



This is a repository copy of *Repeated bilateral transcranial direct current stimulation over auditory cortex for tinnitus treatment: a double-blinded randomized controlled clinical trial.*

White Rose Research Online URL for this paper:

<https://eprints.whiterose.ac.uk/212450/>

Version: Published Version

Article:

Yadollahpour, A. orcid.org/0000-0002-1216-2109, Rashidi, S. orcid.org/0000-0002-5800-6355, Saki, N. et al. (2 more authors) (2024) Repeated bilateral transcranial direct current stimulation over auditory cortex for tinnitus treatment: a double-blinded randomized controlled clinical trial. *Brain Sciences*, 14 (4). 373. ISSN 2076-3425

<https://doi.org/10.3390/brainsci14040373>

Reuse

This article is distributed under the terms of the Creative Commons Attribution (CC BY) licence. This licence allows you to distribute, remix, tweak, and build upon the work, even commercially, as long as you credit the authors for the original work. More information and the full terms of the licence here:

<https://creativecommons.org/licenses/>

Takedown




If you consider content in White Rose Research Online to be in breach of UK law, please notify us by emailing eprints@whiterose.ac.uk including the URL of the record and the reason for the withdrawal request.



eprints@whiterose.ac.uk
<https://eprints.whiterose.ac.uk/>

Article

Repeated Bilateral Transcranial Direct Current Stimulation over Auditory Cortex for Tinnitus Treatment: A Double-Blinded Randomized Controlled Clinical Trial

Ali Yadollahpour ^{1,2}, Samaneh Rashidi ³, Nader Saki ⁴, Pramod Singh Kunwar ⁵ and Miguel Mayo-Yáñez ^{6,7,8,*}

- ¹ Department of Psychology, University of Sheffield, Sheffield S1 2LT, UK; yadollahpour.a@gmail.com
- ² Bioelectromagnetic Clinic, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz 61357-15794, Iran
- ³ Department of Psychology, University of Surrey, Guildford GU2 7XH, UK; samanehrashidi92@gmail.com
- ⁴ Hearing and Speech Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz 61357-15794, Iran; ahvaz.ent@gmail.com
- ⁵ Department of Pharmaceutics and Pharmacy Practice, School of Pharmacy, Mount Kenya University, Thika P.O. Box 342-01000, Kenya; pkunwar@mku.ac.ke
- ⁶ Department of Otorhinolaryngology—Head and Neck Surgery, Complejo Hospitalario Universitario A Coruña (CHUAC), 15006 A Coruña, Spain
- ⁷ Department of Otorhinolaryngology—Head and Neck Surgery, Hospital San Rafael (HSR), 15006 A Coruña, Spain
- ⁸ Otorhinolaryngology—Head and Neck Surgery Research Group, Institute of Biomedical Research of A Coruña (INIBIC), Complejo Hospitalario Universitario de A Coruña (CHUAC), Universidade da Coruña (UDC), 15006 A Coruña, Spain
- * Correspondence: miguel.mayo.yanez@sergas.es

Abstract: Transcranial direct current stimulation (tDCS) is a non-invasive and painless technique of brain neuromodulation that applies a low-intensity galvanic current to the scalp with the aim of stimulating specific areas of the brain. Preliminary investigations have indicated the potential therapeutic efficacy of multisession tDCS applied to the auditory cortex (AC) in the treatment of chronic tinnitus. The aim of this study was to explore the therapeutic effects of repeated sessions of bilateral tDCS targeting the AC on chronic tinnitus. A double-blinded randomized placebo-controlled trial was conducted on patients ($n = 48$) with chronic intractable tinnitus (>2 years duration). Participants were randomly allocated to two groups: one receiving tDCS ($n = 26$), with the anode/cathode placed over the left/right AC, and the other receiving a placebo treatment ($n = 22$). A 20 min daily session of 2 mA current was administered for five consecutive days per week over two consecutive weeks, employing 35 cm² electrodes. Tinnitus handicap inventory (THI) scores, tinnitus loudness, and tinnitus distress were measured using a visual analogue scale (VAS), and were assessed before intervention, immediately after, and at one-month follow-up. Anodal tDCS significantly reduced THI from 72.93 ± 10.11 score to 46.40 ± 15.36 after the last session and 49.68 ± 14.49 at one-month follow-up in 18 out of 25 participants ($p < 0.001$). The risk ratio (RR) of presenting an improvement of ≥ 20 points in the THI after the last session was 10.8 in patients treated with tDCS. Statistically significant reductions were observed in distress VAS and loudness VAS ($p < 0.001$). No statistically significant differences in the control group were observed. Variables such as age, gender, duration of tinnitus, laterality of tinnitus, baseline THI scores, and baseline distress and loudness VAS scores did not demonstrate significant correlations with treatment response. Repeated sessions of bilateral AC tDCS may potentially serve as a therapeutic modality for chronic tinnitus.

Keywords: tinnitus; transcranial direct current stimulation; audiology; intractable; auditory cortex



Citation: Yadollahpour, A.; Rashidi, S.; Saki, N.; Kunwar, P.S.; Mayo-Yáñez, M. Repeated Bilateral Transcranial Direct Current Stimulation over Auditory Cortex for Tinnitus Treatment: A Double-Blinded Randomized Controlled Clinical Trial. *Brain Sci.* **2024**, *14*, 373. <https://doi.org/10.3390/brainsci14040373>

Academic Editors: Eldre W. Beukes and Chantal Delon-Martin

Received: 12 August 2023

Revised: 28 March 2024

Accepted: 3 April 2024

Published: 12 April 2024



Copyright: © 2024 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (<https://creativecommons.org/licenses/by/4.0/>).

1. Introduction

Tinnitus is an auditory condition characterized by a subjective phantom sound sensation in the absence of external sound. It affects 10–15% of the adult population [1,2].

Tinnitus can present in different forms, including pulsatile, hissing, buzzing, ringing, tones, or a combination of these [2,3]. The main causes of tinnitus include trauma to the auditory periphery, such as hearing loss accompanied by noise, or a lesion to an auditory nerve [1], as well as maladaptive plastic changes in the auditory network induced by damage to the early stages of the auditory pathway [2,4,5]. Although clinically positive symptoms of hearing loss are not a necessary precondition for tinnitus, recent studies have shown that different forms of hearing loss which are not detected by conventional audiometric assessments may have some correlation with tinnitus [6]. However, neuroimaging, neuroanatomy, and evoked potential studies have shown that tinnitus-related anomalies are present not only throughout the auditory system, but also in several non-auditory brain areas [2,7–11]. Recent neuroimaging studies have demonstrated that abnormal activity observed in the primary and secondary auditory cortices could underlie the phantom auditory perception itself; whereas the abnormal activities present in the non-auditory areas associated with cognitive, attentional, and limbic processes could be involved in the unpleasant and distressing aspects of tinnitus [12,13]. Therefore, in any therapeutic or management strategy, tinnitus should be regarded as a multifaceted disorder involving an extensive network comprising multiple overlapping brain areas. Typically, this condition is accompanied by various significant comorbidities like depression, anxiety, and sleep disturbances, rendering it a debilitating condition [1,2,14,15]. Numerous pharmaceutical agents are employed in the treatment of tinnitus; nonetheless, a substantial proportion of patients do not respond to treatment [16].

Different non-pharmaceutical techniques for tinnitus treatment have been developed, such as cognitive behavioral therapies [17], noise-masking modality [5], and neurofeedback [18], but their effectiveness remains limited. Transcranial direct current stimulation (tDCS) is a safe and easy to use form of neuromodulation with potential therapeutic efficacy in different neuropsychiatric disorders [5,19–22], as well as the capability to enhance different cognitive functions in healthy individuals [23].

Similar to other neuromodulation and neurostimulation approaches, the main rationale for choosing the site of stimulation as well as the electrode montage in tDCS applications for tinnitus is targeting the affected brain areas to modulate either the tinnitus percept or its affective components through disrupting the underlying pathological neural activity. In this regard, given the associations between tinnitus and the structural and functional abnormalities in the dorsolateral prefrontal cortex (DLPFC) [5,10,24] and auditory cortex (AC) [25,26], these two sites were the main targets in previous studies.

In addition to the therapeutic outcomes that have resulted from disturbing tinnitus-induced impaired neural activities, repeated sessions of tDCS have reportedly reduced or increased neural excitability, depending on the polarity of the electrode persisting beyond the termination of tDCS intervention [27,28]. This altered excitability can lead to neuroplasticity with therapeutic effects for tinnitus. Therefore, abnormal excitability in the auditory pathways and maladaptive plastic changes in auditory and limbic cortical areas in tinnitus have led to the idea of treating tinnitus by modulating these abnormalities through single or repeated sessions of tDCS. Using single and repeated sessions of tDCS targeting either the DLPFC or AC have resulted in immediate beneficiary effects in tinnitus patients; however, most of the observed effects were transient and did not translate into long-term improvements [5,10,24–26,29]. Different review papers have evaluated the efficacy of tDCS for the treatment of tinnitus [30–35]. Initial studies focused on single or few sessions of tDCS over the prefrontal cortex (PFC) [5,24,36] and auditory cortex [25,26,37,38] or left temporal area (LTA) [39–41]. Later studies further focused on repeated sessions of tDCS, especially cathodal tDCS [42]. Based on the theoretical and experimental findings of the initial studies, repeated sessions of cathodal tDCS might have therapeutic effects on tinnitus [38,43–48]. Accordingly, several studies have investigated the effects of repeated sessions, using longer periods in each session and higher intensities of cathodal tDCS in tinnitus [24,37,45,49]. The main target site was the PFC, particularly the dorsolateral PFC (DLPFC), and the most frequent electrode montage was bifrontal [5,10,50,51]. In

bifrontal DLPFC, the electrode montage was either anode left/cathode right DLPFC or anode right/cathode left DLPFC [5,48,52]. Recent studies have used different electrode montages, including high definition (HD) tDCS, for tinnitus treatment and have reported promising though controversial therapeutic effects [53–55]. Further studies are needed to reach a definitive conclusion.

Most of the initial tDCS studies assessed the therapeutic efficacy of a single session of tDCS on tinnitus. Later, several studies investigated the effects of repeated sessions of tDCS on tinnitus symptoms, and most of them targeted the DLPFC [24,52]. Similarly, studies with repeated tDCS sessions as a protocol for tinnitus treatment have been conducted targeting the temporal or temporoparietal (auditory) cortex [37,40,47,56]. The results of these studies have been heterogeneous, necessitating further placebo-controlled randomized studies to reach a decisive conclusion. In addition, most of the previous studies have investigated the transient effects of tDCS, and in most cases the after-effect assessments did not extend beyond some hours.

To our knowledge, this is the first double blinded randomized placebo-controlled trial investigating the effect of repeated sessions of bilateral anodal/cathodal tDCS over left/right AC with one month follow-up for the treatment of chronic intractable tinnitus.

2. Materials and Methods

2.1. Patients

Consecutive patient recruitment was conducted at the clinics of the Tinnitus Clinic at the Khuzestan Cochlear Implant Center (Ahvaz, Iran). The inclusion criteria were idiopathic chronic and medications resistant tinnitus ($\text{THI} \geq 38$) with disease duration of more than 2 years [16], age range of 18 to 65 years old, and no use of medications or sound therapy at the time of intervention. For all patients a wash-out period of 3 months was applied. The choice of a THI score greater than or equal to 38 was based on the recommendations of the British Association of Otolaryngologists, Head and Neck Surgeons. With this score, patients with moderate, severe, and catastrophic tinnitus were included [57].

The exclusion criteria were a history of epileptic seizures, brain trauma, severe psychotic and psychiatric disorders, concurrent severe vertigo, Meniere's disease, severe organic comorbidity, using a pacemaker or defibrillator, a present pregnancy, neurologic disorders such as brain tumors, and individuals being treated for mental disorders.

All prospective subjects underwent complete audiometric and neurologic examinations by experienced specialists. This clinical trial was a part of long-term study designed to comprehensively investigate the efficacy of different tDCS protocols for treatment of chronic and refractory tinnitus by the bioelectromagnetic clinic of Imam Hospital, Ahvaz, Iran.

2.2. Design

This study was designed as a double-blind randomized controlled clinical trial with the aim of investigating the therapeutic effectiveness of administering repeated sessions of anodal tDCS over the AC, totaling 10 sessions, in the context of chronic and intractable tinnitus (see Figure 1). Following the application of predefined inclusion and exclusion criteria, 48 patients were included in the study. These patients were randomly allocated to two groups: one receiving tDCS ($n = 26$), with the anode/cathode placed over the left/right AC, and another receiving a placebo treatment ($n = 22$). The patients were randomly allocated to the two groups; the randomization was performed using a simple randomization process. The two groups were carefully matched in terms of age, gender, and ethnicity. To mitigate potential subjective biases, a comprehensive blinding procedure was implemented. This involved ensuring that patients, the researchers responsible for evaluating outcomes during the experiments and follow-up period, as well as the researcher conducting the statistical analyses, were all unaware of the specific treatment protocol to which each patient was assigned. Prior to enrollment, patients received a clear and detailed explanation of the study's objectives, potential benefits, and possible side effects.

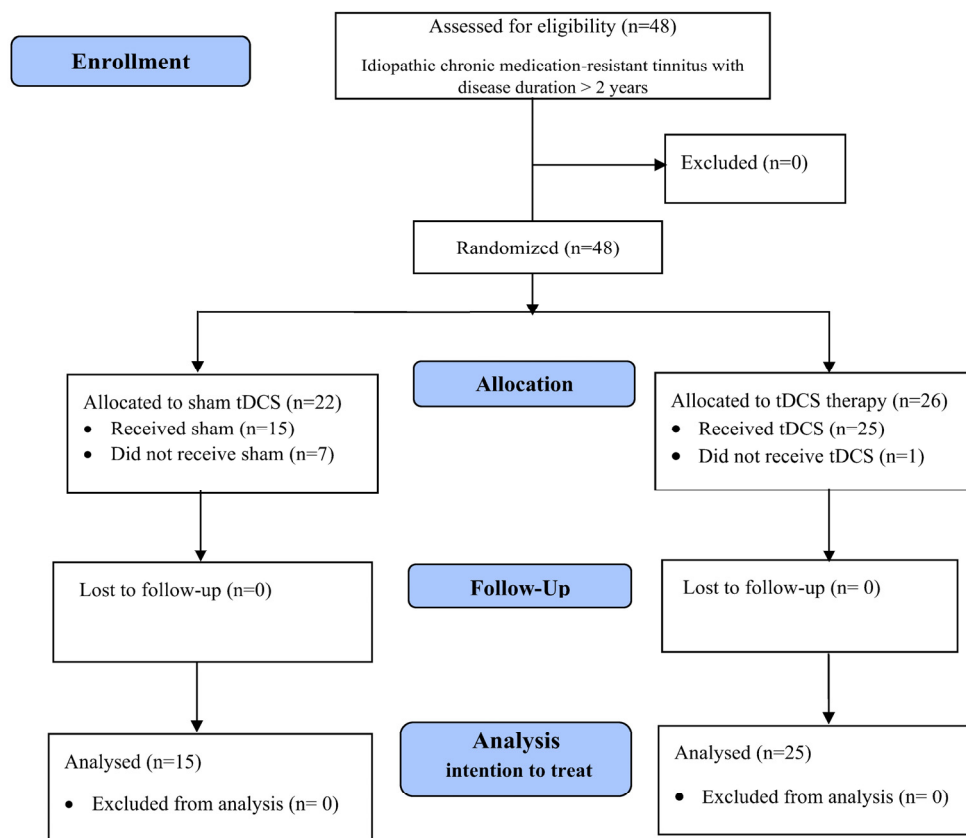


Figure 1. Diagram flow of trial.

2.3. Transcranial Direct Current Stimulation Protocol

tDCS was administered using a pair of surface sponges (35 cm²) soaked in saline solution and delivered via a specially developed battery-powered constant current stimulator capable of a maximum output of 4 mA. The tDCS device utilized in this study was the OASIS Pro™ device manufactured by Mind Alive Inc. (Edmonton, AB, Canada).

The tDCS protocol involved a 2 mA current administered daily for 20 min over five consecutive days per week, for a duration of two consecutive weeks. In the anodal tDCS condition, the anode was positioned over the left auditory cortex (midway between T3 and F7), while the cathode was placed over the right auditory cortex (midway between T4 and F8), using 35 cm² electrodes. The site for stimulation was determined by the International 10–20 Electroencephalogram system, where the left and right AC corresponded to halfway T3–F7 and halfway T4–F8, respectively [58]. According to the tDCS specifications, in both cases, intervention and placebo, the DC current was initially increased in a ramp-like fashion for about 10 s until it reached 2 mA. In the placebo tDCS, the electrode montage was the same as in real tDCS, except that the device was turned off 40–45 s after the start of the session without the patient being aware of this fact. These parameters for placebo stimulation were chosen based on previous reports that the perceived sensations on the skin, such as tingling, usually disappear in the first 30 s after tDCS activation [59,60].

2.4. Evaluations

The tinnitus quality for each patient was determined through a clinical interview by a tinnitus expert otolaryngologist, being categorized as: buzzing, cicadas, high pitch whistling, hissing, humming, ringing, pulsating, thumping, and/or ticking. The class of hearing loss in both ears was assessed, based on the World Health Organization criteria, as normal hearing threshold (<20 dB), mild hearing loss (20–40 dB), moderate hearing loss (41–70 dB), severe hearing loss (70–90 dB), and profound hearing loss (>90 dB). The tinnitus laterality and evolution time were also determined. Pure-tone audiometry was performed

using an AC 40 dual channel Audiometer (Interacoustics Co., Middelfart, Denmark). The hearing thresholds were recorded over the frequency ranges of 250 to 8000 Hz for air conduction and 500 to 4000 Hz for bone conduction pathways, using the modified Hughson–Westlake Method as recommended by the American National Standard Institute ANSI S3.6 (American National Standard Institute, 1996). Pure-tone audiometry was considered normal when the hearing thresholds at all frequencies were below 20 dBHL.

Tinnitus handicap inventory (THI) score was assessed prior to intervention, and then immediately after, 1 h after, and 1 month after the last stimulation [61]. Tinnitus loudness and distress were assessed using a numeric visual analog 0–10 rating scale before intervention, and immediately, one hour, one week, and one month after last stimulation. After the completion of the intervention in the placebo-tDCS, the blinding quality of the study was assessed through asking each patient to determine which type of stimulation they had received.

2.5. Statistical Analysis

The analysis was conducted on an intention-to-treat basis. Statistical analyses were performed using Stata Version 14.2 (StataCorp LLC., College Station, TX, USA). Qualitative variables were expressed as a percentage. Continuous variables were expressed as a mean, median (minimum, maximum), and standard deviation (SD). Baseline characteristics of patients were compared between the two groups using an independent samples student's *t*-test for continuous variables, and a Chi-square test for qualitative variables. Otherwise, Mann-Whitney's test was used with no significant Levene's test variables. Univariate and multivariate logistic regression tests were used to identify a possible association between the basal variables and the efficacy of the therapy, considering this as a decrease in ≥ 20 points between the value of THI pre-intervention versus post-intervention. Statistical significance was determined at $p < 0.05$. Interaction terms inclusion was evaluated by a chunk test based on the likelihood ratio test with a significance level < 0.05 . The presence of possible confounding variables was evaluated, adjusting the model if the changes were $> 10\%$.

3. Results

3.1. Participants

Forty-eight patients (F = 26, M = 22; mean age: 48.67 ± 7.81 years) who met the inclusion criteria of the study were consecutively evaluated for eligibility and entered the study. The patients were randomly divided into two groups of real tDCS (n = 26) and placebo tDCS (n = 22) using simple randomization. One patient from the real tDCS group and seven patients from the placebo tDCS group did not finish the sessions or start the intervention. Twenty-five patients from the real tDCS group (F = 14, M = 11; mean age of 47.52 ± 7.51 years; tinnitus duration time of 7.48 ± 3.99 years) and 15 patients from the placebo tDCS group (F = 8, M = 7; mean age of 47.67 ± 7.96 years; tinnitus duration time of 7.60 ± 3.60 years) finished the study and were considered in the analysis. The evaluation of hearing loss based on laterality is detailed in Table 1 and Supplementary Tables S1 and S2.

Table 1. Distribution of hearing loss.

			TDCS-Group	Placebo-Group	Total
Right ear	Normal	N	10	5	15
		%	40	33.3	37.5
	Mild	N	7	5	12
		%	28	33.3	30
	Moderate	N	5	4	9
		%	20	26.7	22.5
	Profound	N	3	1	4
		%	12	6.7	10

Table 1. Cont.

			TDCS-Group	Placebo-Group	Total
Left ear	Normal	N	11	5	16
		%	44	33.3	40
	Mild	N	10	6	16
		%	40	40	40
	Moderate	N	3	3	6
		%	12	20	15
	Profound	N	1	1	2
		%	4	6.7	5

The distribution of tinnitus localization was 21 (52.5%) cases on the right side, 16 (40%) on the left side, and 3 (7.5%) bilateral. The distribution of tinnitus quality is found in Table 2.

Table 2. Distribution of tinnitus quality.

	N	%
Ringing	12	30
Buzzing	2	5
Hissing	7	17.5
Ticking	2	5
High pitch whistling	5	12
Thumping	2	5
Cicadas	5	12.5
Pulsating	5	12.5

The baseline values of THI, tinnitus loudness, and tinnitus distress are found in Table 3. Sociodemographic and basal variables did not show statistically significant differences between the tDCS group and the placebo group for age ($p = 0.954$), basal THI value ($p = 0.629$), loudness ($p = 0.708$) VAS, or distress VAS ($p = 0.971$) (Table 3). The repeated sessions of tDCS were well-tolerated by all patients; there were no adverse effects reported, and all patients completed the study. No follow-up losses were recorded during the study period.

Table 3. Comparison of the demographic and response variables of the study between the tDCS group and placebo group. The p -values in bold indicate statistical significance.

	Mean \pm SD		p -Value
	tDCS Group	Placebo Group	
Age	47.52 \pm 7.51	47.67 \pm 7.96	0.954
Tinnitus duration since its onset	7.48 \pm 3.99	7.60 \pm 3.60	0.924
Basal THI	72.93 \pm 10.11	71.90 \pm 10.30	0.629
THI post-intervention	46.40 \pm 15.36	66.73 \pm 14.30	<0.001
THI 1-month post-intervention	49.68 \pm 14.49	66.73 \pm 11.97	<0.001
Basal Loudness VAS	7.36 \pm 0.81	7.47 \pm 0.91	0.708
Loudness VAS immediate after last session	5.60 \pm 1.78	6.80 \pm 1.52	0.036
Loudness VAS 1-h post-last session	5.56 \pm 1.78	7.13 \pm 1.40	0.006
Loudness VAS 1-week post-last session	5.68 \pm 1.57	7.40 \pm 1.05	0.001
Loudness VAS 1-month post-last session	6.64 \pm 1.18	7.69 \pm 0.85	0.010
Basal Distress VAS	7.68 \pm 0.55	7.67 \pm 0.61	0.971
Distress VAS immediate after last session	5.92 \pm 1.25	7.07 \pm 1.22	0.008

Table 3. Cont.

	Mean \pm SD		<i>p</i> -Value
	tDCS Group	Placebo Group	
Distress VAS 1-h post-last session	5.92 \pm 1.25	7.40 \pm 1.12	0.001
Distress VAS 1-week post-last session	6.16 \pm 1.24	7.47 \pm 0.83	0.001
Distress VAS 1-month post-last session	6.92 \pm 0.99	7.80 \pm 0.56	0.003

Abbreviations: SD, standard deviation. tDCS, transcranial direct current stimulation. THI, tinnitus handicap index. VAS, visual analog scale.

3.2. Response Variables

Statistically significant differences were found in the response variables. The mean post-intervention THI was 46.40 ± 15.36 for the tDCS group and 66.73 ± 14.30 for the placebo group ($p < 0.001$). These significant differences continued to be present one month after the last tDCS session, with values of 49.68 ± 14.49 for the tDCS group and 66.73 ± 11.97 for the placebo group ($p < 0.001$) (Figure 2). Differences were also found in loudness and distress VAS collected immediately after ($p = 0.008$), after an hour ($p = 0.001$), after a week ($p = 0.001$), and after a month ($p = 0.003$) following the last tDCS session (Table 3).

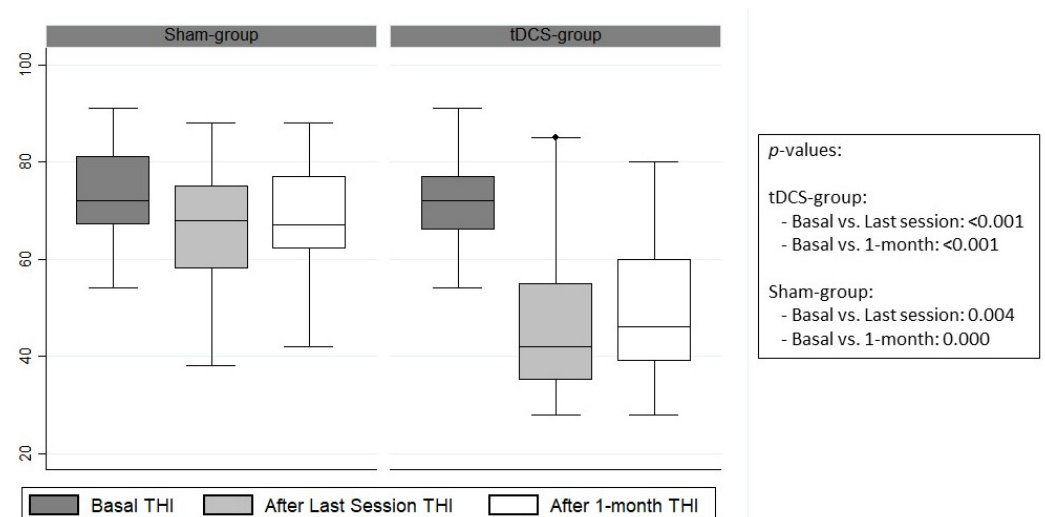


Figure 2. Comparative diagram of THI scores between groups before and after treatment.

The comparison of basal and response variables according to the groups showed that in the tDCS group, there were significant differences comparing pre-intervention data with immediate post-intervention distress VAS and loudness VAS variables ($p < 0.001$), between the basal THI and immediate after last session THI with a $p < 0.001$ (CI 95%, 18.66–31.10), and between the basal THI with after 1 month THI with $p < 0.001$ (CI 95%, 15.96–27.24). In addition, significant differences were also found between the immediate after last session THI and after 1 month THI ($p = 0.011$; CI 95%, -5.75 – -0.81).

On the other hand, in the placebo group, no significant differences were found between basal VAS for loudness and after an hour following the last session ($p = 0.096$; CI 95%, -0.07 – 0.73), after 1 week following the last session ($p = 0.334$; CI 95%, -0.08 – 0.21), and after 1 month following the last session ($p = 0.337$; CI 95%, -0.24 – 0.09). The same pattern occurred with basal VAS for distress and after an hour following the last session ($p = 0.104$; CI 95%, -0.06 – 0.60), after 1 week following the last session ($p = 0.271$; CI 95%, -0.17 – 0.57), and after 1 month following the last session ($p = 0.164$; CI 95%, -0.33 – 0.06). In addition, no significant differences were found between THI immediately following the last session and THI after 1 month following the most recent intervention ($p = 1$; CI 95%, -4.00 – 4.00). Interestingly, in this group, statistically significant differences were found between the

basal THI value and the immediate post-intervention value ($p = 0.004$; CI 95%, 2.32–10.08), the basal THI and the 1 month post-intervention THI value ($p = 0.000$; CI 95%, 4.08–8.32), the immediate loudness VAS ($p = 0.007$; CI 95%, 0.21–1.12), and the immediate distress VAS ($p = 0.007$; CI 95%, 0.19–1.01).

One participant of 15 in the placebo group and 18 of 25 in the tDCS-group underwent an improvement of 20 or more points in THI score immediately after the last stimulation. This improvement was not maintained in the placebo group at the one-month follow-up, whereas in the tDCS group, the improvements persisted for one month in 14 of the subjects (Table 4).

Table 4. Calculation of the risk ratio immediately after the last session and at one month. Note that those with tDCS treatment had a 980% increase in the risk of improving their THI after the last session. After 1 month, no patient in the placebo group showed improvement.

		Improvement of ≥ 20 Points in the THI			Risk Ratio
		Yes	No	Total	
Immediately after	tDCS treatment	18	7	25	10.8 (IC 95%, 1.6–72.88)
	Placebo group	1	14	15	
	Total	19	21	40	
1-month after	tDCS treatment	14	11	25	2.36 (IC 95%, 1.51–3.7)
	Placebo group	0	15	15	
	Total	14	26	40	

3.3. Multivariate Analysis

Considering a reduction of 20 points or more in THI score as the positive treatment response, a logistic regression was performed with the THI values immediately after the last session (Table 5) and with THI values after one month (Table 6) as a dependent variable. The variables selected in the final model, after removing potential confounding factors, were sex, age, tinnitus duration since its onset, basal THI, basal VAS loudness, and basal VAS distress.

Table 5. Results of univariate and multivariate (logistic regression) analysis on possible relationship between the basal variables and the response to tDCS therapy immediately after last session. The p -values in bold indicate statistical significance.

		Improvement ≥ 20 in THI		Immediate after Last Session			
		Yes (N = 18)	No (N = 7)	Univariate Model		Multivariate Model	
				p -Value	OR (IC 95%)	p -Value	OR Adjusted (IC 95%)
Sex	Male	7 (38.89)	4 (57.14)	0.413	0.48 (0.08–2.81)	0.156	0.06 (0.00–2.89)
	Female	11 (61.11)	3 (42.86)	0.413	2.10 (0.36–12.32)	0.156	16.33 (0.35–771.31)
		Mean \pm SD	Mean \pm SD	Univariate Model		Multivariate Model	
				p -Value	OR (IC 95%)	p -Value	OR Adjusted (IC 95%)
	Age	46.72 \pm 7.68	49.57 \pm 7.21	0.392	0.95 (0.84–1.07)	0.325	0.325 (0.70–1.12)
	Tinnitus duration since its onset	6.17 \pm 3.40	10.86 \pm 3.53	0.019	0.71 (0.53–0.95)	0.064	0.64 (0.39–1.03)
	Basal THI	70.94 \pm 11.62	72.14 \pm 7.95	0.795	0.99 (0.91–1.08)	0.900	1.01 (0.88–1.16)
	Basal VAS Loudness	7.17 \pm 0.71	7.86 \pm 0.90	0.071	0.29 (0.08–1.11)	0.166	0.14 (0.01–2.26)
	Basal VAS Distress	7.71 \pm 6.49	7.67 \pm 0.59	0.845	0.85 (0.16–4.43)	0.556	3.36 (0.06–188.8)

Abbreviations: OR, odds ratio. SD, standard deviation. THI, tinnitus handicap index. VAS, visual analog scale.

No statistically significant differences were found in the possible effect of baseline variables on response to treatment, with the exception of the tinnitus duration since its onset. In the univariate model, a possible negative association between the evolution time of tinnitus and the positive response to treatment after the last session (OR = 0.71; $p = 0.019$)

and after one month (OR = 0.73; $p = 0.028$) was observed. This significance was lost in the multivariate model in the first case and maintained in the second (OR = 0.60; $p = 0.027$).

Table 6. Results of univariate and multivariate (logistic regression) analysis on possible relationship between the basal variables and the response to tDCS therapy 1 month after last session. The p -values in bold indicate statistical significance.

		Improvement ≥ 20 in THI after 1-Month					
		Yes (N = 13)	No (N = 12)	Univariate Model		Multivariate Model	
				p -Value	OR (IC 95%)	p -Value	OR Adjusted (IC 95%)
Sex	Male	4 (30.77)	7 (58.33)	0.171	0.32 (0.06–1.64)	0.093	0.09 (0.01–1.50)
	Female	9 (69.23)	5 (41.67)	0.221	3.15 (0.61–16.31)	0.093	11.17 (0.67–187.07)
		Mean \pm SD	Mean \pm SD	Univariate Model		Multivariate Model	
				p -Value	OR (IC 95%)	p -Value	OR Adjusted (IC 95%)
	Age	45.85 \pm 8.63	49.34 \pm 5.91	0.249	0.93 (0.83–1.05)	0.694	0.97 (0.82–1.14)
	Tinnitus duration since its onset	5.62 \pm 2.99	9.5 \pm 4.06	0.028	0.73 (0.55–0.97)	0.027	0.60 (0.38–0.94)
	Basal THI	72.54 \pm 11.11	69.92 \pm 10.26	0.529	1.03 (0.95–1.11)	0.224	1.10 (0.94–1.28)
	Basal VAS Loudness	7.15 \pm 0.69	7.58 \pm 0.90	0.191	0.48 (0.16–1.44)	0.819	0.82 (0.16–4.30)
	Basal VAS Distress	7.54 \pm 0.66	7.83 \pm 0.39	0.199	0.32 (0.06–1.81)	0.120	0.08 (0.00–1.95)

Abbreviations: OR, odds ratio. SD, standard deviation. THI, tinnitus handicap index. VAS, visual analog scale.

4. Discussion

In this study, we evaluated the safety and effectiveness of repeated sessions of tDCS with a combined stimulation approach. Specifically, we conducted 10 tDCS sessions targeting the auditory cortex (AC), with the anode placed over the left AC and the cathode over the right AC, in an effort to alleviate tinnitus symptoms.

Our primary findings indicate that this tDCS protocol had a positive impact on tinnitus symptoms, leading to significant reductions in THI scores, as well as in the VAS assessments of tinnitus loudness and distress. These assessments were conducted immediately following the completion of the last session, as well as at one week and one month after the treatment. It is important to note that comparing these results with previous studies is challenging due to the unique nature of our research. While there have been open trials and randomized controlled tDCS studies targeting either the left temporoparietal area (LTA)/AC [5,26,39,40,56,62,63] or the PFC [10,24,37,51,52,64,65], to the best of our knowledge, this is the first randomized, double-blind, parallel, placebo-controlled tDCS study to employ this specific protocol, including a one-month follow-up. Our approach involved bilateral anodal/cathodal tDCS over the left/right AC. A review of the existing literature reveals only one similar protocol used by Vanneste et al., in which they applied 1.5 mA bilaterally to the AC (T3 + T4), but no statistically significant differences were found in their results [65]. The statistically significant variations in THI found in the placebo group should be taken with caution. One of the strengths of the analysis conducted is to establish a point considered as clinical improvement (a decrease of >20 in THI). Not every statistically significant change translates into a clinically significant change (Figure 2). In fact, Zeeman et al. established a criterion of at least seven points in THI for significant clinical improvement, a value below the one required in our study [66].

Tinnitus research presents a challenge due to the subjective nature of the condition. Determining a clinically significant change in tinnitus is not feasible through objective measures, necessitating reliance on questionnaires by investigators. We chose to utilize the THI as our primary outcome measure, following recommendations from the Tinnitus Research Initiative [67]. While the THI served as our primary outcome measure, we also incorporated a VAS to assess both tinnitus loudness and distress, a methodology employed in previous studies [64]. A reduction in the VAS for distress may suggest an emotional improvement stemming from participation in the study. However, unlike previous interventions, this time the effect was both statistically significant and enduring

over time. In spite of these positive results, data should have been collected in reference to the possible comorbidities suffered by the participants (anxiety, depression . . .) because they may be factors that influenced the outcome. Our positive results are in agreement with those from other studies using VAS as primary outcome measure [10,39,52,68].

We conducted daily 20 min sessions, five days a week, for two consecutive weeks. Previous tDCS studies have noted temporary reductions in tinnitus following stimulation of the AC or PFC, but these effects displayed significant inter-individual variability and were often limited in duration [10,24,26,39,40,51,56,62,64,65,68]. The reductions observed in this study were comparable to those in previous research, with the distinction that they exhibited a more prolonged duration. This contrasts with the findings from multisession tDCS studies; none of them identified long-term reductions in tinnitus severity over time [24,26,39,40,52,56,64]. There is evidence suggesting cumulative effects from repeating interventions, as demonstrated in prior studies [24,52]. However, what distinguishes tDCS in our study is the apparent longevity of its effects. It would be intriguing to investigate whether these effects can be maintained over time through multisession visits at intervals. The maintenance sessions treatment modality has previously been successfully implemented in cases of depression or chronic pain [69,70]. This would provide valuable insights into the extent of improvement participants experience over time without additional sessions, ultimately helping us determine the optimal number of sessions required to alleviate tinnitus and the true duration of the effect.

The results of logistic regression analyses revealed that tinnitus duration since onset as a variable had a significant relationship with the response to tDCS therapy, and this significant effect was statistically significant both immediately after the last session and one month after the last session. This relationship indicates that patients with longer durations of tinnitus were less responsive to the treatment in a way that is clinically significant. This finding could pave the way for developing clinical guidelines to identify the candidacy of patients for tDCS treatment. However, this factor should be considered along with other factors that have significant effects on treatment response. Conducting further studies with larger sample sizes is needed to determine the relationship between tinnitus onset duration and treatment response.

The suitability of patients for clinical intervention is a very important clinical point to make as it provides guidance on candidacy for tDCS.

The concept of maladaptive plasticity suggests that therapeutic stimulation might require an extended duration to induce its intended effects. Following this idea, and based on the existing literature, it would be interesting in the future to combine some drugs that favor neuronal plasticity with tDCS, thus enhancing the benefits through a synergistic effect. One such drug could be Acamprosate; a double-blinded placebo-controlled crossover study has demonstrated its positive effects on tinnitus perception [71]. Specifically, during the active drug period, there was a decrease in tinnitus measures, whereas there was no notable change in these measures during the placebo period.

One limitation of this study to highlight was the non-collection of data relating to changes in auditory threshold and speech perception in order to assess both the safety of tDCS and the possibility of this influencing response to treatment. Regarding the first point, an evidence-based update of this topic has recently been published, confirming the complete safety of the procedure [28]. Consistent with the argument that hearing loss negatively predicts the outcome of stimulation treatment, two recent studies have demonstrated that improvements in tinnitus resulting from multisession tDCS, when combined with either the use of hearing aids [40] or customized notched-music training [56], appear to be unrelated to the number of tDCS sessions administered. Another limitation of this study was that we did not include the variables of quality of tinnitus and hearing loss in the multivariate statistical analysis. In our study, there was no matching based on hearing loss, nor the use of hearing aids. Conducting controlled clinical trials with larger sample sizes is necessary to avoid potential bias. Considering the various types of tinnitus, including ringing, pulsatile, and unilateral versus bilateral, quality of tinnitus as a variable holds

potential value and warrants further exploration through controlled studies with larger sample sizes. Additionally, incorporating objective modalities such as neuroimaging and audiometric assessments could be crucial in developing effective individualized treatment plans. Finally, another limitation of our study was the short follow-up period (1 month) for outcome evaluation. An assessment at 6 or 12 months is necessary in the future to confirm the duration of the effect and the need for further tDCS sessions.

The absence of standardized study methodology presents an additional challenge in tinnitus research. The substantial diversity in design options, such as tDCS, tACS, and tRNS, electrode placements, and stimulation parameters, creates a multitude of potential neuromodulation approaches, which could result in a disorganized collection of data. The therapeutic effectiveness of tDCS remains uncertain until data from larger multicenter randomized controlled trials become available. To address this issue, a systematic approach is essential, accompanied by well-defined methods and outcome measures. The “Evidence-based guidelines on the therapeutic use of transcranial direct current stimulation” concludes that there is a level of evidence in favor of the probable absence of efficacy of anodal tDCS of the left temporo-parietal area to relieve chronic tinnitus [44]. In this scenario, the results of this study are more relevant due to their statistical and clinical significance, the design of the trial, as well as the new placement of the electrodes, opening a new line of research in this regard.

5. Conclusions

This study represents the inaugural double-blinded randomized placebo-controlled trial that delves into the impact of repeated sessions of bilateral anodal/cathodal tDCS over the left/right auditory cortex (AC) with a one month follow-up, aimed at treating chronic intractable tinnitus. The results demonstrate the therapeutic potential of multisession tDCS in alleviating tinnitus symptoms, reducing intensity and distress, and notably, these therapeutic effects persisted for up to one month after intervention. The repeated application of bilateral tDCS appears to hold promise as a potential therapeutic approach for chronic tinnitus. However, further controlled studies are essential to arrive at a definitive conclusion.

Supplementary Materials: The following supporting information can be downloaded at: <https://www.mdpi.com/article/10.3390/brainsci14040373/s1>, Table S1: Participants’ Characteristics of tDCS intervention. Table S2. Participants’ characteristics of sham stimulation.

Author Contributions: Conceptualization, A.Y., S.R., N.S., M.M.-Y. and P.S.K.; methodology, A.Y., S.R. and N.S.; software, A.Y. and M.M.-Y.; validation, A.Y., S.R., N.S., M.M.-Y. and P.S.K.; formal analysis, A.Y., M.M.-Y. and P.S.K.; investigation, A.Y., S.R. and N.S.; resources, A.Y., S.R. and N.S.; data curation, A.Y., M.M.-Y. and P.S.K.; writing—original draft preparation, A.Y., S.R., N.S., M.M.-Y. and P.S.K.; writing—review and editing, A.Y., S.R., N.S., M.M.-Y. and P.S.K.; visualization, M.M.-Y. and P.S.K.; supervision, A.Y., N.S. and M.M.-Y.; project administration, A.Y., S.R., N.S., M.M.-Y. and P.S.K.; funding acquisition, A.Y. and N.S. All authors have read and agreed to the published version of the manuscript.

Funding: This research was financially supported by Ahvaz Jundishapur University of Medical Sciences (Grant no.: HRC-9409).

Institutional Review Board Statement: All of the experimental procedures of the study were approved by local ethical committee of Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran (registration code: IR.AJUMS.REC.1394.635; approval date: 13 February 2016), which were completely in accordance with the ethical standards and regulations of human studies of the Helsinki declaration (1964). The study was registered as a clinical trial in Iranian Registry of Clinical Trials (IRCT2016110124635N6; approval date: 6 December 2016).

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data used in this study are available upon request from the corresponding author due to their containing information that could compromise the privacy of the study participants.

Conflicts of Interest: The authors declare no conflicts of interest.

References

- Kim, H.-J.; Lee, H.-J.; An, S.-Y.; Sim, S.; Park, B.; Kim, S.W.; Lee, J.S.; Hong, S.K.; Choi, H.G. Analysis of the Prevalence and Associated Risk Factors of Tinnitus in Adults. *PLoS ONE* **2015**, *10*, e0127578. [[CrossRef](#)] [[PubMed](#)]
- Smits, M.; Kovacs, S.; De Ridder, D.; Peeters, R.R.; Van Hecke, P.; Sunaert, S. Lateralization of Functional Magnetic Resonance Imaging (fMRI) Activation in the Auditory Pathway of Patients with Lateralized Tinnitus. *Neuroradiology* **2007**, *49*, 669–679. [[CrossRef](#)] [[PubMed](#)]
- Eggermont, J.J. Pathophysiology of Tinnitus. *Prog. Brain Res.* **2007**, *166*, 19–543. [[PubMed](#)]
- De Ridder, D.; Franssen, H.; Francois, O.; Sunaert, S.; Kovacs, S.; Van De Heyning, P. Amygdalohippocampal Involvement in Tinnitus and Auditory Memory. *Acta Oto-Laryngol.* **2006**, *126*, 50–53. [[CrossRef](#)] [[PubMed](#)]
- Vanneste, S.; Plazier, M.; Ost, J.; van der Loo, E.; Van de Heyning, P.; De Ridder, D. Bilateral Dorsolateral Prefrontal Cortex Modulation for Tinnitus by Transcranial Direct Current Stimulation: A Preliminary Clinical Study. *Exp. Brain Res.* **2010**, *202*, 779–785. [[CrossRef](#)] [[PubMed](#)]
- Weisz, N.; Müller, S.; Schlee, W.; Dohrmann, K.; Hartmann, T.; Elbert, T. The Neural Code of Auditory Phantom Perception. *J. Neurosci.* **2007**, *27*, 1479–1484. [[CrossRef](#)]
- Schlee, W.; Hartmann, T.; Langguth, B.; Weisz, N. Abnormal Resting-State Cortical Coupling in Chronic Tinnitus. *BMC Neurosci.* **2009**, *10*, 11. [[CrossRef](#)]
- Langguth, B.; Eichhammer, P.; Kreuzer, A.; Maenner, P.; Marienhagen, J.; Kleinjung, T.; Sand, P.; Hajak, G. The Impact of Auditory Cortex Activity on Characterizing and Treating Patients with Chronic Tinnitus—First Results from a PET Study. *Acta Oto-Laryngol.* **2006**, *126*, 84–88. [[CrossRef](#)]
- Van Der Loo, E.; Congedo, M.; Vanneste, S.; Van De Heyning, P.; De Ridder, D. Insular Lateralization in Tinnitus Distress. *Auton. Neurosci.* **2011**, *165*, 191–194. [[CrossRef](#)]
- Vanneste, S.; De Ridder, D. Bifrontal Transcranial Direct Current Stimulation Modulates Tinnitus Intensity and Tinnitus-distress-related Brain Activity. *Eur. J. Neurosci.* **2011**, *34*, 605–614. [[CrossRef](#)]
- Vanneste, S.; Van de Heyning, P.; De Ridder, D. Contralateral Parahippocampal Gamma-Band Activity Determines Noise-like Tinnitus Laterality: A Region of Interest Analysis. *Neuroscience* **2011**, *199*, 481–490. [[CrossRef](#)] [[PubMed](#)]
- Lewis, J.W.; Beauchamp, M.S.; DeYoe, E.A. A Comparison of Visual and Auditory Motion Processing in Human Cerebral Cortex. *Cereb. Cortex* **2000**, *10*, 873–888. [[CrossRef](#)] [[PubMed](#)]
- Voisin, J.; Bidet-Caulet, A.; Bertrand, O.; Fonlupt, P. Listening in Silence Activates Auditory Areas: A Functional Magnetic Resonance Imaging Study. *J. Neurosci.* **2006**, *26*, 273–278. [[CrossRef](#)] [[PubMed](#)]
- Roberts, L.E.; Eggermont, J.J.; Caspary, D.M.; Shore, S.E.; Melcher, J.R.; Kaltenbach, J.A. Ringing Ears: The Neuroscience of Tinnitus. *J. Neurosci.* **2010**, *30*, 14972–14979. [[CrossRef](#)]
- Nemholt, S.S.; Schmidt, J.H.; Wedderkopp, N.; Baguley, D.M. Prevalence of Tinnitus and/or Hyperacusis in Children and Adolescents: Study Protocol for a Systematic Review. *BMJ Open* **2015**, *5*, e006649. [[CrossRef](#)] [[PubMed](#)]
- Kim, S.H.; Kim, D.; Lee, J.-M.; Lee, S.K.; Kang, H.J.; Yeo, S.G. Review of Pharmacotherapy for Tinnitus. *Healthcare* **2021**, *9*, 779. [[CrossRef](#)] [[PubMed](#)]
- Rauschecker, J.P.; Leaver, A.M.; Mühlau, M. Tuning out the Noise: Limbic-Auditory Interactions in Tinnitus. *Neuron* **2010**, *66*, 819–826. [[CrossRef](#)] [[PubMed](#)]
- Khoramzadeh, S.; Saki, N.; Davoodi, I.; Nosratabadi, M.; Yadollahpour, A. Investigating the Therapeutic Efficacy of Neurofeedback Treatment on the Severity of Symptoms and Quality of Life in Patients with Tinnitus. *Int. J. Ment. Health Addict.* **2016**, *14*, 982–992. [[CrossRef](#)]
- Mondino, M.; Haesebaert, F.; Poulet, E.; Saoud, M.; Brunelin, J. Efficacy of Cathodal Transcranial Direct Current Stimulation over the Left Orbitofrontal Cortex in a Patient with Treatment-Resistant Obsessive-Compulsive Disorder. *J. ECT* **2015**, *31*, 271–272. [[CrossRef](#)]
- Saunders, N.; Downham, R.; Turman, B.; Kropotov, J.; Clark, R.; Yumash, R.; Szatmary, A. Working Memory Training with tDCS Improves Behavioral and Neurophysiological Symptoms in Pilot Group with Post-Traumatic Stress Disorder (PTSD) and with Poor Working Memory. *Neurocase* **2015**, *21*, 271–278. [[CrossRef](#)]
- Baker, J.M.; Rorden, C.; Fridriksson, J. Using Transcranial Direct-Current Stimulation to Treat Stroke Patients with Aphasia. *Stroke* **2010**, *41*, 1229–1236. [[CrossRef](#)] [[PubMed](#)]
- Yadollahpour, A.; Jalilifar, M.; Rashidi, S. Transcranial Direct Current Stimulation for the Treatment of Depression: A Comprehensive Review of the Recent Advances. *Int. J. Ment. Health Addict.* **2017**, *15*, 434–443. [[CrossRef](#)]
- Yadollahpour, A.; Asl, H.M.; Rashidi, S. Transcranial Direct Current Stimulation as a Non-Medication Modality for Attention Enhancement: A Review of the Literature. *Res. J. Pharm. Technol.* **2017**, *10*, 311–316. [[CrossRef](#)]
- Frank, E.; Scheckmann, M.; Landgrebe, M.; Burger, J.; Kreuzer, P.; Poepl, T.B.; Kleinjung, T.; Hajak, G.; Langguth, B. Treatment of Chronic Tinnitus with Repeated Sessions of Prefrontal Transcranial Direct Current Stimulation: Outcomes from an Open-Label Pilot Study. *J. Neurol.* **2012**, *259*, 327–333. [[CrossRef](#)]
- De Ridder, D.; Vanneste, S. EEG Driven tDCS versus Bifrontal tDCS for Tinnitus. *Front. Psychiatry* **2012**, *3*, 84. [[CrossRef](#)] [[PubMed](#)]

26. Fregni, F.; Marcondes, R.; Boggio, P.S.; Marcolin, M.A.; Rigonatti, S.P.; Sanchez, T.G.; Nitsche, M.A.; Pascual-Leone, A. Transient Tinnitus Suppression Induced by Repetitive Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation. *Eur. J. Neurol.* **2006**, *13*, 996–1001. [[CrossRef](#)]
27. Stagg, C.J.; Nitsche, M.A. Physiological Basis of Transcranial Direct Current Stimulation. *Neuroscientist* **2011**, *17*, 37–53. [[CrossRef](#)]
28. Bikson, M.; Grossman, P.; Thomas, C.; Zannou, A.L.; Jiang, J.; Adnan, T.; Mourdoukoutas, A.P.; Kronberg, G.; Truong, D.; Boggio, P.; et al. Safety of Transcranial Direct Current Stimulation: Evidence Based Update 2016. *Brain Stimul.* **2016**, *9*, 641–661. [[CrossRef](#)] [[PubMed](#)]
29. De Ridder, D.; Vanneste, S.; Congedo, M. The Distressed Brain: A Group Blind Source Separation Analysis on Tinnitus. *PLoS ONE* **2011**, *6*, e24273. [[CrossRef](#)]
30. Yuan, T.; Yadollahpour, A.; Salgado-Ramírez, J.; Robles-Camarillo, D.; Ortega-Palacios, R. Transcranial Direct Current Stimulation for the Treatment of Tinnitus: A Review of Clinical Trials and Mechanisms of Action 11 Medical and Health Sciences 1103 Clinical Sciences. *BMC Neurosci.* **2018**, *19*, 66. [[CrossRef](#)]
31. Wang, T.C.; Tyler, R.S.; Chang, T.Y.; Chen, J.C.; Lin, C.D.; Chung, H.K.; Tsou, Y.A. Effect of Transcranial Direct Current Stimulation in Patients with Tinnitus: A Meta-Analysis and Systematic Review. *Ann. Otol. Rhinol. Laryngol.* **2018**, *127*, 79–88. [[CrossRef](#)] [[PubMed](#)]
32. Martins, M.L.; da Silva Souza, D.; Cavalcante, M.E.D.O.B.; Barboza, H.N.; de Medeiros, J.F.; dos Santos Andrade, S.M.M.; da Silva Machado, D.G.; da Rosa, M.R.D. Effect of Transcranial Direct Current Stimulation for Tinnitus Treatment: A Systematic Review and Meta-Analysis. *Neurophysiol. Clin.* **2022**, *52*, 1–16. [[CrossRef](#)] [[PubMed](#)]
33. Sherlock, L.G.P.; Eisenman, D.J. Current Device-Based Clinical Treatments for Tinnitus. *Otolaryngol. Clin. N. Am.* **2020**, *53*, 627–636. [[CrossRef](#)] [[PubMed](#)]
34. Chen, S.; Du, M.; Wang, Y.; Li, Y.; Tong, B.; Qiu, J.; Wu, F.; Liu, Y. State of the Art: Non-Invasive Electrical Stimulation for the Treatment of Chronic Tinnitus. *Ther. Adv. Chronic Dis.* **2023**, *14*, 20406223221148061. [[CrossRef](#)]
35. Labree, B.; Hoare, D.J.; Gascoyne, L.E.; Scutt, P.; Del Giovane, C.; Sereda, M. Determining the Effects of Transcranial Direct Current Stimulation on Tinnitus, Depression, and Anxiety: A Systematic Review. *Brain Sci.* **2022**, *12*, 484. [[CrossRef](#)] [[PubMed](#)]
36. Yadollahpour, A.; Rashidi, S.; Jaberzade, S. Single Session Anodal, Cathodal and Placebo Bifrontal tDCS for Treatment of Intractable Chronic Tinnitus: A Randomized Controlled Clinical Trial. *Brain Stimul. Basic Transl. Clin. Res. Neuromodul.* **2019**, *12*, 406. [[CrossRef](#)]
37. Forogh, B.; Mirshaki, Z.; Raissi, G.R.; Shirazi, A.; Mansoori, K.; Ahadi, T. Repeated Sessions of Transcranial Direct Current Stimulation for Treatment of Chronic Subjective Tinnitus: A Pilot Randomized Controlled Trial. *Neurol. Sci.* **2016**, *37*, 253–259. [[CrossRef](#)] [[PubMed](#)]
38. Rashidi, S.; Yadollahpour, A. Three Weeks Bilateral tDCS over Auditory Cortex Significantly Improves Tinnitus: A Double Blinded Randomized Controlled Clinical Trial. *Brain Stimul.* **2023**, *16*, 403. [[CrossRef](#)]
39. Garin, P.; Gilain, C.; Van Damme, J.P.; de Fays, K.; Jamart, J.; Ossemann, M.; Vandermeeren, Y. Short- and Long-Lasting Tinnitus Relief Induced by Transcranial Direct Current Stimulation. *J. Neurol.* **2011**, *258*, 1940–1948. [[CrossRef](#)]
40. Shekhawat, G.S.; Searchfield, G.D.; Stinear, C.M. Randomized Trial of Transcranial Direct Current Stimulation and Hearing Aids for Tinnitus Management. *Neurorehabil. Neural Repair* **2014**, *28*, 410–419. [[CrossRef](#)]
41. Kikuta, S.; Matsumoto, Y.; Kuboki, A.; Nakayama, T.; Asaka, D.; Otori, N.; Kojima, H.; Sakamoto, T.; Akinori, K.; Kanaya, K.; et al. Longer Latency of Sensory Response to Intravenous Odor Injection Predicts Olfactory Neural Disorder. *Sci. Rep.* **2016**, *6*, 35361. [[CrossRef](#)] [[PubMed](#)]
42. Vanneste, S.; De Ridder, D. Noninvasive and Invasive Neuromodulation for the Treatment of Tinnitus: An Overview. *Neuromodulation Technol. Neural Interface* **2012**, *15*, 350–360. [[CrossRef](#)] [[PubMed](#)]
43. Yadollahpour, A.; Mayo, M.; Saki, N.; Rashidi, S.; Bayat, A. A Chronic Protocol of Bilateral Transcranial Direct Current Stimulation over Auditory Cortex for Tinnitus Treatment: Dataset from a Double-Blinded Randomized Controlled Trial. *F1000Research* **2018**, *7*, 733. [[CrossRef](#)] [[PubMed](#)]
44. Lefaucheur, J.P.; Antal, A.; Ayache, S.S.; Benninger, D.H.; Brunelin, J.; Cogiamanian, F.; Cotelli, M.; De Ridder, D.; Ferrucci, R.; Langguth, B.; et al. Evidence-Based Guidelines on the Therapeutic Use of Transcranial Direct Current Stimulation (tDCS). *Clin. Neurophysiol.* **2017**, *128*, 56–92. [[CrossRef](#)] [[PubMed](#)]
45. Yadollahpour, A.; Bayat, A.; Rashidi, S.; Saki, N.; Karimi, M. Dataset of Acute Repeated Sessions of Bifrontal Transcranial Direct Current Stimulation for Treatment of Intractable Tinnitus: A Randomized Controlled Trial. *Data Brief* **2017**, *15*, 40–46. [[CrossRef](#)]
46. Rashidi, S.; Yadollahpour, A.; Alkahtani, S.A.; Kunwar, P.S.; Robles-Camarillo, D.; Meneses-Flores, A.; Trejo-Macotela, F. The Effects of Acute Multisession Bifrontal Transcranial Direct Current Stimulation on Intractable Tinnitus and Comorbid Depression and Anxiety: A Study Protocol for Randomized Controlled Trial. *Int. Tinnitus J.* **2018**, *22*, 181–187. [[CrossRef](#)]
47. Hyvärinen, P.; Mäkitie, A.; Aarnisalo, A.A. Self-Administered Domiciliary tDCS Treatment for Tinnitus: A Double-Blind Sham-Controlled Study. *PLoS ONE* **2016**, *11*, e0154286. [[CrossRef](#)] [[PubMed](#)]
48. Mares, T.; Albrecht, J.; Buday, J.; Podgorna, G.; Le, T.H.; Magyarova, E.; Poshor, K.; Halik, J.; Buna, J.; Capek, V.; et al. Long-Term Effect of Transcranial Direct Current Stimulation in the Treatment of Chronic Tinnitus: A Randomized, Placebo-Controlled Trial. *Front. Psychiatry* **2022**, *13*, 969800. [[CrossRef](#)] [[PubMed](#)]
49. Bayat, A.; Mayo, M.; Rashidi, S.; Saki, N.; Yadollahpour, A. Repeated Sessions of Bilateral Transcranial Direct Current Stimulation on Intractable Tinnitus: A Study Protocol for a Double-Blind Randomized Controlled Trial. *F1000Research* **2018**, *7*, 317. [[CrossRef](#)]

50. Shekhawat, G.S.; Vanneste, S. Optimization of Transcranial Direct Current Stimulation of Dorsolateral Prefrontal Cortex for Tinnitus: A Non-Linear Dose-Response Effect. *Sci. Rep.* **2018**, *8*, 8311. [[CrossRef](#)]
51. Vanneste, S.; Langguth, B.; De Ridder, D. Do tDCS and TMS Influence Tinnitus Transiently via a Direct Cortical and Indirect Somatosensory Modulating Effect? A Combined TMS-tDCS and TENS Study. *Brain Stimul.* **2011**, *4*, 242–252. [[CrossRef](#)] [[PubMed](#)]
52. Faber, M.; Vanneste, S.; Fregni, F.; De Ridder, D. Top down Prefrontal Affective Modulation of Tinnitus with Multiple Sessions of tDCS of Dorsolateral Prefrontal Cortex. *Brain Stimul.* **2012**, *5*, 492–498. [[CrossRef](#)]
53. Shekhawat, G.S.; Sundram, F.; Bikson, M.; Truong, D.; De Ridder, D.; Stinear, C.M.; Welch, D.; Searchfield, G.D. Intensity, Duration, and Location of High-Definition Transcranial Direct Current Stimulation for Tinnitus Relief. *Neurorehabil. Neural Repair* **2016**, *30*, 349–359. [[CrossRef](#)] [[PubMed](#)]
54. Cardon, E.; Jacquemin, L.; Vermeersch, H.; Joossen, I.; Moyaert, J.; Mertens, G.; Vanderveken, O.M.; Lammers, M.J.W.; Van De Heyning, P.; Van Rompaey, V.; et al. Dual-Site Transcranial Direct Current Stimulation to Treat Tinnitus: A Randomized Controlled Trial. *Brain J. Neurol.* **2022**, *145*, 4222–4231. [[CrossRef](#)]
55. Elyssa Kok, T.; Schaeffe, R.; Shekhawat, G.S. Impact of tDCS and HD-tDCS on Tinnitus Perception: A Scoping Review. *Prog. Brain Res.* **2021**, *262*, 225–244. [[CrossRef](#)] [[PubMed](#)]
56. Teismann, H.; Wollbrink, A.; Okamoto, H.; Schlaug, G.; Rudack, C.; Pantev, C. Combining Transcranial Direct Current Stimulation and Tailor-Made Notched Music Training to Decrease Tinnitus-Related Distress—A Pilot Study. *PLoS ONE* **2014**, *9*, e89904. [[CrossRef](#)]
57. McCombe, A.; Baguley, D.; Coles, R.; McKenna, L.; McKinney, C.; Windle-Taylor, P. Guidelines for the Grading of Tinnitus Severity: The Results of a Working Group Commissioned by the British Association of Otolaryngologists, Head and Neck Surgeons, 1999. *Clin. Otolaryngol. Allied Sci.* **2001**, *26*, 388–393. [[CrossRef](#)]
58. Klem, G.H.; Lüders, H.O.; Jasper, H.H.; 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.
59. Poreisz, C.; Boros, K.; Antal, A.; Paulus, W. Safety Aspects of Transcranial Direct Current Stimulation Concerning Healthy Subjects and Patients. *Brain Res. Bull.* **2007**, *72*, 208–214. [[CrossRef](#)]
60. Paulus, W. Transcranial Direct Current Stimulation (tDCS). *Suppl. Clin. Neurophysiol.* **2003**, *56*, 249–254.
61. Surr, R.K.; Kolb, J.A.; Cord, M.T.; Garrus, N.P. Tinnitus Handicap Inventory (THI) as a Hearing Aid Outcome Measure. *J. Am. Acad. Audiol.* **1999**, *10*, 489–495. [[CrossRef](#)] [[PubMed](#)]
62. Shekhawat, G.S.; Stinear, C.M.; Searchfield, G.D. Transcranial Direct Current Stimulation Intensity and Duration Effects on Tinnitus Suppression. *Neurorehabil. Neural Repair* **2013**, *27*, 164–172. [[CrossRef](#)] [[PubMed](#)]
63. Vanneste, S.; Fregni, F.; De Ridder, D. Head-to-Head Comparison of Transcranial Random Noise Stimulation, Transcranial AC Stimulation, and Transcranial DC Stimulation for Tinnitus. *Front. Psychiatry* **2013**, *4*, 158. [[CrossRef](#)] [[PubMed](#)]
64. Pal, N.; Maire, R.; Stephan, M.A.; Herrmann, F.R.; Benninger, D.H. Transcranial Direct Current Stimulation for the Treatment of Chronic Tinnitus: A Randomized Controlled Study. *Brain Stimul.* **2015**, *8*, 1101–1107. [[CrossRef](#)] [[PubMed](#)]
65. Vanneste, S.; Walsh, V.; Van De Heyning, P.; De Ridder, D. Comparing Immediate Transient Tinnitus Suppression Using tACS and tDCS: A Placebo-Controlled Study. *Exp. Brain Res.* **2013**, *226*, 25–31. [[CrossRef](#)] [[PubMed](#)]
66. Zeman, F.; Koller, M.; Figueiredo, R.; Aazevedo, A.; Rates, M.; Coelho, C.; Kleinjung, T.; de Ridder, D.; Langguth, B.; Landgrebe, M. Tinnitus Handicap Inventory for Evaluating Treatment Effects. *Otolaryngol. Head. Neck Surg.* **2011**, *145*, 282–287. [[CrossRef](#)] [[PubMed](#)]
67. Langguth, B.; Goodey, R.; Azevedo, A.; Bjerne, A.; Cacace, A.; Crocetti, A.; Del Bo, L.; De Ridder, D.; Diges, I.; Elbert, T.; et al. Consensus for Tinnitus Patient Assessment and Treatment Outcome Measurement: Tinnitus Research Initiative Meeting, Regensburg, July 2006. *Prog. Brain Res.* **2007**, *166*, 525–536. [[CrossRef](#)] [[PubMed](#)]
68. Vanneste, S.; Focquaert, F.; Van de Heyning, P.; De Ridder, D. Different Resting State Brain Activity and Functional Connectivity in Patients Who Respond and Not Respond to Bifrontal tDCS for Tinnitus Suppression. *Exp. Brain Res.* **2011**, *210*, 217–227. [[CrossRef](#)] [[PubMed](#)]
69. Wen, Y.-R.; Shi, J.; Hu, Z.-Y.; Lin, Y.-Y.; Lin, Y.-T.; Jiang, X.; Wang, R.; Wang, X.-Q.; Wang, Y.-L. Is Transcranial Direct Current Stimulation Beneficial for Treating Pain, Depression, and Anxiety Symptoms in Patients with Chronic Pain? A Systematic Review and Meta-Analysis. *Front. Mol. Neurosci.* **2022**, *15*, 1056966. [[CrossRef](#)]
70. Le, B.; Alonzo, A.; Bull, M.; Kabourakis, M.; Martin, D.; Loo, C. A Clinical Case Series of Acute and Maintenance Home Administered Transcranial Direct Current Stimulation in Treatment-Resistant Depression. *J. ECT* **2022**, *38*, e11–e19. [[CrossRef](#)]
71. Sharma, D.K.; Kaur, S.; Singh, J.; Kaur, I. Role of Acamprosate in Sensorineural Tinnitus. *Indian J. Pharmacol.* **2012**, *44*, 93–96. [[CrossRef](#)] [[PubMed](#)]

Disclaimer/Publisher’s Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.