Neurol Ther (2025) 14:989–1006
https://doi.org/10.1007/s40120-025-00734-w

ORIGINAL RESEARCH

Effect of Anodal Transcranial Direct Current Stimulation on the Intensity of Post-dural Puncture Headache: Results of Two Randomized Sham Controlled Trials

Bledar Gjikolaj · Mario Stampanoni Bassi · Antonio Bruno · Valeria De Ioanni · Ettore Dolcetti · Sheila Peter · Giovanni Galifi · Antonella Conte · Luana Gilio · Diego Centonze · Fabio Buttari

Received: January 23, 2025 / Accepted: March 13, 2025 / Published online: April 22, 2025

ABSTRACT

Introduction: Post-dural puncture headache (PDPH) is a common complication of diagnostic lumbar puncture (LP), often leading to extended hospitalization and additional medication use. Clinical studies have shown that anodal transcranial direct current stimulation (a-tDCS) is effective against migraine, and thus we decided to assess whether a-tDCS was also effective in treating and preventing PDPH.

Methods: In two independent, randomized, monocentric controlled trials (RCTs), we enrolled 97 hospitalized participants who underwent LP for diagnostic purposes. Patients were randomized to receive either active a-tDCS or sham tDCS over the dominant primary motor cortex (M1) in a therapeutic tDCS (Th-tDCS) or preventive tDCS (Pr-tDCS) study. In the two trials, the primary outcome was the severity of PDPH measured using the Visual Analogue Scale (VAS) for pain. Secondary outcomes included the Brief Pain Inventory (BPI) to evaluate other pain-related symptoms associated with LP.

Results: In the Th-tDCS study, significant differences between groups were observed after tDCS in the VAS ($F = 17.011$, $p < 0.001$), as well as in BPI intensity ($F = 17.006$, $p < 0.001$) and BPI interference ($F = 14.730$, $p < 0.001$). Moreover, in the Pr-tDCS study, VAS analysis showed a significant time × group interaction ($F = 6.918$, $p = 0.002$). Significant differences were also observed in BPI intensity ($F = 17.866$, $p < 0.001$) and BPI interference ($F = 15.520$, $p < 0.001$).

Conclusions: Our findings suggest that a-tDCS may effectively prevent and treat PDPH and alleviate other pain-related symptoms associated with LP. Encouraging results have emerged for the use of a-tDCS in patients undergoing LP, in both experimental research designs (Th-tDCS

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-025-00734-w.

B. Gjikolaj · S. Peter · G. Galifi · D. Centonze (✉) · F. Buttari
Department of Systems Medicine, Tor Vergata University, Rome, Italy
e-mail: centonze@uniroma2.it; diego.centonze@neuromed.it

M. Stampanoni Bassi · A. Bruno · V. De Ioanni · E. Dolcetti · G. Galifi · A. Conte · L. Gilio · D. Centonze · F. Buttari
Unit of Neurology, IRCCS Neuromed, Pozzilli, Isernia, Italy

A. Conte
Department of Human Neurosciences, Sapienza University, Rome, Italy

L. Gilio
Faculty of Psychology, Uninettuno Telematic International University, Rome, Italy

and Pr-tDCS). A non-invasive brain stimulation (NIBS) technique, such as a-tDCS, could have a therapeutic and preventive effect on pain resulting from a LP.
***Trial Registration*:** ClinicalTrials.gov (ID: NCT 06640634) retrospectively registered on October 8, 2024.

PLAIN LANGUAGE SUMMARY

A lumbar puncture can frequently lead to a severe headache known as post-dural puncture headache, which may result in prolonged hospital stay and increased use of pharmacological therapy. We have tested a non-invasive brain stimulation technique, called transcranial direct current stimulation, to reduce the intensity and prevent post-dural puncture headache. Transcranial direct current stimulation may prevent and reduce the intensity of post-dural puncture headache.

Keywords: Headache Neuromodulation; Non-invasive brain stimulation; Post-dural puncture headache; Transcranial direct current stimulation

Key Summary Points

Why carry out this study?

Post-dural puncture headache (PDPH) is a common complication of diagnostic lumbar puncture (LP), often leading to extended hospitalization and additional medication use

Clinical studies have shown that anodal transcranial direct current stimulation (a-tDCS) is effective against migraine

The aim of this study was to explore the efficacy of a-tDCS on the intensity of PDPH and other pain-related symptoms associated with LP

What was learned from this study?

Our findings suggest that a-tDCS may reduce the intensity of PDPH and alleviate other pain-related symptoms associated with LP

A non-invasive brain stimulation (NIBS) technique, such as a-tDCS, could have a therapeutic and preventive effect on pain resulting from a LP

INTRODUCTION

Post-dural puncture headache (PDPH) is the most prevalent complication in patients undergoing diagnostic or therapeutic lumbar puncture (LP) [1]. The pathophysiology of PDPH is primarily attributed to the mechanical traction on pain-sensitive intracranial nerves (e.g., the upper cervical, 5th, 9th, and 10th cranial nerves) and vascular structures, mediated by persistent dural damage leading to cerebrospinal fluid (CSF) leakage and subsequent CSF pressure reduction [2].

According to the International Classification of Headache Disorders 3rd edition (ICHD3), PDPH is classified as a headache subtype due to low CSF pressure. It typically manifests as an orthostatic headache within a few days post-LP, accompanied by symptoms such as neck pain, tinnitus, auditory changes, photophobia, and nausea [3]. While PDPH usually resolves within 7–10 days, it can result in extended hospital stays and increased need for medication. The use of atraumatic needles is the most effective preventive measure for PDPH [1], though other commonly recommended practices such as bed rest, fluid administration, and caffeine have questionable efficacy [1, 4].

Transcranial direct current stimulation (tDCS) is a non-invasive brain stimulation (NIBS) technique that applies low-voltage electrical currents through surface electrodes on the scalp [5,

6]. Depending on the stimulation type (anodal or cathodal), tDCS can induce long-lasting increases or decreases in neuronal excitability and vascular–neuronal activity coupling. Cathodal stimulation leads to hyperpolarization and a reduction in excitability, whereas anodal stimulation induces depolarization and enhances excitability [5, 7]. Research has shown that anodal tDCS (a-tDCS) applied to the primary motor cortex (M1) can alleviate various pain conditions, including fibromyalgia, neuropathic pain, and headaches [8–10]. The pain-relieving effects of M1 a-tDCS are believed to follow the modulation of intracortical inhibitory GABAergic transmission [11], and the descending connections from M1 to the thalamus and periaqueductal gray [12, 13].

Although short-term a-tDCS treatment has shown promise in preventing migraine and medication-overuse headache [14–18], its role in preventing and treating PDPH remains unexplored. This study aims to evaluate the efficacy of preventive and therapeutic a-tDCS applied to M1 in patients undergoing diagnostic LP.

METHODS

Patients and Study Design

A total of 97 patients admitted to the Neurology Unit of the Neuromed Research Institute between January 2022 and April 2024 were enrolled in two independent clinical trials. All patients underwent LP as part of their diagnostic work-up. The study was approved by the Ethics Committee of the IRCCS Neuromed, Pozzilli, Italy, in accordance with the Declaration of Helsinki (approval code: 12-17), and was registered with clinicaltrials.gov (NCT06640634). Written informed consent was obtained from all participants prior to inclusion in the study.

The inclusion criteria were age between 18 and 75 years and the indication to undergo diagnostic LP. Exclusion criteria included any prior exposure to brain stimulation, contraindications to tDCS, a previous diagnosis of migraine or chronic headache, usage of preventive medication at the baseline assessment, history of depression, obesity, multiple LP attempts, or cognitive impairment.

LP was performed after overnight fasting, with patients positioned in the lateral decubitus position, using a Spinal Needle Quincke-Type Point (22 G × 3.50″ × 0.9 mm × 90 mm; Becton Dickinson, Madrid, Spain). A total of 5 ml of CSF was collected for diagnostic purposes.

Two experimental study designs were employed: (1) therapeutic tDCS (Th-tDCS)y and (2) preventive tDCS (Pr-tDCS).

In the Th-tDCS study (see Fig. 1A), patients were randomized after the diagnosis of PDPH, which was made within the first 4 days post-LP according to the International Classification of Headache Disorders, 3rd edition (ICHD-3) criteria. These patients were assigned to either the active a-tDCS group or the sham tDCS group, receiving the intervention for 3 consecutive days. A total of 29 patients were studied in the Th-tDCS study, consisting of 17 females and 12 males, with a mean age of 45.310 years and a standard deviation (SD) of 14.524.

In the Pr-tDCS study (see Fig. 1B), patients were randomized immediately after the LP, and started the active or sham tDCS on the same day (T0), and the treatment continued for 3 consecutive days (T1 and T2). A total of 40 patients were studied in the Pr-tDCS study, consisting of 19 females and 21 males, with a mean age of 51.400 years and a SD of 14.084.

When necessary, patients were allowed to access symptomatic therapy with acetaminophen and anti-emetics (metoclopramide and levosulpiride), for each patient, the type of symptomatic medication, dose, and number of administrations were recorded. No prophylactic therapies, such as anti-epileptics, antidepressants, benzodiazepines, opioids, or steroid drugs, were administered for the treatment of PDPH in the patients included in the two trials. Additionally, no intravenous fluids were given, and the patients included in the two trials were instructed to maintain adequate hydration without any fluid restriction.

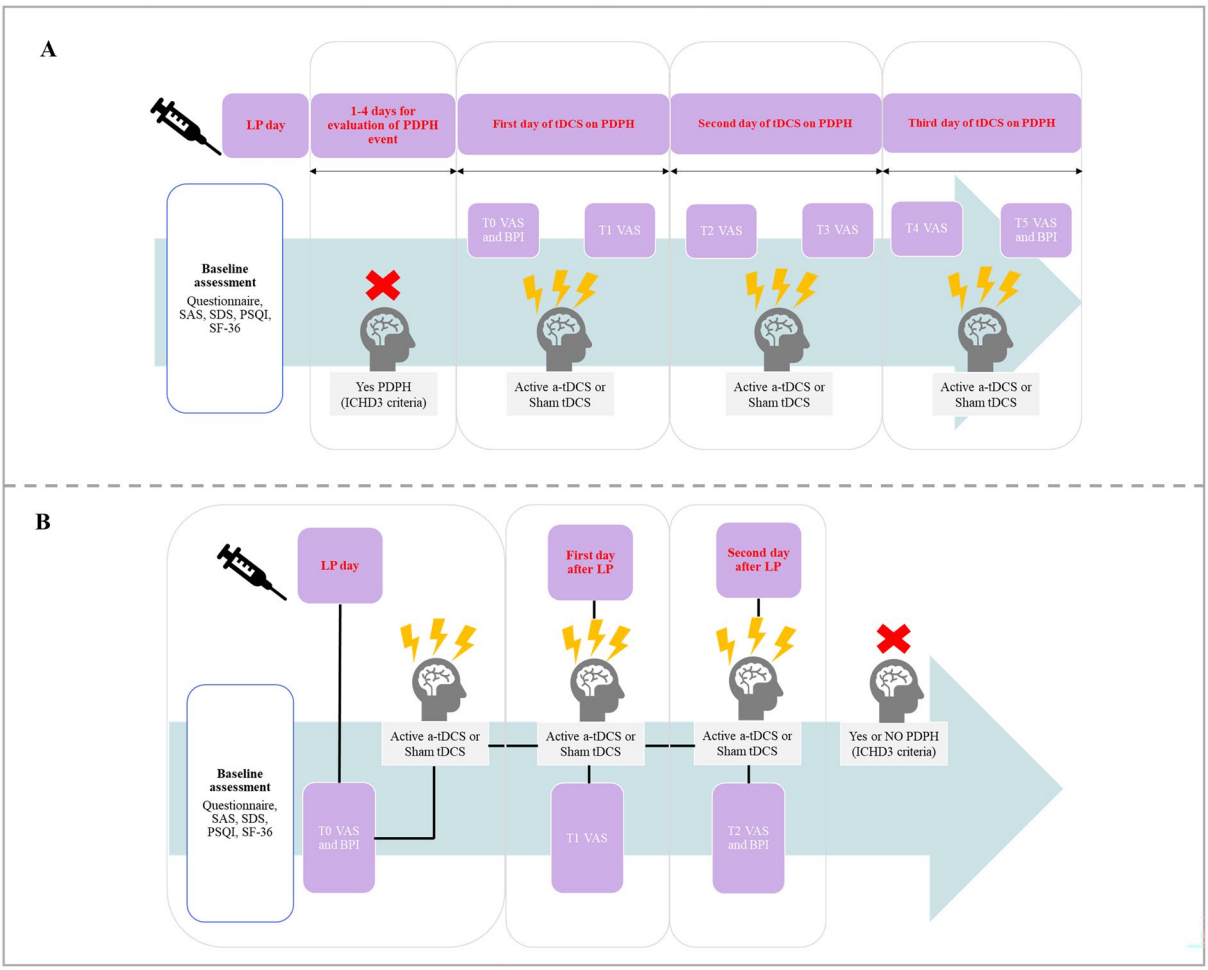

Fig. 1 Study design of the two experimental protocols: **A** therapeutic tDCS (Th-tDCS): baseline, interventions and assessment time points, **B** preventive tDCS (Pr-tDCS): baseline, interventions and assessment time points. *a-tDCS* anodal transcranial direct current stimulation, *BPI* Brief Pain Inventory, *ICHD3* International Classification of Headache Disorders 3rd edition, *LP* lumbar puncture, *PDPH* post-dural puncture headache, *PSQI* Pittsburgh Sleep Quality Index, *SAS* Zung's self-rating anxiety scale, *SDS* Zung's self-rating depression scale, *SF-36* 36-Item Short Form Survey, *T* timepoint, *tDCS* transcranial direct current stimulation, *VAS* Visual Analogue Scale

Randomization and Blinding

Patients in both Th-tDCS and Pr-tDCS studies were randomized (allocation ratio 1:1) into two parallel groups: active a-tDCS or sham tDCS. Blocked randomization was achieved using a computer-generated sequence of binary values (i.e., real or sham). Both patients and investigators involved in clinical evaluations were blinded to the stimulation group assignments. The effectiveness of the blinding was assessed at the end of the stimulation period by asking patients to indicate which treatment they believed they had received (active stimulation, sham stimulation, or do not know). The blinding assessment of Th-tDCS and Pr-tDCS is depicted in Tables S3 and S4 (see the Electronic Supplementary Material).

a-tDCS Protocol

The tDCS protocol was identical for both the Th-tDCS and Pr-tDCS studies. tDCS was delivered using a battery-driven direct current stimulator (HDCstim-DC stimulator; Newronika, Milan, Italy). The current was administered through a pair of saline-soaked surface electrodes. The anode, measuring 3 × 3 cm, was placed over the M1 in the dominant hemisphere. We chose to target the M1 area rather than the primary somatosensory cortex (S1) and the dorsolateral prefrontal cortex (DLPFC), as it has been reported to be more effective [19]. M1 was identified using the International 10–20 EEG system for C3 (left M1) or C4 (right M1). The cathode, measuring 6 × 4 cm, was positioned over the contralateral supraorbital region, immediately below the Fp (frontal pole) position [20].

In the active a-tDCS group, each session consisted of 20-min stimulation with a 2-mA intensity. In the sham tDCS group, the duration and electrodes application were the same, but the current was stopped after 30 s. The subject felt the initial itching sensation, but no changes in cortical excitability were produced [21].

Clinical Assessment

All clinical scales were administered by a neurologist and a trained neuropsychologist.

Primary Outcome

The primary outcome was to assess differences between the two groups (active a-tDCS and sham tDCS) in PDPH-related pain, evaluated using the Visual Analogue Scale (VAS) and referred to pain intensity at that specific moment. The VAS is a self-administered scale in which patients indicate the intensity of pain experienced by selecting a point on a continuous line ranging from 0 to 100 mm, representing the absence of pain to the worst pain, respectively. This scale is widely used in pain studies, with demonstrated validity and reproducibility [22].

In the Th-tDCS study, VAS was administered at T0, before starting tDCS, and 2 h before and 2 h after the tDCS sessions (T1, T2, T3, T4, and T5).

In the Pr-tDCS study, VAS was administered each day at the end of the tDCS sessions (T0, T1, and T2).

Secondary Outcome

As secondary outcome, we analyzed the effects of tDCS on other pain-related symptoms associated with LP, evaluated using the Brief Pain Inventory (BPI). The BPI is a multidimensional measurement tool originally developed to assess the intensity and interference of pain in patients with cancer [23]. In this study, the BPI was used to assess painful symptoms associated with LP, evaluating both the intensity of pain and its interference with affective and activity aspects of the patient's daily life over the past 24 h.

In the Th-tDCS study, the BPI was collected before starting tDCS (T0) and 2 h after the last tDCS stimulation (T5). In the Pr-tDCS study, the BPI was collected before starting tDCS (T0) and 2 h after the last stimulation (T2).

Psychological and Quality of Life Assessments

At baseline in both Th-tDCS and Pr-tDCS, a comprehensive psychological evaluation was conducted, including assessments of depression and anxiety levels using the Zung Anxiety Self-Assessment Scale (SAS) and the Zung Self-Rating Depression Scale (SDS).

The SAS consists of 20 self-report questions measuring anxiety levels across cognitive, autonomic, motor, and central nervous system symptoms [24]. The SDS is an established norm-referenced screening measure used to identify the presence of depressive disorders in adults, and contains 20 items based on the diagnostic criteria for depression [25].

Sleep quality was evaluated using the 19-item Pittsburgh Sleep Quality Index (PSQI), which measures subjective sleep quality over the past month [26]. Quality of life was assessed with the 36-Item Short Form Survey (SF-36), covering eight sections: vitality, physical functioning, bodily pain, general health perceptions, physical

role functioning, emotional role functioning, social role functioning, and mental health [27].

Sample Size

In the Th-tDCS study, the sample size calculation was based on the primary outcome, the VAS scale. The calculation was performed for a two independent sample study (active a-tDCS vs. sham tDCS). According to the literature, we considered the VAS endpoint values reported in similar experiments [28, 29].

The computation was made with the following parameters: confidence interval (two-sided): 95%; alpha: 5%; power: 80%; beta: 20%; ratio of sample size: 1:1; group 1 mean: 51; group 2 mean: 27; standard deviation: 20. The minimum sample size suggested was found to be 22 patients. Considering a 15% possible drop-out rate, the minimum number of patients needed was estimated at 26.

In the Pr-tDCS study, the sample size calculation was based on the primary outcome, the VAS scale. The calculation was performed for a two independent sample study (active a-tDCS vs. sham tDCS). According to literature [28, 29], the computation was made with the following parameters: confidence interval (two-sided): 95%; alpha: 5%; power: 80%; beta: 20%; ratio of sample size: 1:1; mean difference: 1; standard deviation: 2. The minimum sample size suggested was found to be 34 patients. Considering a 15% possible drop-out rate, the minimum number of patients needed was estimated at 40.

Statistical Analysis

The statistical analysis was performed with JAMOVI (version 2.3, The Jamovi Project, Sydney, Australia) and was based on the per-protocol population.

The Shapiro–Wilk test was used to check for normality distribution of continuous data. Data were presented as mean, mean difference (MD), percentage (%), SD, or standard error (SE).

Differences between groups in clinical score analysis were tested by an independent samples t test for non-categorical variables and chi square for categorical variables. Repeated-measures ANOVA was performed with group (active a-tDCS vs. sham tDCS) as between and within subjects factor and time, with Greenhouse–Geisser sphericity correction. Post hoc tests were employed, the p values were adjusted using the Tukey's method, and all p values < 0.05 was considered as significant.

RESULTS

Therapeutic tDCS Study

Clinical Characteristics of the Study Population

A total of 42 patients were initially evaluated for the Th-tDCS study, of which 36 were randomized to receive active a-tDCS or sham tDCS, with 29 completing the study and being analyzed. The CONSORT flow diagram of the Th-tDCS study is shown in Fig. 2A. Patient diagnosis according to the tDCS group is reported in Table S1 (see the Electronic Supplementary Material).

No significant differences were found between the active a-tDCS and sham tDCS groups in age ($p = 0.084$) or sex ($p = 0.786$). Furthermore, no significant differences were found between the two groups in the levels of depression ($p = 0.362$), anxiety ($p = 0.371$), sleep quality ($p = 0.601$), or in quality of life evaluated with the SF-36 (physical functioning $p = 0.462$, role-physical $p = 0.554$, bodily pain $p = 0.668$, general health $p = 0.571$, vitality $p = 0.523$, social functioning $p = 0.469$, role-emotional $p = 0.134$, mental health $p = 0.196$). The clinical and demographic characteristics of patients in the active a-tDCS and sham tDCS groups are shown in Table 1.

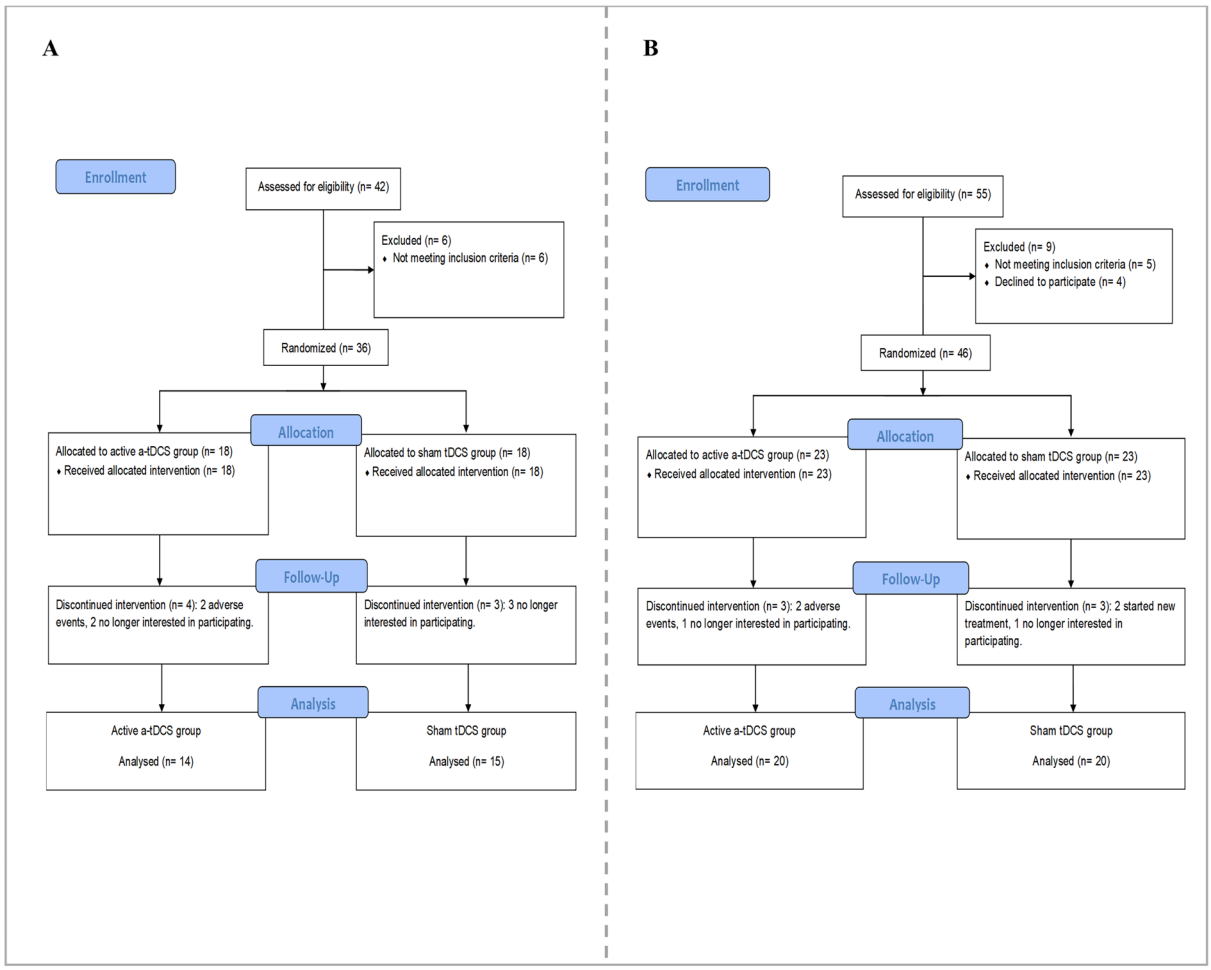

Fig. 2 CONSORT flow diagrams of the two experimental study: **A** therapeutic tDCS (Th-tDCS) study; **B** preventive tDCS (Pr-tDCS) study. *CONSORT* consolidated standards of reporting trials, *a-tDCS* anodal transcranial direct current stimulation, *tDCS* transcranial direct current stimulation

Effects of Therapeutic M1 a-tDCS on PDPH

To explore the effects of a-tDCS on PDPH (main outcome), we first compared the VAS scores between the two groups (active a-tDCS and sham tDCS) (Fig. 3A).

No significant differences were found in the VAS scores between the active and sham tDCS at T0 (T0 VAS score mean ± SD: active group = 65.857 ± 22.698, sham group = 60.333 ± 20.903, p = 1.000). Repeated-measures ANOVA evidenced a significant effect of time [(T0, T1, T2, T3, T4, T5): F = 7.335, p value < 0.001], and a significant effect of group [(a-tDCS vs. sham tDCS): F = 8.662, p value = 0.007]. In addition, a significant interaction time × group was also evidenced (F = 17.011, p value ≤ 0.001). Post hoc comparisons, illustrated in Fig. 3A, indicated significant differences in VAS scores between the two groups at: T3 (VAS score mean ± SD: active group = 39.786 ± 29.548, sham group = 72.267 ± 14.464, p = 0.029), T4 (VAS score mean ± SD: active group = 30.214 ± 24.944, sham group = 66.600 ± 19.257, p = 0.007) and T5 (VAS score mean ± SD: active group = 28.571 ± 27.264, sham group = 69.600 ± 14.411, p = 0.001).

The frequency and categorization of pain are reported in Table 2.

Table 1 Therapeutic tDCS (Th-tDCS) study table: baseline demographic–clinical characteristics and pharmacological therapies of patients according to the allocated group

	Active a-tDCS *n* = 14	Sham tDCS *n* = 15	*p* value
Female, *n* (%)	11 (78.57)	6 (40)	0.786†
Age, mean (SD)	47.00 (14.17)	43.73 (15.15)	0.084
Zung's self-rating anxiety scale (SAS), mean (SD)	41.21 (8.78)	44.60 (11.03)	0.371
Zung's self-rating depression scale (SDS), mean (SD)	40.78 (9.79)	44.93 (13.80)	0.362
Pittsburgh Sleep Quality Index (PSQI), mean (SD)	6.43 (3.89)	7.46 (4.45)	0.601
SF-36 Physical Functioning (PF), mean (SD)	53.92 (33.06)	44.66 (33.67)	0.462
SF-36 Role limitations-physical (RF), mean (SD)	28.57 (41.43)	20.00 (35.60)	0.554
SF-36 Bodily pain (BP), mean (SD)	42.07 (28.61)	47.20 (34.48)	0.668
SF-36 General health (GH), mean (SD)	44.07 (15.39)	48.26 (22.95)	0.571
SF-36 Vitality (VT), mean (SD)	51.42 (18.85)	45.66 (27.89)	0.523
SF-36 Social functioning (SF), mean (SD)	61.500 (24.81)	53.86 (30.55)	0.469
SF-36 Role limitations-emotional (RE), mean (SD)	59.42 (45.64)	33.26 (45.91)	0.134
SF-36 Mental health (MH), mean (SD)	61.14 (21.01)	49.60 (25.46)	0.196
NSAID (acetaminophen), *n* (%)	11 (78.57)	10 (66.66)	0.474†
Anti-emetic, *n* (%)	3 (21.42)	3 (20)	0.924†

a-tDCS anodal-transcranial direct current stimulation, *n* number of subjects, *NSAIDs* non-steroidal anti-inflammatory drugs, *SD* standard deviation, *SF-36* 36-Item Short Form Survey, *tDCS* transcranial direct current stimulation

p value by *t* test and † chi square

The pharmacological therapy administered during hospitalization was not statistically different between the two groups for all drugs ($p > 0.05$; Table 1).

To explore the effects of tDCS on other painful symptoms associated with LP (secondary outcome), we compared the BPI intensity and interference scores collected at T0 and T2 in the two groups (a-tDCS and sham tDCS), and these results are shown in Fig. 3B.

No significant differences were found in the BPI intensity scores between the active and sham tDCS at T0 (T0 BPI intensity score mean ± SD: active group = 5.566 ± 1.835, sham group = 4.928 ± 2.080, $p = 0.819$). Repeated-measures ANOVA did not evidence a significant effect of group [(a-tDCS vs. sham-tDCS): $F = 1.063$, p value = 0.312] and of time [(T0, T5): $F = 0.398$, $p = 0.533$]. Finally, was found a significant interaction time x group ($F = 17.006$, $p < 0.001$).

Post hoc comparisons, illustrated in Fig. 3B, indicated significant differences in BPI intensity scores between the two groups at: T5 (VAS score mean ± SD: active group = 4.064 ± 1.885, sham group = 6.031 ± 1.912, $p = 0.045$).

No significant differences were found in the BPI interference scores between the active and sham tDCS at T0 (T0 BPI interference score mean ± SD: active group = 4.386 ± 1.923, sham group = 4.947 ± 2.418, $p = 0.901$). Repeated-measures ANOVA evidenced a significant effect of groups [(a-tDCS vs. sham-tDCS): $F = 6.409$, p value = 0.017], while there was no significant effect in time [(T0, T5): $F = 0.148$, p value = 0.716]. A significant interaction time × group was also evidenced ($F = 14.730$, p value < 0.001).

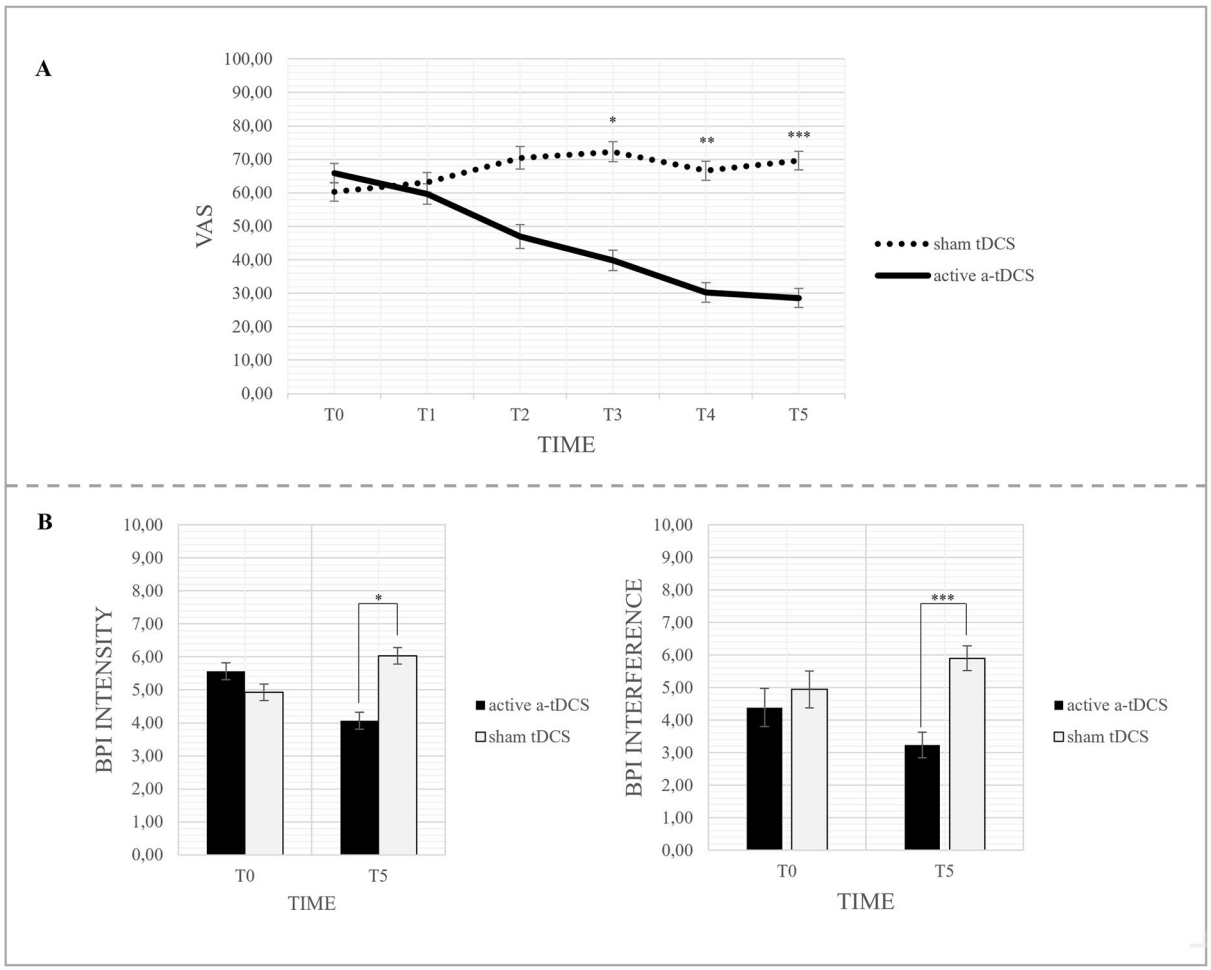

Fig. 3 Repeated-measures ANOVA analysis in the Therapeutic tDCS (Th-tDCS) study evidenced a beneficial effect of M1 a-tDCS in VAS-PDPH and BPI in other pain-related symptoms, in active a-tDCS group versus sham tDCS group: **A** change from baseline in the VAS score; **B** BPI intensity scores change from T0 to T5 and BPI interference scores change from T0 to T5. The graphs show the mean values, standard error (SE) bars, and Tukey's post hoc tests compared to baseline. $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, and $^{***}p \leq 0.001$. *a-tDCS* anodal transcranial direct current stimulation, *BPI* Brief Pain Inventory, *tDCS* transcranial direct current stimulation, *T* timepoint, *VAS* Visual Analogue Scale

Post hoc comparisons, illustrated in Fig. 3B, indicated significant differences in BPI interference scores between the two groups at: T5 (VAS score mean ± SD: active group = 3.231 ± 1.413, sham group = 5.900 ± 1.529, $p < 0.001$).

No significant adverse events were reported and no significant differences emerged in the blinding check ($p > 0.05$) as reported in Table S3 (see the Electronic Supplementary Material).

Preventive tDCS Study

Clinical Characteristics of the Study Population

A total of 55 patients were initially evaluated for the Pr-tDCS study, of which 46 were randomized to receive active a-tDCS or sham tDCS, with 40 completing the study and being analyzed. The CONSORT flow diagram of Pr-tDCS

Table 2 Therapeutic tDCS (Th-tDCS) study table: frequency and categorization of pain, VAS and BPI data was collected at T0, T1 and T2

	Active a-tDCS *n* = 14	Sham tDCS *n* = 15	*p* value
Type of PDPH			
Weight/tension pain, *n* (%)	6 (42.86)	7 (46.66)	0.429
Sharp stabbing pain, *n* (%)	4 (28.57)	3 (20)	0.429
Pulsating pain, *n* (%)	4 (28.57)	5 (33.34)	0.286
Site of PDPH			
Unilateral, *n* (%)	3 (21.42)	4 (26.66)	0.214
Bilateral, *n* (%)	6 (42.85)	5 (33.33)	0.429
Widespread, *n* (%)	5 (35.71)	6 (40)	0.357
Other painful symptoms associated with LP (no PDPH)			
No other symptoms, *n* (%)	0 (0)	0 (0)	N/A
Neck pain, *n* (%)	9 (64.28)	10 (66.66)	0.518
Low back pain, *n* (%)	6 (42.85)	8 (53.33)	0.593
Thoracic back pain, *n* (%)	3 (21.42)	1 (6.66)	0.249
Leg pain, *n* (%)	5 (35.71)	4 (26.66)	0.285
Arm pain, *n* (%)	2 (14.28)	2 (13.33)	0.941
Abdominal pain, *n* (%)	2 (14.28)	3 (20)	0.684
Chest pain, *n* (%)	3 (21.42)	1 (6.66)	0.249

a-tDCS anodal-transcranial direct current stimulation, *BPI* Brief Pain Inventory, *n* number of subjects, *N/A* not applicable, *PDPH* Postdural-puncture headache, *tDCS* transcranial direct current stimulation, *VAS* Visual Analogue Scale

p-value by chi square

is shown in Fig. 2B. Patient diagnosis according to the tDCS group is reported in Table S2 (see the Electronic Supplementary Material).

No significant differences were found between the active a-tDCS and sham tDCS groups in age ($p = 0.628$) and sex ($p = 0.342$). Furthermore, no significant differences were found between the groups in of depression ($p = 0.416$), anxiety ($p = 0.741$), sleep quality ($p = 0.616$), and in quality of life evaluated with the SF-36 (physical functioning $p = 0.474$, role-physical $p = 1.000$, bodily pain $p = 0.443$, general health $p = 0.953$, vitality $p = 0.228$, social functioning $p = 0.211$, role-emotional $p = 0.906$, mental health $p = 0.808$). The clinical and demographic characteristics of patients in the active a-tDCS and sham tDCS groups are shown in Table 3.

Effects of Preventive M1 a-tDCS on PDPH

Within the first 2 days following LP (T1 and T2), 12 patients (30% of the sample) developed PDPH. A significant difference in the occurrence of PDPH events emerged between the two groups, with the active a-tDCS group showing a lower incidence compared to the sham tDCS group. In the sham tDCS group, 8 patients (40%) presented PDPH, while, in the a-tDCS group, 4 patients (20%) presented PDPH (chi-square, $p = 0.046$).

Table 3 Preventive tDCS (Pr-tDCS) study table: baseline demographic-clinical characteristics and pharmacological therapies of patients according to the allocated group

	Active a-tDCS *n* = 20	Sham tDCS *n* = 20	*p* value
Female, *n* (%)	8 (40)	11 (55)	0.342†
Age, mean (SD)	52.50 (13.94)	50.30 (14.50)	0.628
Zung's self-rating anxiety scale (SAS), mean (SD)	36.50 (9.77)	37.55 (10.16)	0.741
Zung's self-rating depression scale (SDS), mean (SD)	36.25 (10.14)	38.80 (9.45)	0.416
Pittsburgh Sleep Quality Index (PSQI), mean (SD)	7.05 (3.65)	8.15 (9.03)	0.616
SF-36 Physical functioning (PF), mean (SD)	60.25 (34.62)	68.00 (33.06)	0.474
SF-36 Role limitations-physical (RF), mean (SD)	37.50 (44.79)	37.50 (40.15)	1.000
SF-36 Bodily pain (BP), mean (SD)	59.35 (29.83)	52.05 (29.68)	0.443
SF-36 General health (GH), mean (SD)	53.35 (21.82)	52.95 (21.01)	0.953
SF-36 Vitality (VT), mean (SD)	55.50 (21.27)	47.75 (18.67)	0.228
SF-36 Social functioning (SF), mean (SD)	55.45 (20.44)	64.15 (22.73)	0.211
SF-36 Role limitations-emotional (RE), mean (SD)	49.85 (45.20)	51.50 (42.54)	0.906
SF-36 Mental health (MH), mean (SD)	61.20 (23.07)	62.80 (17.89)	0.808
NSAID (acetaminophen), *n* (%)	13 (65)	13 (65)	1.000†
Anti-emetic, *n* (%)	5 (25)	5 (25)	1.000†

a-tDCS anodal-transcranial direct current stimulation, *N* number of subjects, *NSAIDs* non-steroidal anti-inflammatory drugs, *SD* standard deviation, *SF-36* the 36-Item Short Form Survey, *tDCS* transcranial direct current stimulation

p value by *t* test and † chi square

To explore the effects of tDCS on PDPH prevention, we first compared the VAS scores between the two groups (active a-tDCS and sham tDCS) (Fig. 4A).

Repeated-measures ANOVA evidenced a significant effect of time [(T0, T1, T2): $F = 17.795$, p value < 0.001], and a significant effect of group [(a-tDCS vs. sham tDCS): $F = 12.057$, p value = 0.001]. In addition, a significant interaction time x group was also evidenced ($F = 6.918$, p value = 0.002). Post hoc comparisons, illustrated in Fig. 4A, indicated significant differences in VAS scores between the two groups at: T1 (VAS score mean ± SD: active group = 6.750 ± 17.035, sham group = 34.150 ± 34.233, $p = 0.030$) and T2 (VAS score mean ± SD: active group = 10.300 ± 25.375, sham group = 41.550 ± 38.403, $p = 0.046$).

The frequency and categorization of pain are reported in Table 4.

The pharmacological therapy administered during hospitalization was not statistically different between the two groups for all drugs ($p > 0.05$; Table 3).

To explore the effects of tDCS on other painful symptoms associated with LP we compared the BPI intensity and interference scores collected at T0 and T2 in the two groups (a-tDCS and sham tDCS), and these results are shown in Fig. 4B.

No significant differences were found in the BPI intensity scores between the active and sham tDCS at T0 (T0 BPI intensity score mean ± SD: active group = 2.425 ± 2.464, sham group = 2.063 ± 1.602, $p = 0.946$). Repeated-measures ANOVA evidenced a significant effect of group [(a-tDCS vs. sham-tDCS): $F = 9.158$,

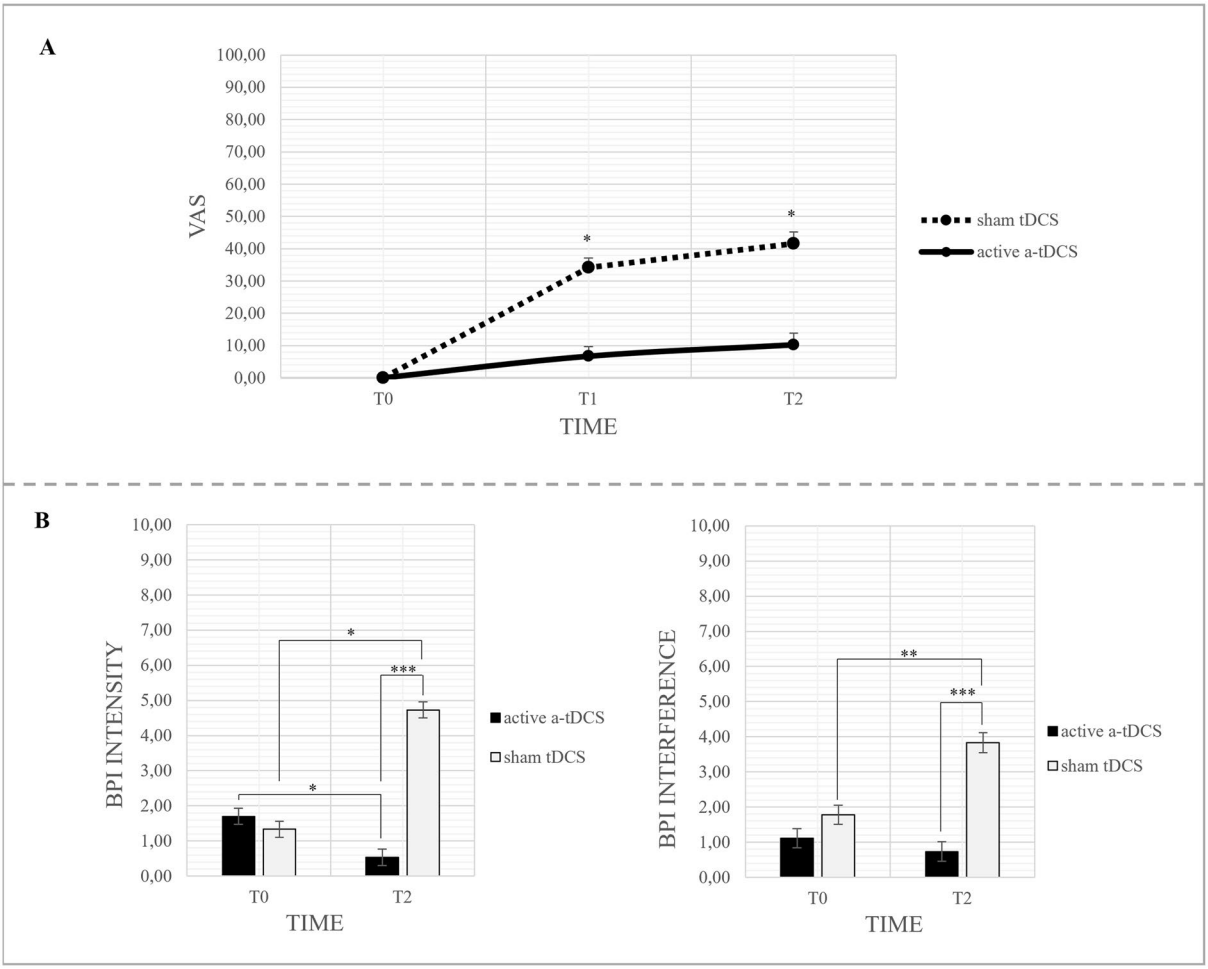

Fig. 4 Repeated-measures ANOVA analysis in the Preventive tDCS (Pr-tDCS) study evidenced a beneficial effect of a-tDCS in VAS-PDPH and BPI in other pain-related symptoms, in active a-tDCS group versus sham tDCS group: **A** change from baseline in the VAS score, **B** BPI intensity scores change from T0 to T2 and BPI interference scores change from T0 to T2. The graphs show the mean values, standard errors (SE) bars, and Tukey's post-hoc tests compared to baseline: $^{*}p \leq 0.05$, $^{**}p \leq 0.01$, and $^{***}p \leq 0.001$. *T* timepoint, *a-tDCS* anodal transcranial direct current stimulation, *tDCS* transcranial direct current stimulation, *VAS* Visual Analogue Scale, *BPI* Brief Pain Inventory

p value = 0.004], while the effect of time was not significant [(T0, T2): $F = 0.000$, $p = 0.989$]. Finally, a significant interaction time x group was also found ($F = 17.866$, $p < 0.001$).

Post hoc comparisons, illustrated in Fig. 4B, indicated significant differences in BPI intensity scores between the two groups at: T2 (VAS score mean ± SD: active group = 0.588 ± 1.223, sham group = 3.913 ± 2.657, $p < 0.001$).

No significant differences were found in the BPI interference scores between the active and sham tDCS at T0 (T0 BPI interference score mean ± SD: active group = 2.053 ± 2.480, sham group = 2.497 ± 2.330, $p = 0.937$). Repeated-measures ANOVA evidenced a significant effect of groups [(a-tDCS vs. sham-tDCS): $F = 8.939$, *p* value = 0.005], while there was no significant effect in time [(T0, T2): $F = 1.169$, *p* value = 0.286]. A significant interaction time x group was also evidenced ($F = 15.520$, *p* value < 0.001).

Table 4 Preventive tDCS (Pr-tDCS) study table: frequency and categorization of pain, VAS and BPI data was collected at T0, T1 and T2

	Active a-tDCS $n = 20$	Sham tDCS $n = 20$	*p*-value
Type of PDPH			
No PDPH, *n* (%)	16 (80)	12 (60)	0.533†
Weight/tension pain, *n* (%)	3 (15)	4 (20)	0.283†
Sharp stabbing pain, *n* (%)	1 (5)	2 (10)	0.117†
Pulsating pain, *n* (%)	0 (0)	2 (10)	0.067†
Site of PDPH			
Unilateral, *n* (%)	0 (0)	2 (10)	0.067†
Bilateral, *n* (%)	2 (10)	4 (20)	0.233†
Widespread, *n* (%)	2 (10)	2 (10)	0.167†
Other painful symptoms associated with LP (no PDPH)			
No other symptoms, *n* (%)	9 (45)	4 (20)	0.091†
Neck pain, *n* (%)	9 (45)	5 (25)	0.185†
Low back pain, *n* (%)	11 (55)	14 (70)	0.327†
Thoracic back pain, *n* (%)	2 (10)	2 (10)	1.000†
Leg pain, *n* (%)	1 (5)	2 (10)	0.548†
Arm pain, *n* (%)	0 (0)	0 (0)	N/A
Abdominal pain, *n* (%)	0 (0)	1 (5)	0.311†
Chest pain, *n* (%)	0 (0)	0 (0)	N/A

a-tDCS anodal-transcranial direct current stimulation, *BPI* Brief Pain Inventory, *n* number of subjects, *N/A* not applicable, *PDPH* Postdural-puncture headache, *tDCS* transcranial direct current stimulation, *VAS* Visual Analogue Scale

p-value by † chi square

Post hoc comparisons, illustrated in Fig. 4B, indicated significant differences in BPI interference scores between the two groups at: T2 (VAS score mean ± SD: active group = 0.918 ± 1.757, sham group = 4.490 ± 3.111, $p < 0.001$).

No significant adverse events were reported and no significant differences emerged in the blinding check ($p > 0.05$) as shown in Table S4 (see the Electronic Supplementary Material).

DISCUSSION

In the present study, we found a preventive and therapeutic effect of a-tDCS applied to the M1 of the dominant hemisphere on PDPH in a heterogeneous cohort of patients undergoing diagnostic LP.

Converging evidence suggests that a-tDCS applied to the M1 of the dominant hemisphere may have beneficial effects on pain due to different clinical conditions [8–10]. Recent meta-analyses have demonstrated that a-tDCS of M1 is an effective, preventive treatment for migraine [30–32]. Accordingly, in patients with episodic migraine, preventive M1 a-tDCS has been associated with a significant reduction of migraine frequency, pain intensity, and analgesic usage (NSAIDs and triptans) compared to pharmacotherapy alone [16, 33–35]. Similar results have been observed in RCTs in patients with chronic migraine (CM) and medication-overuse headache (MOH), with and without allodynia [15, 17, 34, 36]. Specifically, a 3-day consecutive treatment with a-tDCS applied to M1 of the dominant hemisphere significantly reduced the duration, frequency, and intensity of headaches, and the use of symptomatic drug therapy [15, 36]. A recent RCT study in CM patients reported a significant reduction (26.4%) of monthly migraine attacks and a 50% response rate in patients receiving active a-tDCS versus sham stimulation [37].

Several experimental studies have investigated the physiological mechanisms underlying the beneficial effects of M1 a-tDCS for migraine [14, 17, 37–41]. It has been evidenced that a-tDCS of M1 can modulate the activity of several cortical and subcortical brain areas involved in the pain matrix, such as cingulate gyrus, insular cortex, thalamic nuclei, brainstem, supplementary motor area, and prefrontal and orbitofrontal cortices [12, 13, 17]. Functional magnetic resonance imaging studies have shown an alteration

of thalamo-cortical connectivity involving the motor cortex during migraine attacks [38]. A-tDCS of M1 can also strengthen or restore the descending inhibitory controls of nociceptive information transmission, a pathway described as the descending pain modulatory system [39, 40]. Moreover, a-tDCS of M1 may increase the release of endogenous opioids in the nucleus accumbens, in anterior cingulate cortex, in the insula, in the periaqueductal grey matter and in the thalamus in chronic neuropathic and non-cancerous pain [42, 43]. NIBS studies also suggest that other brain areas, such as the DLPFC, may represent an important target for improving pain and the emotional aspects linked to pain [21, 44–46]. Notably, a previous study showed that a-tDCS of M1 induced a greater increase of sensory threshold and pain threshold compared with stimulation of the primary somatosensory cortex (S1) and DLPFC [19].

In our study, 3-day consecutive treatment with a-tDCS applied to M1 of the dominant hemisphere significantly improved pain symptoms in patients with PDPH, as evidenced by reduced VAS scores and BPI intensity and interference scores. In addition, we found that a-tDCS administered prior to the onset of pain symptoms for 3 consecutive days reduced the frequency, and intensity of PDPH.

Based on our results from the Tr-tDCS study, it can be inferred that a-tDCS may serve as an effective symptomatic treatment for PDPH. In addition, the results from the Pr-tDCS study are encouraging in supporting the hypothesis that a-tDCS may have a preventive effect on PDPH, given the significant difference in the occurrence of PDPH events between the two groups.

To our knowledge, this is the first study investigating the role of M1 a-tDCS in the prevention and treatment of PDPH.

The extensive literature on the use of M1 a-tDCS in headache prophylaxis encouraged us to develop a treatment protocol for PDPH. Considering that approximately 90% of PDPHs occur within 72 h after dural puncture, it was essential to use a rapidly effective prophylactic a-tDCS protocol [1, 4, 47, 48]. Without treatment, most PDPH resolve within 1 week, and one-half resolve by 4–5 days after dural puncture [49, 50]. Given that 3 consecutive days of a-tDCS treatment applied to M1 has been reported to be effective [15], we used a 3-day a-tDCS protocol to examine the difference between the two groups in terms of pain onset and severity.

The present study has some important limitations including the low number of patients, a heterogeneous study population including by both central and peripheral nervous system disorders, and the lack of longitudinal follow-up. Further studies are required to clarify the potential therapeutic and preventive effects of a-tDCS, including its application prior to LP, in the treatment of PDPH.

CONCLUSIONS

During the two RCTs with sham-control groups in a population of hospitalized patients with neurological conditions who underwent a diagnostic LP, a-tDCS significantly improved the severity, intensity, and frequency of PDPH and other pain-related symptoms associated with LP.

Encouraging results have emerged for the use of a-tDCS in patients undergoing LP in both experimental research designs, Th-tDCS and Pr-tDCS.

NIBS technique, such as a-tDCS, could have a therapeutic and preventive effect on pain resulting from a LP.

ACKNOWLEDGEMENTS

We thank the participants of the study.

Medical Writing and Editorial Assistance. No medical writing or editorial assistance was received during the writing of this article (including AI).

Author Contributions. Conceptualized and designed the study: Bledar Gjikolaj, Mario Stampanoni Bassi, Antonio Bruno, Antonella Conte, Luana Gilio, Diego Centonze, Fabio Buttari. Methodology: Bledar Gjikolaj, Mario Stampanoni Bassi, Antonio Bruno, Valeria De Ioanni, Giovanni Galifi, Antonella Conte, Luana Gilio, Diego Centonze, Fabio Buttari. Investigation:

Bledar Gjikolaj, Mario Stampanoni Bassi, Antonio Bruno, Valeria De Ioanni, Ettore Dolcetti, Sheila Peter, Giovanni Galifi, Antonella Conte, Luana Gilio, Fabio Buttari. Data curation: Bledar Gjikolaj, Mario Stampanoni Bassi, Antonio Bruno, Valeria De Ioanni, Ettore Dolcetti, Sheila Peter, Giovanni Galifi, Antonella Conte, Luana Gilio, Diego Centonze, Fabio Buttari. Formal analysis: Bledar Gjikolaj, Mario Stampanoni Bassi, Antonio Bruno, Diego Centonze, Fabio Buttari. Writing—original draft preparation: Bledar Gjikolaj, Mario Stampanoni Bassi, Antonio Bruno, Antonella Conte, Luana Gilio, Diego Centonze, Fabio Buttari and all authors commented on previous versions of the manuscript. All authors provided critical review and revision, and final approval of the manuscript.

Funding. The study was supported by Ministero della Salute (Ministry of Health, Italy): Progetto Ricerca Corrente 2024 to IRCCS Neuromed, including the journal's Rapid Service Fee.

Data Availability. The data that support the findings of this study are available on reasonable request from the corresponding author. The datasets generated during and/or analyzed during the current study are not publicly available due to the fact that this information could compromise the privacy of research participants.

Declarations

Conflict of Interest. Bledar Gjikolaj, Mario Stampanoni Bassi, Antonio Bruno, Valeria De Ioanni, Ettore Dolcetti, Sheila Peter, Giovanni Galifi, Antonella Conte, Luana Gilio, Diego Centonze and Fabio Buttari declare that they have no competing interests.

Ethical Approval. The study was approved by the Ethics Committee of the IRCCS Neuromed, Pozzilli, Italy, in accordance with the Declaration of Helsinki (approval code: 12-17) and was registered with clinicaltrials.gov (NCT06640634). Written informed consent was obtained from all participants prior to inclusion in the study.

REFERENCES

1. Cognat E, Koehl B, Lilamand M, Goutagny S, Belbachir A, de Charentenay L, et al. Preventing post-lumbar puncture headache. Ann Emerg Med. 2021;78:443–50. https://linkinghub.elsevier.com/retrieve/pii/S0196064421001517.

2. Li H, Wang Y, Oprea AD, Li J. Postdural puncture headache—risks and current treatment. Curr Pain Headache Rep. 2022;26:441–52. https://link.springer.com/10.1007/s11916-022-01041-x.

3. Headache Classification Committee of the International Headache Society (IHS). The international classification of headache disorders, 3rd edition. Cephalalgia. 2018;38:1–211. https://journals.sagepub.com/doi/10.1177/0333102417738202.

4. Arevalo-Rodriguez I, Ciapponi A, Roqué-Figuls M, Muñoz L, Bonfill Cosp X. Posture and fluids for preventing post-dural puncture headache. Cochrane Database Syst Rev. 2016;2021. http://doi.wiley.com/10.1002/14651858.CD009199.pub3.

5. Nitsche MA, Paulus W. Excitability changes induced in the human motor cortex by weak transcranial direct current stimulation. J Physiol. 2000;527:633–9. https://physoc.onlinelibrary.wiley.com/doi/10.1111/j.1469-7793.2000.t01-1-00633.x.

6. Lefaucheur J-P, Antal A, Ayache SS, Benninger DH, Brunelin J, Cogiamanian F, et al. Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation (tDCS). Clin Neurophysiol. 2017;128:56–92. https://linkinghub.elsevier.com/retrieve/pii/S1388245716306344.

7. Nitsche MA, Fricke K, Henschke U, Schlitterlau A, Liebetanz D, Lang N, et al. Pharmacological modulation of cortical excitability shifts induced by transcranial direct current stimulation in humans. J Physiol. 2003;553:293–301. https://physoc.onlinelibrary.wiley.com/doi/10.1113/jphysiol.2003.049916.

8. Knotkova H, Hamani C, Sivanesan E, Le Beuffe MFE, Moon JY, Cohen SP, et al. Neuromodulation for chronic pain. Lancet. 2021;397:2111–24. https://linkinghub.elsevier.com/retrieve/pii/S0140673621007947.

9. Lefaucheur J-P. Cortical neurostimulation for neuropathic pain. Pain. 2016;157:S81–9. https://journals.lww.com/00006396-201602001-00013.

10. 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;24:256–313. https://academic.oup.com/ijnp/article/24/4/256/5876418.

11. Lefaucheur J-P. Pain. 2013. pp. 423–40. https://linkinghub.elsevier.com/retrieve/pii/B9780444534972000358.

12. Naegel S, Biermann J, Theysohn N, Kleinschnitz C, Diener H-C, Katsarava Z, et al. Polarity-specific modulation of pain processing by transcranial direct current stimulation—a blinded longitudinal fMRI study. J Headache Pain. 2018;19:99. https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-018-0924-5.

13. Meeker TJ, Keaser ML, Khan SA, Gullapalli RP, Seminowicz DA, Greenspan JD. Non-invasive motor cortex neuromodulation reduces secondary hyperalgesia and enhances activation of the descending pain modulatory network. Front Neurosci. 2019;13. https://www.frontiersin.org/article/10.3389/fnins.2019.00467/full.

14. De Icco R, Putortì A, De Paoli I, Ferrara E, Cremascoli R, Terzaghi M, et al. Anodal transcranial direct current stimulation in chronic migraine and medication overuse headache: a pilot double-blind randomized sham-controlled trial. Clin Neurophysiol. 2021;132:126–36. https://linkinghub.elsevier.com/retrieve/pii/S1388245720305290.

15. Cerrahoğlu Şirin T, Aksu S, Hasirci Bayir BR, Ulukan Ç, Karamürsel S, Kurt A, et al. Is allodynia a determinant factor in the effectiveness of transcranial direct current stimulation in the prophylaxis of migraine? Neuromodul Technol Neural Interface. 2021;24:899–909. https://linkinghub.elsevier.com/retrieve/pii/S1094715921062061.

16. Auvichayapat P, Janyacharoen T, Rotenberg A, Tiamkao S, Krisanaprakornkit T, Sinawat S, et al. Migraine prophylaxis by anodal transcranial direct current stimulation, a randomized, placebo-controlled trial. J Med Assoc Thai. 2012;95:1003–12. http://www.ncbi.nlm.nih.gov/pubmed/23061303.

17. DaSilva AF, Mendonca ME, Zaghi S, Lopes M, DosSantos MF, Spierings EL, et al. tDCS-induced analgesia and electrical fields in pain-related neural networks in chronic migraine. Headache J Head Face Pain. 2012;52:1283–95. https://headachejournal.onlinelibrary.wiley.com/doi/10.1111/j.1526-4610.2012.02141.x.

18. Ornello R, Caponnetto V, Ratti S, D'Aurizio G, Rosignoli C, Pistoia F, et al. Which is the best transcranial direct current stimulation protocol for migraine prevention? A systematic review and critical appraisal of randomized controlled trials. J Headache Pain. 2021;22:144. https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-021-01361-0.

19. Vaseghi B, Zoghi M, Jaberzadeh S. How does anodal transcranial direct current stimulation of the pain neuromatrix affect brain excitability and pain perception? A randomised, double-blind, sham-control study. Langguth B, editor. PLoS One. 2015;10:e0118340. https://dx.plos.org/10.1371/journal.pone.0118340.

20. Klem GH, Lüders HO, Jasper HH, Elger C. The ten-twenty electrode system of the International Federation. The International Federation of Clinical Neurophysiology. Electroencephalogr Clin Neurophysiol Suppl. 1999;52:3–6. http://www.ncbi.nlm.nih.gov/pubmed/10590970.

21. Nitsche MA, Cohen LG, Wassermann EM, Priori A, Lang N, Antal A, et al. Transcranial direct current stimulation: state of the art 2008. Brain Stimul. 2008;1:206–23. https://linkinghub.elsevier.com/retrieve/pii/S1935861X08000405.

22. Bolton JE, Wilkinson RC. Responsiveness of pain scales: a comparison of three pain intensity measures in chiropractic patients. J Manip Physiol Ther. 1998;21:1–7. http://www.ncbi.nlm.nih.gov/pubmed/9467094.

23. Caraceni A, Mendoza TR, Mencaglia E, Baratella C, Edwards K, Forjaz MJ, et al. A validation study of an Italian version of the brief pain inventory

(Breve questionario per la valutazione del dolore). Pain. 1996;65:87–92. https://journals.lww.com/00006396-199604000-00015.

24. Dunstan DA, Scott N. Norms for Zung's self-rating anxiety scale. BMC Psychiatry. 2020;20:90. https://bmcpsychiatry.biomedcentral.com/articles/10.1186/s12888-019-2427-6.

25. ZUNG WWK. A self-rating depression scale. Arch Gen Psychiatry. 1965;12:63. http://archpsyc.jamanetwork.com/article.aspx?doi=10.1001/archpsyc.1965.01720310065008.

26. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The Pittsburgh sleep quality index: a new instrument for psychiatric practice and research. Psychiatry Res. 1989;28:193–213. https://linkinghub.elsevier.com/retrieve/pii/0165178189900474.

27. Brazier JE, Harper R, Jones NM, O'Cathain A, Thomas KJ, Usherwood T, et al. Validating the SF-36 health survey questionnaire: new outcome measure for primary care. BMJ. 1992;305:160–4. https://www.bmj.com/lookup/doi/10.1136/bmj.305.6846.160.

28. Ahdab R, Mansour AG, Khazen G, El-Khoury C, Sabbouh TM, Salem M, et al. Cathodal transcranial direct current stimulation of the occipital cortex in episodic migraine: a randomized sham-controlled crossover study. J Clin Med. 2019;9:60. https://www.mdpi.com/2077-0383/9/1/60.

29. Bird SB, Dickson EW. Clinically significant changes in pain along the visual analog scale. Ann Emerg Med. 2001;38:639–43. https://linkinghub.elsevier.com/retrieve/pii/S019606440129670X.

30. Hong P, Liu Y, Wan Y, Xiong H, Xu Y. Transcranial direct current stimulation for migraine: a systematic review and meta-analysis of randomized controlled trials. CNS Neurosci Ther. 2022;28:992–8. https://onlinelibrary.wiley.com/doi/10.1111/cns.13843.

31. Cai G, Xia Z, Charvet L, Xiao F, Datta A, Aroulakis XM. A systematic review and meta-analysis on the efficacy of repeated transcranial direct current stimulation for migraine. J Pain Res. 2021;14:1171–83. https://www.dovepress.com/a-systematic-review-and-meta-analysis-on-the-efficacy-of-repeated-tran-peer-reviewed-fulltext-article-JPR.

32. Raggi A, Leonardi M, Arruda M, Caponnetto V, Castaldo M, Coppola G, et al. Hallmarks of primary headache: part 1—migraine. J Headache Pain. 2024;25:189. https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-024-01889-x.

33. 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. https://linkinghub.elsevier.com/retrieve/pii/S1734114016304613.

34. Andrade SM, de Brito Aranha REL, de Oliveira EA, de Mendonça CTPL, Martins WKN, Alves NT, et al. Transcranial direct current stimulation over the primary motor vs. prefrontal cortex in refractory chronic migraine: a pilot randomized controlled trial. J Neurol Sci. 2017;378:225–32. https://linkinghub.elsevier.com/retrieve/pii/S0022510X17303039.

35. Lefaucheur J-P, André-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). Clin Neurophysiol. 2014;125:2150–206. https://linkinghub.elsevier.com/retrieve/pii/S138824571400296X.

36. Aksu S, Şirin TC, Hasırcı Bayır BR, Ulukan Ç, Soyata AZ, Kurt A, et al. Long-term prophylactic transcranial direct current stimulation ameliorates allodynia and improves clinical outcomes in individuals with migraine. Neuromodul Technol Neural Interface. 2023;26:778–87. Available from: https://linkinghub.elsevier.com/retrieve/pii/S1094715922007590.

37. Hodaj H, Payen J-F, Mick G, Vercueil L, Hodaj E, Dumolard A, et al. Long-term prophylactic efficacy of transcranial direct current stimulation in chronic migraine. A randomised, patient-assessor blinded, sham-controlled trial. Brain Stimul. 2022;15:441–53. https://linkinghub.elsevier.com/retrieve/pii/S1935861X22000407.

38. Amin FM, Hougaard A, Magon S, Sprenger T, Wolfram F, Rostrup E, et al. Altered thalamic connectivity during spontaneous attacks of migraine without aura: a resting-state fMRI study. Cephalalgia. 2018;38:1237–44. https://journals.sagepub.com/doi/10.1177/0333102417729113.

39. Henssen D, Giesen E, van der Heiden M, Kerperien M, Lange S, van Cappellen van Walsum A-M, et al. A systematic review of the proposed mechanisms underpinning pain relief by primary motor cortex stimulation in animals. Neurosci Lett. 2020;719:134489. https://linkinghub.elsevier.com/retrieve/pii/S0304394019305920.

40. Gamal-Eltrabily M, Martínez-Lorenzana G, González-Hernández A, Condés-Lara M. Cortical modulation of nociception. Neuroscience. 2021;458:256–70. https://linkinghub.elsevier.com/retrieve/pii/S0306452221000063.

41. Cheng Y-C, Zeng B-Y, Hung C-M, Su K-P, Wu Y-C, Tu Y-K, et al. Effectiveness and acceptability of noninvasive brain and nerve stimulation techniques for migraine prophylaxis: a network meta-analysis of randomized controlled trials. J Headache Pain. 2022;23:28. https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-022-01401-3.

42. Knotkova H, Nitsche MA, Cruciani RA. Putative physiological mechanisms underlying tDCS analgesic effects. Front Hum Neurosci. 2013;7. http://journal.frontiersin.org/article/10.3389/fnhum.2013.00628/abstract.

43. Plow EB, Obretenova SN, Fregni F, Pascual-Leone A, Merabet LB. Comparison of visual field training for hemianopia with active versus sham transcranial direct cortical stimulation. Neurorehabil Neural Repair. 2012;26:616–26. https://journals.sagepub.com/doi/10.1177/1545968311431963.

44. Fregni F, Boggio PS, Mansur CG, Wagner T, Ferreira MJL, Lima MC, et al. Transcranial direct current stimulation of the unaffected hemisphere in stroke patients. Neuroreport. 2005;16:1551–5. https://journals.lww.com/00001756-200509280-00004.

45. Silva AF, Zortea M, Carvalho S, Leite J, Torres IL da S, Fregni F, et al. Anodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex modulates attention and pain in fibromyalgia: randomized clinical trial. Sci Rep. 2017;7:135. https://www.nature.com/articles/s41598-017-00185-w.

46. Schading S, Pohl H, Gantenbein A, Luechinger R, Sandor P, Riederer F, et al. Tracking tDCS induced grey matter changes in episodic migraine: a randomized controlled trial. J Headache Pain. 2021;22:139. https://thejournalofheadacheandpain.biomedcentral.com/articles/10.1186/s10194-021-01347-y.

47. Vilming ST, Schrader H, Monstad I. The significance of age, sex, and cerebrospinal fluid pressure in post-lumbar-puncture headache. Cephalalgia. 1989;9:99–106. http://cep.sagepub.com/cgi/doi/10.1046/j.1468-2982.1989.0902099.x.

48. Kuntz KM, MD EK, Stevens JC, RN PM, Offord KP, Ho MM. Post-lumbar puncture headaches. Neurology. 1992;42:1884. https://www.neurology.org/doi/10.1212/WNL.42.10.1884.

49. Amorim JA, Gomes de Barros M V, Valença MM. Post-dural (post-lumbar) puncture headache: risk factors and clinical features. Cephalalgia. 2012;32:916–23. https://journals.sagepub.com/doi/10.1177/0333102412453951.

50. Lybecker H, Møller JT, May O, Nielsen HK. Incidence and prediction of postdural puncture headache a prospective study of 1021 spinal anesthesias. Anesth Analg. 1990;70:389–94. http://journals.lww.com/00000539-199004000-00008.