Anaesth Crit Care Pain Med 45 (2026) 1–13

Contents lists available at ScienceDirect

Anaesthesia Critical Care & Pain Medicine

journal homepage: www.elsevier.com

Original Article

Transcranial electrical stimulation (tES) in chronic pain patients: Effects on daily-reported symptoms

Antonio Gil-Ugidos [a,*], Jorge Alcántara-Espinosa [b], Lara Rubal-Otero [a,c], Mónica Mayo-Moldes [d], Noelia Samartin-Veiga [a], María Teresa Carrillo-de-la-Peña [a]

[a] *Brain and Pain lab, Institute of Psychology (IPsiUS), Universidade de Santiago de Compostela, Santiago de Compostela, Spain*
[b] *Group of Nursing Management and Care, Instituto De Investigación Sanitaria (IDIS), Santiago de Compostela, Spain*
[c] *Foundation for Health Research Institute of Santiago de Compostela (FIDIS), Santiago de Compostela, Spain*
[d] *Anesthesiology Department, University Hospital Álvaro Cunqueiro, Vigo, Spain*

ARTICLE INFO

Article history:
Available online 25 September 2025

Keywords:
Chronic pain
Transcranial electrical stimulation
Clinical trial
Home-based intervention
Time series analysis

ABSTRACT

Background: Transcranial electrical stimulation has yielded positive results for relieving pain in patients with chronic pain (CP), but the existing evidence is insufficient. In order to address some gaps in the literature, we conducted a randomized, double blind, sham-controlled clinical trial aimed at evaluating the feasibility and efficacy of home-based neurostimulation in a sample of 120 patients.
Methods: The patients completed 15 self-administered home-based sessions of either transcranial direct current stimulation (tDCS, n = 48), transcranial alternate current stimulation (tACS, n = 48), or sham stimulation (n = 24). The primary outcome variable, *i.e.*, pain intensity, and related variables were assessed online (using numerical rating scales from 0 to 10) throughout 45 days (pre-treatment, treatment, and post-treatment periods each of 15 days).
Results: ANOVA (classical and Bayesian frameworks) and time series analysis consistently showed that both tDCS and tACS decreased the patients' daily reported pain intensity (tDCS: tau = −0.553; $p < 0.001$; tACS: tau = −0.563; $p < 0.001$), pain unpleasantness (tDCS: tau = −0.489; $p < 0.001$; tACS: tau = −0.537; $p < 0.001$), interference due to pain (tDCS: tau = −0.368; $p < 0.001$; tACS: tau = −0.424; p < *0.001), and other symptoms such as fatigue (tDCS: tau = −0.255;* p = *0.02; tACS: tau = −0.556;* p < *0.001) and stress/anxiety (tDCS: tau = −0.245;* p = *0.02; tACS: tau = −0.685;* p < *0.001). No such improvement was observed in the group receiving the sham stimulation. The home-based treatment was associated with low drop-out rates (6.66%) and moderate satisfaction with the procedure (around 5 out of 10 in all groups), and minimal adverse effects of transcranial electrical stimulation were reported.*
Conclusions: tDCS and tACS significantly reduced daily-reported pain in chronic pain patients. Home-based intervention could significantly reduce the high economic burden associated with chronic pain management in healthcare systems. Inclusion of daily reports assessed by time series analysis can improve clinical trials in the field of chronic pain.
Study registration: ClinicalTrials.gov ID number: NCT05099406 (https://clinicaltrials.gov/study/NCT05099406?term=NCT05099406%20&rank=1)

Introduction

Chronic pain (CP) affects about 20% of the European population [1] and has recently begun to be treated as a pathology itself [2,3]. Although there is a very broad spectrum of pathologies characterised by CP, they may share a set of functional and/or structural alterations of the CNS - mainly affecting the descending nociceptive modulation system - which explain why pain becomes chronic [4–6]. In fact, very diverse CP conditions are characterized by impaired conditioned pain modulation [7].

Strategies for managing CP have mainly consisted of pharmacological treatment, despite they have been association with adverse effects, decreased effect over time, and dependency on

* Corresponding author.
E-mail address: antonio.gil.ugidos@usc.es (A. Gil-Ugidos).

https://doi.org/10.1016/j.accpm.2025.101613

analgesics [8–10]. As an alternative or addition, transcranial electric stimulation (tES) has been used to correct the defective central pain-generating mechanisms. The evidence supports that transcranial direct current stimulation (tDCS) over the primary motor cortex (M1) [11–14] has analgesic effects for a wide variety of CP pathologies [15,16]. More recently, transcranial alternating current stimulation (tACS) has been used to modify the cortical networks involved in pain [17,18], proving effective at reducing suffering in problems like chronic back pain [19], although the evidence is scarce and inconclusive [20]. Despite those positive findings, the overall evidence is unsound owing to the heterogeneity and poor methodological quality of the existing studies [21–24]. Particularly, it is necessary to improve the assessment of outcome variables, for instance, using a daily monitoring of symptoms, and to control the placebo effect of tES delivered in the clinic, as reported previously [25]. In this respect, home-based tES interventions (HB-tES) can reduce the placebo effect and also dropout rates [26,27]. Although HB-tES is positively perceived by the patients and families, just a few clinical trials have explored this modality [14,28,29].

In this study, we conducted a clinical trial aimed at evaluating the efficacy and feasibility of HB-tES in a large sample of CP patients. Given that different CP conditions may share common dysfunctional mechanisms and benefit similarly from tES interventions, patients with refractory pain of diverse nature attending the pain units were invited to participate. As a first objective, we compared the effects of tDCS, tACS, and sham stimulation on pain and related symptoms, which were assessed daily for 15 days prior to treatment, 15 days during the treatment, and 15 days post-treatment. To evaluate any changes in the symptoms, we compared the mean values obtained in each period and conducted time series analysis of the data. Our hypothesis was that only patients receiving active tES would improve clinically. Secondly, we aimed to assess the feasibility of HB-tES and the patients' satisfaction with the treatment. We expected a dropout rate of less than 10% and a positive evaluation of the intervention (>5/10 in a NRS scale).

Patients and methods

Participants

The sample comprised 120 patients with CP (23 males, 97 females). The inclusion criteria were as follows: (1) Age between 25 and 65 years old; (2) Diagnosis of any CP disease by a physician; (3) A mean pain intensity score of 4 or more (on a numerical rating scale (NRS) of 10) during the last three months; (4) A mean pain intensity score of 5 or more (on a NRS scale of 10) during the last week; and (5) Stable pharmacological treatment for over 2 months before the trial (except medication for pain that could vary depending on the patients status). Also, the patients had to have access to a smartphone to fill in daily scales and to monitor treatment. Patients who did not have a personal mobile phone compatible with the scales used were also excluded.

Exclusion criteria were the presence of pain caused by a cancer diagnosis, ongoing or planned pregnancy, history of drug abuse, unstable medical conditions, implanted intracranial devices or stimulators, history of neurosurgery, brain injury with loss of consciousness or cortical lesions, family history of epilepsy or active epilepsy, and psychiatric disorders (other than depression and anxiety).

All participants signed an informed consent form prior to the start of the study. Participants' data were coded for pseudonymization. The study complied with the Declaration of Helsinki and was approved by the Research Ethics Committee of Santiago-Lugo (code 2021/021). This study was part of a randomized, double-blind, sham-controlled clinical trial preregistered at https://clinicaltrials.gov/ (ID number: NCT05099406) and conducted in Galicia (NW of Spain) in the period between December 2021 and July 2023[1] .

Design

Patients with refractory, pharmaco-resistant pain meeting the criteria were informed about the study in the Pain Units of the University Hospitals of Santiago de Compostela (CHUS) and Vigo (CHUVI) (Galicia, NW Spain), and if they agreed to participate, they provided consent to contact them by telephone. Other patients who became aware of the study by other channels (local press, social media…) contacted us by telephone and were also included in the trial if they fulfilled the criteria for participation. The evaluations were carried out in the Pain Unit of the CHUVI and in the facilities of the Brain and Pain Lab of the Faculty of Psychology (University of Santiago de Compostela).

To calculate the sample size, we considered the effect size of tES in patients with CP reported in previous studies, the expected number of dropouts, and the objectives of the present study. Several reviews and meta-analyses reported the effect sizes of tDCS produced in specific CP conditions: moderate for fibromyalgia and neuropathic pain [30–32] and large for migraine [33]. Although the evidence for home-based tDCS is preliminary, a large effect size has been reported for patients with fibromyalgia [13]. Regarding tACS, although studies are scarce, the method has shown promising results for pain management [19]. To determine the superiority of either technique, a sample with statistical power sensitive to small effect sizes was needed. Regarding the number of dropouts, we expected a low dropout rate considering the high adherence to home-based tES techniques [13,34].

We therefore calculated the sample size in order to have sufficient power to reach a small-moderate effect size (f = 0.17) by using a linear mixed model ANOVA with the program G*power (v 3.1.9.3) [35; see Supplementary Material]. The minimum estimated sample was 117 participants, but we expanded the sample to 120 to assume a low dropout rate. We divided the total sample (n = 120) into the 3 treatment groups (40% tDCS (n = 48), 40% tACS (n = 48), and 20% sham (n = 24)). We recruited a smaller number of participants in the sham group for ethical reasons, as we considered that a higher proportion of patients should benefit from the likely effective pain treatment based on tES. This decision does not affect the robustness of the study, as even with groups of n = 24 (as in the Sham group), there is sufficient statistical power to detect small to moderate effects (f = 0.25).

Procedure

Potential participants were contacted by phone, and those who agreed to participate and fulfilled the selection criteria were scheduled for an initial evaluation session, during which informed consent was signed. A randomization list was generated by a researcher external to the project, who assigned each participant to the corresponding daily stimulation codes. The researcher who assessed the patients was blind to the treatment condition.

During the first visit, sociodemographic variables and clinical status were assessed using a semi-structured interview and NRS (the full list of variables collected during the clinical interview is provided in the Supplementary Material). In addition, the patients

[1] A full list of the variables included in the trial is presented in the Supplementary material. As the objective of this paper was to assess the daily evolution of symptoms due to the tES intervention, we did not include here variables which could not be assessed on a daily basis.

provided a copy of their medical history and current medication regimen, which was to be kept constant throughout the study period. To complete the pre-treatment assessment, the patients were required to provide a series of daily updates on their health status during a period of 15 days.

After the pretreatment period, the patients returned to our facilities for a second visit and were randomly and blindly assigned to the treatment groups (active tDCS, active tACS, sham tES) with an allocation ratio 2:2:1. The participants undertook the first 20-minute-long tES session under the supervision of the researcher, who explained how to use the delivery device. The tES device (Soterix 1 × 1 tES mini-CT®; https://soterixmedical.com/research/remote/mini-CT) allowed the staff in charge of delivery to be blinded to the treatment being applied, as they simply applied the codes provided by the external researcher without knowing to which treatment group the patients belonged. After this session, the patients were sent a code (by WhatsApp) every day for 14 days to enable them to carry out the treatment at home; they also received a daily link to an online NRS to rate their symptoms and side effects.

After the 15-day-long treatment period, the patients visited the clinical unit for the third assessment. They were then again required to provide daily updates on the different health variables for the following 15 days and to complete an ad-hoc questionnaire about their satisfaction with the treatment. To ensure that the blinding process was successful, participants were also asked which treatment group they believed they had been allocated to (active or sham). Altogether, the patients' symptoms were monitored daily for 45 days, in the pre-treatment, treatment, and post-treatment periods.

Measurements

The main outcome variable was the intensity of pain ("How intense on average has the pain been today?") assessed by a daily NRS (ranging from 0 – No pain - to 10 - Excruciating pain -). As secondary variables, we used daily ad-hoc NRS (0–10) for interference caused by pain ("How much has pain interfered with your daily activities today?"), pain unpleasantness ("How unpleasant has the pain been today?"), stress/anxiety ("What level of stress/anxiety have you experienced today?"), fatigue ("What has been your level of fatigue today?") and sleep quality ("How would you rate your quality of sleep/rest last night?"). Finally, analgesic intake was scored as a dichotomous variable, in which the participants had to report daily whether they had taken any painkillers (1) or not (0). All these variables referred to the previous 24 h and were sent daily throughout the 45 days of the trial.

In addition, participants responded to an *ad-hoc* survey about their satisfaction with the trial. This included 8 NRS (0–10) items (total improvement, emotional improvement, physical improvement, pain reduction, global satisfaction with the study, satisfaction with questionnaires, satisfaction with assessments and repeating the treatment) and 3 dichotomic (Yes/No) items ("Have you noticed any changes after completing the treatment?", "Do you think your symptoms have got worse after completing the treatment?" and "Would you recommend the treatment?").

Treatment with transcranial electrical stimulation (tES)

Patients were randomly assigned to one of the following treatment conditions (see Supplementary Material for more information about the randomization process):

- *Transcranial direct current stimulation (tDCS*; n = 48), applied over the left primary motor cortex (M1; Anode: C3; Cathode: FP2). The parameters for each session were 2 mA for 20 min, ramp-up and ramp-down for 15 seconds at the beginning and end of the stimulation period.
- *Transcranial alternating current stimulation (tACS*; n = 48) over the dorsolateral prefrontal cortex (DLPFC; F3 and F4; Return: Pz). Parameters: 10 Hz, 1 mA intensity (zero-to-peak), 20 min, with ramp-up and ramp-down periods of 15 seconds.
- *Sham stimulation* (n = 24) was considered a placebo-control treatment. Half of the participants received the tDCS montage and the other half the tACS montage. In this case, the current was only delivered during the ramp-up and ramp-down moments.

For all conditions, the researchers explained carefully to the patients how to place the cap using the aid of a mirror and provided a printed guide with explanations and photographs to ensure a correct electrode placement. Besides, we had different cap sizes and selected the ideal one for each patient's skull, to stimulate as precisely as possible in the selected areas. The participants were also instructed to wet the sponge electrodes (5 × 5 cm) with saline solution in the best way (approx. 2.5 mL), and check the impedance before starting the session - the equipment used provides information about the quality of the stimulation, with the green light signifying that the quality is optimal. To activate the device, the patients had to key in the code sent daily by the researcher. After each session, the patients sent back the finalization codes, which indicated to the researcher whether the sessions had been fully completed or if any problem had arisen. Only participants with stimulation sessions who met high-quality standards were included in the analysis.

Data analysis

To maintain randomization and compensate for loss of data due to dropouts, we used an intention-to-treat analysis [36,37]. All randomized subjects (n = 120) were included with their original assignment. The final dataset exhibited very low levels of missingness: 82.35% of the variables had no missing values, 5.88% had exactly one missing value, 5.88% had two missing values, and 5.88% had three missing values. Thus, the overall amount of missing data was negligible - less than 20% -. The missingness was assessed to be Missing Completely at Random (MCAR), because post-study audits confirmed that the data lost were not associated with participant withdrawal, adverse events, or any study procedure; and the quality checks that tracked the full data collection process showed that the missing values were related to external errors (*i.e.*, technical glitches or errors in data recording), and not to participant characteristics or trial implementation. Missing data were imputed using the median method, as it provided the best adjustment for our data. This method involved identifying missing values in each column and replacing them with the respective column's median. This approach is widely recognized in scientific literature due to its key advantages: robustly addressing missing values, preserving the original data distribution, maintaining the study's content integrity, and being suitable for various data types, preventing the loss of valuable information.

The three treatment groups (active tDCS, active tACS, and sham stimulation) were first compared at baseline by using one-way ANOVAs and Pearson's Chi-Square tests to verify that the groups were balanced in the sociodemographic and clinical variables.

Repeated-measures ANOVA was then used to compare the effectiveness of the treatment, with Phase of assessment (2 levels: pre-treatment and post-treatment) included as an intra-subject factor and Group (3 levels: tDCS, tACS, and sham stimulation) as an inter-subject factor. The analyses were performed for the mean of the daily self-reported NRS in each phase (except for analgesic intake, where the sum of days was used), and both classical and Bayesian statistics were used to obtain the most accurate evidence possible. We used Bonferroni-Holm correction for multiple post-hoc comparisons.

To analyse the trends or systematic patterns over time due to the treatment, we also performed a time series analysis for the daily measures (see Supplementary Material for more information about the time-series analysis methodology). We used the following 3 statistical tests:

The Dickey-Fuller Test: This test examines the stationarity of the series, considering unit root properties, which indicate non-stationarity (*i.e.*, changes in the mean and variance of the series over time). A high p-value indicates that the series is non-stationary and may include a trend or a persistent pattern.

The Kwiatkowski-Phillips-Schmidt-Shin (KPSS) Test: This test complements the Dickey–Fuller test by checking for stationarity around a mean or trend. Unlike the Dickey-Fuller test, in which the null hypothesis is the presence of a unit root (indicating non-stationarity), the KPSS test assumes that the null hypothesis is stationarity. A low p-value in the KPSS test would lead us to reject this null hypothesis, indicating that the series is in fact non-stationary and that the mean or variance is not constant over time.

The Mann-Kendall Test: This non-parametric test was used to assess the presence of a monotonic trend within the time series data. A monotonic trend implies consistent movement in one direction, *i.e.*, either an increase or a decrease, but not both. The test provides two key pieces of information: the *p*-value, which indicates the significance of the detected trend, and the tau value, a coefficient that measures the strength of the association. A low *p*-value (typically less than 0.05) indicates that the observed trend is statistically significant, while the tau value provides a measure of the magnitude of the trend.

By applying these tests, we can ascertain the existence or non-stationarity of trends and also their nature and strength. This multi-faceted approach enabled robust analysis of the time series data, thereby enhancing our understanding of the impact of the treatment on pain and its associated symptoms over time. Thus, the aim of this statistical approach was to detect any sustained temporal trends due to treatment, which could differ between the groups.

Finally, we checked whether the blinding was correctly achieved by comparing each participant's belief about which group they belonged to (reported at the end of the treatment) and the actual group they belonged to, using Cohen's Kappa test. We also analyse the global impression of improvement, the satisfaction with the trial, and the adverse effects, by applying one-way ANOVA (factor: treatment group) and Pearson's Chi Square tests to the results of the *ad-hoc* satisfaction with treatment questionnaire and the number of days on which adverse effects were reported during the 15-day treatment period.

Data were analysed by an independent researcher who was blinded to treatment allocation. The statistical tests were run using the SPSS statistical package (v.24.0; IBM Corporation, Armonk, NY, United States), JASP (v.0.18; The JASP Team), and R (v.4.3.2).

Results

Sample characteristics and randomization

The descriptive statistics of the sociodemographic and clinical data and the results of one-way ANOVA tests are summarized in Table 1. The sample was balanced in age (mean: 49.5y). Pearson's Chi-Square tests confirmed that despite having a majority of women (80.8% of the total sample), the 3 treatment groups were sex balanced. The participants were classified according to the ICD-11 criteria: primary pain (55% of the total sample), musculoskeletal pain (19.17%), and neuropathic pain (13.3%) were the 3 most

Table 1
ANOVA results and descriptive statistics: sociodemographic and clinical status at baseline.

	tDCS				tACS				Sham				ANOVA	
	N	M(SD)	Min - Max	CI (95%)	N	M(SD)	Min - Max	CI (95%)	N	M(SD)	Min - Max	CI (95%)	F	Sig.
Age (years)	48	49.81 (7.74)	29 – 65	47.56 – 52.06	48	49.73 (9.05)	27 – 64	47.1 – 52.36	24	48.54 (9.83)	28 – 65	44.39 – 52.69	.192	.826
Weight (kg)	48	70.74 (14.19)	39 – 105	66.62 – 74.86	48	68.01 (15.11)	49 – 112	63.62 – 72.4	24	69.77 (9.93)	50 – 87	65.58 – 73.96	.469	.627
Height (cm)	48	165 (8.79)	149 – 185	162.45 –167.55	48	162.57 (7.29)	147 – 178	160.45 –164.69	24	165.04 (7.87)	150 – 181	161.72 –168.36	1.310	.274
Years feeling pain	48	13.67 (7.94)	1 – 35	11.36 – 15.98	48	16.11 (11.06)	1 – 44	12.9 – 19.32	24	10.74 (7.71)	1 – 30	7.48 – 14	2.661	.074
Years since diagnosis	48	9.77 (6.26)	1 – 25	7.95 – 11.59	48	10.13 (7.61)	1 – 30	7.92 – 12.34	24	7.74 (6.34)	1 – 24	5.06 – 10.42	.992	.374
Pain in the last week (NRS 0–10)	48	7.36 (1.71)	3 – 10	6.86 – 7.86	48	7.25 (1.66)	2 – 10	6.77 – 7.73	24	7.41 (1.67)	5 – 10	6.7 – 8.12	.087	.917
Pain at the time of evaluation (NRS 0–10)	48	6.13 (2.18)	0 – 10	5.5 – 6.76	48	6.27 (2.17)	0 – 10	5.64 – 6.9	24	6.02 (2.87)	0 – 10	4.81 – 7.23	.103	.902
Fatigue in the last week (NRS 0–10)	48	6.57 (2.56)	0 – 10	5.83 – 7.31	48	6.6 (2.53)	0 – 10	5.87 – 7.33	24	6.81 (2.79)	1 – 10	5.63 – 7.99	.073	.930
Fatigue at the time of evaluation (NRS 0–10)	48	5.78 (2.76)	0 – 10	4.98 – 6.58	48	5.93 (2.78)	0 – 10	5.12 – 6.74	24	5.54 (3.16)	0 – 10	4.21 – 6.87	.147	.863
Sleep quality in the last week (NRS 0–10)	48	4.88 (2.58)	0 – 10	4.13 – 5.63	48	4.29 (2.53)	0 – 10	3.56 – 5.02	24	4.5 (2.96)	0 – 10	3.25 – 5.75	.594	.554
Sleep quality today (NRS 0–10)	48	4.57 (2.9)	0 – 10	3.73 – 5.41	48	4.85 (2.84)	0 – 10	4.03 – 5.67	24	4.75 (3.1)	0 – 10	3.44 – 6.06	.113	.893

Note: NRS: Numerical Rating Scale.

Table 2
Pearson's χ^2: **s**ample (n = 120) distribution for the different sociodemographic variables.

Variable	Response	tDCS (N = 48)			tACS (N = 48)			Sham (N = 24)			Pearson's χ^2	
		N	%	CI (95%)	N	%	CI (95%)	N	%	CI (95%)	χ^2	Sig.
Sex	Women	35	72.9	60.3 – 85.5	41	85.4	75.4 – 95.4	21	87.5	74.3 – 100.7	3.28	.194
	Men	13	27.1	14.5 – 39.7	7	14.6	4.6 – 24.6	3	12.5	(–.7) – 25.7		
Civil status	Single	14	29.2	16.3 – 42.0	8	16.7	6.1 – 27.2	9	37.5	18.1 – 56.9	5.84	.441
	Married	24	50	35.9 – 64.1	28	58.3	44.4 – 72.3	13	54.2	34.2 – 74.1		
	Divorced	8	16.7	6.1 – 27.2	10	20.8	9.3 – 32.3	2	8.3	(−2.7) – 19.4		
	Widowed	2	4.2	(−1.5) – 9.8	2	4.2	(−1.5) – 9.8	0	0	0		
Educational level	Elementary school	13	27.1	14.5 – 39.7	6	12.5	3.1 – 21.9	0	0	0	**16.71**	**.033**
	High school	5	10.4	1.8 – 19.1	7	14.6	4.6 – 24.6	4	16.7	1.8 – 31.6		
	Bachelors degree	13	27.1	14.5 – 39.7	18	37.5	23.8 – 51.2	6	25	7.7 – 42.3		
	College degree	16	33.3	20.0 – 46.7	12	25	12.8 – 37.2	13	54.2	34.2 – 74.1		
	Master's degree	1	2.1	(−2.0) – 6.1	5	10.4	1.8 – 19.1	1	4.2	(−3.8) – 12.2		
Occupation	Full-time job	18	37.5	23.8 – 51.2	17	35.4	21.9 – 48.9	4	16.7	1.8 – 31.6	10.64	.387
	Part-time job	3	6.3	(−0.6) – 13.1	4	8.3	.5 – 16.2	2	8.3	(−2.7) – 19.4		
	Student	2	4.2	(−1.5) – 9.8	0	0	0	0	0	0		
	Unemployed	9	18.8	7.7 – 29.8	10	20.8	9.3 – 32.3	3	12.5	(–.7) – 25.7		
	Retired	9	18.8	7.7 – 29.8	10	20.8	9.3 – 32.3	7	29.2	11.0 – 47.4		
	Temporary medical leave	7	14.6	4.6 – 24.6	7	14.6	4.6 – 24.6	8	33.3	14.5 – 52.2		
Disability	Not disabled	29	60.4	46.6 – 74.3	26	54.1	40.1 – 68.3	12	50	30.0 – 70.0	10.72	.218
	Grade II	2	4.2	(−1.5) – 9.8	2	4.2	(−1.5) – 9.8	4	16.7	1.8 – 31.6		
	Grade III	10	20.8	9.3 – 32.3	15	31.3	18.1 – 44.4	5	20.8	4.6 – 37.1		
	Grade IV	7	14.6	4.6 – 24.6	3	6.3	(−0.6) – 13.1	3	12.5	(–.7) – 25.7		
	Grade V	0	0	0	2	4.2	(−1.5) – 9.8	0	0	0		
Inability to work	Absence of inability/DK/NA	41	85.4	75.4 – 95.4	37	77.1	65.2 – 89.0	15	62.5	43.1 – 81.9	5.62	.229
	Total permanent disability	5	10.4	1.8 – 19.1	9	18.8	7.7 – 29.8	6	25	7.7 – 42.3		
	Absolute permanent disability	2	4.2	(−1.5) – 9.8	2	4.2	(−1.5) – 9.8	3	12.5	(−0.7) – 25.7		
Type of chronic pain (ICD-11)	Primary pain	28	58.3	44.4 – 72.3	29	60.4	46.6 – 74.3	9	37.5	18.1 – 56.9	12.74	.388
	Postsurgical/Posttraumatic pain	3	6.3	(−0.6) – 13.1	5	10.4	1.8 – 19.1	2	8.3	(−2.7) – 19.4		
	Neuropathic pain	5	10.4	1.8 – 19.1	5	10.4	1.8 – 19.1	6	25	7.7 – 42.3		
	Headache/Orofacial pain	1	2.1	(−2.0) – 6.1	1	2.1	(−2.0) – 6.1	1	4.2	(−3.8) – 12.2		
	Visceral pain	2	4.2	(−1.5) – 9.8	0	0	0	0	0	0		
	Musculoskeletal pain	9	18.8	7.7 – 29.8	8	16.7	6.1 – 27.2	5	20.8	4.6 – 37.1		
	NA	0	0	0	0	0	0	1	4.2	(−3.8) – 12.2		

frequent diagnostic categories. Anyway, the type of CP was balanced between groups. Also, the groups turned out to be balanced by marital status, occupation, degree of disability, and work incapacity. The only significant difference (X^2 = 16.71; p = 0.033) was in educational level (see Table 2). For the clinical symptoms, no significant differences between the groups at baseline were found.

Comparison between pre- and post-treatment clinical status

The results of the repeated-measures ANOVA for the daily reported symptoms (mean of 15 NRS at pre- and post-treatment) are summarized in Table 3. We found significant effects of Phase for the primary outcome (pain intensity) ($F(1,117)$ = 23.16; $p < 0.001$) and for all other variables under study: pain unpleasantness ($F(1,117)$ = 21,89; $p < 0.001$), interference due to pain ($F(1,117)$=16.64; $p < 0.001$), stress/anxiety ($F(1,117)$ = 29.56; $p < 0.001$), fatigue ($F(1,117)$ = 9.30; p = 0.003), sleep quality ($F(1,117)$ = 432.11; $p < 0.001$) and analgesic intake ($F(1,117)$ = 20.85; $p < 0.001$), mostly with large effect sizes. Only for pain intensity and stress/anxiety we found a significant Phase x Group interaction ($F(2,117)$ = 3.83; p = 0.025 and $F(2,117)$ = 7.34; $p < 0.001$, respectively), although for stress there was also a main effect of Group ($F(2,117)$ = 3.98; p = 0.021) (see effect sizes in Table 3).

Post-hoc tests showed that both tDCS and tACS groups showed significant improvement from pre- to post-treatment in all the clinical variables, while for Sham, only an improvement in sleep quality was observed. Thus, the results showed the superior effects achieved by active tES, with no significant difference between tDCS and tACS.

Using Bayesian statistics, we also found clear evidence of pre-post change for all variables assessed and a Phase x Group interaction only for pain intensity (BF = 1.992; anecdotal evidence) and stress/anxiety (BF = 34.545; extreme evidence), with strong evidence for greater improvement in the tACS group than in the tDCS group for the latter (BF_{10} = 24.038).

Time series analysis: clinical evolution of the patients throughout the clinical trial

To examine the temporal evolution of symptoms, we performed a time series analysis (see Table 4). The three statistical tests used (Dickey-Fuller, KPSS, and Mann-Kendall) yielded consistent results, showing trends (non-stationarity in the data) in all the daily NRS variables, except in sleep quality and analgesic intake. The examination revealed notable decreases in pain-associated indices over time in the tACS and tDCS groups (see Fig. 1), as highlighted by the results of the Mann–Kendall test and the negative tau coefficients for pain intensity (tau = −0.553; $p < 0.001$ in the tDCS and tau = −0.563; $p < 0.001$ in the tACS groups). We found a similar effect for pain unpleasantness, although with slightly higher values for tACS (tau = −0.537; $p < .001$) than tDCS (tau = −0.489; $p < .001$). For pain interference, the evidence was still significant, although less pronounced, with tau values of −0.424 for tACS and −0.368 for tDCS.

For the other symptoms (see Fig. 2), a pronounced negative trend in stress/anxiety was observed along the study in the tACS group (tau = −0.685; $p < 0.001$), which was more moderate for the tDCS group (tau = −0.245; p = 0.02). For fatigue, the results showed significant decreasing trends in both tACS (tau = −0.556;

Table 3
Mixed-model ANOVA and Bayesian ANOVA results on the outcome variables measured daily by Numeric Rating Scales (NRS 0 – 10). Means of 15 days at pre- and post-treatment periods (standard deviations in parentheses) and significance level of the effects.

		tDCS (N = 48)		tACS (N = 48)		Sham (N = 24)		ANOVA results												
								Phase				Phase*Group				Group				
		PRE	POST	PRE	POST	PRE	POST	F	p	Partial η^2	BF	F	p	Partial η^2	BF	F	p	Partial η^2	BF	Post-hoc sig. changes
Pain intensity	Mean (SD)	6.11 (1.53)	5.16 (1.88)	6.43 (1.32)	5.38 (1.76)	5.85 (1.54)	5.79 (2.11)	**23.16**	**<.001**	**.165**	**241150.96**	**3.83**	**.025**	**.061**	**1.99**	.41	.662	.007	.187	?TACS, ?TDCS
	CI 95%	5.67 -6.55	4.61 -5.71	6.05 -6.81	4.87 -5.89	5.20 -6.50	4.90 -6.68													
Pain unpleasantness	Mean (SD)	5.93 (1.69)	4.93 (2.04)	6.23 (1.33)	5.19 (1.93)	5.76 (1.51)	5.58 (2.21)	**21.89**	**<.001**	**.158**	**89152.53**	2.63	.076	.043	.758	.41	.663	.007	.184	?TACS, ?TDCS
	CI 95%	5.44 -6.42	4.34 -5.52	5.84 -6.62	4.63 -5.75	5.12 -6.40	4.65 -6.51													
Pain interference	Mean (SD)	5.61 (1.75)	4.75 (2.02)	5.53 (1.65)	4.79 (2.09)	5.43 (1.71)	5.06 (2.17)	**16.64**	**<.001**	**.125**	**2085.76**	.72	.490	.012	.145	.02	.979	.000	.153	?TACS, ?TDCS
	CI 95%	5.10 -6.12	4.16 -5.34	5.05 -6.01	4.18 -5.40	4.71 -6.15	4.14 -5.98													
Stress	Mean (SD)	5.27 (1.97)	4.63 (1.95)	4.79 (2.01)	3.18 (1.8)	4.29 (1.76)	4.04 (1.89)	**29.56**	**<.001**	**.202**	**1.157e+6**	**7.34**	**<.001**	**.111**	**34.55**	**3.98**	**.021**	**.064**	**3.00**	In PRE: SHAM = TACS < TDCS ?TACS > ?TDCS
	CI 95%	4.70 -5.84	4.06 -5.20	4.21 -5.37	2.66 -3.70	3.55 -5.03	3.24 -4.84													
Fatigue	Mean (SD)	6.33 (1.65)	5.75 (1.69)	6.1 (1.83)	5.43 (2.06)	5.53 (1.75)	5.51 (2.15)	**9.30**	**.003**	**.074**	**89.85**	1.79	.178	.029	.371	.79	.453	.013	.290	?TACS, ?TDCS
	CI 95%	5.85 -6.81	5.26 -6.24	5.57 -6.63	4.83 -6.03	4.79 -6.27	4.60 -6.42													
Sleep quality	Mean (SD)	5.27 (1.29)	5.73 (1.27)	5.11 (1.44)	5.73 (1.57)	4.78 (1.3)	5.57 (1.66)	**432.11**	**<.001**	**.787**	**5946.03**	1.02	.363	.017	.127	.80	.451	.014	.196	?SHAM, ?TACS, ?TDCS
	CI 95%	4.90 -5.64	5.36 -6.10	4.69 -5.53	5.27 -6.19	4.23 -5.33	4.87 -6.27													
Analgesic use	Mean (SD)	7.29 (4.95)	5.33 (5.33)	9.44 (5.04)	6.62 (5.02)	7.37 (5.42)	5.67 (5.75)	**20.85**	**<.001**	**.151**	**8051.43**	.55	.582	.009	.137	1.89	.156	.031	.563	?TACS, ?TDCS
	CI 95%	5.85 -8.73	3.78 -6.88	7.98 -10.90	5.16 -8.08	5.08 -9.66	3.24 -8.10													

Note: All the variables except Sleep Quality should be interpreted to mean that the higher the score (between 0 and 10), the greater the discomfort in the assessed domain. Pain intensity was the primary outcome variable. The results for Analgesic Intake have been obtained using as a variable the sum of the number of days on which patients consumed this type of medication (score between 0 and 15 for this variable).

Table 4
Results obtained for the different statistical tests used in the time series analysis for the variables measured on a day-to-day basis.

	Group	Statistical test used: Dickey-Fuller	KPSS	Mann-Kendall	tau	CI (95%)
Pain intensity	tDCS	**.38**	**<.01**	**<.001**	**–.553**	(–.81) – (–.30)
	tACS	**.67**	**<.01**	**<.001**	**–.563**	(–.82) – (–.31)
	Sham	.32	.10	.27	–.117	(–.37) – .14
Pain unpleasantness	tDCS	**.38**	**<.01**	**<.001**	**–.489**	(–.74) – (–.24)
	tACS	**.72**	**<.01**	**<.001**	**–.537**	(–.79) – (–.28)
	Sham	.09	.10	.07	–.194	(–.45) – .06
Pain interference	tDCS	**.21**	**<.01**	**<.001**	**–.368**	(–.62) – (–.11)
	tACS	**.69**	**<.01**	**<.001**	**–.424**	(–.68) – (–.17)
	Sham	.31	.09	.08	–.772	(–1.03) – (–.52)
Stress	tDCS	.58	**<.01**	**.02**	**–.245**	(–.5) – .01
	tACS	**.27**	**<.01**	**<.001**	**–.685**	(–.94) – (–.43)
	Sham	.47	.10	.13	–.159	(–.41) – .09
Fatigue	tDCS	**.46**	**.05**	**.02**	**–.255**	(–.51) – 0
	tACS	**.06**	**.01**	**<.001**	**–.556**	(–.81) – (–.3)
	Sham	.45	.10	.60	–.056	(–.31) – .2
Sleep quality	tDCS	.06	.10	.49	–.007	(–.26) – .25
	tACS	.17	.10	.24	.012	(–.24) – .27
	Sham	.69	.10	.41	.008	(–.25) – .26
Analgesic use	tDCS	**.19**	**.01**	**<.001**	**–.439**	(–.69) – (–.19)
	tACS	**.52**	**.01**	**.002**	**–.326**	(–.58) – (–.07)
	Sham	**.07**	**.02**	**.001**	**–.343**	(–.6) – (–.09)

$p < 0.001$) and tDCS (tau = –0.255; p = 0.02). The analysis did not uncover any significant trends regarding sleep quality.

In the daily monitoring of analgesic intake (see Fig. 3), there was a decrease in the use of analgesics over time in all groups: sham stimulation (tau = –0.343; p = 0.001), tACS (tau = –326; p = 0.002), and tDCS (tau = –.439; $p < 0.001$).

Feasibility and Satisfaction with the HB-tES treatment

At the end of treatment, the participants answered some questions about their beliefs about the group assignment and their global impression of improvement and satisfaction with the HB-tES. The results confirmed that blinding was very effective: more than 80% of all participants believed they were undergoing active treatment, and only 11.1% of those actually in the sham stimulation group believed they were in that group (see Table 5). Cohen's Kappa statistic (κ = 0.064) made clear the absence of agreement between membership group and treatment belief, which is indicative of the high quality of the blind obtained.

In addition, only 8 (6.66%) participants dropped out of the study, 3 (2.5%) after the pre-treatment assessment phase and 5 (4.16%) during the active treatment phase. No serious adverse effects were reported. Mild effects such as itching of the scalp or visualisation of slight flashes during the session, and slight headaches, fatigue, and dizziness after the session were scarcely reported (mean below 3 days out of 15). There were no significant differences (F (2,117) = 1.08; p = 0.344) between the groups.

The groups did not differ in the global impression of improvement, emotional improvement, or physical improvement (see Table 6). Regarding the perception of pain reduction, the sham group (mean: 1.83 ± 1.79) was the least satisfied, followed by the tDCS group (mean: 2.02 ± 2.79) and then tACS group (mean: 2.31 ± 2.71), although the differences were not statistically significant. Although the mean perception of improvement was low (around 2.5–3) the global satisfaction with the study (mean: sham = 5.13 ± 2.51; tACS = 4.75 ± 2.96; tDCS = 5 ± 3.5) and the likelihood of continued participation in the study (mean: sham = 7.21 ± 2.99; tACS = 6.46 ± 3.46; tDCS = 7.69 ± 2.83) were

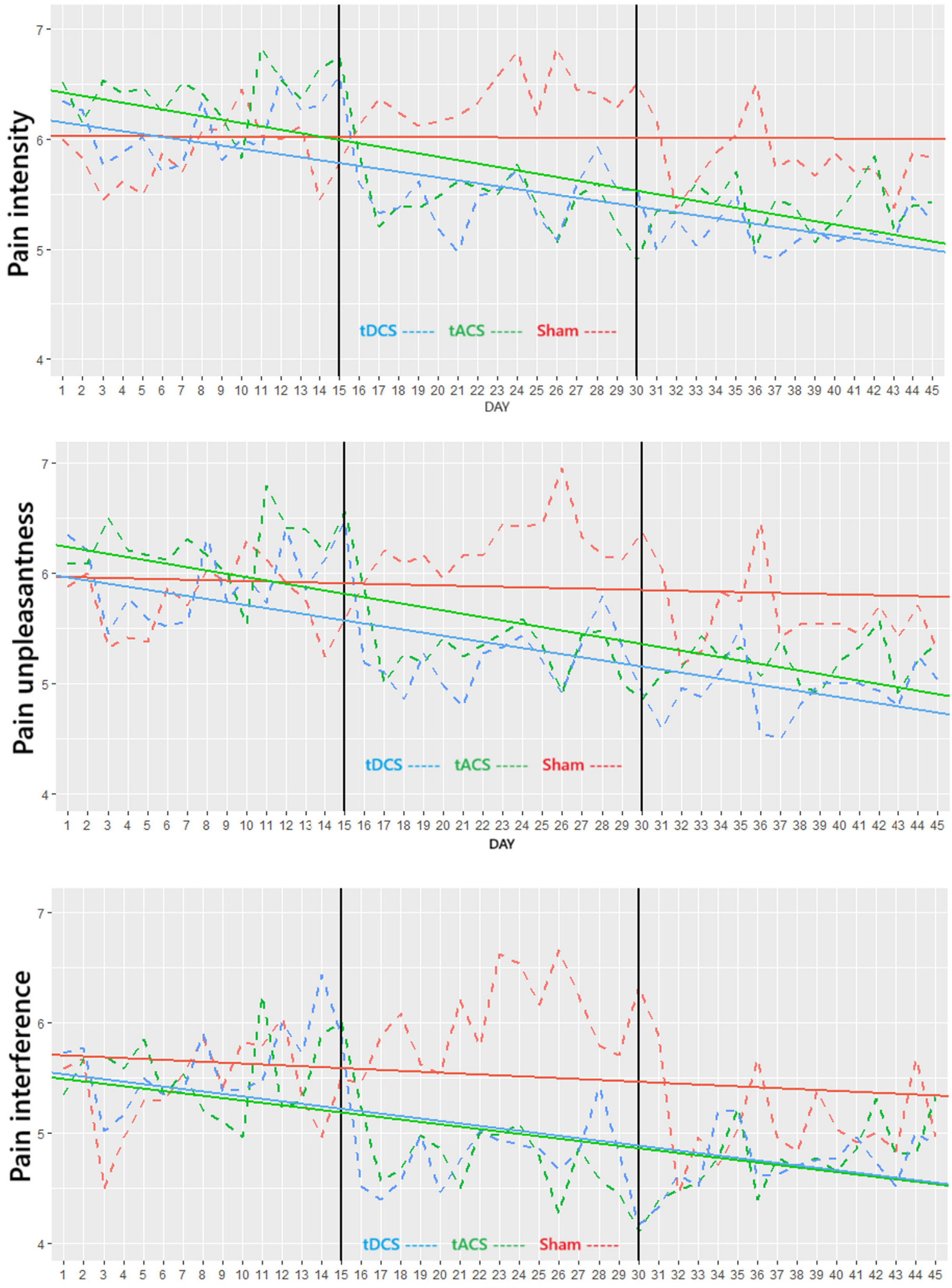

Fig. 1. Comparison of changes in pain related measures between tDCS, tACS and Sham groups over 45 days. All the variables should be interpreted to mean that the higher the score (between 0 and 10), the greater the discomfort in the assessed domain. Days 1 to 15 correspond to the pre-treatment period, days 16 to 30 to the treatment period, and days 31 to 45 to the post-treatment period.

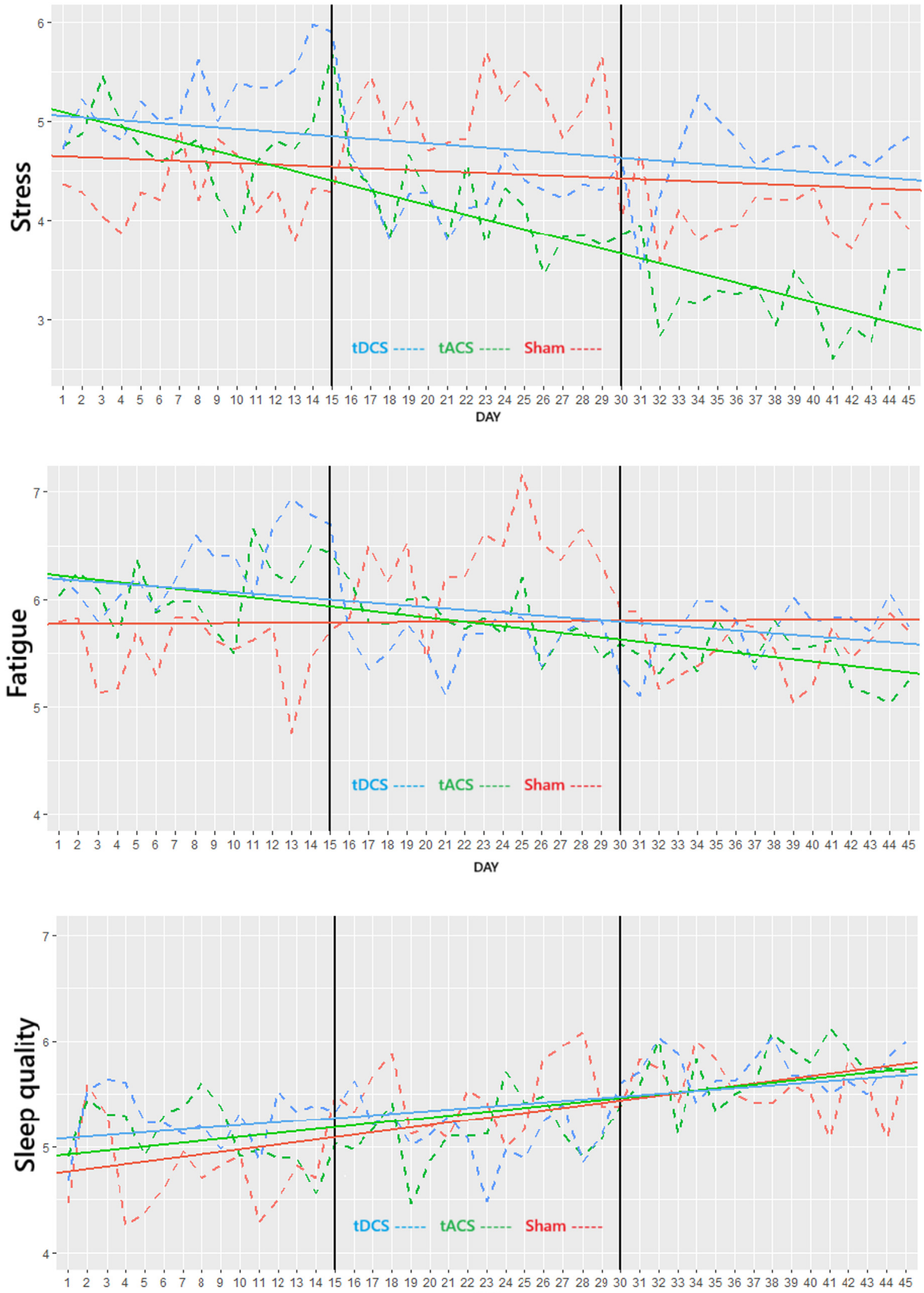

Fig. 2. Comparison of changes in pain unrelated measures between tDCS, tACS and Sham groups over 45 days. All the variables except Sleep Quality should be interpreted to mean that the higher the score (between 0 and 10), the greater the discomfort in the assessed domain. Days 1 to 15 correspond to the pre-treatment period, days 16 to 30 to the treatment period, and days 31 to 45 to the post-treatment period.

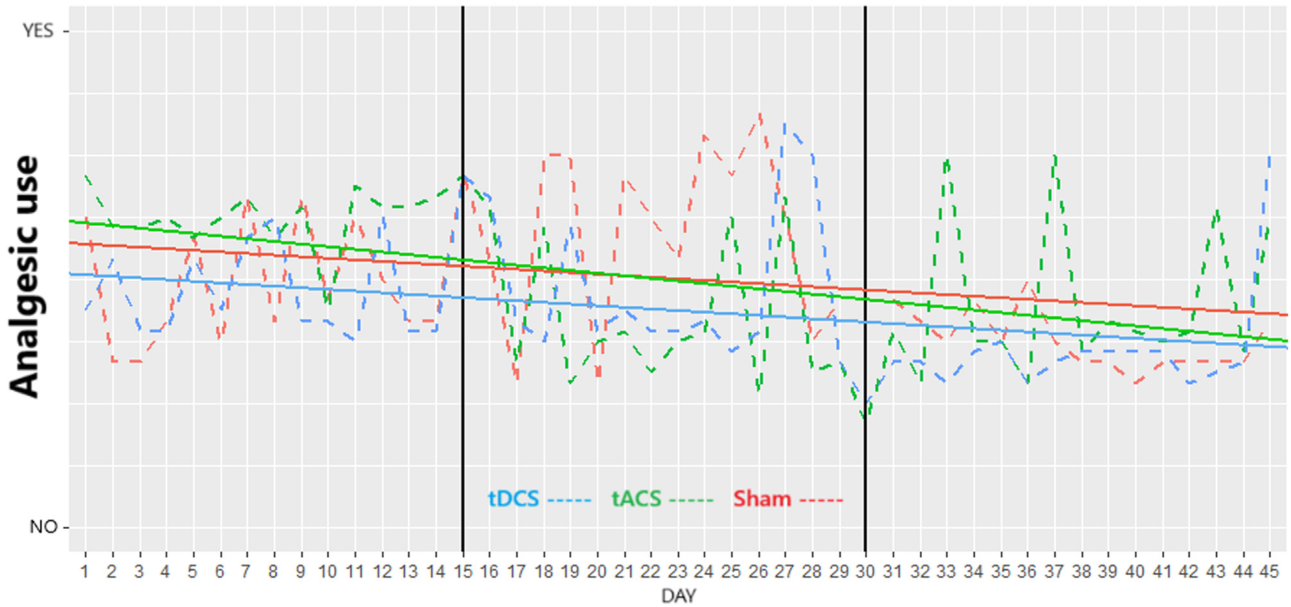

Fig. 3. Comparison of changes in analgesic intake between tDCS, tACS and Sham groups over 45 days. This variable reflects the sum of the number of days on which patients consumed analgesic medication (score between 0 and 15 for this variable). Days 1 to 15 correspond to the pre-treatment period, days 16 to 30 to the treatment period, and days 31 to 45 to the post-treatment period.

Table 5
Distribution of participants based on their belief of active/sham treatment group membership at the end of the study (n = 85).

	Active Group (N = 72)	Sham Group (N = 13)	Cohen's Kappa
Active belief (N = 49)	40 (81.7%)	9 (18.3%)	.064
Sham belief (N = 36)	32 (88.9%)	4 (11.1%)	

from moderate to high, with no significant differences between the groups.

The tDCS group included a higher proportion of people who did not perceive any change (54.2% in sham stimulation, 60.4% in tACS, and 68.8% in tDCS), but the Chi-Square value was not significant (see Table 7). Overall, 85% of the participants would recommend the treatment, and only 5 (4.2% of the 120 participants) reported feeling worse after the treatment.

Table 6
ANOVA results and descriptive statistics: satisfaction with treatment questionnaire.

	tDCS (N = 48)			tACS (N = 48)			Sham (N = 24)			ANOVA	
	M(SD)	Min - Max	CI (95%)	M(SD)	Min - Max	CI (95%)	M(SD)	Min - Max	CI (95%)	F	Sig.
Total improvement	2.67 (3.02)	0 – 9	1.79 – 3.55	2.67 (2.48)	0 – 10	1.95 – 3.39	2.71 (1.9)	0 – 6	1.91 – 3.51	.002	.998
Emotional improvement	2.65 (2.78)	0 – 8	1.84 – 3.46	2.69 (2.71)	0 – 10	1.90 – 3.48	2.96 (2.37)	0 – 8	1.96 – 3.96	.117	.890
Physical improvement	2.19 (2.64)	0 – 8	1.42 – 2.96	2.06 (2.63)	0 – 10	1.30 – 2.82	2.46 (2.4)	0 – 8	1.45 – 3.47	.187	.830
Pain reduction	2.02 (2.79)	0 – 8	1.21 – 2.83	2.31 (2.71)	0 – 9	1.52 – 3.10	1.83 (1.79)	0 – 6	1.07 – 2.59	.310	.734
Global satisfaction with the study	5 (3.5)	0 – 10	3.98 – 6.02	4.75 (2.96)	0 – 10	3.89 – 5.61	5.13 (2.51)	1 – 10	4.07 – 6.19	.139	.870
Satisfaction with questionnaires	6.52 (3.02)	0 – 10	5.64 – 7.40	6.38 (2.55)	0 – 10	5.64 – 7.12	6.21 (2.09)	1 – 10	5.33 – 7.09	.113	.893
Satisfaction with assessments	7.67 (2.74)	0 – 10	6.87 – 8.47	7.94 (2.4)	0 – 10	7.24 – 8.64	8.21 (1.93)	2 – 10	7.40 – 9.02	.407	.667
Would you repeat the treatment?	7.69 (2.83)	0 – 10	6.87 – 8.51	6.46 (3.46)	0 – 10	5.46 – 7.46	7.21 (2.99)	0 – 10	5.95 – 8.47	1.869	.159
Days with reported adverse effects	2.42 (3.72)	0 – 14	1.34 – 3.50	1.69 (2.68)	0 – 12	0.91 – 2.47	2.92 (3.39)	0 – 11	1.49 – 4.35	1.265	.286

Table 7
Pearson's χ^2: distribution for changes noticed, worsening after treatment and recommendation for others.

		tDCS (N = 48)			tACS (N = 48)			Sham (N = 24)			Pearson's χ^2	
	Response	N	%	CI (95%)	N	%	CI (95%)	N	%	CI (95%)	χ^2	Sig.
Have you noticed any changes after doing the treatment?	Yes	15	31.3	18.1 – 44.4	19	39.6	25.7 – 53.4	11	45.8	25.9 – 65.8	1.60	.449
	No	33	68.8	55.6 – 81.9	29	60.4	46.6 – 74.3	13	54.2	34.2 – 74.1		
Do you think you've gotten worse after treatment?	Yes	3	6.3	(−.6) – 13.1	2	4.2	(−1.5) – 9.8	0	0	(−3.5) – 7.5	1.57	.457
	No	45	93.8	86.9 – 100.6	46	95.8	90.2 – 101.5	24	100	92.5 – 103.5		
Would you recommend the treatment?	Yes	44	91.7	83.8 – 99.5	40	83.3	72.8 – 93.9	23	95.8	87.8 – 103.8	3.11	.212
	No	4	8.3	.5 – 16.2	8	16.7	6.1 – 27.2	1	4.2	(−3.8) – 12.2		

Discussion

We conducted a randomized clinical trial of home-based transcranial electric stimulation (HB-tES), as a complementary treatment to relieve CP, comparing tDCS, tACS, and a sham condition. We monitored the symptoms online to minimize the placebo effect and biases such as the social desirability effect. To achieve a more robust main outcome, we measured the variables daily 15 days before, 15 days during, and 15 days after the treatment. We analysed daily reported symptoms by two different approaches: ANOVAs (classical and Bayesian) to test for any differences in the mean scores for pre- and post-treatment periods, and time series analyses to examine the evolution of symptoms over time.

For our primary outcome variable (pain intensity), repeated measures ANOVA revealed a significant phase by group interaction (with a medium effect size), reflected in pain intensity reductions after treatment only in the active groups. Post-hoc tests did not detect any significant difference between tDCS and tACS. Our results appear consistent with previous application of tDCS on the M1 area, resulting in pain relief [24,38,39]. Although the physiological mechanism by which stimulation in motor areas causes this effect is not fully understood, it may be due to the close relationship between the motor and somatosensory regions [40] or their projections to the thalamus, which could reduce nociceptive inputs and modulate the discriminative/sensory dimension of pain [41–43]. In addition, M1 projections to the prefrontal cortex and regions involved in nociception, such as the insula and cingulate gyrus, and brainstem structures involved in analgesic regulation [44], can influence the affective dimension of pain.

tDCS has proved effective for a wide ranging of pain conditions-such as fibromyalgia [13,24,28,29,39,45–48], knee osteoarthritis [12,14,49,50], chronic low back pain [51–54], migraine [33,55,56], temporomandibular disorders [57], multiple sclerosis [58,59], chikungunya illness [60], or phantom limb pain [61], suggesting that different CP disorders may share common dysfunctional pain modulation mechanisms [62]. Using a heterogeneous sample in terms of diagnosis, our results also support the efficacy of tES techniques in a wide range of CP conditions. As said above, the available evidence suggests that, despite the diagnosis, very diverse CP pathologies may share common dysfunctional pain modulation mechanisms, and this could explain why they all can benefit from tES. In spite of this cumulative evidence for the analgesic effect of tDCS over M1, previous studies have questioned whether the effect found is not always superior to sham or peripheral stimulation [50,63–65]. In a recent clinical trial with tES delivered at the clinic [25], we found significant improvements both in the active and sham conditions. As the daily visits and contact with the researchers could have unspecific therapeutic effects, in this trial, we used a home intervention with remote daily assessments along a 45-day period and found differences between the active and sham tES groups. Our results cannot completely rule out a placebo effect, but provide insights into how to improve clinical trials in CP.

Regarding tACS over the DLPFC, our results reinforce previous evidence of a positive effect in pain reduction, in CP conditions such as fibromyalgia [66], low back pain [67], and migraine [68]. This effect could be mediated by modulation of brain oscillatory activity in the cortical networks involved in pain perception [17,18,69]. Interestingly, we found similar results to those obtained with tDCS, despite the different type of current and montage. Both types of stimulation affect modulation of the DLPFC, suggesting a role of this region in modifying the activity of areas involved in the affective processing of pain or in descendent inhibitory regulation [70]. Nevertheless, despite the positive and encouraging results obtained with tACS, the evidence must be further strengthened before firmer conclusions can be drawn.

Besides pain reduction, we found that the intervention had a positive effect on all the secondary outcome variables. In general, the analyses did not reveal significant interactions between phase and group, but post-hoc tests revealed significant improvements in pain unpleasantness, daily interference due to pain, fatigue, and analgesic intake only for the active treatment groups, as in previous research [13,28,71]. For sleep quality, the finding is at odds with previous research [13,19], as we found an improvement also in the sham group. Stress/anxiety was the only secondary variable affected by a significant Phase and Group interaction, showing a significant decrease after treatment only for the active tES groups. This result is in line with recent evidence pointing to the usefulness of tES in reducing anxiety and depression in patients with CP [72,73].

Also, we performed repeated-measures ANOVA tests with Bayesian statistics for all the clinical variables, and the results replicated those of classical statistics. Nevertheless, it should be noted that the evidence for the Phase and Group interaction in pain intensity was anecdotal.

On the other hand, we analysed the changes in the daily-reported symptoms by time series analysis. While ANOVA provides a "static" view of mean differences, analysis of the changes in the trends of symptoms can give a more approximate picture of the real responses. For pain intensity, the results indicated a change in trend in the active treatment groups, not observed in the sham. We observed a similar effect for pain unpleasantness, pain interference, and fatigue. Altogether, the results confirmed that the treatment led to an improvement in the pain felt and related effects. This pattern was not confirmed for sleep quality, as the values remained quite stable over time in all the groups, with a slight improvement in the sham. For stress/anxiety, this trend was only significant in the tACS group. Finally, for analgesic intake, we found a significant decline for all groups, which could be due to a placebo effect caused by the patient's participation in the study.

Considering all the above, the results obtained using different statistical approaches are robust and support the effectiveness of active tES. As far as we know, this is the only study to date using daily assessment for such a long period and applying time series analysis to the data. This approach allows us to assess the subjectivity of the painful experience, but largely solving the problems of low reliability or stability over time that characterize self-report-based pain indices [74]. Time-series analysis allows researchers to see how variables evolve daily across the intervention phases, revealing progressive trends, such as steady improvements, delayed effects, plateaus, or rebounds, that simple pre-post analyses would have missed. Thus, with its implementation in clinical trials, it would be possible to address many existing gaps in the field, complementing the traditional data analyses in clinical trials.

Lastly, the results obtained supported the feasibility of HB-tES for patients with CP. The patients reported minimal adverse effects after the stimulation sessions. We obtained low rates of attrition and moderate satisfaction with the treatment, even though the perception of improvement was low. It is possible that only a percentage of the participants responded to the treatment, and thus it would be interesting to delve into their profiles. This modality of treatment (HB-tES) reduces the time spent and enables the patients to be more independent. Home-based interventions with remote online monitoring, such as the one we have carried out, could lead to a significant improvement in intervention efficiency, reducing the number of medical appointments and travel times, and providing greater flexibility for professionals and patients through continuous follow-ups and effective communication. Thus, such protocols could improve access to care for CP populations, with mobility difficulties or living in geographically dispersed regions, and enhance treatment adherence, as well as reduce the high medical and social costs associated with CP management in healthcare systems [75].

Regarding the study limitations, there is an over-representation of women - although this is in line with the gender imbalance of CP prevalence [76] - and patients with primary pain in the sample – using the ICD-11 classification [77], based on diagnostic categories -, which may reduce the generalizability of results to men and other CP types. Perhaps using another type of classification or with a broader and more balanced sample, it would have been possible to analyse subgroups and arrive at more individualised conclusions on the effectiveness of treatment in relation to these subgroups. In addition, although we conducted daily monitoring to determine whether the stimulation session had been completed, we cannot discard that some factors beyond our control may have influenced the treatment implementation and consequently the results. Although the daily trend clearly indicated a reduction in pain in the active groups, we cannot rule out a placebo effect. Finally, the measurement of "analgesic intake" - consisting of a question about the daily use of painkillers but not whether intake increased or decreased from the baseline level- may explain the lack of differences between sham and active groups. In future trials, a standardised scale such as the Medication Quantification Scale (MQS-4.0) [78] should be used.

Conclusions

Our results indicate that the HB-tES techniques are feasible and effective for treating pain in patients with CP. Using an innovative two-pronged approach combining ANOVAs and time series analysis, we obtained robust evidence that the tES treatments decrease patients' daily pain intensity and other core CP symptoms such as pain interference, pain unpleasantness, fatigue, and stress, relative to sham-tES stimulation. Both tDCS and tACS treatments produced similar results, although the characteristics and area of stimulation were different.

CRediT authorship contribution statement

MC designed the study. AG-U, LR-O, and MM recruited the participants. AG-U and LR-O made the assessments and monitored the treatment delivery. AG-U, JA-E, and MC analyzed and interpreted data. AG-U and JA-E wrote the first draft of the manuscript, and MC, MM and NS-V corrected it. AG-U and MC wrote the last version of the manuscript. All authors approved the submitted version.

Funding

This study was funded by the Spanish State Research Agency (Call: Retos 2019. Project reference: PID2019-107986RB-I00). AG-U was supported by a grant from the Spanish Government (Ministerio de Ciencia e Innovación; grant number PRE2020-091845).
Funding for open access charge: Universidade de Santiago de Compostela/CISUG.

Data availability statement

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

Study pre-registration statement

The study was preregistered at https://clinicaltrials.gov/ (ID number: NCT05099406).

Declaration of competing interest

The authors declare no competing interests.

Acknowledgements

Our thanks to all those who volunteered to participate in this study. We would like to thank Diego Pinal Fernández for his advice in the elaboration of the final version of the figures.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.accpm.2025.101613.

References

[1] Breivik H, Collett B, Ventafridda V, Cohen R, Gallacher D. Survey of chronic pain in Europe: prevalence, impact on daily life, and treatment. Eur J Pain 2006;10(4):287. http://dx.doi.org/10.1016/j.ejpain.2005.06.009.
[2] Domenichiello AF, Ramsden CE. The silent epidemic of chronic pain in older adults. Prog Neuro-Psychopharmacol Biol Psychiatry 2019;93:284–90. http://dx.doi.org/10.1016/j.pnpbp.2019.04.006.
[3] Mills SEE, Nicolson KP, Smith BH. Chronic pain: a review of its epidemiology and associated factors in population-based studies. Br J Anaesth 2019;123(2):e273–83. http://dx.doi.org/10.1016/j.bja.2019.03.023.
[4] Apkarian AV, Reckziegel D. Peripheral and central viewpoints of chronic pain, and translational implications. Neurosci Lett 2019;702:3–5. http://dx.doi.org/10.1016/j.neulet.2018.11.040.
[5] Chen Q, Heinricher MM. Descending control mechanisms and chronic pain. Curr Rheumatol Rep 2019;21(5):13. http://dx.doi.org/10.1007/s11926-019-0813-1.
[6] Barroso J, Branco P, Apkarian AV. Brain mechanisms of chronic pain: critical role of translational approach. Transl Res 2021S1931524421001444. http://dx.doi.org/10.1016/j.trsl.2021.06.004.
[7] Ramaswamy S, Wodehouse T. Conditioned pain modulation—A comprehensive review. Neurophysiol Clin 2021;51(3):197–208. http://dx.doi.org/10.1016/j.neucli.2020.11.002.
[8] Hochberg MC, Altman RD, April KT, Benkhalti M, Guyatt G, McGowan J, et al. American College of Rheumatology 2012 recommendations for the use of nonpharmacologic and pharmacologic therapies in osteoarthritis of the hand, hip, and knee. Arthritis Care Res 2012;64(4):465–74. http://dx.doi.org/10.1002/acr.21596.
[9] Chaparro LE, Furlan AD, Deshpande A, Mailis-Gagnon A, Atlas S, Turk DC. Opioids compared with placebo or other treatments for chronic low back pain: an update of the cochrane review. Spine 2014;39(7):556–63. http://dx.doi.org/10.1097/BRS.0000000000000249.
[10] Reinecke H, Weber C, Lange K, Simon M, Stein C, Sorgatz H. Analgesic efficacy of opioids in chronic pain: recent meta-analyses. Br J Pharmacol 2015;172(2):324–33. http://dx.doi.org/10.1111/bph.12634.
[11] Lefaucheur J-P. A comprehensive database of published tDCS clinical trials (2005–2016). Neurophysiol Clin 2016;46(6):319–98. http://dx.doi.org/10.1016/j.neucli.2016.10.002.
[12] Ahn H, Sorkpor S, Miao H, Zhong C, Jorge R, Park L, et al. Home-based self-administered transcranial direct current stimulation in older adults with knee osteoarthritis pain: an open-label study. J Clin Neurosci 2019;66:61–5. http://dx.doi.org/10.1016/j.jocn.2019.05.023.
[13] Brietzke AP, Zortea M, Carvalho F, Sanches PRS, Silva DPJ, Torres ILS, et al. Large treatment effect with extended home-based transcranial direct current stimulation over dorsolateral prefrontal cortex in fibromyalgia: a proof of concept sham-randomized clinical study. J Pain 2020;21(1–2):212–24. http://dx.doi.org/10.1016/j.jpain.2019.06.013.
[14] Martorella G, Mathis K, Miao H, Wang D, Park L, Ahn H. Self-administered transcranial direct current stimulation for pain in older adults with knee osteoarthritis: a randomized controlled study. Brain Stimulation 2022;15(4):902–9. http://dx.doi.org/10.1016/j.brs.2022.06.003.
[15] Vaseghi B, Zoghi M, Jaberzadeh S. Does anodal transcranial direct current stimulation modulate sensory perception and pain? A meta-analysis study. Clin Neurophysiol 2014;125(9):1847–58. http://dx.doi.org/10.1016/j.clinph.2014.01.020.
[16] Antal A, Alekseichuk I, Bikson M, Brockmöller J, Brunoni AR, et al. Low intensity transcranial electric stimulation: safety, ethical, legal regulatory and application guidelines. Clin Neurophysiol 2017;128(9):1774–809. http://dx.doi.org/10.1016/j.clinph.2017.06.001.
[17] Woods AJ, Antal A, Bikson M, Boggio PS, Brunoni AR, Celnik P, et al. A technical guide to tDCS, and related non-invasive brain stimulation tools. Clin Neurophysiol 2016;127(2):1031–48. http://dx.doi.org/10.1016/j.clinph.2015.11.012.

[18] Peng W, Tang D. Pain related cortical oscillations: methodological advances and potential applications. Front Comput Neurosci 2016;10. http://dx.doi.org/10.3389/fncom.2016.00009.
[19] Ahn S, Prim JH, Alexander ML, McCulloch KL, Fröhlich F. Identifying and engaging neuronal oscillations by transcranial alternating current stimulation in patients with chronic low back pain: a randomized, crossover, double-blind, sham-controlled pilot study. J Pain 2018;20(3):277.e1–277.e11. http://dx.doi.org/10.1016/j.jpain.2018.09.004.
[20] Chang MC, Briand MM, Boudier-Revéret M, Yang S. Effectiveness of transcranial alternating current stimulation for controlling chronic pain: a systematic review. Front Neurol 2023;141323520. http://dx.doi.org/10.3389/fneur.2023.1323520.
[21] O'Connell NE, Marston L, Spencer S, DeSouza LH, Wand BM. Non-invasive brain stimulation techniques for chronic pain. Cochrane Database Syst Rev 2018. http://dx.doi.org/10.1002/14651858.CD008208.pub4.
[22] Wen YR, Shi J, Hu ZY, Lin YY, Lin YT, Jiang X, et al. Is transcranial direct current stimulation beneficial for treating pain, depression, and anxiety symptoms in patients with chronic pain? A systematic review and meta-analysis. Front Mol Neurosci 2022;15. http://dx.doi.org/10.3389/fnmol.2022.1056966.
[23] Shlobin NA, Wu C. Current neurostimulation therapies for chronic pain conditions. Curr Pain Headache Rep 2023;27(11):719–28. http://dx.doi.org/10.1007/s11916-023-01168-5.
[24] Teixeira PE, Pacheco-Barrios K, Branco LC, de Melo PS, Marduy A, Caumo W, et al. The analgesic effect of transcranial direct current stimulation in fibromyalgia: a systematic review, meta-analysis, and meta-regression of potential influencers of clinical effect. Neuromodulation 2023;26(4):715–27. http://dx.doi.org/10.1016/j.neurom.2022.10.044.
[25] Samartin-Veiga N, Pidal-Miranda M, González-Villar AJ, Bradley C, Garcia-Larrea L, O'Brien AT, et al. Transcranial direct current stimulation of 3 cortical targets is no more effective than placebo as treatment for fibromyalgia: a double-blind sham-controlled clinical trial. Pain 2022;163(7):e850–61. http://dx.doi.org/10.1097/j.pain.0000000000002493.
[26] Palm U, Kumpf U, Behler N, Wulf L, Kirsch B, Wörsching J, et al. Home use, remotely supervised, and remotely controlled transcranial direct current stimulation: a systematic review of the available evidence. Neuromodulation 2018;21(4):323–33. http://dx.doi.org/10.1111/ner.12686.
[27] Garcia-Larrea L, Perchet C, Hagiwara K, André-Obadia N. At-home cortical stimulation for neuropathic pain: a feasibility study with initial clinical results. Neurotherapeutics 2019;16(4):1198–209. http://dx.doi.org/10.1007/s13311-019-00734-3.
[28] Caumo W, Alves RL, Vicuña P, Alves CF, da S, Ramalho L, et al. Impact of bifrontal home-based transcranial direct current stimulation in pain catastrophizing and disability due to pain in fibromyalgia: a randomized, double-blind sham-controlled study. J Pain 2022;23(4):641–56. http://dx.doi.org/10.1016/j.jpain.2021.11.002.
[29] Caumo W, Ramos RL, Serrano PV, da Silveira Alves CF, Medeiros L, Ramalho L, et al. Efficacy of home-based transcranial direct current stimulation over the primary motor cortex and dorsolateral prefrontal cortex in the disability due to pain in fibromyalgia: a factorial sham-randomized clinical study. J Pain 2024;25(2):376–92. http://dx.doi.org/10.1016/j.jpain.2023.09.001.
[30] Boldt I, Eriks-Hoogland I, Brinkhof MW, De Bie R, Joggi D, Von Elm E. Non-pharmacological interventions for chronic pain in people with spinal cord injury. Cochrane Database Syst Rev 2014. http://dx.doi.org/10.1002/14651858.CD009177.pub2.
[31] Mehta S, McIntyre A, Guy S, Teasell RW, Loh E. Effectiveness of transcranial direct current stimulation for the management of neuropathic pain after spinal cord injury: a meta-analysis. Spinal Cord 2015;53(11):780–5. http://dx.doi.org/10.1038/sc.2015.118.
[32] Fregni F, El-Hagrassy MM, Pacheco-Barrios K, Carvalho S, Leite J, Simis M, et al. Evidence-based guidelines and secondary meta-analysis for the use of transcranial direct current stimulation in neurological and psychiatric disorders. Int J Neuropsychopharmacol 2021;24(4):256–313. http://dx.doi.org/10.1093/ijnp/pyaa051.
[33] Shirahige L, Melo L, Nogueira F, Rocha S, Monte-Silva K. Efficacy of noninvasive brain stimulation on pain control in migraine patients: a systematic review and meta-analysis. Headache 2016;56(10):1565–96. http://dx.doi.org/10.1111/head.12981.
[34] Carvalho F, Brietzke AP, Gasparin A, dos Santos FP, Vercelino R, Ballester RF, et al. Home-based transcranial direct current stimulation device development: an updated protocol used at home in healthy subjects and fibromyalgia patients. J Visualized Exp 2018;13757614. http://dx.doi.org/10.3791/57614.
[35] Faul F, Erdfelder E, Lang A-G, Buchner A. G*Power 3: a flexible statistical power analysis program for the social, behavioral, and biomedical sciences. Behav Res Methods 2007;39(2):175–91. http://dx.doi.org/10.3758/BF03193146.
[36] Gupta SK. Intention-to-treat concept: a review. Perspect Clin Res 2011;2(3):109. http://dx.doi.org/10.4103/2229-3485.83221.
[37] McCoy CE. Understanding the intention-to-treat principle in randomized controlled trials. Western J Emerg Med 2017;18(6):1075. http://dx.doi.org/10.5811/westjem.2017.8.35985.
[38] Knotkova H, Nitsche MA, Cruciani RA. Putative physiological mechanisms underlying tDCS analgesic effects. Front Hum Neurosci 2013;7. http://dx.doi.org/10.3389/fnhum.2013.00628.
[39] Lloyd DM, Wittkopf PG, Arendsen LJ, Jones AKP. Is Transcranial Direct Current Stimulation (tDCS) effective for the treatment of pain in fibromyalgia? A systematic review and meta-analysis. J Pain 2020;21(11–12):1085–100. http://dx.doi.org/10.1016/j.jpain.2020.01.003.
[40] Gordon EM, Chauvin RJ, Van AN, Rajesh A, Nielsen A, Newbold DJ, et al. A somato-cognitive action network alternates with effector regions in motor cortex. Nature 2023;617(7960):351–9. http://dx.doi.org/10.1038/s41586-023-05964-2.
[41] Boggio PS, Zaghi S, Lopes M, Fregni F. Modulatory effects of anodal transcranial direct current stimulation on perception and pain thresholds in healthy volunteers. Eur J Neurol 2008;15(10):1124–30. http://dx.doi.org/10.1111/j.1468-1331.2008.02270.x.
[42] Polanía R, Paulus W, Nitsche MA. Modulating cortico-striatal and thalamo-cortical functional connectivity with transcranial direct current stimulation. Hum Brain Mapp 2012;33(10):2499–508. http://dx.doi.org/10.1002/hbm.21380.
[43] Castillo-Saavedra L, Gebodh N, Bikson M, Diaz-Cruz C, Brandao R, Coutinho L, et al. Clinically effective treatment of fibromyalgia pain with high-definition transcranial direct current stimulation: phase II open-label dose optimization. J Pain 2016;17(1):14–26. http://dx.doi.org/10.1016/j.jpain.2015.09.009.
[44] De Ridder D, Adhia D, Vanneste S. The anatomy of pain and suffering in the brain and its clinical implications. Neurosci Biobehav Rev 2021;130:125–46. http://dx.doi.org/10.1016/j.neubiorev.2021.08.013.
[45] Villamar MF, Wivatvongvana P, Patumanond J, Bikson M, Truong DQ, Datta A, et al. Focal modulation of the primary motor cortex in fibromyalgia using 4× 1-ring high-definition transcranial direct current stimulation (HD-tDCS): immediate and delayed analgesic effects of cathodal and anodal stimulation. J Pain 2013;14(4):371–83. http://dx.doi.org/10.1016/j.jpain.2012.12.007.
[46] Khedr EM, Omran EA, Ismail NM, El-Hammady DH, Goma SH, Kotb H, et al. Effects of transcranial direct current stimulation on pain, mood and serum endorphin level in the treatment of fibromyalgia: a double blinded, randomized clinical trial. Brain Stimulation 2017;10(5):893–901. http://dx.doi.org/10.1016/j.brs.2017.06.006.
[47] Cheng YC, Hsiao CY, Su MI, Chiu CC, Huang YC, Huang WL. Treating fibromyalgia with electrical neuromodulation: a systematic review and meta-analysis. Clin Neurophysiol 2023;148:17–28. http://dx.doi.org/10.1016/j.clinph.2023.01.011.
[48] Moshfeghinia R, Shekouh D, Mostafavi S, Hosseinzadeh M, Bahadori AR, Abdollahifard S, et al. The effects of transcranial direct-current stimulation (tDCS) on pain intensity of patients with fibromyalgia: a systematic review and meta-analysis. BMC Neurol 2023;23(1):395. http://dx.doi.org/10.1186/s12883-023-03445-7.
[49] Ahn H, Woods AJ, Kunik ME, Bhattacharjee A, Chen Z, Choi E, et al. Efficacy of transcranial direct current stimulation over primary motor cortex (anode) and contralateral supraorbital area (cathode) on clinical pain severity and mobility performance in persons with knee osteoarthritis: an experimenter-and participant-blinded, randomized, sham-controlled pilot clinical study. Brain Stimulation 2017;10(5):902–9. http://dx.doi.org/10.1016/j.brs.2017.05.007.
[50] Comino-Suárez N, Serrano-Muñoz D, Beltran-Alacreu H, Belda-Pérez P, Avendaño-Coy J. Efficacy of transcranial direct current stimulation on pain intensity and functionality in patients with knee osteoarthritis: a systematic review and meta-analysis. Am J Phys Med Rehabil 2023;10:1097. http://dx.doi.org/10.1097/phm.0000000000002386.
[51] Straudi S, Buja S, Baroni A, Pavarelli C, Pranovi G, Fregni F, et al. The effects of transcranial direct current stimulation (tDCS) combined with group exercise treatment in subjects with chronic low back pain: a pilot randomized control trial. Clin Rehabil 2018;32(10):1348–56. http://dx.doi.org/10.1177/0269215518777881.
[52] Jafarzadeh A, Ehsani F, Yosephi MH, Zoghi M, Jaberzadeh S. Concurrent postural training and M1 anodal transcranial direct current stimulation improve postural impairment in patients with chronic low back pain. J Clin Neurosci 2019;68:224–34. http://dx.doi.org/10.1016/j.jocn.2019.07.017.
[53] Jiang N, Wei J, Li G, Wei B, Zhu FF, Hu Y. Effect of dry-electrode-based transcranial direct current stimulation on chronic low back pain and low back muscle activities: a double-blind sham-controlled study. Restor Neurol Neurosci 2020;38(1):41–54. http://dx.doi.org/10.3233/RNN-190922.
[54] Hazime FA, Baptista AF, De Freitas DG, Monteiro RL, Maretto RL, Hasue RH, et al. Treating low back pain with combined cerebral and peripheral electrical stimulation: a randomized, double-blind, factorial clinical trial. Eur J Pain 2017;21(7):1132–43. http://dx.doi.org/10.1002/ejp.1037.
[55] Przeklasa-Muszyńska A, Kocot-Kępska M, Dobrogowski J, Wiatr M, Mika J. Transcranial direct current stimulation (tDCS) and its influence on analgesics effectiveness in patients suffering from migraine headache. Pharmacol Rep 2017;69:714–21. http://dx.doi.org/10.1016/j.pharep.2017.02.019.
[56] Rahimi MD, Fadardi JS, Saeidi M, Bigdeli I, Kashiri R. Effectiveness of cathodal tDCS of the primary motor or sensory cortex in migraine: a randomized controlled trial. Brain Stimulation 2020;13(3):675–82. http://dx.doi.org/10.1016/j.brs.2020.02.012.
[57] Kim DJ, Nascimento TD, Lim M, Danciu T, Zubieta JK, Scott PJ, et al. Exploring HD-tDCS effect on μ-opioid receptor and pain sensitivity in temporomandibular disorder: a pilot randomized clinical trial study. J Pain 2024;25(4):1070–81. http://dx.doi.org/10.1016/j.jpain.2023.11.001.
[58] Ayache SS, Palm U, Chalah MA, Al-Ani T, Brignol A, Abdellaoui M, et al. Prefrontal tDCS decreases pain in patients with multiple sclerosis. Front Neurosci 2016;10:147. http://dx.doi.org/10.3389/fnins.2016.00147.
[59] Hadoush H, Alawneh A, Kassab M, Al-Wardat M, Al-Jarrah M. Effectiveness of non-pharmacological rehabilitation interventions in pain management in patients with multiple sclerosis: systematic review and meta-analysis. NeuroRehabilitation 2022;50(4):347–65. http://dx.doi.org/10.3233/NRE-210328.

[60] De Souza CG, Pegado R, Costa J, Morya E, Baptista AF, Unal G, et al. Alternate sessions of transcranial direct current stimulation (tDCS) reduce chronic pain in women affected by chikungunya. A randomized clinical trial. Brain Stimulation 2021;14(3):541–8. http://dx.doi.org/10.1016/j.brs.2021.02.015.

[61] Navarro-Lopez V, Manuel DEL, Fernandez-Vazquez D, Fernandez-Gonzalez P, Carratala-Tejada M, Molina-Rueda F. Transcranial direct current stimulation in the management of phantom limb pain: a systematic review of randomized controlled trials. Eur J Phys Rehabil Med 2022;58(5):738–48. http://dx.doi.org/10.23736/S1973-9087.22.07439-1.

[62] Arendt-Nielsen L, Morlion B, Perrot S, Dahan A, Dickenson A, Kress HG, et al. Assessment and manifestation of central sensitization across different chronic pain conditions. Eur J Pain 2018;22(2):216–41. http://dx.doi.org/10.1002/ejp.1140.

[63] Alwardat M, Pisani A, Etoom M, Carpenedo R, Chinè E, Dauri M, et al. Is transcranial direct current stimulation (tDCS) effective for chronic low back pain? A systematic review and meta-analysis. J Neural Transm 2020;127(9):1257–70. http://dx.doi.org/10.1007/s00702-020-02223-w.

[64] Evers S. Non-invasive Neurostimulation methods for acute and preventive migraine treatment—a narrative review. J Clin Med 2021;10(15):3302. http://dx.doi.org/10.3390/jcm10153302.

[65] Li L, Huang H, Yu Y, Jia Y, Liu Z, Shi X, et al. Non-invasive brain stimulation for neuropathic pain after spinal cord injury: a systematic review and network meta-analysis. Front Neurosci 2022;15800560. http://dx.doi.org/10.3389/fnins.2021.800560.

[66] Lin AP, Chiu CC, Chen SC, Huang YJ, Lai CH, Kang JH. Using high-definition transcranial alternating current stimulation to treat patients with fibromyalgia: a randomized double-blinded controlled study. Life 2022;12(9):1364. http://dx.doi.org/10.3390/life12091364.

[67] Prim JH, Ahn S, Davila MI, Alexander ML, McCulloch KL, Fröhlich F. Targeting the autonomic nervous system balance in patients with chronic low back pain using transcranial alternating current stimulation: a randomized, crossover, double-blind, placebo-controlled pilot study. J Pain Res 2019;3265–77. http://dx.doi.org/10.2147/JPR.S208030.

[68] Antal A, Bischoff R, Stephani C, Czesnik D, Klinker F, Timäus C, et al. Low intensity, transcranial, alternating current stimulation reduces migraine attack burden in a home application set-up: a double-blinded, randomized feasibility study. Brain Sci 2020;10(11):888. http://dx.doi.org/10.3390/brainsci10110888.

[69] Fröhlich F. Experiments and models of cortical oscillations as a target for noninvasive brain stimulation. Progress Brain Res 2015;222:41–73. http://dx.doi.org/10.1016/bs.pbr.2015.07.025.

[70] Yang S, Chang MC. Chronic pain: structural and functional changes in brain structures and associated negative affective states. Int J Mol Sci 2019;20(13):3130. http://dx.doi.org/10.3390/ijms20133130.

[71] Hernandez-Tejada MA, Cherry KE, Rauch SAM, Acierno R, Fries GR, Muzzy W, et al. Management of chronic pain and PTSD in veterans with tDCS+Prolonged Exposure: a pilot study. Mil Med 2023;188(11–12):3316–21. http://dx.doi.org/10.1093/milmed/usac200.

[72] Naji F, Sharbafchi MR, Khorvash F, Maracy MR, Abadi NGM. The efficacy of repetitive transcranial magnetic stimulation (rTMS) versus transcranial direct-current stimulation (tDCS) on migraine headaches: a randomized clinical trial. Adv Biomed Res 2024;13:7. http://dx.doi.org/10.4103/abr.abr14223.

[73] Wen YR, Shi J, Hu ZY, Lin YY, Lin YT, Jiang X, et al. Is transcranial direct current stimulation beneficial for treating pain, depression, and anxiety symptoms in patients with chronic pain? A systematic review and meta-analysis. Front Mol Neurosci 2022;15. http://dx.doi.org/10.3389/fnmol.2022.1056966.

[74] Chiarotto A, Maxwell LJ, Ostelo RW, Boers M, Tugwell P, Terwee CB. Measurement properties of visual analogue scale, numeric rating scale, and pain severity subscale of the brief pain inventory in patients with low back pain: a systematic review. The Journal of Pain 2019;20(3):245–63. http://dx.doi.org/10.1016/j.jpain.2018.07.009.

[75] Leadley RM, Armstrong N, Lee YC, Allen A, Kleijnen J. Chronic diseases in the European Union: the prevalence and health cost implications of chronic pain. J Pain Palliat Care Pharmacother 2012;26(4):310–25. http://dx.doi.org/10.3109/15360288.2012.736933.

[76] Tsang A, Von Korff M, Lee S, Alonso J, Karam E, Angermeyer MC, et al. Common chronic pain conditions in developed and developing countries: gender and age differences and comorbidity with depression-anxiety disorders. The Journal of Pain 2008;9(10):883–91. http://dx.doi.org/10.1016/j.jpain.2008.05.005.

[77] Treede RD, Rief W, Barke A, Aziz Q, Bennett MI, Benoliel R, et al. Chronic pain as a symptom or a disease: the IASP classification of chronic pain for the International Classification of Diseases (ICD-11). Pain 2019;160(1):19–27. http://dx.doi.org/10.1097/j.pain.0000000000001384.

[78] De Clifford-Faugère G, Nguefack HLN, Godbout-Parent M, Diallo MA, Guénette L, Pagé MG, et al. The medication quantification scale 4.0: an updated index based on prescribers' perceptions of the risk associated with chronic pain medications. J Pain 2024;25(2):508–21. http://dx.doi.org/10.1016/j.jpain.2023.09.010.