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Effect of high-definition transcranial direct current stimulation among late-subacute and chronic stroke survivors with fatigue: A randomized-controlled crossover trial protocol

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ABSTRACT

Post-stroke fatigue (PSF) is a commonly overlooked symptom that impacts daily functioning and quality of life. It is caused by altered functional connectivity within the brain networks, which can potentially be influenced by neuromodulation. Multiple cortical regions have been targeted to reduce PSF, but the most efficient ones remain uncertain. Therefore, we aim to identify the most appropriate cortical stimulation site to reduce PSF. Twenty participants with PSF will be included in this cross-over trial. Each participant will receive one session of active anodal high definition- transcranial direct current stimulation (HD-tDCS) over three different cortical areas and one session of sham tDCS in a cross-over manner, with a two-week of washout period in between. Pre- and post- fatigue will be assessed using Fatigue Severity Scale and fatigability using electromyography by determining the time to task failure. Resting-state electroencephalography will be performed before and after each stimulation session to determine the functional connectivity of the cortical areas stimulated.

Specifications Table

Subject area:	Neuroscience
More specific subject area:	Stroke
Name of your method:	Randomized-controlled crossover trial protocol
Name of your protocol:	Effect of high-definition transcranial direct current stimulation among late-subacute and chronic stroke survivors with fatigue: A randomized-controlled crossover trial protocol.
Reagents/tools:	• Fatigue Severity Scale • Electromyography (Delsys, Trigno wireless EMG 8 channel AD instrument, USA) • Hand-held dynamometer (Chatillon®, a registered trademark of AMETEK, Inc., USA) • Electroencephalography (Starstim 32, Neuroelectrics, Spain)

(*continued on next page*)

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Experimental design:	This randomized controlled cross-over trial will include 20 participants with poststroke fatigue (Fatigue Severity Scale-7 ≥ 4). All the participants will receive one session of three blocks of active anodal high-definition tDCS (1.5 mA for 20 min) over three cortical areas (dorsolateral prefrontal, motor, and parietal) and one block of sham tDCS in a cross-over manner with a washout period of two weeks. Pre- and post-fatigue will be assessed using Fatigue Severity Scale and fatigability will be assessed using electromyography. Resting-state electroencephalography will be performed before and after each stimulation session to determine the functional connectivity of the cortical areas stimulated.
Trial registration:	This trial is registered in Clinical Trial Registration- India (CTRI/2022/02/040657).
Ethics:	Written informed consent will be obtained from all subjects before the commencement of the study.
Value of the Protocol:	• This study will be able to determine the optimal cortical stimulation site to effectively reduce fatigue among late subacute and chronic stroke survivors living in the community. • The cross-over method implemented in this study will eliminate the potential subjective differences from the overall treatment effect enhancing the statistical power and determining the most suitable cortical area to target fatigue. • The findings will contribute to advancing the development of improved treatment protocols for mitigating fatigue among stroke survivors.

Introduction

Stroke has globally emerged as the primary cause of adult disability and mortality, experiencing a 12% rise in low- and middle-income countries over the past two decades [1]. Motor disabilities are evident and apparent among stroke survivors, but non-motor symptoms such as fatigue interfere maximally with daily activities even though the patient does not have any noticeable physical disability [2]. Post-stroke fatigue (PSF) is an exceedingly common but neglected symptom that is also a significant predictor of functional disability among stroke survivors [3]. The prevalence of PSF is observed to be 46.79% globally [4]. Even if we consider the lowest prevalence rates, a large population of stroke survivors suffers from PSF.

PSF is considered a consequence of brain injury rather than a secondary symptom following a stroke. The precise mechanism underlying the development of this symptom is still being investigated. Fatigue is believed to arise from a complex and multifaceted process that intersects with other stroke symptoms. Existing literature suggests that PSF predominantly originates from issues within the central brain regions, including altered functional activity in frontal, prefrontal, and fronto-striato-thalamic networks [5–7], altered processing of sensory input [8,9], reduced excitability in the primary motor regions [10], and inflammation [8,11]. However, the neurophysiological mechanism that leads to the persistence of PSF is not yet fully comprehended [10].

Given the multidimensional nature of fatigue, several pharmacological, physical, and psychological interventional approaches have been implemented to manage PSF, but none have demonstrated substantial effectiveness [12–14]. This is because most of the therapies did not directly target the compromised cortical connectivity identified as a contributing factor. Moreover, the lack of consensus and limited evidence in this area have left the optimal management approach for PSF largely unexplored [15].

Transcranial direct current stimulation (tDCS) is a non-invasive type of brain stimulation that uses low-intensity direct current to modulate the activity of key neuronal networks. It has been shown to impact various cell and molecular pathways involved with inflammation, neuroplasticity, neurogenesis, and angiogenesis [16]. In multiple sclerosis, tDCS has been recognized as an effective strategy for managing fatigue. In stroke, tDCS has been explored for the recovery of motor [17] and language functions [18] but there are only limited studies focusing on reducing PSF [19–21]. Furthermore, the distinct cortical regions targeted in these studies exhibit considerable diversity [22]. The outcomes of these studies have demonstrated varying results, underscoring the need for additional exploration. Taking these considerations into account, our study aims to investigate the impact of tDCS on PSF through the sequential stimulation of multiple cortical areas in a cross-over manner. Concurrently, we aim to gain insights into the performance of the brain network across the diverse stimulated regions, utilizing electroencephalography for analysis.

Study design

This randomized controlled crossover trial will be conducted at the Neuromotor control training unit within the physiotherapy department of a tertiary care hospital in South Karnataka. Study participants involve late subacute and chronic community-living stroke survivors who report fatigue as one of their symptoms. This protocol adheres to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [23] and CONSORT 2010 statement [24]. Institutional Ethical Committee clearance (IEC:627/2021) is obtained and the trial is registered in Clinical Trial Registration- India (CTRI/2022/02/040657).

Patient population

A total sample of 20 late subacute and chronic stroke survivors aged between 18- and 65- years reporting fatigue (FSS7 ≥4), capable of understanding and signing the informed consent, able to read Kannada or English, and can voluntarily move the affected upper and lower limb (VCG≥3) will be included in the study.

The criteria for exclusion will be individuals with coexisting disorders of other systems influencing fatigue, such as chronic fatigue syndrome, neoplasms, and asthma; coexisting other neurological conditions; undergoing treatment with centrally acting medications or immune modulatory drugs affecting the level of fatigue; epilepsy; cognitive disorders (MoCA<24); depression (PHQ≥10) and reduced sleep quality (ESS≥10); skin problems, such as dermatitis, psoriasis, eczema; recurrent/bilateral/operated/infratentorial stroke; presence of metal implants (around head and neck region)/cardiac pacemakers/defibrillators; and recurrent or current pregnancy.

Table 1
Randomization sequence of cortical areas.

RANDOMIZATION SEQUENCE OF CORTICAL AREAS							
BASELINE	→	**POST TWO WEEKS**	→	**POST FOUR WEEKS**	→	**POST-SIX WEEKS**
Primary motor cortex	2 WEEKS WASHOUT	Dorsolateral prefrontal cortex	2 WEEKS WASHOUT	Parietal cortex	2 WEEKS WASHOUT	Sham
Dorsolateral prefrontal cortex		Parietal cortex		Sham		Primary motor cortex
Parietal cortex		Sham		Primary motor cortex		Dorsolateral prefrontal cortex
Sham		Primary motor cortex		Dorsolateral prefrontal cortex		Parietal cortex

Recruitment and study enrolment

The recruitment of participants will predominantly target individuals from the community or those visiting the physiotherapy department of a tertiary care hospital. The primary investigator (PI) will screen the participants for the selection criteria before enrolment. Volunteering participants who fit the criteria will be given detailed information regarding the study both verbally and through the participant information sheet for a better understanding of the intervention. Written informed consent will be obtained before baseline testing. The basic demographic details of the participants will be recorded, following which they will be randomly assigned to any of the four treatment sequences that were predetermined (Table 1).

Randomization, allocation concealment, and blinding

A simple randomization method will be used for the process of allocating the participants to each sequence. Sequentially numbered opaque sealed envelopes (SNOSE) will be prepared by an independent party who is not involved in subject recruitment, treatment procedures, or outcome assessment. Randomization code will be written on paper and placed inside an opaque envelope. During the recruitment process, the envelopes will be opened to allocate the participants to a particular sequence. The participants and outcome assessors will be blinded to the allocated sequence.

Outcomes

Fatigue Severity Scale: The FSS evaluates how fatigue impacts an individual's daily activities and overall quality of life. This 7-point Likert scale rates the severity of fatigue, where 1 indicates strongly disagree and 7 indicates strongly agree. A total score of ≥4 indicates fatigue. The Kannada version of FSS has proven to be valid ($r = 0.71$) and reliable (ICC= 0.91) among the Kannada-speaking neurological population [25].

Electromyography (EMG): Delsys, Trigno wireless EMG system 8 channel AD instruments, USA will be used to obtain the activities of Biceps Brachii (BB) and Rectus Femoris (RF) muscles of the affected side. Trigno wireless EMG sensors of size 27 × 37 × 13 mm will be selected. The stimulation area will be made visible with the participant's consent, and the skin will be cleansed using an alcohol-based rub to prevent electrode and skin impedance and ensure proper fixation. The participants will be positioned in sitting with their upper limbs resting over the arm of the chair. The recording sensors will be sited over the motor points of BB and RF with proper fixing ensured using Trigno sensor adhesive. The positioning of the sensors will be parallel to the direction of the muscle fibre arrangement in reference to SENIAM guidelines [26].

The participants will be asked to perform the maximum amount of elbow flexion and knee extension against resistance using an isometric hand-held dynamometer (Chatillon®, a registered trademark of AMETEK, Inc., USA) to objectively measure the peak amplitude (Maximum Voluntary Contraction- MVC). Following the identification of peak amplitude, participants will be asked to contract these muscles against resistance at 20%, 40%, and 60% of the baseline MVC. Participants will be instructed to maintain the contraction for 30 s or until voluntary task termination to record the% increase in the duration of the MVC.

Electroencephalography (EEG): During this procedure, participants will be seated comfortably in a quiet room with back and arm support. Resting-state EEG recordings will be taken for 10 min using a 32-channel electrode system (Starstim 32, Neuroelectrics, Spain) following the standard International 10–20 EEG electrode placement. To ensure accuracy, participants will be instructed to avoid consuming any caffeinated beverages 12 h before the EEG recording. Raw EEG data will be analysed using whole brain analysis,

region of interest analysis, and lagged-phased connectivity with a detailed description outlined in the study protocol by Adhia DB et al., 2022 [27].

Intervention

A battery-driven portable 32-channel transcranial electrical stimulation (Starstim 32, Neuroelectrics, Spain) device will be used to deliver high-definition tDCS (HD-tDCS) and measure resting-state EEG. The participants will be seated comfortably on a chair with a back and armrest and eyes closed in a quiet room. Alcohol wipes will be used to clean the participant's scalp. A neoprene head cap will be fitted with 32 electrodes to record the resting state EEG and deliver the stimulation. Resting-state EEG recording will be performed for 10 min before the stimulation to determine the connectivity of the targeted cortical area. The HD system focally targets the specified brain regions using arrays of several small NG Pitstim electrodes (~4 cm2). The brain regions that will be targeted in this study will include the dorsolateral prefrontal cortex, primary motor cortex, and parietal cortex of the affected side. The placement of tDCS electrodes to target selected brain regions is shown in Fig. 1.

The reference electrode will be secured to the right ear lobe using an ear clip. Electrode gel will be applied at the electrode locations to minimize impedance. The NIC2 software will evaluate impedance levels using a traffic light signal system (red, yellow, green) to achieve optimal impedance (green) for all electrodes. Following this, appropriate cables will be connected to their respective

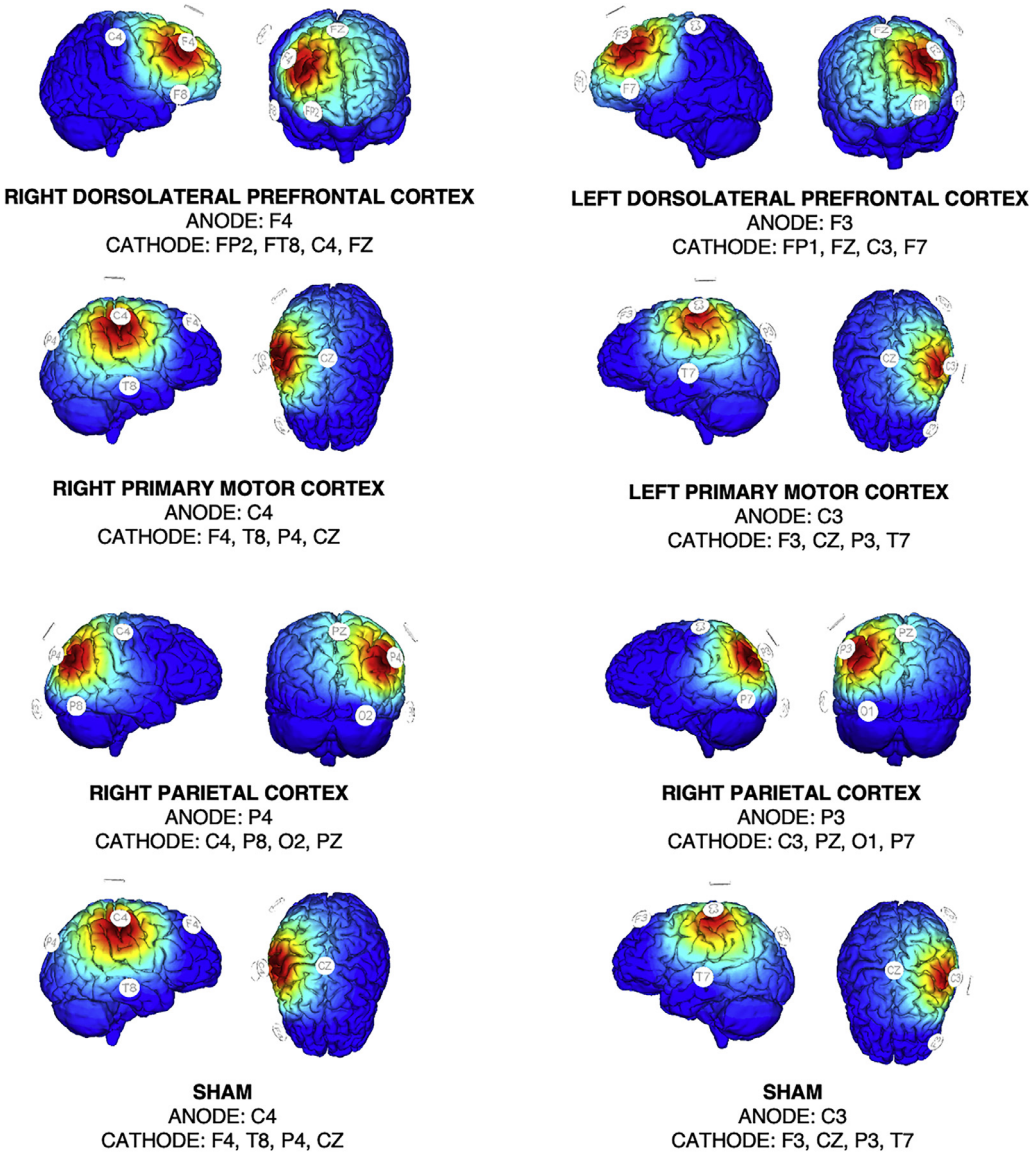

Fig. 1. Cortical areas and their electrode placements according to the 10-20 International EEG system.

Table 2
Study timeline for each participant.

DAY	1	2 WEEKS WASHOUT	14-16	2 WEEKS WASHOUT	28-30	2 WEEKS WASHOUT	42-45	2 WEEKS WASHOUT	56-60
BASELINE	• FSS • %MVC+ TTF • RS-EEG (10 min)		• FSS • %MVC+ TTF • RS-EEG (10 min)		• FSS • %MVC+ TTF • RS-EEG (10 min)		• FSS • %MVC+ TTF • RS-EEG (10 min)		FSS
INTERVENTION	HD-tDCS PMC (1.5mA for 20 min)		HD-tDCS DLPFC (1.5mA for 20 min)		HD-tDCS PC (1.5mA for 20 min)		Sham-tDCS PMC (1.5mA for 20 min)		
IMMEDIATE POST	• RS-EEG (10 min) • %MVC+ TTF		• RS-EEG (10 min) • %MVC+ TTF		• RS-EEG (10 min) • %MVC+ TTF		• RS-EEG (10 min) • %MVC+ TTF		

FSS- Fatigue Severity Scale; MVC- Maximum Voluntary Contraction; TTF- Time to task failure; RS-EEG- Resting State Electroencephalography; HD-tDCS- High-definition Transcranial direct current stimulation; PMC- Primary Motor Cortex; mA- milli ampere; DLPFC- Dorsolateral prefrontal cortex; PC- Parietal Cortex.

electrodes and the neuroelectric control box (Necbox). To ensure smooth connectivity, the stimulator will be connected to the NIC2 software via Wi-Fi.

Participants will randomly receive one session of three blocks of active anodal HD-tDCS + 1 block of sham stimulation over four areas at an intensity of 1.5 mA for 20 min in a crossover manner. For active HD-tDCS, the current will be ramped up and down for 60 s at the start and end of each session, while maintaining continuous stimulation in between. This intervention dosage was selected based on previous transcranial electrical stimulation (tES) studies, following safety guidelines [20]. For the sham stimulation group, the current will be applied for 30 s ramping up and 30 s ramping down at the beginning of each stimulation session, followed by no stimulation for the remaining time to produce a comparable skin sensation as the active group. The duration of the sham session will align with that of the active HD-tDCS to ensure effective blinding. The PI will ensure that the treatment is administered consistently and according to the schedule at each session. The treatment delivered at each session for all the participants will be saved in the NIC2 computer software.

The EEG recordings and fatigability (using EMG) will be reassessed after each session of the intervention. Fatigability will be assessed by an outcome assessor blinded to the allocation of the participants. Participants will be asked to fill out a tDCS adverse event questionnaire one hour after the intervention to assess and monitor for any adverse events [28]. FSS will be recorded after a week of intervention and after the washout period of two weeks. All the participants will be assessed at the same time of the day to avoid diurnal variations. The data obtained will be stored and analysed to identify the stimulation area with the most reduction of fatigue. The study timeline for each participant is outlined in Table 2.

Participants will continue to receive standard stroke care throughout the study duration, and comprehensive documentation of their care will be maintained. In case of any adverse event or if the patient wishes to discontinue/withdraw from the trial, they will be allowed to do so. The reasons if provided will be documented appropriately.

Data collection and management

The principal investigator (PI) will have full access to the data, and confidentiality will be ensured by assigning a unique identification code to each participant. This code will be used to identify and link the participants' data. All data will be stored in a secured cabinet within a protected environment at the study centre. Only authorized personnel, including the research team, ethics committee, and regulatory bodies, will have access to the information. Raw data generated by EMG and EEG devices will be handled exclusively by the PI or their authorized representatives and will not be shared with any third party. Any personal information collected, such as telephone numbers or addresses, will be destroyed at the end of the study. In compliance with the ethical policy of the university, study-related documents will be securely maintained and stored at the Institutional Ethical Committee office and archival

sites for five years. These storage systems will ensure confidentiality and enable retrieval at any time. After the retention period, the documents will be appropriately destroyed.

Data monitoring body

The institutional ethical committee will oversee data safety throughout the study period. A formal data monitoring committee will not be appointed for this study since the intervention provided is of low intensity and administered for a single session of a short duration.

Sample size estimates

By controlling for multiple comparisons, the sample size was determined using Cohen's d effect size with reported minimal clinically important difference (MCID) and standard deviation (SD) of Fatigue Severity Scale (FSS) scores for persons with stroke. With the level of significance (Z1-$\alpha/2$) set at 1.96, power (Z1-β) at 80%, SD of 0.63, and MCID value of 0.85, the sample size required was five for each of the four sequences and thus the total sample size estimated was 20. The PI will oversee screening, providing intervention, maintaining the intervention adherence of all the participants, and reminding them to visit the investigation site for timely follow-up through telephone calls.

Statistical analyses

SPSS version 24 will be used for data analysis. Descriptive statistics will be used to describe all the demographic characteristics. The continuous variables (e.g., age, sleep duration, poststroke duration, FSS scores. MVC duration, etc.) will be summarized using the mean and standard deviation or median and interquartile range. The categorical variables (e.g., gender, marital status, level of education, occupational status, comorbidities, stroke type, side of the lesion, pre-stroke fatigue, etc.) will be summarized using frequency and percentage. A linear mixed-method model or a relevant nonparametric test will be used with Post FSS and EMG as the dependent variable and Pre FSS, EMG, stimulus & area effect, area × treatment as a covariate. The interaction term area × treatment will be analysed for which area has more reduction in fatigue and fatigability scores for each of the stimuli. The missing data will be addressed using multiple imputations. The level of significance will be set at $p < 0.05$. The EEGLAB function in MATLAB and sLORETA will be used to explore the effects of HD-tDCS on cortical activity and connectivity using three analyses: whole-brain analysis, region of interest analysis, and lagged-phase connectivity.

Ethics and dissemination

The research study obtained ethical approval from the Kasturba Medical College and Kasturba Hospital Institutional Ethics Committee and was registered in the Clinical Trials Registry-India. If any modifications to the study protocol are required based on emerging evidence or expert opinions, the relevant parties, including the institutional research committee, ethical committee, clinical trial registry, trial participants, and journals, will be duly informed. The progress and findings of the study will be updated in the Clinical Trial Registry India. The results of the study will be shared through publications in reputable peer-reviewed journals and presentations at national and international conferences, ensuring widespread dissemination.

Discussion

Poststroke fatigue (PSF) has negative effects on patient's mobility, quality of life, and survival, making it crucial to find effective treatment approaches [29]. Unlike current treatment methods, tDCS focuses on targeting the impaired neuronal networks in the brain, showing promise as a management technique for PSF. To effectively target PSF, it is essential to stimulate the specific cortical networks associated with this symptom. Previous evidence points to various cortical regions, including the left DLPFC, bilateral primary motor cortex, bilateral somatosensory cortex, and parietal cortex, being involved in fatigue across different neurological conditions, including stroke [19–21]. However, there is still uncertainty about which cortical region to stimulate for the most effective reduction of PSF. This study will enable us to pinpoint the cortical networks involved in the development of fatigue in stroke survivors.

The perception of fatigue varies from person to person [30]. To address this, our study will employ a crossover trial to determine the most suitable cortical area to target fatigue. By using the crossover method, we aim to eliminate potential subjective differences in treatment effects, thereby enhancing statistical power in our analysis. Additionally, we will use resting-state EEG to assess the accuracy of the stimulated cortical area. Electroencephalography is an excellent tool for evaluating brain network performance and identifying cortical regions. By implementing EEG to study functional connectivity before and after tDCS stimulation, we can better understand the brain mechanism of this treatment on fatigue.

Fatigue in the diseased population can manifest as either perceptual or physical [31]. Most previous studies assessing PSF have relied on subjective patient-reported outcome measures, which offer insights into the perception of fatigue. However, objective assessment of fatigue has been mostly limited to evaluating physical fatigue in conditions such as multiple sclerosis, with a gap in research for stroke. Our study will address this by utilizing EMG measures of affected side elbow flexors and knee extensors to objectively quantify fatigue. This objective approach will provide us with a more comprehensive understanding of the symptoms. A potential constraint within this study is the likelihood of observing diminished fatigue in more than one area over time. Nevertheless, the cortical region manifesting a more notable reduction in fatigue would be identified as the primary contributor to fatigue alleviation.

Summary and conclusion

This randomized, controlled crossover trial aims to elucidate the influence of tDCS on PSF, offering valuable insights into the functional connectivity of the stimulated cortical networks. This study will also contribute essential knowledge regarding the cortical region most implicated in the reduction of PSF.

Supplementary material and/or additional information [OPTIONAL]

SPIRIT Checklist

Declaration of competing interest

Please tick the appropriate statement below (please do not delete either statement) and declare any financial interests/personal relationships which may affect your work in the box below.

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

CRediT authorship contribution statement

Akhila Jagadish: Methodology, Investigation, Writing – original draft, Visualization, Project administration. **Manikandan Natarajan:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision. **Divya Bharatkumar Adhia:** Methodology, Validation, Resources, Writing – review & editing, Supervision. **Annapoorna Kuppuswamy:** Methodology, Validation, Writing – review & editing, Supervision. **Vasudeva Guddattu:** Formal analysis, Supervision. **John M. Solomon:** Conceptualization, Methodology, Validation, Resources, Writing – review & editing, Supervision.

Data availability

No data was used for the research described in the article.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.mex.2024.102629.

References

[1] V.L. Feigin, B.A. Stark, Johnson CO, G.A. Roth, C. Bisignano, G.G. Abady, et al., Global, regional, and national burden of stroke and its risk factors, 1990–2019: a systematic analysis for the Global Burden of Disease Study 2019, Lancet Neurol. 20 (2021) 795–820, doi:10.1016/S1474-4422(21)00252-0.

[2] K.J. Becker, Inflammation and the silent sequelae of stroke, Neurotherapeutics 13 (2016) 801–810, doi:10.1007/s13311-016-0451-5.

[3] E.L. Glader, B. Stegmayr, K. Asplund, Poststroke fatigue: a 2-year follow-up study of stroke patients in Sweden, Stroke 33 (2002) 1327–1333, doi:10.1161/01.str.0000014248.28711.d6.

[4] J. Zhan, P. Zhang, H. Wen, Y. Wang, X. Yan, L. Zhan, et al., Global prevalence estimates of poststroke fatigue: a systematic review and meta-analysis, Int. J. Stroke (2022) 17474930221138701, doi:10.1177/17474930221138701.

[5] A.A. Jolly, A. Zainurin, G. Mead, H.S. Markus, Neuroimaging correlates of post-stroke fatigue: a systematic review and meta-analysis, Int. J. Stroke (2023) 17474930231192214, doi:10.1177/17474930231192214.

[6] G. Cotter, M. Salah Khlif, L. Bird, M. E Howard, A. Brodtmann, N Egorova-Brumley, Post-stroke fatigue is associated with resting state posterior hypoactivity and prefrontal hyperactivity, Int. J. Stroke 17 (2022) 906–913, doi:10.1177/17474930211048323.

[7] X. Zhang, H. Fang, D. Ma, Y. Duan, Z. Wang, N. Zhang, et al., Risk factors and imaging mechanisms of fatigue after mild ischemic stroke: an exploratory study from a single Chinese center, Front. Neurol. 12 (2021) 649021, doi:10.3389/fneur.2021.649021.

[8] W. De Doncker, R. Dantzer, H. Ormstad, A. Kuppuswamy, Mechanisms of poststroke fatigue, J. Neurol. Neurosurg. Psychiatry 89 (2018) 287–293, doi:10.1136/jnnp-2017-316007.

[9] C.H. Wu, W. De Doncker, A. Kuppuswamy, Electroencephalography-Derived functional connectivity in sensorimotor networks in post stroke fatigue, Brain Topogr. 36 (2023) 727–735, doi:10.1007/s10548-023-00975-8.

[10] S. Ondobaka, W. De Doncker, N. Ward, A. Kuppuswamy, Neural effective connectivity explains subjective fatigue in stroke, Brain 145 (2022) 285–294, doi:10.1093/brain/awab287.

[11] J. Wan, Z. Qin, P. Wang, Y. Sun, X. Liu, Muscle fatigue: general understanding and treatment, Exp. Mol. Med. 49 (2017) e384 e384, doi:10.1038/emm.2017.194.

[12] G. Andersen, D. Christensen, M. Kirkevold, S.P. Johnsen, Post-stroke fatigue and return to work: a 2-year follow-up, Acta Neurol. Scand. 125 (2012) 248–253, doi:10.1111/j.1600-0404.2011.01557.x.

[13] F. Khan, B. Amatya, Management of fatigue in neurological disorders: implications for rehabilitation, J. Int. Soc. Phys. Rehab. Med. 1 (2018) 9, doi:10.4103/ijprm.ijprm_5_18.

[14] G. Aali, A. Drummond, R. das Nair, F. Shokraneh, Post-stroke fatigue: a scoping review, F1000Res 9 (2020) 242, doi:10.12688/f1000research.22880.2.

[15] C. English, D.B. Simpson, S.A. Billinger, L. Churilov, K.G. Coupland, A. Drummond, et al., A roadmap for research in post-stroke fatigue: consensus-based core recommendations from the third stroke recovery and rehabilitation roundtable, Neurorehabil. Neural Repair (2023) 15459683231209170, doi:10.1177/15459683231209170.

[16] S.J. Pelletier, F. Cicchetti, Cellular and molecular mechanisms of action of transcranial direct current stimulation: evidence from in vitro and in vivo models, Int. J. Neuropsychopharmacol. 18 (2014) pyu047, doi:10.1093/ijnp/pyu047.
[17] G. Orrù, C. Conversano, P.K. Hitchcott, A. Gemignani, Motor stroke recovery after tDCS: a systematic review, Rev. Neurosci. 31 (2020) 201–218, doi:10.1515/revneuro-2019-0047.
[18] E. Biou, H. Cassoudesalle, M. Cogné, I. Sibon, I. De Gabory, P. Dehail, et al., Transcranial direct current stimulation in post-stroke aphasia rehabilitation: a systematic review, Ann. Phys. Rehabil. Med. 62 (2019) 104–121, doi:10.1016/j.rehab.2019.01.003.
[19] W. De Doncker, S. Ondobaka, A. Kuppuswamy, Effect of transcranial direct current stimulation on post-stroke fatigue, J. Neurol. 268 (2021) 2831–2842, doi:10.1007/s00415-021-10442-8.
[20] X.L. Dong, X. Sun, W.M. Sun, Q. Yuan, G.H. Yu, L. Shuai, et al., A randomized controlled trial to explore the efficacy and safety of transcranial direct current stimulation on patients with post-stroke fatigue, Medicine 100 (2021) e27504, doi:10.1097/MD.0000000000027504.
[21] K.M. Ulrichsen, K.K. Kolskår, G. Richard, M.L. Pedersen, D. Alnaes, E.S. Dørum, et al., No add-on effect of tDCS on fatigue and depression in chronic stroke patients: a randomized sham-controlled trial combining tDCS with computerized cognitive training, Brain Behav. 12 (2022) e2643, doi:10.1002/brb3.2643.
[22] A. Jagadish, A.M. Shankaranarayana, M. Natarajan, J.M. Solomon, Transcranial direct current stimulation for fatigue in neurological conditions: a systematic scoping review, Physiother. Res. Int. (2023) e2054, doi:10.1002/pri.2054.
[23] A.W. Chan, J.M. Tetzlaff, P.C. Gotzsche, D.G. Altman, H. Mann, J.A. Berlin, et al., SPIRIT 2013 explanation and elaboration: guidance for protocols of clinical trials, BMJ 346 (2013) e7586 e7586, doi:10.1136/bmj.e7586.
[24] K.F. Schulz, D.G. Altman, D. Moher, the CONSORT Group, CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials, BMC Med. 8 (2010) 18, doi:10.1186/1741-7015-8-18.
[25] A. Jagadish, M. Natarajan, J.M. Solomon, Cross-Cultural Adaptation and validation of the Kannada version fatigue severity scale among Kannada-speaking individuals with neurological disorders: a cross-sectional study done in South India, DCID 32 (2021) 51, doi:10.47985/dcidj.450.
[26] H.J. Hermens, B. Freriks, C. Disselhorst-Klug, G. Rau, Development of recommendations for SEMG sensors and sensor placement procedures, J. Electromyogr. Kinesiol. 10 (2000) 361–374, doi:10.1016/S1050-6411(00)00027-4.
[27] D.B. Adhia, R. Mani, J.N.J. Reynolds, S. Vanneste, D. De Ridder, High-definition transcranial infraslow pink noise stimulation for chronic low back pain: protocol for a pilot, safety and feasibility randomised placebo-controlled trial, BMJ Open 12 (2022) e056842, doi:10.1136/bmjopen-2021-056842.
[28] A.R. Brunoni, J. Amadera, B. Berbel, M.S. Volz, B.G. Rizzerio, F. Fregni, A systematic review on reporting and assessment of adverse effects associated with transcranial direct current stimulation, Int. J. Neuropsychopharmacol. 14 (2011) 1133–1145, doi:10.1017/S1461145710001690.
[29] M. Rahamatali, N. De Bont, M. Valet, V. Halkin, P. Hanson, T. Deltombe, et al., Post-stroke fatigue: how it relates to motor fatigability and other modifiable factors in people with chronic stroke, Acta Neurol. Belg. 121 (2021) 181–189, doi:10.1007/s13760-020-01453-9.
[30] I.J. Skogestad, M. Kirkevold, P. Larsson, C.R. Borge, B. Indredavik, C.L. Gay, et al., Post-stroke fatigue: an exploratory study with patients and health professionals to develop a patient-reported outcome measure, J. Patient Rep. Outcomes 5 (2021) 35, doi:10.1186/s41687-021-00307-z.
[31] B.M. Kluger, L.B. Krupp, R.M. Enoka, Fatigue and fatigability in neurologic illnesses: proposal for a unified taxonomy, Neurology 80 (2013) 409–416, doi:10.1212/WNL.0b013e31827f07be.