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Non-invasive brain stimulation for fatigue in post-acute sequelae of SARS-CoV-2 (PASC)

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ABSTRACT

Background: and purpose: Fatigue is among the most common persistent symptoms following post-acute sequelae of Sars-COV-2 infection (PASC). The current study investigated the potential therapeutic effects of High-Definition transcranial Direct Current Stimulation (HD-tDCS) associated with rehabilitation program for the management of PASC-related fatigue.

Methods: Seventy patients with PASC-related fatigue were randomized to receive 3 mA or sham HD-tDCS targeting the left primary motor cortex (M1) for 30 min paired with a rehabilitation program. Each patient underwent 10 sessions (2 sessions/week) over five weeks. Fatigue was measured as the primary outcome before and after the intervention using the Modified Fatigue Impact Scale (MFIS). Pain level, anxiety severity and quality of life were secondary outcomes assessed, respectively, through the McGill Questionnaire, Hamilton Anxiety Rating Scale (HAM-A) and WHOQOL.

Results: Active HD-tDCS resulted in significantly greater reduction in fatigue compared to sham HD-tDCS (mean group MFIS reduction of 22.11 points vs 10.34 points). Distinct effects of HD-tDCS were observed in fatigue domains with greater effect on cognitive (mean group difference 8.29 points; effect size 1.1; 95% CI 3.56−13.01; $P < .0001$) and psychosocial domains (mean group difference 2.37 points; effect size 1.2; 95% CI 1.34−3.40; $P < .0001$), with no significant difference between the groups in the physical subscale (mean group difference 0.71 points; effect size 0.1; 95% CI 4.47−5.90; $P = .09$). Compared to sham, the active HD-tDCS group also had a significant reduction in anxiety (mean group difference 4.88; effect size 0.9; 95% CI 1.93−7.84; $P < .0001$) and improvement in quality of life (mean group difference 14.80; effect size 0.7; 95% CI 7.87−21.73; $P < .0001$). There was no significant difference in pain (mean group difference −0.74; no effect size; 95% CI 3.66−5.14; $P = .09$).

Conclusion: An intervention with M1 targeted HD-tDCS paired with a rehabilitation program was effective in reducing fatigue and anxiety, while improving quality of life in people with PASC.

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1. Introduction

Post-acute sequelae of Sars-CoV-2 infection (PASC) is an umbrella term for the wide range of multisystemic symptoms that are present four or more weeks after SARS-CoV-2 infection, independent of infection severity [1]. Fatigue is among the most reported PASC symptoms and has been associated with significant burden and disability [2]. The pathophysiological mechanisms of PASC remain poorly understood, but persistent immune activation has been regarded as a major player [3]. Currently, there are no established treatments for PASC and thus a large patient population seeking effective therapies [4].

Transcranial direct current stimulation (tDCS) is a type of noninvasive brain stimulation using low amplitude sustained currents [5]. High Definition tDCS (HD-tDCS) allows current steering to targeted brain regions [6–8]. tDCS is appealing as a non-pharmacological intervention and has been proposed for both COVID-19 acute illness and PASC-related conditions [9,10]. tDCS has been shown to reduce fatigue in a range of neurologic and immune diseases [11–13] and recently proposed as a therapeutic strategy for PASC-related fatigue [14–17].

Preliminary findings have demonstrated that PASC patients with fatigue exhibit abnormal motor cortex neurophysiological excitability. In these patients, inadequate input from brain regions upstream of M1 and/or reduced excitability of motor cortex could cause inadequate descending drive to the α-motor neurons thus contributing to the central fatigue [18,19]. Brain imaging and neurophysiology studies have indicated M1 is strongly involved in fatigue control [20,21] and prior studies revealed that changes in cortical excitability after tDCS were significantly correlated with fatigue improvement [22,23].

Given the need to develop effective strategies against PASC-related fatigue and the emerging role of tDCS in the treatment of fatigue, we developed this trial. The main objective of this randomized, sham-controlled trial was to evaluate the efficacy of M1 HD-tDCS associated with rehabilitation in PASC patients with fatigue. We postulated that, compared to sham stimulation, active stimulation during rehabilitation would improve fatigue (primary outcome), related symptoms (anxiety and pain) improving quality of life of patients with PASC.

2. Methods

2.1. Study design

This was a prospective, double-blind, randomized, sham-controlled clinical trial (NCT05289115) approved by the National Health Service Research Ethics Committee and conducted according to the Declaration of Helsinki. All patients enrolled provided written informed consent. Every patient received two sessions/week over five weeks (10 sessions).

2.2. Participants

Seventy patients fulfilling the criteria were enrolled. Eligible participants were aged 18–80 years, had diagnosis of PASC-related fatigue, and were followed in an outpatient clinic. Participants were required to be three to 12 months after acute confirmed SARS-CoV-2 infection, according to the CDC criteria [24]. The diagnosis of post-infectious fatigue following COVID-19 was performed according to the Academy of Physical Medicine and Rehabilitation recommendations [25]. Patients were screened for fatigue patterns to help guide activity and monitor the response to initiating and escalating activity as well as monitor the effects on daily functioning. Additionally, we compare their current symptoms with their pre illness functional status and use standardized functional assessment tools to monitor the patient's progress over time. As part of the evaluation, we also determine whether the patient has any conditions that may exacerbate or lead to fatigue, including system dysfunctions, sleep disorders and medication use/polypharmacy [26].

Potential participants were excluded if they had severe depression (a score >30 in the Beck Depression inventory) [27]; history of alcohol abuse or substance harmful use or dependence; severe/life-threatening medical conditions and concomitant neuropsychiatric disorders such traumatic brain injury, stroke, epilepsy; and specific contraindications for brain stimulation (e.g., implanted metallic devices in the brain).

2.3. Randomization, allocation and blinding

Participants are randomized in accordance with a computer generated list at www.random.org (1:1 ratio) to receive active or sham HD-tDCS. After the randomization process, a blind researcher (not involved with the recruitment, data collection, or intervention) conducted the allocation of participants between the groups. Treatment assignments were concealed from patients and the personnel applying the stimulation sessions were blinded to the treatment group. Raters were also blinded to allocation group status.

2.4. Intervention

The experimental procedures and experimental profiles are shown in Fig. 1. We employed a 4 × 1 HD tDCS montage (mini-CT with 4 × 1 adaptor, Soterix Medical, New York, NY, USA). Based on the past neurophysiological studies on disruptive functional changes in fatigue-related to PASC [18,19], we positioned the center electrode over the left motor cortex (M1). Four return electrodes were placed in a ~7.5 cm radius. In the sham condition, the device provided a 30-s ramp-up period to the full 3 mA, followed immediately by a 30-s ramp down. For those in the active group, the electrical current was delivered with a ramp-up time of 30 s, held at 3 mA for 30 min, and then ramped down over 30 s. Each set of five

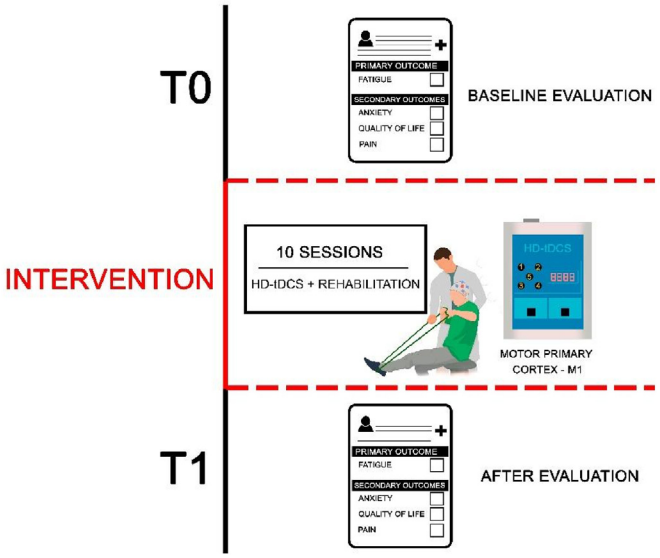

Fig. 1. Experimental design of HD-tDCS plus rehabilitation program for fatigue in Post-Acute Sequelae of SARS-CoV-2 (PASC). The treatment protocol was composed by 10 sessions of HD-tDCS associated to rehabilitation program. The primary and secondary outcomes were measured at the baseline (T0) and at the endpoint (T1). HD-tDCS = High-Definition transcranial Direct Current Stimulation.

electrodes was used for 10 sessions, rotating which electrode was in the center position [28,29] 4 × 1 HD-tDCS allows for both cortically targeted and sub-threshold (DC) modulation (PMID: 23149292) and is well tolerated and blinded under the conditions tested [[28]. 30 min is a typical duration used in neuropsychiatric interventions [28,30] Our overall approach adapts our previously successful intervention in critically-ill COVID-19 patients [9].

During each session, all participants (active or sham) also received an individually tailored rehabilitation program based on the consensus guidance statement for treatment of PASC-related fatigue [25]. The protocol comprised submaximal levels (Rate of Perceived Exertion 9–11 score/Very Light-Light), gradual stretching, breathing exercise and resistance training. The Borg breathlessness scale and rate of perceived exertion were used alongside self-reported symptoms (including fatigue) to determine progression of the exercises [31]. All exercise training and counseling sessions were conducted by a physical therapist at the Department of Rehabilitation at University Medical Center. All patients underwent an educational program focused on treatment options for alleviating symptoms, taking account of the orientations and recommendations promoted by WHO on the education of health care providers and of patients. Therapeutic patient education is designed therefore to train patients in the skills of self-managing or adapting treatment to their particular condition, and in coping processes and skills It is therefore a continuous process, integrated in health care. It is patient-centered; it includes awareness, learning, psychosocial support, prescribed treatment, organizational information, and behavior related to health and illness [32].

2.5. Outcomes

The primary efficacy outcome was fatigue severity as assessed by the Modified Fatigue Impact Scale (MFIS) [33] at the end of the treatment. The MFIS is a self-report inventory of fatigue severity that results in a total score and scores for three subscales: cognitive (9 items), psychosocial (10 items) and physical (2 items) components of fatigue.

Secondary outcomes included the evaluation of anxiety symptoms with the Hamilton Anxiety Rating Scale (HAM-A) [34], quality of life using WHOQOL-bref [35], and pain by the McGill Questionnaire [36]. Clinical response, as defined as 5-point reduction of the baseline MFIS score, according to the reliable change index was also determined. A change in 5–6 points represents statistically meaningful change at the 0.90 and 0.95 confidence interval [37]. To assess tolerability, we used a questionnaire based on previously reported adverse events [38].

2.6. Statistical analysis

The sample size was estimated based on a minimal clinically important difference (5-point reduction on MFIS score from the baseline) in the outcome of fatigue [37] and previous research by Mortezanejad et al. [12] that evaluated the effect of tDCS on fatigue (mean of 31.0 SD of 4.0). Considering an effect size of 0.80 and drop rate of 10%, a total sample size of 44 were required.

All data analyses were performed using the GraphPad Prism software version 8.0 for Mac (GraphPad Software, San Diego, CA, USA). All tests were performed with a two tailed $p < .05$. Descriptive statistics were run as frequencies and percentages for categorical variables; means and standard deviations were calculated for the continuous variables.

Mean differences between groups with 95% confidence intervals (CI) and effect sizes were calculated for the primary and secondary outcomes. Adjustment for multiple comparisons was performed using Bonferroni correction. Chi-square tests were used to compare the number of clinically improved patients between the active and sham group. The effect size was measured in terms of odds ratios, and we estimated the number needed to treat (NNT) based on the odds ratios for clinical response.

In addition, we constructed mixed linear models controlling for age and baseline measures (anxiety, depression, and sleep disorder), since these factors are related to fatigue. We used the Hamilton Anxiety Rating Scale [34] and the Beck Depression Inventory [39] to assess anxiety and depression, respectively. Sleep quality was assessed with the Sleep Quality Scale [40]. Adverse events are expressed as counts and percentages and compared between groups using the $\chi 2$ test.

3. Results

3.1. Participants

Out of 226 patients who were initially assessed for eligibility, 156 were excluded (135 did not meet eligibility criteria and 21 withdrew consent) (Fig. 2). The demographic characteristics and clinical variables were similar between groups at baseline (Table 1).

3.2. Primary outcome

The active HD-tDCS group had significantly greater reduction in fatigue (mean group difference 14.03 points; effect size 1.2; 95% CI 7.78–20.28; $P < .001$) compared to the sham group at the end of the five-week intervention. MFIS subscale analyses found that the reduction in fatigue was found in both the cognitive (mean group difference 8.29 points; effect size 1.1; 95% CI 3.56–13.01; $P < .001$) and psychosocial subscales (mean group difference 2.37 points; effect size 1.2; 95% CI 1.34–3.40; $P < .001$). No difference was observed between groups on physical fatigue (mean group difference 0.71 points; effect size 0.1; 95% CI 4.47–5.90; $P = .09$) (Table 2) (Fig. 3).

3.3. Secondary outcomes

The secondary outcomes were anxiety (HAM-A scores), quality of life (WHOQOL-bref scores) and pain (McGill scores). The mean differences favored the active group for anxiety (mean group difference 4.88; effect size 0.9; 95% CI 1.93–7.84; $P < .001$) and quality life (mean group difference 14.80; effect size 0.7; 95% CI 7.87–21.73; $P < .001$) compared to sham group. For pain, there was no significant difference between groups (mean group difference −0.74; no effect size; 95% CI 3.66–5.14; $P = .09$) (Fig. 4).

Results indicated that the proportion of clinically improved participants in the active group was significantly larger than in the sham group (77.14% vs 45.71%; NNT = 3; odds ratio = 0.24; 95% CI, 0.08–0.70; $P < .001$).

3.4. Exploratory analysis

Our exploratory analysis showed that age, sleep disorder and depression were not predictors of response. Anxiety severity at baseline was associated with lower response ($P = .3$). A significant regression equation was found ($F(7,54) = 17.40$, $P < .001$), with an adjusted R^2 of 0.69 (Table 3).

3.5. Adverse effects

Skin redness was the only adverse event that differed significantly between groups: there were 37 occurrences in the active group compared to 13 in the sham group ($P < .001$). No serious adverse events were reported.

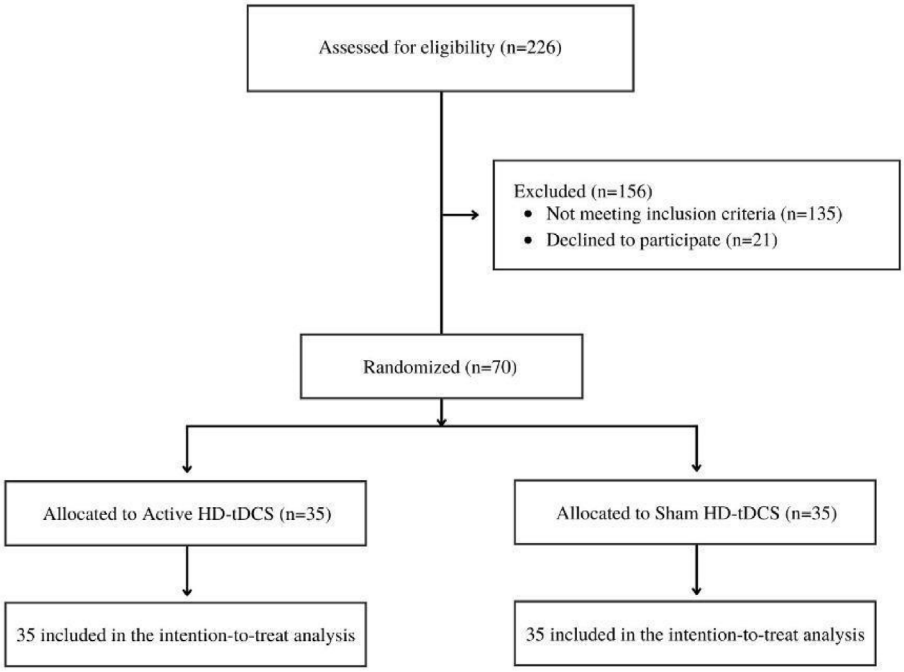

Fig. 2. Screening, Randomization, and Follow-up of Patients in the HD-RECOVERY trial. HD-tDCS = High-Definition transcranial Direct Current Stimulation.

4. Discussion

This is the first randomized, double-blind, sham-controlled clinical trial assessing the efficacy of HD-tDCS for the treatment of PASC-related fatigue. Consistent with the larger HD-tDCS (with rehabilitation) literature, the intervention is well-tolerated [41,42]. We found that active vs. sham HD-tDCS sessions combined with the rehabilitation program resulted in significant fatigue reduction after the five-week intervention. Our results are encouraging because combining rehabilitation with HD-tDCS is feasible, well-tolerated and a potential useful treatment to many patients with fatigue.

There are several candidate mechanisms for tDCS benefit in fatigue. Previous reports documented that tDCS can induce neuroplastic after-effects and may exert a 'top-down' influence including along the ascending midbrain-thalamic-cingulate

Table 1
Demographics and clinical characteristics of participants in baseline.

	Group		P value
	Active (n = 35)	Sham (n = 35)	
Age[a], years	51.63 [15.87]	54.46 [19.01]	0.50
Women, No. [%]	24 [69]	21 [60]	0.45
Comorbidities, No. [%]			
Hypertension	5 [14]	7 [20]	0.45
Chronic heart disease	3 [9]	2 [5]	0.64
Pulmonary disease	4 [11]	0 [0]	0.04
Diabetes	6 [17]	4 [11]	0.49
Rheumatic disease	3 [9]	2 [6]	0.64
Acute Phase Characteristics, No. [%]			
Asymptomatic	3 [9]	3 [9]	1.http://0.0.0.0/00[c]
Home-isolated with symptoms	25 [71]	26 [74]	0.79[c]
Hospitalized needing O2	2 [6]	3 [9]	0.64[c]
Hospitalized needing NIV	4 [11]	2 [6]	0.39[c]
Hospitalized needing respirator	3 [9]	4 [11]	0.69[c]
Length of hospital stay[a]	2.86 [8.14]	3.34 [11.32]	0.84[b]
Long COVID Symptoms, No. [%]			
Headache	12 [34]	9 [26]	0.43[c]
Weakness	19 [54]	16 [46]	0.47[c]
Sleep difficulty	15 [43]	12 [34]	0.46[c]
Cough	22 [63]	15 [43]	0.09[c]
Gastrointestinal symptoms	14 [40]	11 [31]	0.45[c]
Breathlessness	14 [40]	17 [49]	0.47[c]

No. or n = number of participants; NIV: Non-Invasive Ventilation.
[a] Continuous variables are presented as mean (SD) unless otherwise indicated.
[b] Chi-square analysis.
[c] Independent *t*-test analysis.

Table 2
Clinical outcomes.

Variables	Group		ANOVA [F(1,68)/P value]		
			Acute treatment period		
	Active (n = 35)	Sham (n = 35)	Active vs Sham	Time effects	Time × group interaction
Primary Outcome[a]					
MFIS-Cognitive					
Baseline	31.60 [9.10]	33.66 [8.27]			
Week 5	17.14 [8.7]	26.46 [7.56]	7,82/0.0067[b]	115,8/0.0001	10,56/0.0018
MFIS-Psychosocial					
Baseline	6.54 [2.05]	5.91 [1.67]			
Week 5	2.66 [2.14]	5.03 [1.67]	26,58/0.0237[b]	199,2/0.001	78,75/0.001
MFIS-Physical					
Baseline	19.03 [10.97]	18.23 [9.66]			
Week 5	15.26 [8.70]	15.97 [8.61]	0.000/0.985	28.93/0.001	1.82/0.181
MFIS total					
Baseline	57.17 [14.95]	57.8 [7.91			
Week 5	35.06 [12.22]	47.46 [8.48]	9.69/0.0027[b]	140.8/0.001	21.76/0.001
Secondary Outcomes[a]					
McGill Questionnaire					
Baseline	11.8 [11.39]	10.94 [9.03]			
Week 5	7.46 [6.04]	8.49 [5.95]	0.06/0.801	6.46/0.013	0.11/0.740
HAM-A					
Baseline	25.93 [5.98]	25.95 [4.75]			
Week 5	18.66 [5.84]	23.57 [5.19]	4.55/0.036[b]	60.74/0.0001	15.37/0.0002
WHOQoL-bref					
Baseline	57.51 [12.60]	59.71[13.32]			
Week 5	80.89 [12.10]	66.09 [13.24]	5.49/0.022[b]	101.9/0.0001	33.28/0.0001

[a] Continuous variables are presented as mean (SD).
[b] Statistically significantn = number of participants; MFIS = Modified Fatigue Impact Scale; HAM-A = Hamilton anxiety rating scale; WHOQol-brief = World Health Organization quality of life questionnaire (brief version).

pathway through descending fibers from the motor cortex [43–45]. The therapeutic efficacy of tDCS is, at least partly, due to its capacity to induce neural plasticity in different clinical conditions [45–47]. Additionally, M1 stimulation has been used for treating fatigue [22,48], decreasing the threshold for perceived effort [23] and performance fatigability [15]. The suggested modulation of inflammatory processes by tDCS, either by direct brain stimulation [49,50] or top-down (vagal) processes, may be a parallel therapeutic mechanism [17,22]. As a further explanation of our study outcomes, rehabilitation programs are known to decrease

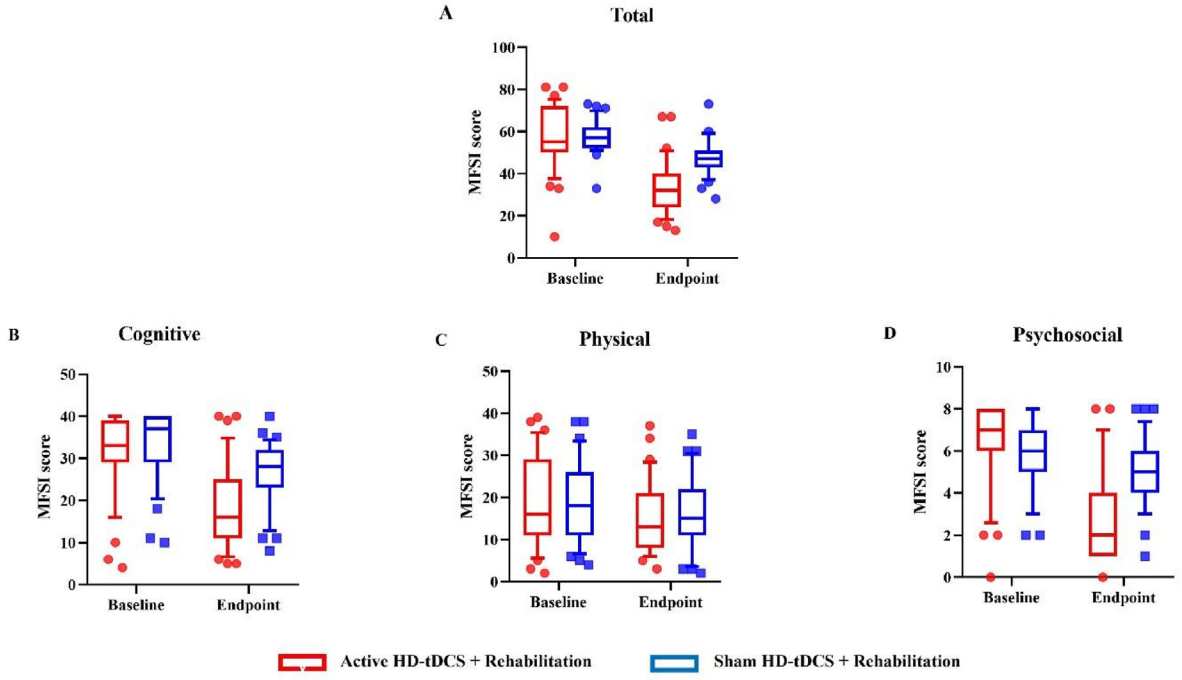

Fig. 3. Primary fatigue Outcomes of HD-tDCS plus rehabilitation program in Post-Acute Sequelae of SARS-CoV-2 (PASC). Boxplots presenting changes in fatigue severity, (A) and regarding to cognitive, (B) psychosocial, (C) and physical fatigue domains, (D) from baseline to endpoint (week 5). A MFIS score reduction represents decrease fatigue severity after treatment. The HD-tDCS plus rehabilitation program on fatigue ratings were greater for the active group than for the sham group (fatigue total, cognitive and psychosocial domains). No significant effect was observed for physical fatigue between the two groups. MFIS = Modified Fatigue Impact Scale; HD-tDCS = High-Definition transcranial Direct Current Stimulation.

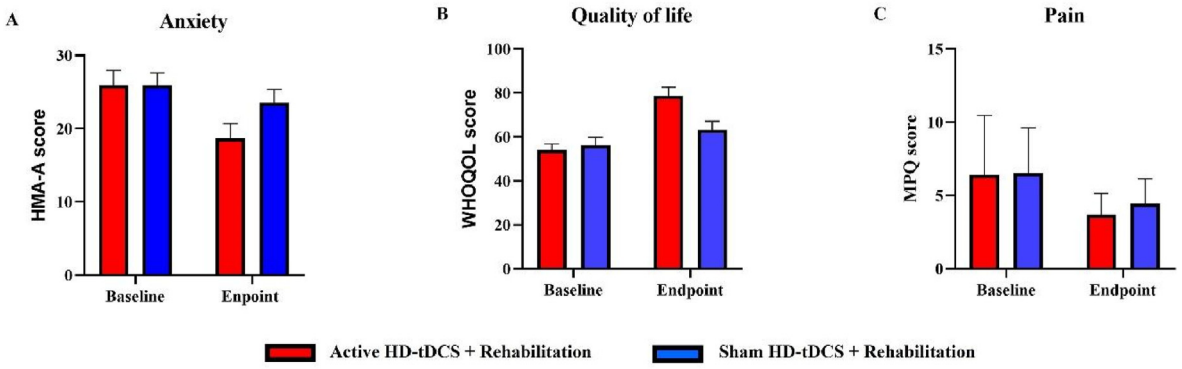

Fig. 4. Secondary Outcomes. Panels showing changes in anxiety severity, A, quality of life, B and pain level, C from baseline to endpoint (week 5). Compared with sham group, the effect of attenuating anxiety symptoms and improve quality of life ratings were marginally greater for the active group. There was no statistically significant difference between the treatment groups in pain change. HAM-A = Hamilton anxiety rating scale; WHOQol-brief = World Health Organization quality of life questionnaire (brief version); MPQ = McGill Pain Questionnaire HD-tDCS = High-definition transcranial direct current stimulation.

sensation of fatigue accompanied by brain functional reorganization in the sensory-motor network [49–51] and tDCS enhances sensoriomotor activities and plasticity [52,53].

Our effort build on decades of work indicating the potential for tDCS for range of neurological and psychiatric conditions [28,54–58] with symptoms relevant to PASC. Trials of 4 × 1 HD-tDCS has spanned cognitive dysfunction [59] and neuropsychiatric disorders [60,61], pain [62,63], motor learning [64], and exercise performance [65].

Adjuvant treatments to improve the effects of rehabilitation are challenging, mainly due to the heterogeneity and complexity of fatigue-related to PASC conditions. Therefore, the results of this trial may result in an important advance in the healthcare setting. HD-tDCS associated with the rehabilitation protocol is feasible to a real clinical scenario, since the protocol allows brain stimulation during rehabilitation procedures, without increasing the human resource costs (physiotherapy time). Taken together, HD-tDCS and rehabilitation improves the chances of recovery, offer incentives to treatment compliance and may have an impact on public health costs.

Improvements of anxiety and quality of life, but not pain, were also observed with active HD-tDCS. Anxiety is reported to be associated with fatigue on a broad range of clinical conditions [66,67]. Since frontal and central areas are dysfunctional after COVID-19 infection [68,69], modulation of motor targets could lead not only to changes in fatigue but also in anxiety. The effects of HD-tDCS indeed affect distinct cortical and subcortical circuits, which could influence both motor and cognitive areas [43,46]. Further studies are necessary to investigate whether changes in anxiety occur simultaneously to fatigue or if improvements in cognitive symptoms mediates PASC outcomes. There is evidence showing the relationship between PASC-related fatigue and quality of life [70,71]. In other clinical conditions, such as multiple sclerosis, for instance, the increase in neuronal activity following demyelination of some neurons, leads to deterioration of physical abilities, inducing fatigue and subsequently decreasing quality of life [12,71]. Therefore, the improvement of quality of life effect may be secondary to the effect of HD-tDCS on fatigue. Because patients had lower pain scores at baseline their scores might have not improved after treatment (despite a sustained response) owing to a "ceiling effect". Finally, given that both groups improved their fatigue, the rehabilitation program might have an effect that was augmented by the HD-tDCS, as suggested by previous studies [47,72,73].

Study limitations and opportunities should be underscored. First, acute phase parameters of COVID-19 and premorbid conditions are factors non controlled during the current study. Second, absence of MRI precludes computational models of the role of individual anatomy in brain electric field intensity, however use of 4 × 1 HD-tDCS ensures consistent spatial targeting across subjects [74,75]. Third, PASC is a multifactorial condition suggesting customized treatment strategies - to this end our inclusion of subjects with specific symptom profiles and application of indication-targeted HD-tDCS and rehabilitation is consistent with developing socialized interventions. Finally, notwithstanding high compliance in our ten protocol sessions, due the barriers associated with consecutive visits to clinic/hospital and considering the large number of people affected by PASC remotely supervised home-based tDCS can be considered (and is feasible) to investigate extended treatment protocols [17,76–78].

Table 3
Multiple linear regression results with the change in MFIS as the outcome variable.

	Beta coefficient	95% CI	P value
Intercept	58.84	45.32 to 72.37	<0.0001[a]
Group	−14.22	−17.96 to −10.49	<0.0001[a]
Age	−0.08	−0.23 to 0.07	0.29
Sleep difficulty	−0.01	−0.54 to 0.51	0.96
Depression	−0.26	−0.62 to 0.10	0.15
Anxiety	−0.46	−0.89 to −0.03	0.04[a]

Table includes beta coefficients. 95% confidence intervals and the associated p values for each predictor.
CI confidence interval.
MFIS = Modified Fatigue Impact Scale.
[a] Statistically significant.

5. Conclusion

In this sham-controlled randomized trial, we found that 10 sessions of M1 HD-tDCS paired with a rehabilitation program led to significant reduction of PASC-related fatigue. Although strengths of our study are the relatively large sample size and also its pragmatic aspect, enrolling fatigued patients that present mixed symptoms, further studies should acknowledge the specifically effects of treatment on patients with higher pain level and physical impairment related to fatigue to consolidate these exploratory findings. These findings along with the low cost of the therapy and its tolerability suggests its potential application in the clinical practice for the treatment of PASC.

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CRediT authorship contribution statement

Kelly Santana: Conceptualization, Methodology, Validation, Formal analysis, Data curation, Writing – original draft. **Eduardo França:** Conceptualization, Methodology, Supervision, Writing – review & editing. **João Sato:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Ana Silva:** Investigation, Writing – review & editing. **Maria Queiroz:** Investigation, Writing – review & editing. **Julia de Farias:** Investigation, Writing – review & editing. **Danniely Rodrigues:** Investigation, Writing – review & editing. **Iara Souza:** Investigation, Writing – review & editing. **Vanessa Ribeiro:** Conceptualization, Methodology, Resources, Writing – review & editing. **Egas Caparelli-Dáquer:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Antonio L. Teixeira:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Leigh Charvet:** Conceptualization, Methodology, Supervision, Writing – review & editing. **Abhishek Datta:** Designed the experiment. **Marom Bikson:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Supervision, Project administration, Writing – original draft. **Suellen Andrade:** Conceptualization, Methodology, Validation, Formal analysis, Data curation, Supervision, Project administration, Writing – original draft.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: The City University of New York holds patents on brain stimulation with MB as inventor.MB has equity in Soterix Medical Inc. MB consults, received grants, assigned inventions, and/or serves on the SAB of SafeToddles, Boston Scientific, GlaxoSmithKline, Biophysics, Mecta, Lumenis, Halo Neuroscience, Google-X, i-Lumen, Humm, Allergan (Abbvie), Apple. AD is an employee and has equity in Soterix Medical Inc.

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