



STUDY PROTOCOL

Repeated sessions of bilateral transcranial direct current stimulation on intractable tinnitus: a study protocol for a double-blind randomized controlled trial [version 1; referees: 2 approved]

Arash Bayat¹, Miguel Mayo ², Samaneh Rashidi³, Nader Saki¹,
Ali Yadollahpour ^{3,4}

¹Hearing Research Center, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, 61357-15794, Iran

²Department of Otorhinolaryngology, A Coruña University Hospital Complex, A Coruña, 15006, Spain

³Bioelectromagnetic Clinic, Imam Khomeini Hospital, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, 61936-73111, Iran

⁴Department of Medical Physics, School of Medicine, Ahvaz Jundishapur University of Medical Sciences, Ahvaz, 61357-33118, Iran

v1 First published: 14 Mar 2018, 7:317 (doi: [10.12688/f1000research.13558.1](https://doi.org/10.12688/f1000research.13558.1))
Latest published: 14 Mar 2018, 7:317 (doi: [10.12688/f1000research.13558.1](https://doi.org/10.12688/f1000research.13558.1))

Abstract

Background: Transcranial Direct Current Stimulation (tDCS) is reportedly a potential treatment option for chronic tinnitus. The main drawbacks of previous studies are short term follow up and focusing on the efficacy of single session tDCS. This study aims to investigate the therapeutic efficacy, adverse effects (AEs) and tolerability of repeated sessions of bilateral tDCS over auditory cortex (AC) on tinnitus symptoms

Methods: This will be a double-blinded randomized placebo controlled parallel trial on patients (n=90) with intractable chronic tinnitus (> 2 years) randomly divided into three groups of anodal, cathodal, and sham tDCS. In the sham treatment, after 30 sec the device will be turned OFF without informing the patients. The tDCS protocol consists of 10 sessions (daily 20 min session; 2 mA current for 5 consecutive days per week and 2 consecutive weeks) applied through 35 cm² electrodes. The primary outcome is tinnitus handicap inventory (THI) which will be assessed pre- and post-intervention and at one month follow-up. The secondary outcomes are tinnitus loudness and distress to be assessed using a visual analogue scale (VAS) pre-intervention, and immediately, one hour, one week, and one month after last stimulation. The AEs and tolerability of patients will be evaluated after each session using a customized questionnaire. Possible interactions between the disease features and treatment response will be evaluated.

Discussion: To our knowledge this is the first study to investigate the effects of repeated sessions of tDCS on chronic tinnitus symptoms with one month follow-up. In addition, the AEs, and tolerability of patients will be studied. In addition, the possible interactions between the disease specific features including the hearing loss, laterality, type of tinnitus, and treatment response will be evaluated.

Trial registration: The study has been registered as a clinical trial in Iranian Registry of Clinical Trial ([IRCT2016110124635N6](https://www.clinicaltrials.gov/ct2/show/study?term=IRCT2016110124635N6)) on the 01/06/2017.

Open Peer Review

Referee Status:

	Invited Referees	
	1	2
version 1 published 14 Mar 2018	 report	 report

- 1 **Leonid S. Godlevsky** , Odessa National Medical University, Ukraine
- 2 **Daniel Robles-Camarillo**, Polytechnic University of Pachuca, Mexico

Discuss this article

Comments (0)

Corresponding author: Ali Yadollahpour (Yadollahpour.a@gmail.com)

Author roles: **Bayat A:** Formal Analysis, Resources, Validation, Writing – Original Draft Preparation; **Mayo M:** Data Curation, Formal Analysis, Validation, Writing – Original Draft Preparation, Writing – Review & Editing; **Rashidi S:** Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Writing – Original Draft Preparation; **Saki N:** Funding Acquisition, Project Administration, Resources, Supervision, Validation; **Yadollahpour A:** Conceptualization, Data Curation, Investigation, Methodology, Project Administration, Supervision, Writing – Review & Editing

Competing interests: No competing interests were disclosed.

How to cite this article: Bayat A, Mayo M, Rashidi S *et al.* **Repeated sessions of bilateral transcranial direct current stimulation on intractable tinnitus: a study protocol for a double-blind randomized controlled trial [version 1; referees: 2 approved]** *F1000Research* 2018, 7:317 (doi: [10.12688/f1000research.13558.1](https://doi.org/10.12688/f1000research.13558.1))

Copyright: © 2018 Bayat A *et al.* This is an open access article distributed under the terms of the [Creative Commons Attribution Licence](https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Grant information: This study is financially supported by Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran (Grant No: HRC-9409). The AJUMS has no role in the design of the study, collection of data, analyses, and interpretation of data as well as in composing the manuscript. It, as the external funding body has reviewed the study in a double blinding peer review policy and it was approved by the editorial board member of the University.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

First published: 14 Mar 2018, 7:317 (doi: [10.12688/f1000research.13558.1](https://doi.org/10.12688/f1000research.13558.1))

Abbreviations

tDCS: transcranial direct current stimulation; AC: auditory cortex; DLPFC: dorsolateral prefrontal cortex; THI: tinnitus handicap inventory; BDI-II: Beck Depression inventory; BAI: Beck Anxiety Inventory; dBHL: decibels hearing level.

Background

Tinnitus is a subjective auditory phantom perception without an external physical sound source¹, which exists in different forms including pulsatile or continuous, buzzing, ringing, hissing, tone, or a combination of them². It is a relatively common disorder with 10–15% prevalence among adults worldwide. Tinnitus is a debilitating condition which severely affects the quality of life. It is accompanied by different comorbidities such as anxiety, depression, and sleep disturbances³.

There is no definitive treatment for tinnitus and a large proportion of tinnitus become intractable^{1,3}. During the recent years, different non-pharmacological techniques have been developed for treatment of chronic tinnitus including cognitive behavioral therapies, hearing aids, neurofeedback, and noise-masking techniques^{4–6}. Although some of these techniques have shown therapeutic outcomes, the therapeutic efficacies of these techniques are limited and studies to develop more efficient techniques are ongoing.

Transcranial direct current stimulation (tDCS) is a non-invasive neuromodulation technique and recent studies have reported promising therapeutic outcomes in improving cognitive functions in healthy individuals⁷ as well as symptoms of different neuropsychiatric disorders such as depression⁸, obsessive compulsive disorder⁹ auditory-verbal hallucinations¹⁰, and chronic pain¹¹. Several studies have investigated the therapeutic efficacy of different tDCS protocols in chronic tinnitus^{11–15}. Results were in general promising, despite some controversial findings. In treating tinnitus with tDCS, there are two main targets as the site of stimulation including the dorsolateral prefrontal cortex (DLPFC)^{16,17}, and the auditory cortex^{18–20}. The neural anomalies, hyperactivity, or maladaptive plasticity of the primary and secondary auditory cortices have been reportedly the main causes of tinnitus loudness and disturbances in non-auditory structures and networks such as anterior cingulate cortex, and particularly DLPFC are the main causes of distress or annoyance experienced in tinnitus^{2,3,21}. The main hypothesis for therapeutic application of tDCS in tinnitus is disturbing ongoing abnormal neural activities responsible for tinnitus. According to this approach, the areas involved in the pathophysiology of tinnitus are targeted by tDCS. The other hypothesis of eliciting therapeutic outcomes from tDCS is inducing plastic changes to alter the maladaptive plasticity of the involved regions. The important point for treatment of tinnitus is that there is a large network consisting of different auditory and non-auditory regions with overlapping functions^{22–24}.

Most of the studies performed to date, have focused on the effects of single tDCS session on tinnitus symptoms, with short term follow ups ranging some hours to some days. To our knowledge,

there is no published study investigating the effect of repeated sessions of tDCS over the auditory cortex (AC) on tinnitus symptoms as well as the AEs of and tolerability to the tDCS with one month follow up. This study aims to investigate the effects of repeated sessions of tDCS on tinnitus symptoms with one month follow-up. Our main hypothesis is that repeated sessions will lead to aggregative therapeutic effects on tinnitus. In addition, we want to evaluate possible association between treatment response, and patient's and tinnitus specific characteristics including gender, THI basal score, laterality, tinnitus quality, duration, hearing loss class, etc.

Methods/design

Participants

This is a part of a larger project which is designed to comprehensively investigate the efficacy of different tDCS protocols at different sites of brain for treatment of intractable chronic tinnitus. In this double blinded placebo controlled randomized trial will be conducted on intractable tinnitus patients (n=90) who will be randomly divided into three groups of anodal (anode/cathode on left/right AC), cathodal (cathode/anode on left/right AC, and sham (anode/cathode on left/right AC) tDCS. In the sham treatment, after 30 sec the device will be turned off without informing the patients. The experimental procedures of the study including tDCS interventions and the evaluations of the outcomes will be performed in the Bioelectromagnetic Clinic in Ahvaz Imam Hospital, Ahvaz, Iran. Patients with intractable chronic tinnitus (> 2 years) will be enrolled in this study. This is a single-center, non-stratified, with balanced randomization [1:1:1], double-blind, placebo-controlled, parallel-group study conducted in Bioelectromagnetic Clinic, Imam Khomeini Hospital, Ahvaz, Iran. Allocation concealment will be performed by random allocation cards using computer-generated random numbers. The patients will be randomly assigned into three groups of cathodal, anodal, or placebo tDCS.

Ethics approval and consent to participate

All of the experimental procedures of this study were approved by the local ethics committee of Ahvaz Jundishapur University of Medical Sciences, Ahvaz, Iran (registration code: IR.AJUMS.REC.1394.639) which were in complete accordance with the ethical standards and regulations of human studies of the Helsinki declaration (2014)²⁵. After enrolment and before the start of the study, researcher will clearly explain the experimental procedures, the objectives, possible benefits, and side effects of the study to the patients and then all participants will fill and sign a written consent form for contribution in the study. The study was registered as a clinical trial in the Iranian registry of clinical trials ([IRCT2016110124635N6](https://www.irct.ir/trial/2016110124635N6)).

Inclusion and exclusion criteria

The patients should meet specific criteria for inclusion in this project. The primary criteria will be evaluated during the neurological and otolaryngological examinations by experienced specialists. The patients will be selected among the tinnitus patients referred to the Tinnitus Clinic in the Khuzestan Cochlear Implant Center, Ahvaz, Iran. After the start of the study

and anytime during the study, patients have the right to leave the study. In case of any significant adverse effects (AEs), the procedures for the respective patients will be terminated.

Inclusion criteria

- Idiopathic chronic and medication-resistant tinnitus (more than 2 years)
- Age range of 18 to 70 years old
- No use of medications at the time of intervention

Exclusion criteria

- History of epileptic seizures, brain trauma
- Severe psychotic and psychiatric disorders
- Concurrent severe vertigo
- Meniere's disease
- Severe organic comorbidity
- Using pacemaker or defibrillator
- Present pregnancy, neurologic disorders such as brain tumors,
- Concurrent treatment for mental disorders.

All prospective subjects will undergo complete audiometric and neurologic examinations by experienced specialists. The experimental procedures of the study including tDCS interventions and the evaluations of the outcomes will be performed in the Bioelectromagnetic Clinic in Ahvaz Imam Hospital, Ahvaz, Iran.

Study protocol

This study is a double-blind randomized controlled clinical trial design and patients will be randomly assigned into three groups of anodal and cathodal tDCS and sham tDCS. The random allocation will be performed based on balanced randomization [1:1:1] where the allocation concealment will be applied by random allocation cards using computer-generated random numbers. The three groups will be matched for age, gender, ethnicity, and audiometric main characteristics. To reduce the procedure and subjective bias, the patients, the researchers who will evaluate the outcomes, and the researchers who perform data

analyses will be blinded on the type of protocol. In addition, the blinding quality of the study will be assessed after completion of the intervention.

Transcranial direct current stimulation protocol

The direct current will be applied through a saline-soaked pair of surface electrodes (35 cm²) and delivered by a tDCS device which is a specially developed, battery-driven, constant current stimulator with a maximum output of 2 mA. The tDCS device used in this study will be an OASIS Pro™ device by Mind Alive Inc (Edmonton, Alberta, Canada). Anodal and cathodal tDCS groups will consist of daily 20-min sessions of 2 mA current for five consecutive days per week and for 2 consecutive weeks (10 sessions in total). In anodal tDCS, the anode and cathode will be respectively centered over left AC (halfway T3 - F7) and right AC (halfway T4 - F8). In the cathodal tDCS the electrodes position will be reversed where cathode and anode will be respectively centered over left AC (halfway T3-F7) and right AC (halfway T4-F8). The site of electrodes will be selected according to the [International 10-20 electroencephalography system](#). In the sham tDCS group, the electrode montage will be the same as the anodal tDCS, but the device will be turned off after 30 s without the knowledge of the participant. These parameters for sham stimulation were chosen based on previous reported findings where the perceived sensations of stimulation on the skin, such as tingling, usually disappear in the first 30 s of active tDCS^{23,26} (Table 1).

Adverse effects and tolerability

The previous studies on the safety and tolerability of tDCS have shown that the 2 mA current applied in 20 minutes are associated with no serious AEs^{24,26}. The common reported AEs are itching or tingling sensation, mild headache or fatigue and local burns at the site of stimulation. However, most of the AEs and tolerability assessments have been performed on the tDCS were for single session ranging 20–30 minutes and current of 1 to 2 mA. In our study, we will use repeated sessions of tDCS (2 mA current for 20 minute, total 10 sessions, daily one session, five consecutive days per week and 2 consecutive weeks), thus the reported AEs in the previous studies may be intensified. Therefore, we will assess the AEs using a customized questionnaire ([Supplementary File 1](#)). The questionnaire will be performed during and after each tDCS session to record all the perceived AEs from the patients in all three tDCS groups.

Table 1. Setting for anodal, cathodal, and sham Transcranial Direct Current Stimulation (tDCS).

	Anodal tDCS	Cathodal tDCS	Sham tDCS
Current density	57.1 $\mu\text{A}/\text{cm}^2$	57.1 $\mu\text{A}/\text{cm}^2$	57.1 $\mu\text{A}/\text{cm}^2$
Electrode montage	Anode left (halfway T3 - F7) and cathode right AC (halfway T4 - F8)	Cathode left (halfway T3 - F7) and anode right AC (halfway T4 - F8)	Anode left (halfway T3 - F7) and cathode right AC (halfway T4 - F8)
Duration	20 min	20 min	20 min*

Note: * 30 seconds after the start of the stimulation the device will be turned off without the knowledge of patient.

Outcome assessments

Baseline evaluations

There will be different evaluations before the intervention. After enrollment, the patients will undergo complete audiometric and neurological assessments by expert specialties. The tinnitus severity for each patient will be determined through asking the patient and confirming the class by an expert otolaryngologist as buzzing, cicadas, high pitch whistling, hissing, humming, ringing, pulsating, thumping, and ticking. The tinnitus laterality and duration will be also determined.

Hearing assessment

Hearing assessments will be performed in an acoustically isolated chamber (ISO 8253–1:2010). Pure-tone audiometry will be performed using AC 40 dual channel Audiometer (Intracoustics Co., Denmark). The hearing thresholds will be 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 per recommended by ANSI 1997²⁷. Pure-tone audiometry is considered normal when the hearing thresholds at all frequencies are below 20 decibels hearing level (dBHL). Hearing loss will be classified according

to the type and degree²⁸. The class of hearing loss in both ears will be assessed 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 hearing class is determined as the average of threshold in 250 Hz, 1000, 2000, and 4000 Hz. The possible interactions of the aforementioned variables and the amount of each primary or secondary outcome will be studied.

Outcomes assessments

The primary and secondary outcomes will be measured in two main time points: pre- and post-intervention. The pre-intervention assessments of the outcomes will be performed at the first day of the intervention before tDCS stimulation (T₁). There will be four time points of post-intervention assessments as T₂, T₃, T₄, and T₅ corresponding to the immediately after last session, one hour, one week, and one month after last tDCS session. Table 2 represents the SPIRIT schematic protocol of the study and timing of the assessments.

Primary outcome. Tinnitus handicap inventory (THI) score will be the primary outcome. The THI is a 25-item questionnaire and

Table 2. Standard Protocol Items: Recommendations for Interventional Trials of this study.

	Enrolment	Allocation	Pre-intervention	Intervention	Post-intervention			
TIME POINT	-T ₁	T ₀	T ₁		T ₂	T ₃	T ₄	T ₅
ENROLMENT:								
Eligibility screen	X							
Informed consent	X							
Demographic information	X							
Allocation		X						
INTERVENTIONS:								
real (anodal and cathodal) tDCS				↔				
Sham tDCS				↔				
ASSESSMENTS:								
Neurological and audiological assessments	X							
Hearing loss assessment	X							
Primary outcome: THI			X		X			X
Secondary outcomes: loudness			X		X	X	X	X
Distress			X		X	X	X	X
AEs and Tolerability				↔	X			

Note: THI: tinnitus handicap inventory; AEs: adverse effects, -T₁: one month before intervention, T₀: one day before intervention, T₁: 5 min before intervention, T₂: immediately after last session, T₃: at hour after last session, T₄: one week, and T₅: at month after last tDCS session. Real tDCS refers to anodal and cathodal tDCS groups.

commonly used as self-reporting inventory for disabling level of tinnitus. The THI items are grouped into three subscales: Functional (11 items), emotional (9 items), and catastrophic (5 items) subscales. Each item is three point Likert type scale with three alternative assessments: yes (4 points), sometimes (2 points), and no (0 point). The questionnaire yields scores for each subscale and a total score that ranges 0 to 100, where higher score means more severe tinnitus or a greater handicap²⁹. The THI is widely used as the primary outcome measure in double-blind trials with a control group to assess the effect of pharmacological or non-pharmacological agents in tinnitus patients. The functional subscale items reflect the effect of tinnitus on mental, social, occupational, and physical functioning. The emotional subscale items probe the individual's emotional reactions to the tinnitus and the catastrophic response items address whether tinnitus makes the respondent feel desperate, trapped, hopeless or out of control. In this study, the THI will be assessed prior to intervention, and immediately, and at one month after the last tDCS session. Response to treatment is defined as a reduction of equal or more than 20 points in THI score (Pre-treatment THI – Post-treatment THI \geq 20). This cut-off value for treatment response to tDCS is generally considered as significant clinical improvement in the previous similar studies^{15,30}.

Secondary outcomes

Tinnitus loudness and distress. The tinnitus loudness and distress will be assessed using a numeral 0–10 visual analogue scale rating scale before intervention, and immediately, one hour, one week, and one month after last tDCS session. For tinnitus loudness and distress a 10 percent or 2 point reduction of 0–10 scale will be considered as treatment response^{31,32}.

Blinding assessment

The previous studies have shown that the experience of the sensations induced by tDCS are usually fade out after 30 seconds; thus, we will use this period in the sham tDCS group, to evaluate the blinding quality of the study design, after completion of the intervention we will ask the patients whether they know which type of stimulation, real or sham tDCS, they received. This assessment will be performed after each tDCS session in all groups.

Adverse effects and tolerability. Previous studies have reported no severe AEs of tDCS for different protocols. However, most of the previous studies used single session tDCS. For this study, considering the multisession protocol of tDCS, the AEs of and tolerability to the repeated sessions of tDCS will be assessed using a customized questionnaire (Supplementary File 1) which will be applied after the last session.

Statistical assessments

All statistical tests will be performed using SPSS (V20.0, IBM Corporation, New York, USA). To determine whether the anodal, cathodal, and sham tDCS groups are well-matched in terms of

age, sex, quality of tinnitus, tinnitus laterality, THI score, and duration and class of hearing loss, these dependent variables will be compared between the three groups using independent samples t-tests.

For nominal data like gender and class of hearing loss, Chi-square tests will be conducted across groups. Independent sample t-tests were also used to determine if individual baseline measures differed between groups (THI, tinnitus loudness, and distress). Prior to conducting *t*-tests, Levene's test for equality of variances was used. In no instance was Levene's test violated; thus, equality of variances was assumed. The number of female and male participants and the quality of tinnitus symptoms, across each group will be compared using Pearson Chi-square tests. Mixed repeated-measure ANOVAs with the within-subject factor time and the between-subject factor stimulation were performed for evaluating changes in THI, tinnitus loudness, tinnitus distress, BDI and BAI scores. For the ANOVAs, sphericity was tested with the Mauchly's test, and in the event of a violation of Mauchly's test, the Greenhouse-Geisser correction was applied. In case of significant effects, follow-up post-hoc *t*-tests were carried out using LSD adjustments for multiple comparisons to examine if tDCS caused a significant difference relative to sham or baseline. An analysis of covariance will be performed with Time as within-subject factor, Stimulation as between-subject factor, and gender, laterality of tinnitus, duration of tinnitus as covariates. In addition, we will calculate Pearson's correlations between change of THI and tinnitus loudness and distress values from pre- to post-stimulation.

Finally, we will examine the number of responders versus non-responders under each treatment condition (anodal, cathodal, and sham). This will be accomplished by calculating change scores between the pre-treatment and post-treatment THI values (Pre-treatment – Post-treatment). Responders will be considered individuals who showed reductions in THI score of equal or more than 20 points in the THI score (Pre-treatment THI – Post-treatment THI \geq 20). For tinnitus loudness and distress a 10 percent or 2-point reduction of 0–10 scale is considered as treatment response. Pearson's chi-square tests will be used to evaluate whether there are differences in the proportion of responders versus non-responders under each condition. For all statistical tests the P-value < 0.05 is defined as statistically significant level.

Sample size calculation

The sample size of this study was calculated using the standard sample size formula (represented in Equation 1). The study of Shakhawat *et al.* was considered as the basic study to determine the sample size of our study with the predetermined power and level of significance. Considering the power of 85 percent and for confidence interval of 95 percent, the sample size of this study is 22 patients. We will use 25 patients in each group so that future attrition of the patients due to long term period of the tDCS sessions will be compromised.

$$n = \frac{(z_{1-\alpha/2} + z_{1-\beta})^2 (S_1^2 + S_2^2)}{(\bar{X}_1 - \bar{X}_2)^2} \quad \text{Equation 1}$$

Discussion

Recent studies have shown beneficial effects of tDCS in improving cognitive functions in healthy individuals⁷ and also symptoms of different neuropsychiatric disorders such as depression⁸, obsessive compulsive disorder⁹, auditory-verbal hallucinations¹⁰, and chronic pain¹¹. The therapeutic effects of tDCS in tinnitus have been reported by several studies; however, the findings are heterogeneous and controversial. In addition, most of the conducted studies have focused on single session tDCS, with short follow-up periods ranging some hours, to a few days^{13,16,33}. The present study aims to investigate the therapeutic efficacies of repeated sessions of bilateral tDCS (anodal/cathodal over the left/right AC) on tinnitus symptoms, its loudness, and distress in patients with intractable chronic tinnitus. The main advantage of this study is that it is a double blinded which will remove the placebo effects of the tDCS. The other main advantage of this study is the one month follow-up which is relatively long period, compared to the previous studies. Moreover, we aim to evaluate the possible interactions between the disease specific features and treatment response to develop a more specific and disease oriented tDCS protocol. To our knowledge this will be the first study of repeated sessions of tDCS with one month follow-up. Considering the repeated sessions of tDCS in this study, we will investigate the AEs of and tolerability of the patients in this study.

Trial status

To date, the enrollment of the patients has been performed and the allocation will be performed in the near future. The study is supposed to be started in end of January and finished in August 2018.

Supplementary materials

Supplementary File 1: The customized questionnaire of adverse effects of and tolerability to Transcranial Direct Current Stimulation (tDCS). The assessments of AEs and tolerability will be performed during and after each session.

[Click here to access the data.](#)

Dissemination of findings

The data collection of this study is supposed to be completed August 2018 and the results of this trial will be communicated to the external funding body through a formal report. In addition, the trial results will be communicated to the public through publishing as dataset and original research in the relevant scientific journals. There is no limit in the publication of the trial results.

Data availability

All data underlying the results are available as part of the article and no additional source data are required

Competing interests

The authors declare that they have no competing interests.

Grant information

This study is financially supported by Ahvaz Jundishapur University of Medical Sciences (AJUMS), Ahvaz, Iran (Grant No: HRC-9409). The AJUMS has no role in the design of the study, collection of data, analyses, and interpretation of data as well as in composing the manuscript. It, as the external funding body has reviewed the study in a double blinding peer review policy and it was approved by the editorial board member of the University.

The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Acknowledgements

The authors would like to thank the staff of the Khuzestan cochlear center, Ahvaz, Iran for their assistance in performing the audiometric assessments.

References

- Sanchez L: **The epidemiology of tinnitus.** *Audiol Med.* 2004; **2**(1): 8–17. [Publisher Full Text](#)
- Eggermont JJ: **Pathophysiology of tinnitus.** *Prog Brain Res.* 2007; **166**: 19–35. [PubMed Abstract](#) | [Publisher Full Text](#)
- Vanneste S, Plazier M, der Loo Ev, *et al.*: **The neural correlates of tinnitus-related distress.** *Neuroimage.* 2010; **52**(2): 470–80. [PubMed Abstract](#) | [Publisher Full Text](#)
- khoramzadeh S, Saki N, Davoodi I, *et al.*: **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**(6): 982–92. [Publisher Full Text](#)
- Langguth B, Kreuzer PM, Kleinjung T, *et al.*: **Tinnitus: causes and clinical management.** *Lancet Neurol.* 2013; **12**(9): 920–30. [PubMed Abstract](#) | [Publisher Full Text](#)
- Hobson J, Chisholm E, El Refaie A: **Sound therapy (masking) in the management of tinnitus in adults.** *Cochrane Database Syst Rev.* 2010; (12): CD006371. [PubMed Abstract](#) | [Publisher Full Text](#)
- Yadollahpour A, Asl HM, 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**(1): 311–6.
[Publisher Full Text](#)
8. 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**(2): 434–43. [cited 2017 Mar 24].
[Publisher Full Text](#)
 9. Mondino M, Haesebaert F, Poulet E, *et al.*: **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**(4): 271–2.
[PubMed Abstract](#) | [Publisher Full Text](#)
 10. Shiozawa P, da Silva ME, Cordeiro Q, *et al.*: **Transcranial direct current stimulation (tDCS) for the treatment of persistent visual and auditory hallucinations in schizophrenia: a case study.** *Brain Stimul.* 2013; **6**(5): 831–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 11. Kuo MF, Paulus W, Nitsche MA: **Therapeutic effects of non-invasive brain stimulation with direct currents (tDCS) in neuropsychiatric diseases.** *Neuroimage.* 2014; **85 Pt 3**: 948–60.
[PubMed Abstract](#) | [Publisher Full Text](#)
 12. Hyvärinen P, Mäkitie A, Aarnisalo AA: **Self-Administered Domiciliary tDCS Treatment for Tinnitus: A Double-Blind Sham-Controlled Study.** *PLoS One.* 2016; **11**(4): e0154286.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 13. Joos K, De Ridder D, Van de Heyning P, *et al.*: **Polarity Specific Suppression Effects of Transcranial Direct Current Stimulation for Tinnitus.** *Neural Plast.* 2014; **2014**: 930860, 1–8. [cited 2017 Jun 1].
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 14. Shekhawat GS, Sundram F, Bikson M, *et al.*: **Intensity, Duration, and Location of High-Definition Transcranial Direct Current Stimulation for Tinnitus Relief.** *Neurorehabil Neural Repair.* 2016; **30**(4): 349–59. [cited 2017 Jun 1].
[PubMed Abstract](#) | [Publisher Full Text](#)
 15. Forogh B, Mirshaki Z, Raisi GR, *et al.*: **Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: a pilot randomized controlled trial.** *Neurol Sci.* 2016; **37**(2): 253–9.
[PubMed Abstract](#) | [Publisher Full Text](#)
 16. Frank E, Scheckmann M, Landgrebe M, *et al.*: **Treatment of chronic tinnitus with repeated sessions of prefrontal transcranial direct current stimulation: outcomes from an open-label pilot study.** *J Neurol.* 2012; **259**(2): 327–33.
[PubMed Abstract](#) | [Publisher Full Text](#)
 17. Vanneste S, Focquaert F, Van de Heyning P, *et al.*: **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**(2): 217–27.
[PubMed Abstract](#) | [Publisher Full Text](#)
 18. Shekhawat GS, Stinear CM, Searchfield GD: **Modulation of Perception or Emotion? A Scoping Review of Tinnitus Neuromodulation Using Transcranial Direct Current Stimulation.** *Neurorehabil Neural Repair.* 2015; **29**(9): 837–46. [cited 2017 Jun 1].
[PubMed Abstract](#) | [Publisher Full Text](#)
 19. Yadollahpour A, Bayat A, Rashidi S, *et al.*: **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.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 20. Vanneste S, De Ridder D: **Bifrontal transcranial direct current stimulation modulates tinnitus intensity and tinnitus-distress-related brain activity.** *Eur J Neurosci.* 2011; **34**(4): 605–14. [cited 2017 Jun 3].
[PubMed Abstract](#) | [Publisher Full Text](#)
 21. Elgoyhen AB, Langguth B, De Ridder D, *et al.*: **Tinnitus: perspectives from human neuroimaging.** *Nat Rev Neurosci.* 2015; **16**(10): 632–42.
[PubMed Abstract](#) | [Publisher Full Text](#)
 22. De Ridder D, Fransen H, Francois O, *et al.*: **Amygdalohippocampal involvement in tinnitus and auditory memory.** *Acta Otolaryngol Suppl.* 2006; **126**(sup556): 50–3.
[PubMed Abstract](#) | [Publisher Full Text](#)
 23. Paulus W: **Transcranial direct current stimulation (tDCS).** *Suppl Clin Neurophysiol.* 2003; **56**: 249–54.
[PubMed Abstract](#)
 24. Boggio PS, Rigonatti SP, Ribeiro RB, *et al.*: **A randomized, double-blind clinical trial on the efficacy of cortical direct current stimulation for the treatment of major depression.** *Int J Neuropsychopharmacol.* 2008; **11**(2): 249–54. [cited 2017 Jun 7].
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)
 25. General Assembly of the World Medical Association: **World Medical Association Declaration of Helsinki: ethical principles for medical research involving human subjects.** *J Am Coll Dent.* 2014; **81**(3): 14–8. [cited 2017 Jun 28].
[PubMed Abstract](#)
 26. Poreisz C, Boros K, Antal A, *et al.*: **Safety aspects of transcranial direct current stimulation concerning healthy subjects and patients.** *Brain Res Bull.* 2007; **72**(4–6): 208–14.
[PubMed Abstract](#) | [Publisher Full Text](#)
 27. Lloyd LL, Kaplan H: **Audiometric interpretation: a manual of basic audiometry.** University Park Press; 1: 1978.
[Reference Source](#)
 28. American Speech-Language-Hearing Association: **Guidelines for manual pure-tone threshold audiometry.** 2005.
[Reference Source](#)
 29. Newman CW, Jacobson GP, Spitzer JB: **Development of the tinnitus handicap inventory.** *Arch Otolaryngol Head Neck Surg.* 1996; **122**(2): 143–8.
[PubMed Abstract](#) | [Publisher Full Text](#)
 30. Shekhawat GS, Stinear CM, Searchfield GD: **Transcranial Direct Current Stimulation Intensity and Duration Effects on Tinnitus Suppression.** *Neurorehabil Neural Repair.* 2013; **27**(2): 164–72. [cited 2017 Jun 1].
[PubMed Abstract](#) | [Publisher Full Text](#)
 31. Vanneste S, Plazier M, Ost J, *et al.*: **Bilateral dorsolateral prefrontal cortex modulation for tinnitus by transcranial direct current stimulation: a preliminary clinical study.** *Exp Brain Res.* 2010; **202**(4): 779–85.
[PubMed Abstract](#) | [Publisher Full Text](#)
 32. Vanneste S, Heyning PV, Ridder DD: **Contralateral parahippocampal gamma-band activity determines noise-like tinnitus laterality: a region of interest analysis.** *Neuroscience.* 2011; **199**: 481–90.
[PubMed Abstract](#) | [Publisher Full Text](#)
 33. Garin P, Gilain C, Van Damme JP, *et al.*: **Short- and long-lasting tinnitus relief induced by transcranial direct current stimulation.** *J Neurol.* 2011; **258**(11): 1940–8.
[PubMed Abstract](#) | [Publisher Full Text](#) | [Free Full Text](#)

Open Peer Review

Current Referee Status:  

Version 1

Referee Report 04 April 2018

doi:[10.5256/f1000research.14726.r32356](https://doi.org/10.5256/f1000research.14726.r32356)



Daniel Robles-Camarillo

Graduate and Research Department, Polytechnic University of Pachuca, Zempoala, Hidalgo, Mexico

1. Summary

This protocol aims to research the therapeutic effect of tDCS, adverse effects and tolerability of bilateral tDCS over auditory cortex on tinnitus symptoms, applied on a very specific group of patients with intractable chronic tinnitus. It is proposed an interesting a double blinded experiment with three patient groups that consider the electrodes allocation: cathodal, anodal, or placebo. The three groups will be matched for age, gender, ethnicity, and audiometric main characteristics.

It is a novel treatment of daily 20-min sessions for five consecutive days per week and for 2 consecutive weeks. It is very well described the inclusion-exclusion criteria, the selection of patients' groups and the analysis of electrophysiological and subjective findings, which are done by statistical methods. Authors consider baseline evaluations, hearing assessment, primary and secondary outcomes. In difference to other studies, authors gave one-month follow-up period, in order to study the AEs of and tolerability of the patients

2. General comments

Protocol design: the inclusion and exclusion criteria are well structured. Pre-treatment complete audiometric and neurologic examinations by experienced specialists was a good establishment. The balanced random allocation performed by cards using computer-generated random numbers, is a good idea, because it considers the age, gender, ethnicity, and audiometric main characteristics. As a part of a larger experiment, final results will be deterministic in intractable tinnitus treatment. The sample size may be greater than $n=90$, to improve the statistical significance

3. Constructive criticism

It should be very interesting if authors show their data in corresponding plots to clearly visualize the patients' distribution, electrophysiological and subjective readings and findings, pre- and post-treatment. This study purposes the application of tDCS electric parameters. Authors use a specific device (by Mind Alive Inc.), it will be desirable if they show the precise electrical plot parameters (voltage, current, power and frequency) against time, performed with this device used.

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.**I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.**

Referee Report 23 March 2018

doi:[10.5256/f1000research.14726.r31942](https://doi.org/10.5256/f1000research.14726.r31942)**Leonid S. Godlevsky** 

Ministry of Public Health, Odessa National Medical University, Odessa, Ukraine

Proposed protocol of investigation aims for the clinical effectiveness of tDCS in patients suffered from resistant to current therapy tinnitus assessment. Both cathode and anode role is in interest to verify based on the double blind method exploration.

Hence, one month follow up along with filtering informative data from placebo effects and identification of adverse effects of tDCS are advantages of this protocol. Besides, two daily trials of tDCS during 5 days also points on the novelty of approach on the way of therapeutic potential of tDCS estimation in patients suffered from tinnitus.

Such advantages of the protocol correspond to perfectly described methods, design, criteria on inclusion and exclusion, study protocol and outcomes assessments. Technology of tDCS is clear and reliable; all steps are controlled by researches. Statistical assessments are explicit for data gained in observations. Authors carefully consider all adverse effects which might encounter in tDCS delivering and must identify in their investigation.

THI along with distress level will be used for the evaluation of the clinical effectiveness of tDCS. Meanwhile, background of the project contains data on quality of life (QL) worsening of patients with tinnitus. Despite QL is in good correlation with distress [1], it could be interesting to hear why just only distress was in scope and QL was not. QL was investigated by others cited authors just for estimation effectiveness of tinnitus treatment (N4 from list of literature- Khoramzadeh S. et al., 2016). The same question is for other disturbances mentioned in background chapter – such as sleep deteriorations, anxiety and depression development.

It would be of worth to delineate criteria on resistance of patients suffered from tinnitus. Thus, it is interesting to hear details on their negative experience during previous drug treatment.

Some notions on electrodes planned to use rose. In accordance to protocol the location of electrodes corresponds to 10-20 system of EEG electrode location. It is not enough for better imagine of the brain structures topography affected with your stimulations. Shape of electrodes is also important with such

respect. Besides due to a flexibility of large electrodes the problem on non uniformity of currents under 3D electrodes leads to the increase of risks of burning of underlying tissues [2]. Hence, explanations on avoiding this problem are quite desirable. Also manufacturer of electrodes should be mentioned.

It should to note that authors [3] did not use intensity of current higher than 1.5 mA when delivered stimulations through 35 cm² electrodes and emphasized on adverse effects of tDCS. What is the reason for treating patients with higher intensity of electric current in your protocol? Parameters and regimes of planned interventions should have better ground. Namely, why you have justified 10 sessions? Is it settled for other brain pathology treatment?

30 s period, which is planned to use for sham-stimulated patients might be distinguishable by them in the course of delivering 10 trials. Hence, proposed control via asking patients if they know what type of influence is going on looks rather reliable procedure for verifying blind type of investigation. But it should be mentioned if the moment of turning of stimulator was soundless or not, just for prevention patients training for the distinguishing between types of stimulation.

General conclusion is that description of protocol on the tDCS treatment of patients suffered from tinnitus is rather convincing and deserves publication in highly ranked journal. Above mentioned minor remarks do not make serious impact upon very positive general estimation of proposed protocol of investigations. New and promising alternative for patients with tinnitus treatment is expected as result of its realization.

References

1. Hoffmann K, Kamp M, Steiger HJ, Sabel M, Rapp M: Correlation of psychooncological distress-screening and quality of life assessment in neurosurgical patients. *Oncotarget*. 2017; **8** (67): 111396-111404 [PubMed Abstract](#) | [Publisher Full Text](#)
2. Lenninger M, Froeis T, Scheiderbauer M, Grabher G, Bechtold T: High current density 3D electrodes manufactured by technical embroidery. *Journal of Solid State Electrochemistry*. 2013; **17** (8): 2303-2309 [Publisher Full Text](#)
3. Turi Z, Ambrus GG, Ho KA, Sengupta T, Paulus W, Antal A: When size matters: large electrodes induce greater stimulation-related cutaneous discomfort than smaller electrodes at equivalent current density. *Brain Stimul*. **7** (3): 460-7 [PubMed Abstract](#) | [Publisher Full Text](#)

Is the rationale for, and objectives of, the study clearly described?

Yes

Is the study design appropriate for the research question?

Yes

Are sufficient details of the methods provided to allow replication by others?

Yes

Are the datasets clearly presented in a useable and accessible format?

Yes

Competing Interests: No competing interests were disclosed.

Referee Expertise: Neurophysiology

I have read this submission. I believe that I have an appropriate level of expertise to confirm that it is of an acceptable scientific standard.

The benefits of publishing with F1000Research:

- Your article is published within days, with no editorial bias
- You can publish traditional articles, null/negative results, case reports, data notes and more
- The peer review process is transparent and collaborative
- Your article is indexed in PubMed after passing peer review
- Dedicated customer support at every stage

For pre-submission enquiries, contact research@f1000.com

F1000Research