RESEARCH REPORT

Combined transcranial and trans-spinal direct current stimulation in chronic headache: A feasibility and safety trial for a novel intervention

Ghufran Alhassani, B.Med.Sc (Hons) [a], Julia Treleaven, PhD [b], Siobhan S.M. Schabrun, PhD [a],*

[a] Brain Rehabilitation and Neuroplasticity Unit, Western Sydney University, Sydney, New South Wales, Australia
[b] School of Health and Rehabilitation Science, The University of Queensland, Brisbane, Queensland, Australia

Abstract   Background: Chronic primary headache disorders are associated with frequent, severe pain and significant functional impairment, with treatment remaining challenging.
Objective: We examined the feasibility and safety of a novel brain [transcranial direct current stimulation (tDCS)] and spinal cord stimulation [trans-spinal cord direct current stimulation (tsDCS)] treatment in chronic headache.
Methods: Nine participants (3 males; aged, 40 ± 15 years) suffering from chronic daily headache, chronic tension-type headache, or chronic migraine received the combined brain and spinal cord intervention for 5 consecutive days. Stimulation was applied for a total of 40 minutes (20 minutes of tDCS followed by 20 minutes of tsDCS) at 1 mA. Pain sensitivity and headache symptoms (frequency, severity, duration, and medications recorded via a headache diary, 4 weeks before and after treatment) were assessed.
Results: The treatment was safe, feasible, and well tolerated. Headache frequency was reduced following the treatment ($p = 0.026$) in chronic tension-type headache and chronic migraine, but not in chronic daily headache. Headache severity was reduced immediately post-treatment in 67% of sessions. A trend towards a reduction in medication use was observed ($p = 0.075$). No changes in headache severity ($p = 0.16$) or duration ($p = 0.34$) were present.
Conclusion: These data suggest that combined tDCS and tsDCS intervention is safe and feasible, and may improve headache frequency in patients with chronic primary headache disorders.
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 * Corresponding author. Brain Rehabilitation and Neuroplasticity Unit, Western Sydney University, Campbelltown Campus, Locked Bag 1797, Penrith, New South Wales 2751, Australia.
   E-mail address: s.schabrun@westernsydney.edu.au (S.S.M. Schabrun).

Introduction

Chronic primary headache disorders are associated with frequent, severe pain and significant functional impairment, and are now viewed as a global health disorder, with migraine ranking sixth highest in terms of years lived with disability [1]. Despite this, treatment remains challenging, with many individuals failing to respond to preventative medication or experiencing adverse effects [2,3]. Recent studies suggest that increased sensitivity of cortical and spinal neurons to sensory stimuli (termed central sensitisation) and malfunction of descending pain pathways are key features of chronic primary headache disorders [e.g., chronic migraine (CM), chronic tension-type headache (CTTH), and chronic daily headache (CDH)] [4–6]. Indeed, previous studies have suggested that central sensitisation is a common mechanism of chronification that can explain clinical similarities across various forms of chronic headaches [4–6]. In addition, previous studies have shown a reduction in the nociceptive flexor withdrawal reflex, a spinally mediated reflex measured from biceps femoris, in various types of chronic headache [4]. As the nociceptive flexor withdrawal reflex is related to A-delta fibre activation, this finding has led to the suggestion that there may be increased input to the trigeminal complex that arises in the spinal cord, possibly as a result of impaired descending pain control, in chronic headache [7]. Novel treatments with the potential to target mechanisms of central sensitisation and pain system dysfunction at both spinal and cortical level may, therefore, have a positive impact on clinical outcomes in a range of chronic headache types.

Applications of weak direct currents over the scalp [transcranial direct current stimulation (tDCS)] and spinal cord [trans-spinal direct current stimulation (tsDCS)] are two interventions with the potential to reduce central sensitisation and improve descending pain control via complementary mechanistic pathways. Preliminary evidence suggests that anodal tDCS applied to the primary motor cortex can improve pain via direct effects on the cortex and thalamus [8–14] as well as downstream effects on the anterior cingulate and upper brainstem [15,16]. More recent work has also suggested that tDCS may influence pain perception by regulation of endogenous opioid release [17]. Conversely, direct current applied to the spinal cord can improve pain perception through the induction of long-lasting changes in ascending pain pathways and activation of supraspinal loops involved in descending pain control systems [18–20]. Synergistic treatments that modify ascending inputs at the level of the spinal cord (tsDCS) and treatments that modify processing of these inputs at the supraspinal level (tDCS) may summate to produce greater mechanistic and clinical effects. In addition, tDCS has the potential to increase the brain's receptiveness to other interventions by increasing cortical excitability, a phenomenon known as priming [21]. Thus, tDCS may optimise the responsiveness of the brain to tsDCS to produce mechanistic and clinical benefits in various forms of chronic headache.

To our knowledge, no study has combined brain and spinal cord direct current stimulation in chronic pain, despite evidence of pain-relieving effects when each technique is applied alone. However, preliminary evidence using other combined interventions supports the hypothesis that synergistic mechanistic effects are achieved when the brain and spinal cord are targeted simultaneously [22–26]. For example, additive effects on pain thresholds are reported in healthy individuals with a combined tDCS and central pain modulation intervention [23]. Similarly, tDCS combined with peripheral electrical stimulation of the back muscles improves central sensitisation, motor cortical organisation, and persistent low back pain beyond that of either technique applied alone [25].

As this is the first study to combine tDCS and tsDCS in humans, a pilot feasibility trial was conducted. The aims were as follows: (1) to determine the feasibility, safety, and perceived patient response to a combined tDCS and tsDCS intervention in chronic primary headache disorders; (2) to examine the effect of a combined tDCS and tsDCS intervention on mechanisms of central sensitisation; and (3) to provide data to support a sample size calculation for a fully powered, controlled trial should trends of effectiveness be present.

Methods

Study design

This is a pilot feasibility study designed to generate data that can be used to inform a future randomised controlled trial should the intervention appear feasible and safe, and show trends of effectiveness. The study design involved three phases consisting of an initial baseline phase without intervention for 4 weeks, an intervention phase lasting 1 week (5 consecutive daily sessions), and a final baseline phase of 4 weeks in which the intervention was withdrawn (Figure 1). As the study is a pilot trial there was no prospective randomised control group. The study protocol was approved by the Institutional Human Research Ethics Committee, and it complied with the Declaration of Helsinki. All participants provided written, informed consent.

Participants

Adult participants with chronic headache of any type were screened from the general community using advertisements and social media during the period from June 2014 to May 2015, with the research conducted at the university. Participants were screened according to the International Classification of Headache Disorders, second edition, and were included if they were older than 18 years and experienced symptom onset before the age of 50 years, reported headaches that were present on 4 or more days per month and lasted 4 or more hours when left untreated, did not use prophylactic migraine medication, did not have metal objects or stimulators in the head that might pose a hazard during tDCS, were not pregnant, and had no known neurological or psychiatric conditions.

Intervention

The intervention included five consecutive daily sessions of 40-minute duration consisting of 20 minutes of tDCS,
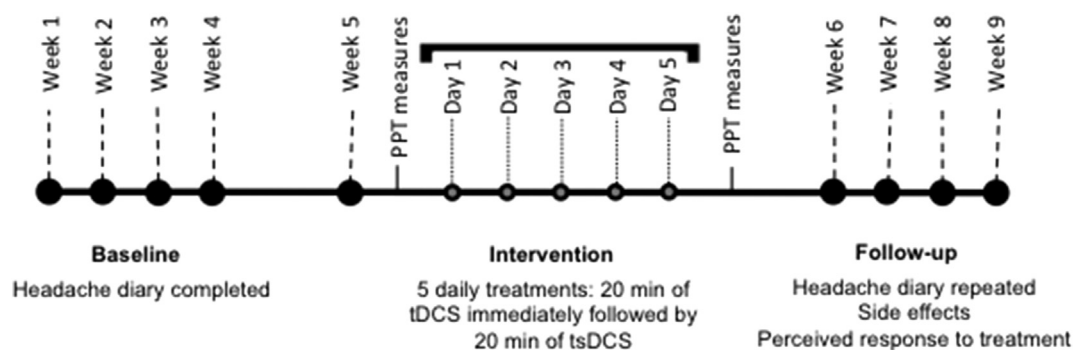
Figure 1. Experimental protocol. The experiment protocol consisted of a 4-week baseline phase where headache symptoms were recorded via a headache diary, a 5-day treatment phase where the combined tDCS and tsDCS intervention was administered, and a 4-week follow-up phase where headache symptoms were again recorded via a headache diary. Sensitivity to mechanical stimuli was assessed at the beginning and end of the 5-day treatment period. PPT = pressure pain threshold; tDCS = transcranial direct current stimulation; tsDCS = trans-spinal direct current stimulation.

immediately followed by 20 minutes of tsDCS; tDCS was applied prior to tsDCS based on a previous research in stroke patients that indicates clinical benefits are greatest when tDCS precedes a second therapy [27]. Indeed, when tDCS was applied during or after therapy, it conferred no additional advantage [27]. The treatment dose was based on early evidence that consecutive daily sessions maximise the effects of tDCS [28].

Transcranial direct current stimulation

Anodal tDCS was delivered using two 35 cm^2 (5 cm × 7 cm) saline-soaked surface electrodes and a battery-operated unit (NeuroConn DC-STIMULATOR PLUS, NeuroConn GmbH, Ilmenau, Germany). Current was applied with the anode positioned over the left primary motor cortex (M1), determined using the International 10—20 system for C3, and the cathode positioned over the contralateral supraorbital region (10/20 location approximately Fp2) [29]. This configuration has been used previously in individuals with CM and other chronic pain conditions [9,10,30—33]. Further, the majority of studies investigating the effect of tDCS in bilateral chronic pain conditions have applied unilateral stimulation [9,10,30,34,35]. Prior to application, the skin was inspected for pre-existing lesions and was cleaned with a mildly abrasive skin preparation cream. A direct current of 1 mA (ramped up and down over 10 seconds) was applied for 20 minutes.

Trans-spinal direct current stimulation

Anodal tsDCS was delivered using two saline-soaked surface electrodes (35 cm^2) and a battery-operated unit (Neuro-Conn DC-STIMULATOR PLUS, NeuroConn GmbH, Ilmenau, Germany). Current was applied with the anode positioned longitudinally over the spinous process of the 10th thoracic vertebrae (T10) and the cathode positioned over the right shoulder [18,36]. This configuration has been shown to reduce pain sensitivity [37], alter processing of nociceptive stimuli [36], and increase pain tolerance [18] in previous studies. Prior to application, the skin was inspected for pre-existing lesions and was cleaned with a mildly abrasive skin preparation cream. A direct current of 1 mA (ramped up and down over 10 seconds) was applied for 20 minutes.

Outcome measures

Feasibility and safety

Feasibility was measured as (1) the number of sessions attended by each participant and (2) the proportion of participants recruited from the total number screened. Safety was determined as the frequency and duration of any adverse reaction reported verbally by the participant at each session. An adverse reaction is defined by the World Health Organisation as "a response to a drug [intervention] which is noxious and unintended, and which occurs at doses normally used in man for the prophylaxis, diagnosis, or therapy of disease, or for the modification of physiological function" and that likely has a causal relationship with the intervention [38]. A mild tingling or itching sensation under the electrodes, fatigue, headache, nausea, and insomnia have been reported as potential adverse reactions in response to direct current stimulation [39].

Headache symptoms

A headache diary was completed for the 4 weeks immediately before and after the 5-day intervention. The diary included information on headache frequency (days per month), severity [recorded on a numerical rating scale (NRS) where 0 indicated no pain and 10 the worst pain imaginable], duration of each headache episode, triggers, and use of medication/other nonpharmacological treatments.

Headache severity immediately following each intervention session

Headache severity was assessed immediately before and after each 40-minute intervention session using an 11-point NRS as above. The NRS is a reliable and valid tool for the assessment of pain severity [40].

Sensitivity to mechanical stimuli

Pressure pain thresholds (PPTs) were measured using a hand-held pressure algometer (FORCE TEN FDX compact digital force gauge; Wagner Instruments, Greenwich, Connecticut, USA). The probe (size 1 cm^2) was applied perpendicular to the skin (rate 5.8 lb/s) until the

participant first reported that the sensation of pressure changed to pain. PPTs were measured bilaterally at each of the following sites: (1) anterior temporalis muscle; (2) upper trapezius muscle (measurements made at the insertion of the muscle at the medial superior nuchal line); and (3) thumbnail [41]. Three recordings were made at each site and the mean was calculated.

Perceived response to therapy

A 7-point Likert Scale was used to assess the perceived response to therapy according to the Global Perceived Effects Scale [42]. The scale ranges from completely recovered, moderately recovered, and somewhat recovered to unchanged, somewhat worsened, moderately worsened, and vastly worsened. Participants were asked to rate the outcome of the intervention on completion of the 4-week follow-up phase.

Analysis

Data for feasibility and safety are presented using descriptive statistics. Data for headache duration and severity were averaged over the 4-week baseline and follow-up periods for each participant. Pharmacological and nonpharmacological treatments were analysed as number of uses. To determine whether the intervention had an effect on headache parameters (frequency, duration, severity, treatment use, or mechanical sensitivity) a paired t test was performed (factor time: baseline vs. follow-up) for each variable. Normality was assessed using Shapiro—Wilk tests. Significance was set at $p < 0.05$. As this was a pilot trial not powered to detect a difference in response to treatment between headache types (CTTH, CM, and CDH), these data are presented descriptively in the text. To estimate the sample size needed to detect a significant treatment effect for a future powered trial, a power analysis was conducted using G*POWER 3.1.9.2 (Universitat Dusseldorf, Germany) for outcomes showing a

significant, or a trend towards a significant improvement following the combined stimulation.

Results

Feasibility and safety

Seventeen participants were screened for eligibility. One participant did not meet the inclusion criteria for headache frequency during the baseline phase, and four participants withdrew before the start of the treatment week with no reasons stated. Thus, 12 participants entered the treatment stage. Of these, two participants withdrew after the first treatment session due to personal commitments. Ten participants completed baseline, intervention, and withdrawal phases, but one participant attended only three treatment sessions. Thus, nine participants attended all five treatment sessions and were included in the analysis (Figure 2).

The intervention was well received. Mild side effects included a tingling sensation at the beginning of both stimulations or during the session that faded away (49% of tDCS sessions and 47% of tsDCS sessions), itching under the electrode at the start of stimulation (16% of tDCS sessions and 16% of tsDCS sessions), a sensation of pins and needles that faded away during the session (4% of tDCS sessions and 4% of tsDCS sessions), pain following tDCS sessions that faded away after a few seconds or with the start of tsDCS (7%), a slight burning sensation felt with tsDCS (4%), and nausea at the start of tDCS (4%). Other side effects included one episode of drowsiness and headache with tDCS that resolved with the start of tsDCS.

Participant characteristics at baseline

Nine participants (3 with CM, 3 with CTTH, and 3 with CDH) completed all phases of the study including the 4-week
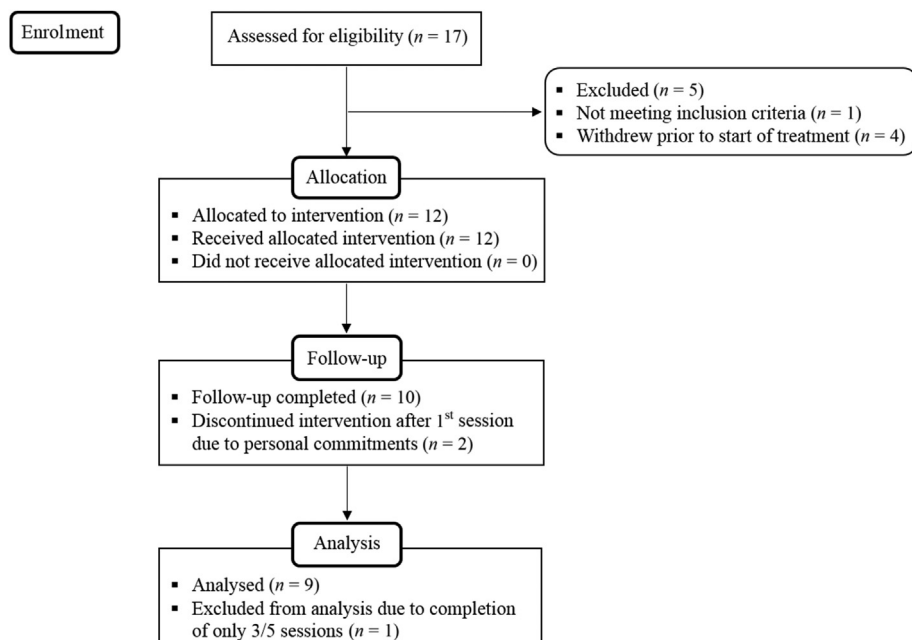

Figure 2.   Consolidated Standards of Reporting Trials (CONSORT) flow chart of participants through the study.

follow-up. These participants ranged in age from 22 years to 59 years [mean ± standard deviation (SD): 40 ± 15 years] and comprised three males and six females. The time since first onset of chronic headaches ranged from 2 years to 36 years, with a mean and SD of 14.9 ± 12.2 years. The most common headache trigger was bad sleep reported by 67% of participants, followed by technology use including computers, mobile phones, and iPads (56%); stress (44%); muscular tension (44%); cold/flu (33%); excessive work (33%); light (22%); tiredness (22%); hunger (22%); and exercise (11%). Participant demographics are provided in Table 1.

Headache symptoms

Individual results for headache symptoms pre- and post-intervention are presented in Table 2.

Headache frequency
The number of headaches reported during the 4-week baseline period ranged from nine to 28, with a mean of 20 ± 8 headaches per month. The number of headaches reported at baseline differed based on headache type, with 20 ± 2 headaches in CTTH, 11 ± 3 headaches in CM, and 28 ± 0 in CDH (Figure 2). Following the 5-day combined tDCS and tsDCS intervention, there was a reduction in headache frequency ($p = 0.026$). Descriptive examination of these data reveals an average reduction in headache frequency in participants with CTTH and CM of 54 ± 24% following treatment, but no reduction in headache frequency in participants with CDH (Figure 3).

Headache duration
The duration of each headache episode at baseline ranged from 2.5 hours to 7.3 hours (mean ± SD: 6.2 ± 1.8 hours) in those with CTTH and CM. All participants with CDH reported continuous headache (24 hours a day) at baseline. Headache duration was unaltered following the combined tDCS and tsDCS intervention ($p = 0.34$; Table 2).

Headache severity
Average headache severity in the 4-week baseline period ranged from 3.3 to 7.2 out of 10 on the NRS, with a mean

**Table 1** Participant demographics.

Participant	Gender	Age (y)	Headache type	Time since onset of headaches (y)
1	F	58	CTTH	25
2	M	32	CTTH	24
3	M	59	CTTH	21
4	F	37	CM	5
5	F	33	CM	3
6	F	33	CDH	14
7	M	28	CDH	4
8	F	60	CDH	36
9	F	22	CM	2

CDH = chronic daily headache; CM = chronic migraine; CTTH = chronic tension-type headache; F = female; M = male.

Table 2 Headache frequency, average headache duration, severity, and use of medication and other treatments for each participant in the 4 weeks before and after the intervention.

Participant	Headache type	Frequency (d/mo)		Duration (h) (mean ± SD)		Severity (NRS) (mean ± SD)		Medication use (frequency)		Other treatments (frequency)	
		Pre	Post	Pre	Post	Pre	Post	Pre	Post	Pre	Post
1	CTTH	18	15	6.5 ± 6.1	7.3 ± 5.6	4.8 ± 2.1	4.3 ± 1.4	7	8	7	9
2	CTTH	22	6	6.9 ± 5.4	6.4 ± 4.9	3.3 ± 2.3	4.5 ± 1.6	7	5	2	0
3	CTTH	19	3	2.5 ± 0.6	3.3 ± 1.5	4.3 ± 1.4	5.0 ± 1.7	14	3	18	0
4	CM	9	5	6.9 ± 5.3	12.8 ± 7.4	6.3 ± 1.3	4.2 ± 1.8	8	4	1	0
5	CM	15	8	7.3 ± 5.3	6.0 ± 4.2	3.7 ± 1.3	4.1 ± 1.2	7	6	0	0
6	CDH	28	28	23.0 ± 0	23.0 ± 0	4.5 ± 1.8	3.3 ± 1.1	0	0	13	13
7	CDH	28	28	23.0 ± 0	23.0 ± 0	7.2 ± 0.8	4.3 ± 0.6	28	28	0	0
8	CDH	28	28	23.0 ± 0	23.0 ± 0	6.9 ± 0.5	7.1 ± 0.4	0	0	0	0
9	CM	10	4	7.1 ± 5.2	7.0 ± 0.7	7.2 ± 1.2	2.9 ± 0.9	10	4	2	1

CDH = chronic daily headache; CM = chronic migraine; CTTH = chronic tension-type headache; NRS = numerical rating scale.
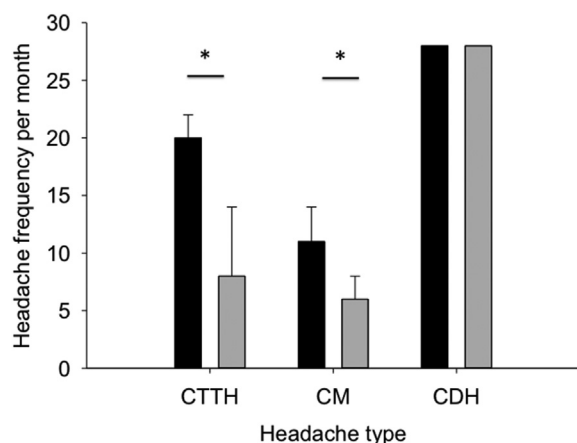
Figure 3. Group data (mean and standard deviation) for headache frequency in the 4 weeks before (black bars) and after (grey bars) the combined tDCS and tsDCS intervention split by headache type (CTTH, CM, and CDH). Following the 5-day combined tDCS and tsDCS intervention, there was a reduction in headache frequency in participants with CTTH and CM, but not in those who experienced CDH. * $p < 0.05$. CDH = chronic daily headache; CM = chronic migraine; CTTH = chronic tension-type headache; tDCS = transcranial direct current stimulation; tsDCS = trans-spinal direct current stimulation.

severity of 5.4 ± 1.5 across participants. There was no change in headache severity following the combined tDCS and tsDCS intervention ($p = 0.16$; Table 2).

Headache severity immediately after each intervention session

Immediately before and after each intervention session, participants rated the severity of their headache on the NRS. Across the five sessions, the average headache severity was 2.7 ± 0.40 points immediately before treatment and 2.0 ± 0.24 points immediately after treatment. The combined stimulation produced immediate reductions in headache severity in 67% of sessions, with 18% of these resulting in a headache severity rating of 0/10 immediately after treatment.

Use of medication and nonpharmacological treatments

Medication use varied, with some participants reporting no use of medication and others reporting medication use with every headache episode (mean $\pm$ SD of 9 ± 8 uses in the 4-week baseline period). Medications included antidepressants and over-the-counter pain medications such as paracetamol. There was a trend towards a decrease in the use of medications following the combined tDCS and tsDCS intervention, but this did not reach statistical significance ($p = 0.075$; Table 2).

Nonpharmacological treatments were used from zero to 18 times over the 4-week baseline period (mean $\pm$ SD of 4.8 ± 6.6 uses). Treatments included massage, rest, sleep,

heat packs, showers, distractions, and exercise/stretching. There was no change in the use of other treatments following the combined intervention ($p = 0.15$; Table 2).

Perceived response to therapy

Four weeks following cessation of the intervention, 78% of participants reported that their headaches had improved. Four participants (44%), including two with CTTH, one with CDH, and one with CM, scored headache improvement as "moderately improved" (a score of $+2$). Three participants (33%), including one with CTTH, one with CM, and one with CDH, rated their overall headache improvement as "somewhat improved" (a score of $+1$), and two participants (22%; 1 with CM and 1 with CDH) rated their headaches as unchanged (a score of 0) on the Global Perceived Effects Scale.

Sensitivity to mechanical stimuli

The combined tDCS and tsDCS intervention did not alter sensitivity to mechanical stimuli at any site (p value range, $0.11-0.94$).

Sample size calculation

A sample size calculation was performed for a fully powered trial using the following parameters: $\alpha = 0.05$, power of 0.8, and effect size for the variables of headache frequency (Cohen's $d = 0.59$) and medication use (Cohen's $d = 0.31$), resulting in required sample sizes of 20 and 66 for each outcome, respectively.

Discussion

To our knowledge, this is the first study to investigate the use of direct current stimulation applied in combination to the brain and spinal cord in any pain condition. Our data demonstrate that a combined tDCS and tsDCS intervention is feasible, safe, and well received by individuals who experience chronic headaches. In addition, we provide early evidence for an immediate effect of combined stimulation on headache severity following treatment and an overall effect on headache frequency in individuals with CTTH and CM, but not in those with CDH. A trend towards a reduction in medication use was also observed. Contrary to our hypothesis, the combined stimulation did not appear to influence sensitivity to mechanical stimuli. These preliminary findings provide data to inform a fully powered, randomised controlled trial of this novel intervention in chronic headache.

The dropout rate for the current study (25%) is similar to that reported in other trials of noninvasive brain stimulation interventions [9,25,43,44]. Adherence to the intervention was high with 83% of scheduled sessions completed. Transient side effects such as tingling under the electrodes were experienced by many participants; however, these were mild and consistent with those reported in previous studies [45]. Seven of nine participants reported an improvement in their headaches following the intervention.

Notably, two participants who, on the headache diary, did not report differences in headache symptoms following the intervention, reported an improvement in their headaches using the Global Perceived Effects Scale. Outcome measures such as the headache disability index, headache impact test, or the McGill pain questionnaire, which detect more subtle changes in headache symptoms that the participant may perceive to be large, may be useful in future trials.

The combined brain and spinal cord direct current intervention had positive effects on headache frequency that on average (54 ± 24%) exceeded the threshold for clinically meaningful change [46]. Reduced headache frequency is reported to be an important indicator for successful treatment in headache patients [47]. Notably, improvements in headache frequency were reported in individuals with CTTH and CM, but not in those with CDH, suggesting that some forms of chronic headache may be more receptive to direct current stimulation interventions than others. In one participant (Participant #1, Table 2), the reduction in headache frequency coincided with a slight increase in headache duration and treatment. Despite this, the participant reported headaches to be "moderately improved" on the Global Perceived Effects Scale. It is unknown what individual factors may influence the response to treatment, and this pilot trial was not powered to examine this question. One possibility is that the older age of this participant and a longer history of headaches (relative to other CTTH and CM participants) may have influenced the response to treatment. Future, fully powered trials should seek to examine the relationship between individual factors and treatment response.

Headache severity was reduced immediately following the 5-day treatment period, but this was not maintained at the 4-week follow-up. A longer intervention period may be required to induce long-lasting effects on headache severity. Indeed, some studies have shown that an intervention period of 10 consecutive working days has greater effects on pain severity than five consecutive sessions, with effects maintained up to 2 months [48]. Finally, our data reveal a trend towards a reduction in medication use in the 4 weeks following treatment that should be further explored in future studies.

Central sensitisation is hypothesised to play a role in a range of chronic headache types [4–6], and there is evidence that tDCS applied to both brain [30] and spinal cord [49,50] may target this mechanism. Here, we failed to detect a change in sensitivity to mechanical stimuli (PPT), a measure thought to provide an index for central sensitisation [41,51], following treatment. Interestingly, a previous study suggested that PPT is related to headache parameters of severity and frequency [52]. It is possible that the unaltered headache severity scores in this study were also related to the unaltered change in sensitivity. To see the effects on pain sensitivity, a longer intervention time, as suggested for headache severity, may be required. Alternatively, a reduction in central sensitisation may take time to develop following a direct current stimulation intervention, and a longer follow-up period may be required to see the changes in this parameter in future trials.

As the combination of brain and spinal direct current stimulation has not, to our knowledge, been trialled in any previous study, the purpose of this work was to provide data on feasibility and safety in order to support a fully powered, randomised, controlled trial of this novel intervention in future. As such, this study was not designed or powered to determine the effect of treatment on clinical outcomes. Key limitations include a small sample size; variability of headache types across participants; lack of participant, assessor, or therapist blinding; and the absence of a sham control. Although previous studies investigating pain have shown greater mechanistic and/or clinical benefits when tDCS and a second therapy (e.g., peripheral electrical stimulation, aerobic exercise, or active stretching) are combined than when either treatment is given alone, this pilot study is unable to determine whether the combined effect of tDCS and tsDCS was greater than that of tDCS or tsDCS applied alone. Future studies will require individual controls for the brain and spinal stimulations to determine whether the combined treatment has greater effects on clinical outcomes than either intervention applied alone. Despite these limitations, this study provides valuable proof-of-concept data to inform a rigorous clinical trial in future.

Conclusion

This study is the first to investigate the use of a combined brain and spinal cord stimulation in any chronic pain population. Our data suggest that a combined tDCS and tsDCS intervention is safe, feasible, and well tolerated by individuals with chronic headache. Although this pilot trial suggests that our novel intervention may improve clinical outcomes in chronic headache, further studies that are appropriately powered, randomised, and blinded, and include suitable control groups are required before conclusions regarding clinical efficacy can be drawn. Future studies should include additional neurophysiological measures that may underpin any clinical improvements observed and longer follow-up periods to capture any slowly developing effects on central sensitisation mechanisms.

Conflicts of interest

Funding/support

Authors' contributions

Treleaven contributed to the conception and design of the study, data interpretation, reviewing of the article and final approval of the version to be published.

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