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CLINICAL TRIAL

Dual-site transcranial direct current stimulation to treat tinnitus: a randomized controlled trial

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Transcranial direct current stimulation (tDCS) has been proposed as a potential intervention for subjective tinnitus, but supporting evidence remains limited. We aimed to investigate the effect of anodal high-definition tDCS of the left temporal area and right dorsolateral prefrontal cortex on tinnitus severity.

This double-blind randomized controlled trial included 77 patients (age range 18–79, 43 male) with chronic subjective tinnitus as their primary complaint. Thirty-eight subjects received six consecutive sessions of dual-site sequential high-definition-tDCS with electrodes positioned over the left temporal area and right dorsolateral prefrontal cortex. Both areas were stimulated for 15 min per session, with total stimulation time amounting to 30 min. Thirty-nine subjects received sham stimulation. The primary outcome measure was the change in tinnitus severity, as evaluated by the Tinnitus Functional Index, from baseline to a follow-up visit at 8 ± 2 weeks after treatment completion. Secondary outcomes included changes in perceived tinnitus loudness, as measured with a visual analogue scale and a tinnitus matching procedure, as well as scores on the Hospital Anxiety and Depression Scale, and the Hyperacusis Questionnaire.

No differences in Tinnitus Functional Index change scores were identified between the active treatment and sham control groups (linear regression: $P = 0.86$). The Tinnitus Functional Index scores decreased significantly over time in both groups ($P = 0.0012$), indicating the presence of a considerable placebo effect. These change scores were significantly influenced by sex (linear regression: $P = 0.037$) and baseline symptoms of anxiety (linear regression: $P = 0.049$) in both groups. In general, Tinnitus Functional Index scores decreased more profoundly in males and in subjects with a higher degree of anxiety at baseline. None of the included secondary measures differed significantly between experimental arms.

Our results suggest that dual-site sequential high-definition-tDCS of the left temporal area and right dorsolateral prefrontal cortex does not alleviate tinnitus severity. Interestingly, in our study population, fluctuations in tinnitus severity were influenced by gender and concurrent mental condition. It is therefore important to take these factors into account when conducting or planning randomized controlled trials in tinnitus populations.

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Introduction

Tinnitus, defined as the perception of a sound with no corresponding external source, is a highly prevalent symptom present in 12 to 30% of the worldwide adult population.[1,2] Whereas some subjects suffer from objective tinnitus and perceive sounds generated by physiological events within the body, the large majority of patients experience subjective tinnitus, perceiving a sound without any corresponding sound source. The severity of tinnitus and its accompanying symptoms varies greatly. Subjects suffering from tinnitus may experience one or a combination of a plethora of accompanying non-specific symptoms, such as annoyance, irritability, anxiety, depression, hyperacusis, hearing impairment, insomnia and cognitive difficulties.[3–6] An estimated 1% of the total population perceives their tinnitus as a significant burden with a considerable impact on quality of life.[2]

There is no curative treatment for tinnitus, and currently, the only evidence-based tinnitus management strategy is cognitive behavioural therapy (CBT).[7,8] Psycho-social treatment options such as CBT are indeed able to reduce tinnitus-associated distress. However, they cause little or no reduction of the underlying tinnitus loudness, and evidence for their long-term effects is lacking. The success of other tinnitus treatments often depends on the presence and severity of accompanying symptoms. For instance, patients for whom tinnitus is paired with varying degrees of hearing loss may experience significant tinnitus relief when using hearing aids, cochlear implants or auditory brainstem implants.[9–12] Meanwhile, subjects with concomitant cervical or temporomandibular dysfunctions can achieve beneficial results with physical therapy such as orofacial treatment.[13] Thus, the large heterogeneity in tinnitus presentation requires a personalized, patient-tailored treatment plan.[14] Overall, existing management strategies more often target accompanying symptoms other than the underlying pathophysiology of the tinnitus percept itself.

While tinnitus is often preceded by some form of cochlear damage, the relationship between tinnitus and hearing loss is not straightforward. A dominant theory for the formation of tinnitus is the central gain hypothesis, which postulates that reduced somatosensory input leads to amplified spontaneous firing at the level of the auditory neurons, which is then relayed to higher order nuclei and the auditory cortex.[15,16] This hypothesis has been demonstrated in animal models of tinnitus[17,18] and is consistent with findings of hyperactivity in auditory cortex illustrated by human MRI and EEG studies.[19,20] However, recent research has offered important counterpoints to this bottom-up central gain hypothesis, such as the relative absence of tonotopic map changes in auditory cortex of hearing-impaired individuals with tinnitus.[21] Consequently, researchers have begun proposing alternative or additional theoretical models of tinnitus generation. One hypothesis is the predictive coding theory, which posits that the perception of tinnitus relies on higher perceptual networks recognizing auditory activity as an auditory entity instead of noise, regardless of the level of cochlear damage.[22] Overall, the influence of top-down processes contributing to the tinnitus percept is increasingly being recognized, as the importance of other cortical regions such as prefrontal cortex, parahippocampus, anterior cingulate cortex and insula becomes clear.[19,23–25]

Overall, a large body of evidence on tinnitus-related aberrant activity and connectivity in both auditory and non-auditory brain areas exists. As the extent of these cortical irregularities is illuminated, researchers have begun exploring the targeting of such aberrant brain activity as a therapeutic option.[26,27] Acts of modifying underlying neural activity, often with the aim of achieving a therapeutic benefit, fall under the heading of neuromodulation. The induction of neuroplastic changes via neuromodulation may interrupt the observed aberrant neural activity and, thus, alter or reduce the tinnitus percept.[28] Non-invasive neuromodulation can be performed using several different modalities. For instance, repeated electromagnetic pulses may be delivered by a coil producing magnetic fields in a procedure known as repetitive transcranial magnetic stimulation (rTMS). Some studies have demonstrated that rTMS is capable of suppressing tinnitus symptoms, but its therapeutic effect is often partial and transient.[29,30] A potential alternative approach is the direct delivery of low-intensity electric currents to the brain via scalp electrodes. The technique using direct currents is known as transcranial direct current stimulation (tDCS). Immediate effects of tDCS are usually less marked than those elicited by rTMS, as this technique does not elicit action potentials, but rather modulates subthreshold cortical excitability. The mechanisms of action of tDCS remain to be elucidated. Initial investigations of tDCS of the motor cortex have led to the assumption that anodal tDCS increases and cathodal tDCS decreases the excitability of the underlying cortex.[31] However, this does not function as a general rule, as numerous factors have been shown to influence tDCS polarity effects, including dendritic orientation, baseline activity, and current intensity.[32] Despite the considerable degree of uncertainty regarding the exact mechanisms of action, tDCS has been suggested as a potential therapeutic application in many different domains,[33] and researchers generally agree that the weak currents delivered by tDCS are able to influence oscillatory neural behaviour and affect cortical connectivity.[34,35]

In existing trials investigating tDCS as an experimental treatment for tinnitus, electrodes have often been placed over the left temporal area (LTA), which comprises the auditory cortex. Initial studies applying anodal tDCS over the LTA found preliminary results showing transient tinnitus suppression in up to 40% of participants.[36,37] However, more recent trials have not been able to conclusively replicate these findings.[38,39] A different area of interest for tDCS in tinnitus trials is the right dorsolateral prefrontal cortex (rDLPFC). Stimulation of this area has been proposed to strengthen deficient inhibitory top-down mechanisms, as well as interfere with the emotional response to the tinnitus percept.[40] Pilot studies applying anodal tDCS over the rDLPFC reported promising effects,[41–43] but the evidence remains too preliminary to make definitive recommendations.[33] A direct comparison between stimulation of both areas yielded no difference in effect, although it is not unthinkable that the targeting of different cortical areas acts on the tinnitus percept via different mechanisms.[44] The recent introduction of

high-definition (HD) tDCS, which uses small ring electrodes allowing for more focal stimulation, has opened up the possibility of stimulating both areas within one session.[45] Such a dual-site stimulation protocol may have more profound and longer-lasting effects on underlying cortical excitability.[44,46,47] However, this has not yet been investigated in a tinnitus population.

Overall, current trials into the effects of tDCS on tinnitus are characterized by a considerable degree of variability and a low quality of evidence. Many of the published studies lack a sham arm, although placebo effects in patients with tinnitus are well documented and should undoubtedly be taken into account.[48,49] Several sham-controlled studies have investigated the effect of only one tDCS session on tinnitus,[50,51] although it has been suggested that a single session of tDCS is not sufficient to elicit long-term effects.[43] Some sham-controlled trials investigating the effects of multiple sessions of tDCS on tinnitus exist, but they are characterized by small sample sizes (generally, 11 to 15 subjects are included in each group) and a high degree of between-study heterogeneity concerning electrode placement and used tDCS protocol.[38,39,41,52] Summarizing the existing evidence, a recent meta-analysis found a small to moderate, but ultimately non-significant, effect of active versus sham tDCS on tinnitus.[49] The authors found no compelling evidence that active tDCS diminishes tinnitus symptoms, but nevertheless reported a clinically significant mean change of tinnitus standardized questionnaire scores. Thus, some uncertainty regarding potential tDCS effects on tinnitus still remains.

We performed a randomized controlled trial into the effects of dual-site HD-tDCS of the LTA and rDPLFC in a well-defined study population of patients with chronic subjective tinnitus as their primary complaint. Our primary aim was to investigate the therapeutic effect of HD-tDCS on tinnitus severity and its impact on quality of life, as measured by the Tinnitus Functional Index (TFI). In addition, we examined HD-tDCS effects on secondary outcomes including tinnitus loudness, hyperacusis and concurrent symptoms of anxiety and depression.

Materials and methods

The full protocol of this clinical trial has been published elsewhere.[53] The study has been registered at ClinicalTrials.gov (protocol number: NCT03754127) since 22 November 2018.

Subjects

Patients were recruited at the tertiary tinnitus clinic (TINTRA—Tinnitus Treatment and Research Center Antwerp) at the ENT department of the Antwerp University Hospital (UZA). Inclusion and exclusion criteria were chosen in order to guarantee that all subjects experienced subjective tinnitus as their primary complaint. All patients experienced chronic tinnitus lasting for at least 6 months, with tinnitus duration ranging from 6 months to 50 years. A full overview of all inclusion and exclusion criteria is provided in Table 1. Tinnitus patients presenting themselves at the ENT department who met all inclusion criteria were informed about the clinical trial and invited to participate.

Table 1 Overview of all inclusion and exclusion criteria

Inclusion	Exclusion
Chronic (> 6 months) subjective tinnitus	Somatosensory tinnitus
24 < TFI score < 90	Pregnancy
HADS scores:[a]	Active middle ear pathology
Depression subscale <12	Hearing implants
Anxiety subscale <12	Known tumours in the head/neck region
HQ score < 40	Patient having already had any other tinnitus treatment within the last 2 months

[a]Not applicable for subjects with TFI scores between 75 and 90.

All procedures were approved by the Ethical Committee of Antwerp University Hospital on September 3, 2018 (file number: B300201837315). All participants provided full informed consent. Patient recruitment started in January of 2019, with the first patient being included on 17 January. Recruitment was completed on 29 September 2021.

A sample size calculation was performed based on the minimal clinically relevant difference in TFI scores, i.e. 13 points.[54] Assuming a standard deviation (SD) of 20 points, as found in international literature,[55] a sample size of 39 participants per group was deemed appropriate to detect this difference with 80% power.[53]

Recruitment was intended to progress evenly across three different categories of tinnitus severity, i.e. grade 2 (light to moderate tinnitus distress, 25 < TFI < 50), grade 3 (moderate to severe tinnitus distress, 50 < TFI < 75) and grade 4 (severe tinnitus distress, 75 < TFI < 90).[53] This precautionary measure was taken on account of a previous suggestion that baseline tinnitus severity may impact tDCS effects.[42] However, after approximately 18 months of patient recruitment, it became apparent that full inclusion for subjects with grade 4 tinnitus distress would not be met. Nearly every subject experiencing severe tinnitus distress was excluded from the trial due to scores on the Hospital Anxiety and Depression Scale (HADS) exceeding 11, indicating the putative presence of concurrent symptoms of anxiety and/or depression. In consultation with all involved researchers, it was decided that an amendment would be put in place allowing an additional group of subjects, with TFI scores between 75 and 90 and one or both HADS subscale scores exceeding 11, to be submitted to the same trial protocol. This decision was made to guarantee that sufficient data would be collected from subjects in grade 4, corresponding to severe tinnitus distress. This amendment was approved by the Ethical Committee of Antwerp University Hospital on November 19, 2020. Data from this group of subjects were handled separately in all analyses unless statistical equivalence between both groups could be proven.

Study design

Participants were invited for a first study visit consisting of audiometric measurements and questionnaires to gauge tinnitus severity and the presence and degree of confounding factors. All measurements were performed by ICH-GCP accredited researchers (including masters in audiology and a master in biomedical sciences). After this baseline visit, patients were randomized into the active HD-tDCS group or control group. Six sessions of sequential dual-site HD-tDCS (or sham stimulation) were planned after the baseline visit. The primary follow-up time point was planned at 8 (±2) weeks after the last HD-tDCS session. Audiometric tests and questionnaires included in this follow-up visit were identical to the baseline visit.

Assignment of interventions

Participants were randomized into the active HD-tDCS or sham control group in a 1:1 ratio. Stratified randomization—according to sex and grade of tinnitus severity based on TFI scores—was performed. Patients were categorized in three groups according to their TFI score

as described above. As such, a total of six strata were defined. Patient enrollment and allocation was performed by an independent researcher using QMinim Online Minimization©.

The researcher performing all baseline and follow-up measurements was blind to the allocation of the patients to avoid test bias. As it is not possible to blind the person administering the HD-tDCS, for each patient, this member of the research team differed from the researcher performing baseline and follow-up measurements. Both the participant and the researcher were blinded until the primary follow-up time point, after which they were unblinded by an independent researcher with access to the allocation list.

High-definition transcranial direct current stimulation

All parameters concerning the execution of the HD-tDCS were in accordance with guidelines extracted from optimization studies.[45] Six 30-min sessions of HD-tDCS (or sham stimulation) were provided within a period of 3 weeks, with a minimum interval of 1 day between subsequent sessions. Electrode positioning was performed according to the 10/20 international system for EEG electrode placement, with electrodes placed at the rDLPFC and LTA. Central anodes were placed at F4 (rDLPFC) and CP5 (LTA), with adjoining cathodes at F2, F6, FC4 and AF4 (rDLPFC) and C5, TP7, CP3 and P5 (LTA). A constant current of 2 mA was applied at each site for 15 min, with a fade-in and fade-out time of 20 s. The order of stimulation was randomized. For the sham stimulation, constant current was only applied for the first 20 s as described previously.[56] Direct current was applied via sintered Ag/AgCl ring electrodes with an inner radius of 6 mm and outer radius of 12 mm and delivered via a battery-driven 1 × 1 tDCS low-intensity stimulator and 4 × 1 multichannel stimulation adaptor (Soterix Medical Inc.). Ring electrodes were stabilized using HD-electrode holders anchored in a Soterix Medical HD-cap and filled with EEG electrode gel (Neurax) following the guidelines for 4 × 1 HD-tDCS stimulation.[57]

Primary outcome

The primary outcome measure was the change in TFI scores from baseline to follow-up. The TFI is a self-reported questionnaire to gauge severity of the tinnitus and its impact on daily life.[54,58] This questionnaire consists of 25 questions which must be answered on a Likert scale ranging from 0 to 10. The total score is calculated as the mean of all scores multiplied by 10 and expressed as a number from 0 to 100, with a score of 0 corresponding to the absence of any tinnitus complaint. Next to the total score, results of the TFI include eight subscales: intrusiveness, sense of control, cognition, sleep disturbance, auditory difficulties, relaxation, quality of life and emotional distress.

Secondary outcomes

Questionnaires

A visual analogue scale (VAS) was used to determine the subjective maximum loudness of the tinnitus sound. Patients were asked to rate the loudness of their tinnitus on a scale from 0 (no tinnitus) to 100 (tinnitus cannot possibly be any louder). The degree of subjective tinnitus loudness as measured via this VAS will henceforth be referred to as 'VAS loudness'.

The Hospital Anxiety and Depression Scale (HADS) is a screening tool to detect states of anxiety and depression.[59] Subjects were asked to answer a total of 14 questions, with seven questions belonging to the subscale 'anxiety' and the other seven to the subscale 'depression'. Scores lower than 8 indicate non-cases, while borderline abnormal cases score between 8 and 10 and cases score higher than 10 out of a possible 21 for each scale.

The Hyperacusis Questionnaire (HQ) was used to investigate hypersensitivity to sound.[60] The HQ is a 14-item self-report questionnaire assessing three dimensions of hyperacusis (attentional, social and emotional). A score of 28 or more out of a possible 42 indicates the presence of clinically significant hyperacusis.

Audiometric tests

Pure-tone linear audiometry was performed in a soundproof booth according to current clinical standards [International Organization for Standardization (ISO) 8253-1:2010]. Air conduction thresholds were measured at 125 Hz, 250 Hz, 500 Hz, 1 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz and 8 kHz using a two-channel AC-40 audiometer (Interacoustics). Pure tone averages (PTA) were calculated based on the thresholds at 1, 2 and 4 kHz. In cases of unilateral tinnitus, PTA of the tinnitus ear was chosen for further analysis. Otherwise, an average PTA of both ears was calculated.

In addition, a two-alternative forced choice matching procedure was used to establish the psychoacoustic characteristics of the tinnitus sound. First, pairs of pure tones or noises at differing frequencies were presented to the subject, who was asked to indicate which of the stimuli best resembled the tinnitus sound. This procedure was then repeated in order to obtain the closest possible match of the tinnitus frequency. Then, tinnitus loudness, i.e. the perceptual correlate of sound intensity, was determined via a similar forced choice procedure. The tone or noise defined as the tinnitus match was repeatedly presented to the subject at two different intensity levels, until the closest loudness match was identified. Final loudness levels were expressed as dB sensation level, calculated as the difference between the absolute level of the loudness match and the auditory threshold at the tinnitus frequency. This psychoacoustic measure of tinnitus loudness will henceforth be referred to as 'matched loudness'.

Data collection and management

Data were stored using OpenClinica LLC, a software packet designed for electronic data storage and management in a clinical setting. This program allows for the use of validation checks, such as range checks for date values, so that the number of mistakes in manually entering the data is minimized. The database was password-protected, with only the principal investigators being granted access. Information collected in the study was kept strictly confidential. Data were coded and pseudonymized.

Study monitoring

An independent Data and Safety Monitoring Board at the Antwerp University Hospital met twice a year to monitor the clinical trial for adherence to the protocol and potential adverse events. No major issues were identified during these meetings.

Statistical analysis

The primary outcome was the change in TFI scores from baseline to follow-up (ΔTFI). This ΔTFI score was compared between the sham and active group in a linear regression model using R (version 4.0.5, The R Foundation for Statistical Computing, 2021). ΔTFI was chosen

as the outcome variable, while treatment group (active versus sham) was the predictor variable. A backwards stepwise elimination was performed to correct for putative confounding effects of age, sex, PTA, HADS scores, HQ scores, tinnitus characteristics and TFI grade at baseline.

To analyse the secondary outcomes, similar linear regression models were constructed with matched loudness, VAS loudness, HADS scores and HQ scores as outcome variable and treatment group as predictor variable. A Holm-Bonferroni correction for multiple comparisons was applied to the resulting *P*-values of these linear regression models.

As mentioned above, an additional group of subjects experiencing severe tinnitus distress (75 < TFI < 90) and signs of anxiety and/or depression (one or both HADS subscale scores > 11) was included in the protocol. As a rule, data from this group of subjects were handled separately, unless statistical equivalence could be proven. Equivalence between both groups was investigated using two one-sided tests equivalence testing in R. For the primary outcome measure and all secondary outcome measures, statistical equivalence between both groups could be demonstrated. Therefore, data from both groups were combined for the final data analyses.

Data availability

The data that support the findings of this study are available upon motivated request in Zenodo (doi:10.5281/zenodo.5913674).

Results

Seventy-seven participants completed the full clinical trial

A total of 101 tinnitus patients were invited to participate in the clinical trial. Nineteen patients did not meet the inclusion criteria and were excluded from the trial. Five subjects dropped out of the study before completing the full treatment, three of whom did not receive the allocated treatment, and two were lost to follow-up. Thus, the final analyses were performed on a group of 77 participants. A consort flow diagram can be found in Fig. 1.

An overview of baseline characteristics of all participants can be found in Table 2. No significant differences between active and control groups for any of these baseline characteristics were identified.

Side effects of the tDCS were monitored during treatment and at follow-up. A total of eight study participants (10.4%) reported side effects. In the active HD-tDCS group, two subjects reported light, transient headaches after the stimulation sessions. In the sham control group, four subjects reported light, transient headaches, one subject reported more serious migraine-like headaches and one subject reported tingling sensations in the extremities after each session. No significant differences in the presence of side effects were found between the active and control groups ($P = 0.18$).

Blinding success was assessed by asking participants whether they believed to have received active or sham stimulation after completion of the treatment. Seventeen participants in the active HD-tDCS group (44.7%) and 13 participants in the sham control group (33.3%) believed to have received the active treatment. No significant differences in these proportions were found between both groups ($P = 0.30$).

TFI change scores did not differ significantly between active and sham treatments

TFI scores decreased significantly from baseline to follow-up (paired *t*-test: $t = 3.38$, $P = 0.0012$) across all participants (Fig. 2A). On average, TFI scores decreased with 5.7 points, corresponding to an effect size of 0.36. A linear regression model was constructed to investigate the effect of treatment group on ΔTFI scores, i.e. the differences between TFI scores at baseline and follow-up. ΔTFI scores did not differ significantly between participants receiving active and sham treatments [$F(3,70) = 0.033$, $P = 0.86$] (Fig. 2B). This linear regression model included a correction for confounding factors. Sex was found to have a significant independent effect on ΔTFI scores [$F(3,70) = 4.52$, $P = 0.037$], with males displaying higher ΔTFI scores (average ΔTFI scores in males: 8.6; in females: 2.0). Additionally, a significant effect of HADS anxiety subscale scores on ΔTFI scores was found [$F(3,70) = 3.99$, $P = 0.049$]. Larger ΔTFI scores were found in participants with higher HADS anxiety subscale scores at baseline. No significant effect on ΔTFI scores was found for any of the remaining putative confounding factors (age, hearing level, tinnitus characteristics, baseline HADS depression subscale scores, baseline HQ scores and TFI grade at baseline).

No secondary outcomes differed between the active treatment and sham control groups

Loudness of the tinnitus percept was determined via a tinnitus matching procedure at baseline and follow-up. Only in the active HD-tDCS group, matched loudness decreased from baseline to follow-up (Fig. 3A). A linear regression model was constructed to investigate the effect of treatment group on Δ matched loudness, i.e. the differences between matched loudness at baseline and follow-up. These Δ matched loudness levels differed between participants receiving active and sham treatments [$F(1,75) = 5.41$] (Fig. 3B). Average Δ matched loudness levels in the active treatment group were equal to 4.16 dB compared with −0.51 dB in the sham control group, corresponding to an effect size of 0.53. However, this effect did not survive the applied Holm-Bonferroni correction for multiple comparisons ($P_{corr} = 0.11$). No significant effect on Δ matched loudness levels was found for any of the putative confounding factors (age, sex, hearing level, tinnitus duration, baseline HADS scores, baseline HQ scores and TFI grade at baseline).

The remaining secondary outcomes included VAS loudness, subscale scores on the HADS and the HQ. These scores did not differ between baseline and follow-up. Linear regression models were also constructed for the change scores of these secondary outcomes, i.e. ΔVAS loudness, ΔHADS and ΔHQ scores. No significant differences between active and sham HD-tDCS groups were found.

Discussion

Here, we present the results of a randomized controlled trial into the effects of HD-tDCS on chronic subjective tinnitus. Our most important finding was that dual-site HD-tDCS of the LTA and rDLPFC did not affect tinnitus severity in this selected sample of patients with chronic subjective tinnitus. Rather, tinnitus severity decreased similarly in the active treatment and sham control group.

Existing trials investigating tDCS as a tinnitus treatment option have generally used a current strength of 2 mA, informing the choice of stimulation intensity used in this study. Early research has suggested that a current intensity of 2 mA may have a more pronounced effect on tinnitus severity than lower intensities such as 1 mA.[45,61] However, it has been suggested that increasing tDCS intensity might lead to a directional shift of underlying cortical excitability.[32,62] Thus, direct comparisons between different stimulation intensities should be interpreted with caution, and more research on the underlying tDCS physiological effects is

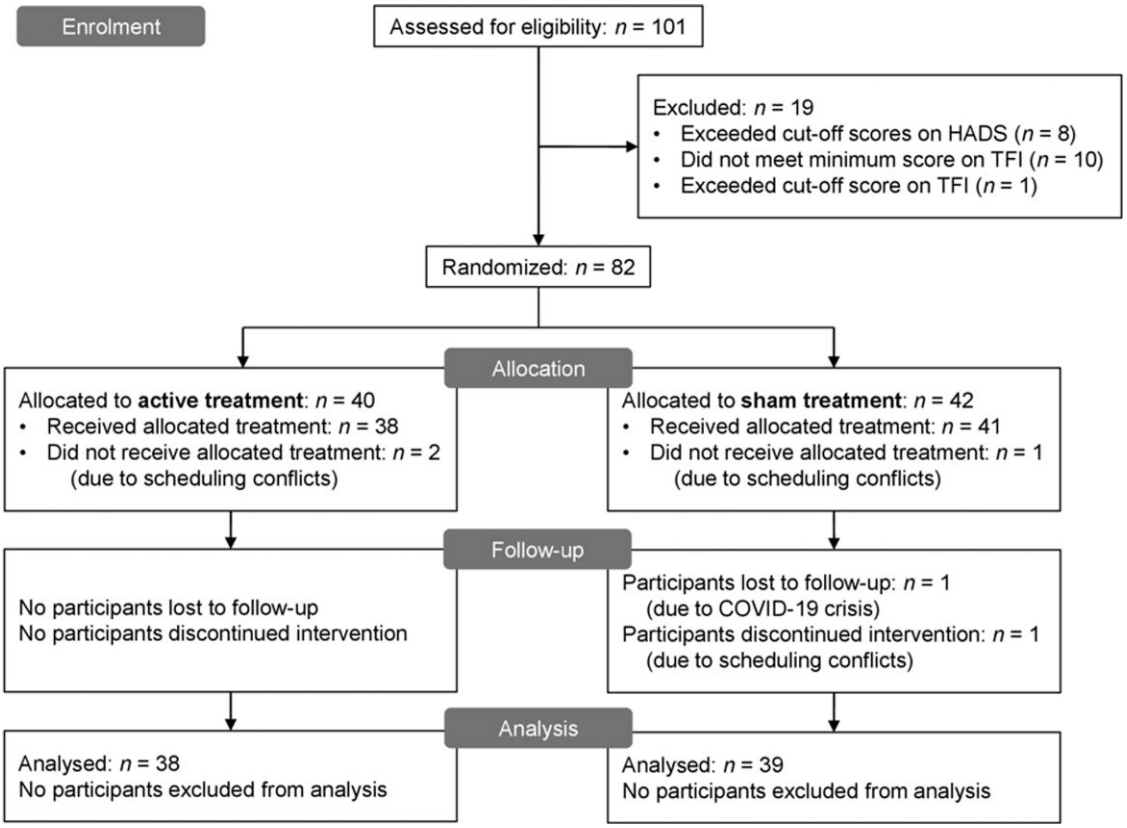

Figure 1 Consort flow diagram. Trial profile of 101 patients who were screened for eligibility. A total of 77 participants completed the study.

Table 2 Overview of baseline characteristics of all participants

	Overall (*n* = 77)	Active (*n* = 38)	Sham (*n* = 39)	*P*-value[a]
Demographic variables				
Age: mean (SD)	52.70 (14.06)	53.47 (14.39)	51.95 (13.87)	0.6372
Sex: number of males/females	43/34	20/18	23/16	0.5751
Hearing level: mean $PTA_{1–2–4\ kHz}$ (SD)	24.53 (17.93)	27.30 (17.66)	21.84 (18.02)	0.1830
Tinnitus characteristics				
Tinnitus type (*n*):				
Pure tone/noise/polyphonic	42/21/14	23/7/8	19/14/6	0.2194
Tinnitus laterality (*n*):				
Right/left/bilateral/central	8/12/28/29	1/7/17/13	7/5/11/16	0.0722
Tinnitus aetiology[b] (*n*):				
Otological/idiopathic/psychological/non-otological	39/34/3/1	18/18/2/0	21/16/1/1	0.4994
Tinnitus duration, years: mean (SD)	9.57 (10.35)	10.36 (9.50)	8.79 (11.19)	0.5106
Matched loudness, dB SL: mean (SD)	10.21 (7.62)	11.00 (9.77)	9.42 (4.58)	0.3700
Matched frequency, kHz: mean (SD)	5.80 (3.74)	5.17 (3.89)	6.43 (3.53)	0.1426
Questionnaire scores				
TFI scores: mean (SD)	57.61 (17.66)	55.34 (16.92)	59.83 (18.30)	0.2675
VAS loudness: mean (SD)	76.79 (19.22)	75.82 (19.81)	77.74 (18.84)	0.6629
HADS scores: mean (SD)				
Anxiety subscale	7.55 (3.64)	7.21 (3.67)	7.87 (3.63)	0.4291
Depression subscale	5.56 (4.23)	4.87 (4.46)	6.23 (3.94)	0.1589
HQ scores: mean (SD)	19.82 (8.04)	19.58 (5.77)	20.05 (9.83)	0.7985

dB SL = dB sensation level; $PTA_{1–2–4\ kHz}$ = pure tone average of hearing thresholds at 1, 2 and 4 kHz.

[a]Participants in active and sham control group were compared using *t*-tests; resulting *P*-values are shown in the right-hand column.

[b]Otological aetiology was defined as a tinnitus that became noticeable after a decrease in hearing ability. Idiopathic aetiology signifies that the tinnitus appeared suddenly without a specific event. Psychological aetiology indicates that the tinnitus stems from a stressful event, while a physical problem outside the ear was referred to as a non-otological aetiology.

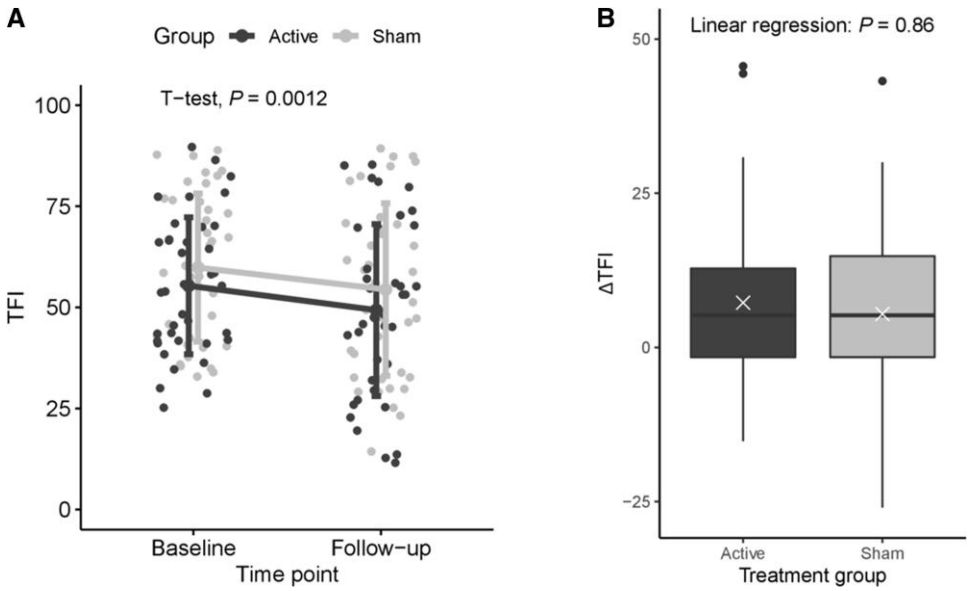

Figure 2 Evolution of TFI scores from baseline to follow-up. (**A**) In both active and sham HD-tDCS groups, TFI scores decreased significantly from baseline to follow-up (paired *t*-test for all participants: $P = 0.0012$). (**B**) ΔTFI scores, i.e. the difference in TFI scores from baseline to follow-up, did not differ significantly between active and sham HD-tDCS groups (linear regression model: $P = 0.86$).

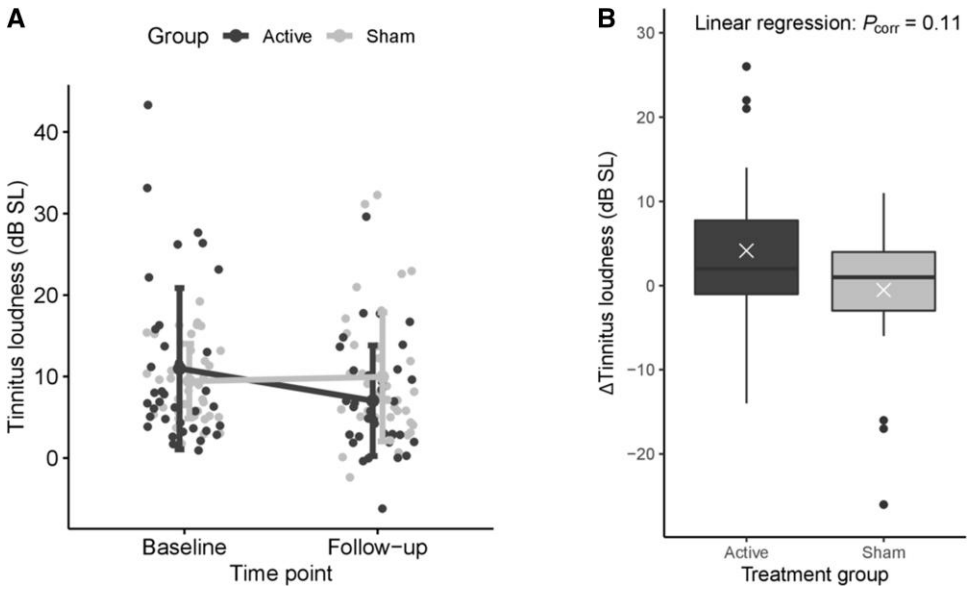

Figure 3 Evolution of matched loudness from baseline to follow-up. (**A**) Only in the active treatment group, matched loudness levels decreased from baseline to follow-up. (**B**) Δ Matched loudness levels, i.e. the difference in matched loudness from baseline to follow-up, differed significantly between active and sham HD-tDCS groups (linear regression model: $P_{corr} = 0.11$). Matched loudness levels are presented in dB sensation level (dB SL).

crucial. Moreover, previous trials have targeted either the LTA or the rDLPFC, with compelling rationale for both areas. The LTA comprises the auditory cortex, which has been proven to be hyperactive in patients with tinnitus and therefore constitutes a logical therapeutic target.[20] Meanwhile, tDCS of the rDLPFC is suggested to minimize the emotional response to the tinnitus percept, and has also been implemented in other therapeutic areas such as pain management.[33] Accordingly, in this trial, electrodes were positioned over both the LTA and the rDLPFC. As it has been suggested that the stimulation of these areas might have different mechanisms of action and, therefore, benefit different subtypes of patients,[44] we chose to stimulate both areas sequentially within each session. Ultimately, we conclude that in this optimally selected sample of chronic subjective tinnitus patients, sequential HD-tDCS of the LTA and rDLPFC did not affect tinnitus severity.

Our primary outcome measure was the change in TFI scores between baseline and follow-up. The TFI is a standardized questionnaire that is well-accepted by the broad tinnitus community. Specifically, it has been suggested that this questionnaire is highly sensitive towards treatment-induced changes in tinnitus severity and shows high agreement with the self-perceived tinnitus burden.[63] We observed that, while TFI scores decreased significantly from baseline to follow-up in all participants, HD-tDCS treatment did not cause a more pronounced treatment effect compared to

sham stimulation. This seems to echo findings from a recent systematic review and meta-analysis of sham-controlled trials, in which the authors state that tDCS effects on tinnitus severity are small and non-significant.[49] The observed mean difference in TFI scores between baseline and follow-up in this trial is comparable with results from previous, non-sham controlled trials aimed at comparing different target areas and/or tDCS techniques.[44,45] Our current results strongly suggest that placebo results contributed significantly to these earlier reports. The generalized decrease in TFI scores from baseline to follow-up observed in this trial may have several causal factors that are difficult to disentangle. Non-specific placebo effects may be intertwined with the unavoidable effects of the act of therapy which participants received during their multiple study visits. Moreover, a significant contribution of regression to the mean cannot be ruled out.

Regarding secondary outcomes, we observed a possible effect of HD-tDCS on tinnitus loudness levels as measured via a tinnitus matching procedure. No spontaneous decrease of matched loudness was observed in the sham control group, while loudness levels showed a decreasing trend in the active treatment group. The difference between both groups corresponded to a moderate effect. However, this group difference did not prove significant after applying a necessary correction for multiple comparisons. Psychoacoustic measures, such as matched pitch or loudness, have often been suggested as a 'semi-objective' parameters for tinnitus assessment, but conflicting results regarding these measures should be noted.[64] It has been suggested that tinnitus loudness does not necessarily have an impact on tinnitus-related distress and its subjective severity.[65,66] As a result, most researchers agree that changes in tinnitus loudness do not necessarily reflect a benefit for patients' quality of life.[67,68] Regarding potential tDCS effects on tinnitus loudness, a 2012 systematic review and meta-analysis reported a significant mean tinnitus intensity reduction of 13.5%,[69] but a more recent meta-analysis found no significant effects of tDCS on tinnitus loudness.[70] The latter review included a greater number of studies and acknowledged the presence of a large heterogeneity among them. Potential tDCS effects on loudness of the tinnitus percept remain to be elucidated, but generally, a putative decrease in tinnitus loudness is not expected to have an immediate effect on its severity.

The current trial represents the first adequately powered sham-controlled trial into the effects of HD-tDCS on chronic subjective tinnitus. A major strength of this trial is its ability to conclusively assess the putative effects of confounding factors. For example, regardless of treatment effect, we found an important influence of sex on fluctuations in TFI scores. TFI change scores were higher in males, indicating that the impact of tinnitus on quality of life decreased more in males from baseline to follow-up. Moreover, participants with higher levels of anxiety at baseline were found to have a more pronounced decrease in TFI scores, regardless of treatment group. Interestingly, a systematic review investigating sex differences in the placebo effect in pain research reported that males respond more strongly to placebo treatment than females, and that these differences may be importantly mediated by anxiety levels.[71] Overall, the important mediating effect of psychological complaints, including anxiety and depression, on tinnitus is well established.[72] Several previously published studies of tDCS for tinnitus have reported on the evolution of psychological complaints as secondary outcome measures,[39,41] and a recent meta-analysis noted the absence of any effect of tDCS on psychiatric symptoms in tinnitus populations.[73] However, effects of baseline anxiety or depression are seldomly taken into account in these studies. Our results show that effects of sex and concurrent anxiety levels, whether on spontaneous or treatment-elicited changes in tinnitus severity, remain important to take into account.[74]

Some limitations of the current study should be noted. Although our initial sample size calculations yielded a minimum sample of 78,[53] we could only analyse data from 77 participants who underwent the full study protocol, including the primary end point. We chose to recruit participants equally over different categories of baseline tinnitus severity, as it has been shown that the baseline grade of tinnitus distress may have important effect on tDCS trial outcomes.[42] Moreover, taking into account possible sex effects, we sought to recruit a similar number of males and females. As the trial progressed, these stringent recruitment criteria were found to be incongruent with the clinical reality, as tinnitus patients who presented themselves spontaneously to the tinnitus center were predominantly male and often had TFI scores lower than 75. Particularly, we found that almost all subjects experiencing severe tinnitus distress (i.e. TFI scores between 75 and 90) also experienced signs of elevated anxiety and/or depression (i.e. HADS scores higher than 11), indicating that patients confronted with severe tinnitus generally experience concurrent psychological complaints. We strongly urge researchers conducting future randomized controlled trials in tinnitus populations to take this major overlap into account when designing their study and deciding on appropriate inclusion and exclusion criteria.

In conclusion, we report that dual-site HD-tDCS of the LTA and rDLPFC did not have a significant treatment effect on tinnitus severity or loudness. Tinnitus severity decreased similarly in the active and sham control groups, suggesting a considerable placebo effect. The use of other forms of transcranial electrical stimulation, such as alternating current or random noise stimulation, may form the object of further investigation. We suggest that future randomized controlled studies in tinnitus populations carefully take into account potential confounding factors, particularly sex and concurrent psychological complaints.

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Competing interests

The authors report no competing interests.

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