



BRIEF REPORT

Multitarget Transcranial Electrical Stimulation for Freezing of Gait: A Randomized Controlled Trial

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ABSTRACT: Background: Treatments of freezing of gait (FOG) in Parkinson's disease are suboptimal.

Objective: The aim of this study was to evaluate the effects of multiple sessions of transcranial direct current stimulation (tDCS) targeting the left dorsolateral prefrontal cortex and primary motor cortex (M1) on FOG.

Methods: Seventy-seven individuals with Parkinson's disease and FOG were enrolled in a double-blinded randomized trial. tDCS and sham interventions comprised 10 sessions over 2 weeks followed by five once-weekly sessions. FOG-provoking test performance (primary outcome), functional outcomes, and self-reported FOG severity were assessed.

Results: Primary analyses demonstrated no advantage for tDCS in the FOG-provoking test. In secondary analyses, tDCS, compared with sham, decreased self-reported FOG severity and increased daily living

step counts. Among individuals with mild-to-moderate FOG severity, tDCS improved FOG-provoking test time and self-report of FOG.

Conclusions: Multisession tDCS targeting the left dorsolateral prefrontal cortex and M1 did not improve laboratory-based FOG-provoking test performance. Improvements observed in participants with mild-to-moderate FOG severity warrant further investigation. © 2021 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; freezing; noninvasive brain stimulation; tDCS; physical activity

Freezing of gait (FOG) is one of the most debilitating Parkinson's disease (PD) symptoms.¹ Current treatments are limited, and new therapies are needed.^{2–4} In addition to subcortical dysfunction within the striatum and cerebellar locomotor regions, recent studies suggest that FOG is also associated with dysfunction within prefrontal–cognitive and sensorimotor networks.^{3,5–9}

Transcranial direct current stimulation (tDCS) modulates the excitability of cortical neurons and their connected neural networks.^{10–12} Pilot work suggests that tDCS designed to facilitate the excitability of the primary motor cortex (M1) reduces FOG,¹³ that tDCS targeting the left dorsolateral prefrontal cortex (dlPFC) may improve executive function¹⁴ and gait under cognitively demanding “dual-task” conditions,¹⁵ and that tDCS may improve self-reported FOG severity.¹⁶ In a pilot study that we conducted in 20 patients with PD with FOG,¹⁷ a single session of tDCS that targeted both the left dlPFC and M1 significantly reduced the severity of FOG immediately after stimulation, compared with M1 or sham stimulation. Based on this evidence and the putative role of cognitive–motor links in FOG,^{1,3,18} we conducted a randomized-controlled trial to test the hypothesis that a multisession tDCS intervention that targets the left dlPFC and M1 would reduce FOG and improve related outcomes.

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Relevant conflicts of interest/financial disclosures: A.P.-L. has a sponsored research agreement with Neuroelectronics for home-based

transcranial current stimulation and Electrical GEODESICS Incorporated (EGI) for high-density electroencephalography in cognitive disability. The other authors declare no conflict of interest.

Received: 8 June 2021; **Revised:** 23 July 2021; **Accepted:** 26 July 2021

Published online in Wiley Online Library
 (wileyonlinelibrary.com). DOI: 10.1002/mds.28759

Patients and Methods

A sham-controlled, double-blinded, randomized trial was conducted (ClinicalTrials.org: NCT02656316). After providing informed written consent, 77 subjects completed the baseline assessment and were randomized to either tDCS or sham stimulation (Supporting Information Figs. S1 and S2), stratified by site and sex. The tDCS intervention was designed to facilitate the excitability of the left dlPFC and the bilateral leg region of M1¹⁷ (Supporting Information Fig. S3). Subjects in each arm underwent an intensive phase of 10 stimulation sessions over 2 weeks, followed by a “maintenance” phase of once-weekly sessions for 5 weeks. Follow-up assessments were performed after the intensive phase, after the maintenance phase, and 5 weeks later (10-week follow-up; Supporting Information Fig. S2). Motivated by the positive effects of our pilot study,^{17,19} the primary FOG outcome was the FOG-provoking test performance score (FOG severity score) after the intensive phase (ie, after 10 sessions of tDCS given over 2 weeks) in the *on* medication state.¹⁹ Secondary outcomes included additional measures derived from the FOG-provoking test (ie, FOG episodes number, percentage total test time frozen, and total time to complete the test²⁰), the Movement Disorder Society Unified Parkinson’s Disease Rating Scale, Part III,²¹ the Timed Up and Go,²² a computerized executive function battery (Neurotrax Inc.),²³ and an accelerometer that captured 7-day daily living step counts.²⁴ If patients agreed, the assessment was also completed in the *off* medication state for exploratory analyses. Mixed-effects negative-binomial regression models evaluated the primary outcome and other measures derived from the FOG-provoking test. See Supporting Data for additional details.

Results

The tDCS and sham groups were similar in age, sex distribution, education, body mass index, and years since PD diagnosis (Supporting Information Tables S1 and S2). The FOG severity score and the average number of identified FOG episodes experienced during the FOG-provoking test were noticeably higher in those randomized to tDCS compared with sham (Table 1). All subsequent statistical analyses considered these baseline measures. Retention to the assessment immediately after the intensive phase (the primary endpoint) was high (97%), with no significant differences between treatment arms for the side effects which were transient and mild (Supporting Information Figs. S1 and S4). Blinding was achieved; the proportion of participant guesses regarding whether they received real or sham stimulation was not statistically different between

groups (tDCS: 49% guessed tDCS; sham: 35% guessed tDCS; $P = 0.77$).

Effects of tDCS on FOG-Provoking Test Outcomes

In the tDCS arm, the median FOG severity score was 15 at baseline and 12, 12, and 10 at the immediate, 5-week, and 10-week follow-ups, respectively (Table 1). Similar trajectories were observed for the other secondary outcomes derived from the FOG-provoking test (Table 1). Nonetheless, neither model-adjusted nor unadjusted comparisons of change in FOG severity score showed statistically significant differences between the tDCS and sham groups at the three follow-up evaluations (all $P > 0.11$).

Secondary Outcomes

More participants reported a reduction in FOG severity on a Likert global impression scale in the tDCS group than in the sham group (58% vs. 35%; $P = 0.05$; Fig. 1). Compared with sham, tDCS also increased daily living step counts from baseline to the immediate ($P = 0.04$) and 10-week follow-up ($P = 0.03$) assessments. tDCS did not offer statistically significant advantage over sham stimulation on other secondary outcomes.

Influence of Baseline FOG Severity

Because participants had a wide range of FOG severity at baseline and previous work suggested that individuals with more advanced FOG may be less responsive to interventions,^{26–28} we conducted exploratory analyses stratifying participants into mild-to-moderate and severe FOG subgroups (based on tertiles of baseline FOG-provoking score). In participants with mild-to-moderate FOG severity (baseline FOG severity score < 16), tDCS compared with sham resulted in a 10% reduction in the total time taken to complete the FOG-provoking test at the immediate follow-up (means ratio = 0.9; 95% confidence interval = 0.8–1.0; $P = 0.048$) (Supporting Information Fig. S5 and Table S4). The effects of tDCS on the number of FOG episodes and percent time frozen were not significant (Supporting Information Fig. S5 and Table S4). In participants with mild-to-moderate FOG severity, those who received tDCS as compared with sham self-reported greater improvement in FOG severity after the intensive intervention (Likert global impression scale; $P = 0.05$). In this subgroup, tDCS was also associated with a reduction ($P = 0.03$) in the new freezing of gait questionnaire total score at the 10-week follow-up (Supporting Information Table S4). No other group differences in the change from baseline to any follow-up assessment were observed. For the most severe FOG tertile group, unadjusted and adjusted analysis of

TABLE 1 Key outcomes assessed in the on medication state by study visit and by treatment arm

	Treatment Arm				
	tDCS			Sham	
	Baseline	Immediate	5 Weeks	10 Weeks	
Completed visits, n (%)	37 (100%)	35 (95%)	29 (78%)	21 (57%)	21 (58%)
FOG-provoking test outcomes					
FOG severity score	15 (11–19)	12 (6–15)	12 (6–16)	10 (4–13)	7 (3–17)
Total number of FOG episodes	5 (1–8)	3 (0–10)	2 (0–8)	2 (0–6)	0 (0–4)
Average % time frozen	15 (2–28)	5 (0–22)	6 (0–32)	7 (0–23)	0 (0–18)
Test duration, s	140 (111–191)	116 (90–154)	124 (82–223)	105 (87–175)	115 (84–147)
PD severity, functional outcomes, and subjective FOG severity					
MDS-UPDRS-III	38 (32–45)	35 (29–49)	37 (29–44)	36 (31–43)	40 (30–52)
TUG, s	13 (10–16)	12 (10–14)	13 (9–18)	11 (9–15)	11 (9–16)
Neurotrax EF score	98 (82–109)	97 (86–101)	94 (81–106)	98 (86–107)	102 (88–106)
Daily living step count, per day	5850 ± 3982	6672 ± 4666*	6749 ± 5015	8596 ± 5045*	6364 ± 3183
N-FOG questionnaire total score	20 ± 4	20 ± 3	19 ± 5	19 ± 5**	18 ± 4

Outcomes are presented as mean ± SD or median (interquartile interval). Data include participants who satisfy the modified Intent to Treat (mITT) criterion. No missing data were imputed. Note that the scores on the FOG-provoking test decreased by at least 3 points, the minimum clinically meaningful amount,²⁸ at each follow-up as compared with baseline in the tDCS arm.

* $P < 0.05$, ** $P < 0.01$; asterisks indicate outcomes and visits for which the raw change from baseline in the tDCS arm was different from the raw change from baseline in the sham arm.

tDCS, transcranial direct current stimulation; FOG, freezing of gait; PD, Parkinson's disease; MDS-UPDRS, Movement Disorder Society Revised Unified Parkinson's Disease Rating Scale; TUG, Timed Up and Go test; EF, executive function; N-FOG, new freezing of gait.

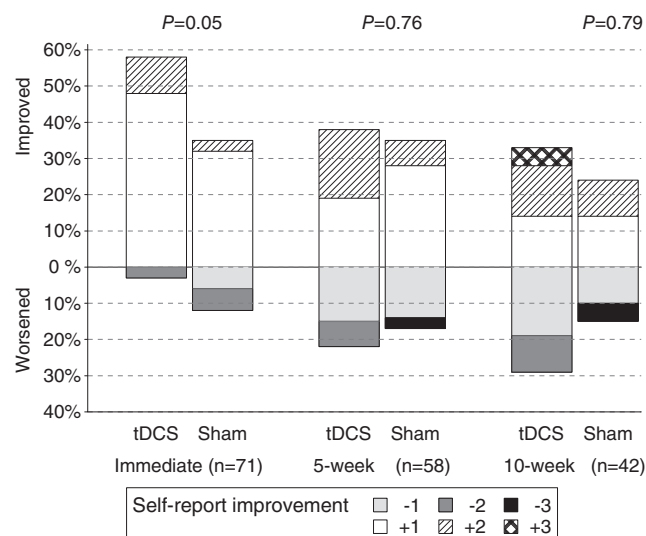


FIG. 1. The effects of transcranial direct current stimulation (tDCS) or sham stimulation on self-reported severity of freezing of gait (FOG). Participants were asked to rate their change in FOG severity using a Likert scale ranging from -3 (significantly worsened) to +3 (significantly improved), with 0 indicating no change. The tDCS intervention, as compared with sham, was associated with greater percentage (y axis) of participants reporting improvement in FOG at the immediate follow-up ($P = 0.05$), yet not at the 5-week or 10-week follow-up. Very similar results ($P = 0.045$) were obtained using the Wilcoxon test, which treats the values as a numeric Likert score.

FOG-provoking test performance and self-reported FOG severity revealed no significant effects of the intervention on any outcome (Supporting Information Table S5 and Fig. S5).

The Off Medication State

Exploratory analyses of the *off* medication data suggested no association between the tDCS intervention and any outcome measures in the subgroup of participants who agreed to be tested in the *off* medication state (Supporting Information Table S6).

Discussion

The 2-week tDCS intervention followed by five once-weekly booster sessions did not significantly reduce the severity of FOG observed during an in-laboratory FOG-provoking test, over and above that of the sham intervention, in contrast with the pilot results.¹⁷ The primary outcome was not met. This suggests that tDCS did not induce permanent changes in brain function sufficient to create a measurable reduction in FOG severity across the entire cohort.

Secondary analyses suggested that as compared with sham, tDCS resulted in greater participant-reported improvement in FOG severity immediately after the intensive phase, as well as greater daily living step counts at both the immediate (ie, after 2 weeks of stimulation) and 10-week follow-ups. Exploratory analyses also revealed that the time to complete the FOG-provoking test improved specifically among those

participants with mild-to-moderate FOG severity at baseline (FOG severity score < 16). Such results were not observed in participants with more severe FOG. Thus, despite lack of observed benefit on the primary FOG outcome, continued study of tDCS may be warranted, particularly in patients who suffer from relatively mild-to-moderate FOG.

Although tDCS did not affect FOG-provoking test performance, it was associated with reduced self-reported FOG severity immediately after the intervention. This discrepancy between in-laboratory tests and self-report is not surprising because low correlations between the two forms of evaluation have been reported previously.^{20,29} Although self-reported outcomes may be prone to relatively large test-retest error,²⁹ these results suggest that tDCS might be able to positively impact FOG, but that a larger “dose” (ie, the number, intensity, and/or frequency of stimulation sessions) may be needed to induce larger between-group changes within laboratory-based FOG-provoking tests. Future trials should consider the use of longer interventions, additional methods of capturing FOG including the percent of freezing during daily living activities,^{30,31} and diaries by participants and/or their caregivers.³²

The tDCS group exhibited evidence of increased daily living step counts (after 2 weeks of stimulation and 10 weeks later), as compared with the sham group. Conclusions regarding the retention of observed immediate effects are limited by smaller sample sizes at later assessments, and the clinical meaningfulness of changes in daily living step counts has not yet been established for PD. Future work should also check that these

increases do not simply reflect FOG (see Supporting Data). Still, these results provide preliminary evidence of a potential way to improve physical activity in this population who suffer from sedentary lifestyles.

Exploratory analyses revealed that the tDCS intervention appeared to reduce self-reported FOG severity, increase daily living step counts, and potentially improve FOG-provoking test performance in those with mild-to-moderate FOG severity (changes that were similar to those observed among all subjects), but *not* in those with severe FOG. This observation is consistent with the possibility that earlier treatment may lead to better outcomes and that mild FOG may be relatively more responsive to therapy.^{26–28} Perhaps, patients with more severe disease and associated neurodegeneration may not be able to respond to tDCS. Alternatively, they may require a larger dose than that provided in the current trial. Also, different mechanisms may drive mild-to-moderate FOG as opposed to advanced FOG.^{33,34} Future studies using noninvasive brain stimulation should consider tailoring the tDCS to FOG severity, stratifying by disease severity, or focusing exclusively on patients with mild-to-moderate FOG. Additional research is needed to address these issues.

tDCS was designed to simultaneously facilitate the excitability of the left dlPFC and the leg regions of M1. Although this intervention may have benefited some aspects of motor function (eg, step counts), positive effects on executive function were not consistently observed. Targeting additional or other cortical networks that have been implicated in FOG, including the limbic^{34–36} and/or cerebellar locomotor networks,^{8,37} may thus be needed to exert an optimal effect on FOG. Future trials may also consider using tDCS optimization techniques to tailor interventions to individual brain anatomy^{38,39} and consider possible effects of peripheral nerve stimulation.⁴⁰

The tDCS intervention was well tolerated and well attended within the intensive 2-week phase. Although some participants did not complete later follow-ups (Supporting Information Fig. S1), loss to later follow-up was largely similar across arms (Supporting Information Table S3). Eligibility criteria resulted in larger-than-expected interparticipant variance in baseline FOG severity, as well a percentage of participants who exhibited minimal FOG episodes within the baseline FOG-provoking test. Larger trials should carefully consider eligibility criteria and the stratification of randomization (beyond only site and sex as done in the current trial because of sample size constraints) to ensure balance between arms. This trial provides preliminary data suggesting that multitarget tDCS is safe, and that multiple sessions may potentially improve FOG-related outcomes. Nonetheless, additional research is needed to optimize tDCS and determine if and in whom this form of brain stimulation ameliorates FOG. ■

Acknowledgments: This work was supported by The Michael J. Fox Foundation for Parkinson's Research project grant number 11774.

Data Availability Statement

Data available on request due to privacy/ethical restrictions The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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Author Roles

1. Research project: A. Conception, B. Organization, C. Execution;
2. Statistical Analysis: A. Design, B. Execution, C. Review and Critique;
3. Manuscript: A. Writing of the first draft, B. Review and Critique.
B.M.: 1A, 1B, 1C, 2A, 2C, 3A, 3B
M.D.: 1A, 1B, 1C, 2C, 3A, 3B
T.H.: 1B, 1C, 3B
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V.V.: 1A, 3B
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Financial Disclosures

This work was supported by The Michael J. Fox Foundation (grant number 11174). B.M. was also supported by grants from the National Institutes of Health (1 R01 AG059089-01A1, 1R21 AG064575-01, and 3 P30 AG031679-09S1). N.G. also received support from the National Parkinson Foundation, the European Union, and the Israel Science Foundation, as well as from Teva NNE program, Biogen, and Ionis. He receives support from the Sieratzki Family Foundation and the Aufzien Academic Center in Tel-Aviv University. He serves as consultant to Sionara, NeuroDerm, Pharma2B, Denali, Neuron23, Sanofi-Genzyme, Biogen, and AbbVie. He receives royalties from Lysosomal Therapeutics and payment for lectures at AbbVie, Sanofi-Genzyme, and Movement Disorder Society. A.P.-L. was also supported by grants from the National Institutes of Health (R24AG06142 and P01 AG031720) and the Barcelona Brain Health Initiative (La Caixa and Institute Guttmann), as well as sponsored research agreements with Neuroelectrics for home-based transcranial current stimulation and EGI for high-density electroencephalography in cognitive disability. He is listed as an inventor on several issued and pending patents on the real-time integration of noninvasive brain stimulation with electroencephalography and magnetic resonance imaging. He is co-founder of Linus Health and TI Solutions AG and serves on the scientific advisory boards for Starlab Neuroscience, Magstim Inc., Nexstim, and MedRhythms. T.G.T. was also supported by the Biostatistical Design and Analysis Core of the Boston Older Americans Independence Center (P30 AG031679). L.A.L. was also supported by the Irving and Edyth S. Usen and Family Chair in Geriatric Medicine at Hebrew SeniorLife. J.M.H. was also supported by Mobilise-D, which has received funding from the Innovative Medicines Initiative 2 Joint Undertaking (JU) under grant agreement number 820820. The JU receives support from the European Union's Horizon 2020 research and innovation program and EFPIA. He is also received support from the Israel Science Foundation, The Israel Ministry of Health, subcontracts from the NIH, and from the National Multiple Sclerosis Society. V.V. was also supported by NINDS R01 NS079623, Dystonia Medical Research Foundation, NIA R01 AG047976, NIH U54 DK104310, NHLBI 2P01 HL09549. She is a consultant to Takeda.