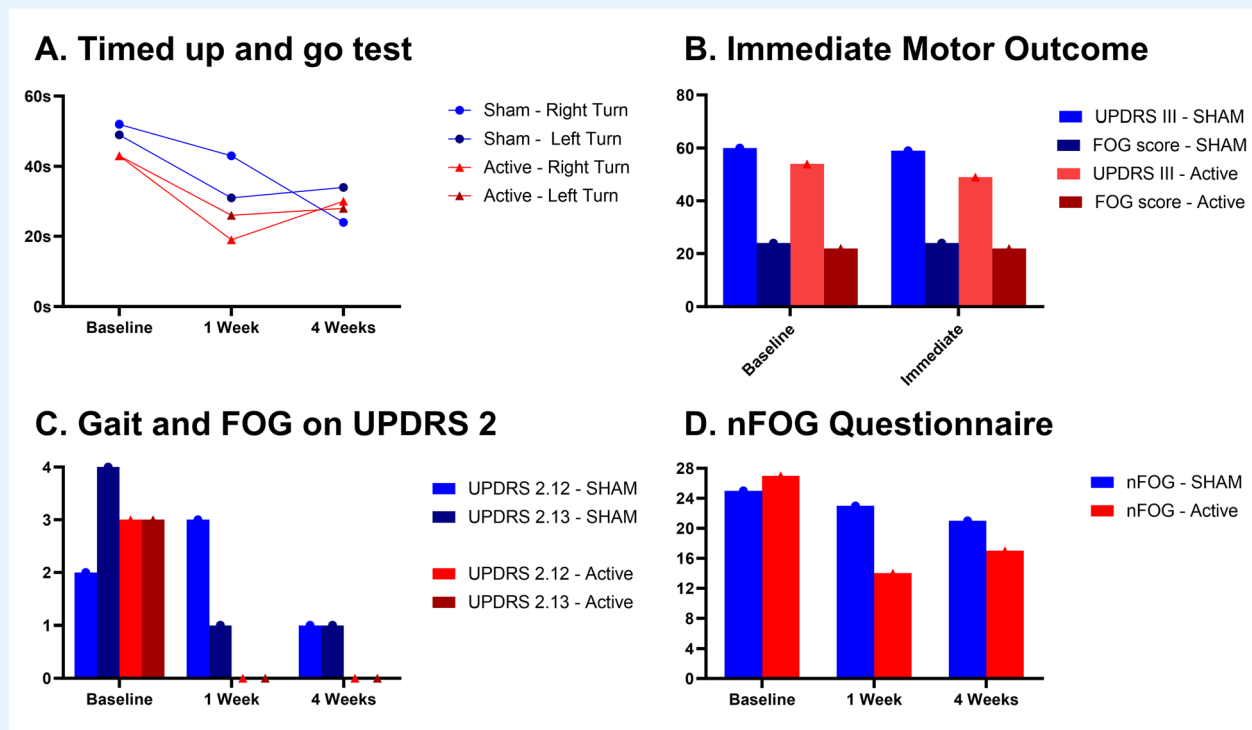


Figure 1. (A) Timed up and go test, (B) new freezing of gait Questionnaire (nFOG), and (C) Unified Parkinson's Disease Rating Scale (UPDRS) Part 2 items 12 (gait) and 13 (freezing of gait) before stimulation, 1 week after stimulation and 4 weeks after stimulation for sham and active phases. (D) 1 week after stimulation and 4 weeks after stimulation for the sham and active phases. (D) FoG Score and UPDRS part III (motor evaluation) before and immediately after stimulation.

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Video 1. Patient gait at baseline with deep brain stimulation turned off, under regular deep brain stimulation, one week after sham stimulation and one week after trans-spinal magnetic stimulation. Video content can be viewed at <https://onlinelibrary.wiley.com/doi/10.1002/mdc3.14137>

only in the active phase, while the UPDRS part 3 was unchanged in both settings. Regarding blinding, the patient reported receiving active stimulation during sham phase and vice versa. However, post-experiment, the patient correctly identified the active session, attributing it to perceived gait improvement after 1 week.

As no effective strategies have been reported for GPi DBS-induced dystonia other than altering stimulation settings,

TsMS offers a new possible alternative to reduce stimulation-induced FoG without sacrificing dystonia improvement. While TsMS would be expected to only provide short-lasting effects, the apparently sustained FoG benefit at 4 weeks was surprising and would suggest additional mechanisms, involving either secondary gain from the briefly improved mobility or yet to be confirmed as longer-lasting circuitry changes.

Although we could only include a single patient because of the rarity of DBS-induced FoG, these findings documented an improvement in FoG scores, suggesting that TsMS might be useful as a strategy for dystonic patients with secondary parkinsonism or FoG.

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; (3) Manuscript Preparation: A. Writing of the first draft, B. Review and Critique.

G.A.N: 1AB, 2ABC, 3A.

R.B.C: 1AB, 2C, 3A.

C.L: 1B, 2A, 3B.

S.M: 1B, 1C, 2B.

J.S.S: 1B, 2C.

A.C.R: 1C, 2C.

J.R.M: 2C, 3B.
 E.R.B:1B, 3B.
 R.G.C: 1AB, 2C, 3B.

Disclosures

Ethical Compliance Statement: Study approval statement: The study was approved by Institutional Review Board from the University of São Paulo (CAPPesq: 16233819.8.0000.0068). Consent to participate statement: All participants provided written informed consent before implementing any study protocol. We confirm that we have read the Journal's position on issues involved in ethical publication and affirm that this work is consistent with those guidelines.

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