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.

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 function[14] 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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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 M1[17] (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 test[20]), 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**	**Baseline**	**Immediate**	**5 Weeks**	**10 Weeks**
Completed visits, n (%)	37 (100%)	35 (95%)	29 (78%)	21 (57%)	36 (100%)	36 (100%)	29 (81%)	21 (58%)
FOG-provoking test outcomes								
FOG severity score	15 (11–19)	12 (6–15)	12 (6–16)	10 (4–13)	10 (6–16)	8 (4–16)	11 (5–17)	7 (3–17)
Total number of FOG episodes	5 (1–8)	3 (0–10)	2 (0–8)	2 (0–6)	2 (0–6)	2 (0–5)	1 (0–5)	0 (0–4)
Average % time frozen	15 (2–28)	5 (0–22)	6 (0–32)	7 (0–23)	5 (0–22)	3 (0–15)	1 (0–13)	0 (0–18)
Test duration, s	140 (111–191)	116 (90–154)	124 (82–223)	105 (87–175)	125 (93–190)	127 (98–157)	113 (92–159)	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)	37 (21–45)	30 (25–45)	33 (24–47)	40 (30–52)
TUG, s	13 (10–16)	12 (10–14)	13 (9–18)	11 (9–15)	12 (11–14)	12 (10–15)	13 (10–15)	11 (9–16)
Neurotrax EF score	98 (82–109)	97 (86–101)	94 (81–106)	98 (86–107)	96 (86–105)	99 (90–106)	97 (91–107)	102 (88–106)
Daily living step count, per day	5850 ± 3982	6672 ± 4666★	6749 ± 5015	8596 ± 5045★	5977 ± 4099	5359 ± 3744	5937 ± 3780	6364 ± 3183
N-FOG questionnaire total score	20 ± 4	20 ± 3	19 ± 5	19 ± 5★★	18 ± 5	19 ± 5	18 ± 5	18 ± 4

Outcomes are presented as mean ± SD or median (intraquartile 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,[25] at each follow-up as compared with baseline in the tDCS arm.

★$P < 0.05$, ★★$P < 0.1$; 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.

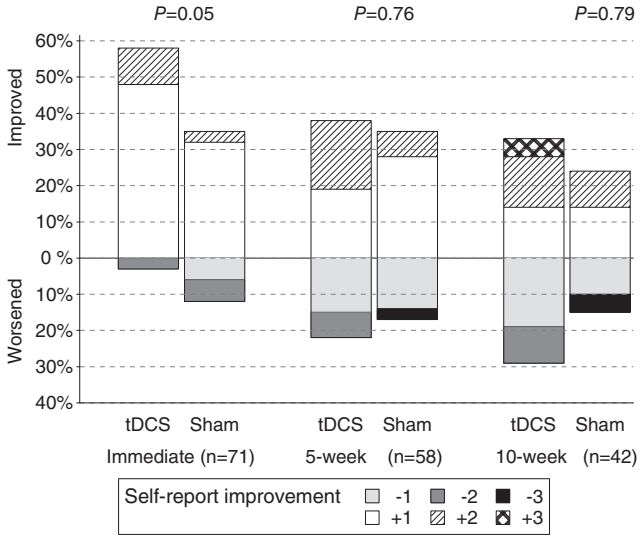

FIG. 1. The effects of transcranial direct current stimulation (tDCS) or sham stimulation on self-reported severity of freezing of gait (FOG). Participants were asked to rate their change in FOG severity using a Likert scale ranging from −3 (significantly worsened) to +3 (significantly improved), with 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. ●

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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.

References

1. Weiss D, Schoellmann A, Fox MD, et al. Freezing of gait: understanding the complexity of an enigmatic phenomenon. Brain 2020; 143:14–30.
2. Gilat M, Lígia Silva de Lima A, Bloem BR, Shine JM, Nonnekes J, Lewis SJG. Freezing of gait: promising avenues for future treatment. Parkinsonism Relat Disord 2018;52:7–16.
3. Nutt JG, Bloem BR, Giladi N, Hallett M, Horak FB, Nieuwboer A. Freezing of gait: moving forward on a mysterious clinical phenomenon. Lancet Neurol 2011;10:734–744.
4. Delgado-Alvarado M, Marano M, Santurtún A, Urtiaga-Gallano A, Tordesillas-Gutierrez D, Infante J. Nonpharmacological, nonsurgical treatments for freezing of gait in Parkinson's disease: a systematic review. Mov Disord 2020;35:204–214.
5. Ehgoetz Martens KA, Hall JM, Georgiades MJ, et al. The functional network signature of heterogeneity in freezing of gait. Brain 2018; 141:1145–1160.
6. Lewis SJ, Shine JM. The next step: a common neural mechanism for freezing of gait. Neuroscientist 2016;22:72–82.
7. Shine JM, Matar E, Ward PB, et al. Exploring the cortical and subcortical functional magnetic resonance imaging changes associated with freezing in Parkinson's disease. Brain 2013;136:1204–1215.
8. Gilat M, Dijkstra BW, D'Cruz N, Nieuwboer A, Lewis SJG. Functional MRI to study gait impairment in Parkinson's disease: a systematic review and exploratory ALE meta-analysis. Curr Neurol Neurosci Rep 2019;19:49.
9. Snijders AH, Takakusaki K, Debu B, et al. Physiology of freezing of gait. Ann Neurol 2016;80:644–659.
10. Stagg CJ, Antal A, Nitsche MA. Physiology of transcranial direct current stimulation. J ECT 2018;34:144–152.
11. Lefaucheur JP, Wendling F. Mechanisms of action of tDCS: a brief and practical overview. Neurophysiol Clin 2019;49:269–275.
12. Chhatbar PY, Kautz SA, Takacs I, et al. Evidence of transcranial direct current stimulation-generated electric fields at subthalamic level in human brain in vivo. Brain Stimul 2018;11:727–733.
13. Valentino F, Cosentino G, Brighina F, et al. Transcranial direct current stimulation for treatment of freezing of gait: a cross-over study. Mov Disord 2014;29:1064–1069.
14. Bueno MEB, do Nascimento Neto LI, Terra MB, Barboza NM, Okano AH, Smaili SM. Effectiveness of acute transcranial direct current stimulation on non-motor and motor symptoms in Parkinson's disease. Neurosci Lett 2019;696:46–51.
15. Putzolu M, Pelosin E, Ogliastro C, et al. Anodal tDCS over prefrontal cortex improves dual-task walking in parkinsonian patients with freezing. Mov Disord 2018;33:1972–1973.
16. Lee HK, Ahn SJ, Shin YM, Kang N, Cauraugh JH. Does transcranial direct current stimulation improve functional locomotion in people with Parkinson's disease? A systematic review and meta-analysis. J Neuroeng Rehabil 2019;16:84.
17. Dagan M, Herman T, Harrison R, et al. Multitarget transcranial direct current stimulation for freezing of gait in Parkinson's disease. Mov Disord 2018;33:642–646.
18. Walton CC, Mowszowski L, Gilat M, et al. Cognitive training for freezing of gait in Parkinson's disease: a randomized controlled trial. NPJ Parkinsons Dis 2018;4:15.

19. Ziegler K, Schroeteler F, Ceballos-Baumann AO, Fietzek UM. A new rating instrument to assess festination and freezing gait in parkinsonian patients. Mov Disord 2010;25:1012–1018.

20. Herman T, Dagan M, Shema-Shiratzky S, et al. Advantages of timing the duration of a freezing of gait-provoking test in individuals with Parkinson's disease. J Neurol 2020;267:2582–2588.

21. Goetz CG, Fahn S, Martinez-Martin P, et al. Movement Disorder Society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): process, format, and clinimetric testing plan. Mov Disord 2007;22:41–47.

22. Podsiadlo D, Richardson S. The timed "up & go": a test of basic functional mobility for frail elderly persons. J Am Geriatr Soc 1991; 39:142–148.

23. Weiss A, Herman T, Giladi N, Hausdorff JM. Association between community ambulation walking patterns and cognitive function in patients with Parkinson's disease: further insights into motor-cognitive links. Parkinsons Dis 2015;2015:547065.

24. Weiss A, Herman T, Giladi N, Hausdorff JM. New evidence for gait abnormalities among Parkinson's disease patients who suffer from freezing of gait: insights using a body-fixed sensor worn for 3 days. J Neural Transm 2015;122:403–410.

25. Fietzek UM, Schulz SJ, Ziegler K, Ceballos-Baumann AO. The Minimal Clinically Relevant Change of the FOG Score. J Parkinsons Dis 2020;10:325–332. https://doi.org/10.3233/JPD-191783

26. Olson M, Lockhart TE, Lieberman A. Motor learning deficits in Parkinson's disease (PD) and their effect on training response in gait and balance: a narrative review. Front Neurol 2019;10:62.

27. Heremans E, Nackaerts E, Vervoort G, Broeder S, Swinnen SP, Nieuwboer A. Impaired retention of motor learning of writing skills in patients with Parkinson's disease with freezing of gait. PLoS One 2016;11:e0148933.

28. Vandenbossche J, Deroost N, Soetens E, et al. Impaired implicit sequence learning in Parkinson's disease patients with freezing of gait. Neuropsychology 2013;27:28–36.

29. Scully AE, Hill KD, Tan D, Clark R, Pua YH, de Oliveira BIR. Measurement properties of assessments of freezing of gait severity in people with Parkinson disease: a COSMIN review. Phys Ther 2021; 101. https://doi.org/10.1093/ptj/pzab009

30. Mancini M, Shah VV, Stuart S, et al. Measuring freezing of gait during daily-life: an open-source, wearable sensors approach. J Neuroeng Rehabil 2021;18:1.

31. Mancini M, Bloem BR, Horak FB, Lewis SJG, Nieuwboer A, Nonnekes J. Clinical and methodological challenges for assessing freezing of gait: future perspectives. Mov Disord 2019;34:783–790.

32. Montgomery GK, Reynolds NC Jr. Compliance, reliability, and validity of self-monitoring for physical disturbances of Parkinson's disease. The Parkinson's symptom diary. J Nerv Ment Dis 1990; 178:636–641.

33. Nonnekes J, Bloem BR. Biphasic levodopa-induced freezing of gait in Parkinson's disease. J Parkinsons Dis 2020;10:1245–1248.

34. Ehgoetz Martens KA, Shine JM, Walton CC, et al. Evidence for subtypes of freezing of gait in Parkinson's disease. Mov Disord 2018; 33:1174–1178.

35. Ehgoetz Martens KA, Peterson DS, Almeida QJ, Lewis SJG, Hausdorff JM, Nieuwboer A. Behavioural manifestations and associated non-motor features of freezing of gait: a narrative review and theoretical framework. Neurosci Biobehav Rev 2020;116: 350–364.

36. Chow R, Tripp BP, Rzondzinski D, Almeida QJ. Investigating therapies for freezing of gait targeting the cognitive, limbic, and sensorimotor domains. Neurorehabil Neural Repair 2021;35:290–299.

37. Fasano A, Laganiere SE, Lam S, Fox MD. Lesions causing freezing of gait localize to a cerebellar functional network. Ann Neurol 2017;81:129–141.

38. Mosayebi-Samani M, Jamil A, Salvador R, Ruffini G, Haueisen J, Nitsche MA. The impact of individual electrical fields and anatomical factors on the neurophysiological outcomes of tDCS: a TMS-MEP and MRI study. Brain Stimul 2021;14:316–326.

39. Martens G, Ibáñez-Soria D, Barra A, et al. A novel closed-loop EEG-tDCS approach to promote responsiveness of patients in minimally conscious state: a study protocol. Behav Brain Res 2021;409:113311.

40. van Boekholdt L, Kerstens S, Khatoun A, Asamoah B, Mc LM. tDCS peripheral nerve stimulation: a neglected mode of action? Mol Psychiatry 2021;26:456–461.

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
N.A.G.: 2A, 2B, 2C, 3A, 3B
V.V.: 1A, 3B
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