

Repeated sessions of transcranial direct current stimulation for treatment of chronic subjective tinnitus: a pilot randomized controlled trial

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Abstract Subjective tinnitus is an auditory phantom sensation characterized by the perception of sound in the absence of an identifiable external source. This distressing audiological symptom can severely affect the quality of life. Transcranial direct current stimulation (tDCS) is a noninvasive technique that can induce short-term relief in tinnitus in some patients. The purpose of this pilot double-blind randomized controlled trial was to investigate whether repeated application of anodal tDCS over left temporoparietal area could induce long-lasting relief in patients with chronic tinnitus. Twenty-two patients with chronic tinnitus for at least 6 months were randomly allocated into two groups and received five sessions of anodal ($N = 11$) or sham ($N = 11$) stimulation in five consecutive days. A current intensity of 2 mA for 20 min was used for anodal stimulation. Outcomes were assessed using Persian version of tinnitus handicap inventory (THI), loudness and distress visual analog scale (VAS) scores and clinical global impression (CGI) scale. The trial is registered at the Iranian Registry of Clinical Trials (IRCT) with the reference ID of IRCT2014082018871N1. No statistically significant difference was found between anodal and sham stimulation regarding either immediate or long-lasting

effects over the 2 weeks follow-up period. Deterioration of symptoms and alteration in tinnitus characteristics were reported by a few patients. There were no significant long-term beneficial effects following tDCS of the left temporoparietal area.

Keywords Tinnitus · Treatment · Transcranial direct current stimulation · tDCS · Temporoparietal area · Neuromodulation

Introduction

Subjective tinnitus is an auditory phantom sensation characterized by the perception of sound in the absence of an identifiable external source. This distressing audiological symptom is experienced by 15–20 % of adults and severely affects the quality of life in 1 % of population [1]. Currently no efficient evidence-based treatment option is available for this disabling condition. Although the precise pathophysiologic mechanism of tinnitus is not currently revealed, it is hypothesized that tinnitus perception results from maladaptive plastic changes involving a wide network of cortical and subcortical brain areas [2]. Few neuroimaging studies have documented an overactivation of left temporoparietal area in tinnitus patients. Considering the fact that tinnitus is frequently accompanied by hearing loss, it is postulated that deafferentation of peripheral input from auditory system may trigger such plastic changes [3]. The discovery of such abnormal cortical excitability leads to the formation of the novel hypothesis that tinnitus symptoms may be relieved by modulating the activity of malfunctioned brain structures. Consistent with this notion, invasive and noninvasive neuromodulation techniques such as implantable cortical electrodes, transcranial magnetic

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stimulation (TMS) and transcranial direct current stimulation (tDCS) were used [2]. Single sessions of TMS were used to induce transient tinnitus suppression [3, 4]. To achieve a longer lasting relief. This short-term beneficial effect was successfully extended using repeatedly applied TMS [5, 6].

tDCS uses a weak direct electrical current which is usually delivered via two surface electrodes. The modulating effect of tDCS depends on the polarity of stimulation; while anodal tDCS increases the excitability of the underlying cortex by depolarizing neurons, cathodal tDCS causes hyperpolarization and hence induces inhibition [2]. Early studies showed that a single session of tDCS applied over either left temporoparietal area or bilateral dorsolateral prefrontal cortex (DLPFC) can induce transient relief of tinnitus in some patients [2, 3, 7, 8]. Two sham-controlled trials investigating single sessions of anodal or cathodal stimulation of left temporoparietal area found that the anodal stimulation is the most effective one; however, suppression of tinnitus was partial and transient [2, 3]. The purpose of this study is to investigate if repeated sessions of anodal tDCS over left temporoparietal area induce longer lasting relief of symptoms in patients with chronic tinnitus.

Materials and methods

Subjects

Patients over age of 18 with chronic tinnitus for at least 6 months were included in the study. Exclusion criteria were as follows: fluctuating audition, Meniere disease, history of traumatic brain injury, epilepsy, intake of ototoxic, antipsychotic and antiepileptic medications, tricyclic antidepressants or benzodiazepines within 1 month prior to the study, previous experience of receiving tDCS, cochlear implants, cardiac pacemakers and pregnancy.

The study protocol was approved by the local ethics committee at Iran University of Medical Sciences and performed in accordance with the ethical standards of the Helsinki Declaration. The procedure was explained to the patients and written informed consent was signed by all patients before participation in the study. The trial is registered at the Iranian Registry of Clinical Trials (IRCT) with the reference ID IRCT2014082018871N1.

Study design

This double-blind sham-controlled trial investigated the efficacy of multisession anodal tDCS of left temporoparietal area to treat tinnitus.

Patients were allocated into real or sham treatment groups using a simple randomization method. Participants and rater were both blinded to the treatment. Patients were told that they may receive active or sham stimulation. Each patient received five sessions of stimulation in five consecutive days.

Procedure

Eleven patients were assigned to active treatment group and 11 patients to sham treatment group. For all patients irrespective of tinnitus laterality, the anode electrode was positioned over left temporoparietal area that is localized as halfway between C3 and T5 using international 10–20 electroencephalogram system. The cathode electrode was placed over right supraorbital area.

Direct electrical current was generated by a battery-driven direct current stimulator (Activadose II) with a maximum current output of 4 mA and was transmitted through two pairs of 35 CM2 rubber electrodes covered with 0.9 % saline soaked sponges.

In both conditions the direct current was ramped up to 2.0 mA within 30 s. Patients in anodal tDCS group received 20 min of stimulation with a current intensity of 2 mA. In sham condition, after the initial ramp-up, the current was directly ramped down to 0, as patients felt a tingling sensation at the beginning and received no more stimulation in the remaining time of the session. The ramp-down time was 4 s in both conditions. The stimulator was placed behind and out of sight of the patients.

Evaluation

CGI (clinical global impression) scale was used as the primary outcome measure to evaluate the global change in tinnitus. CGI is rated from 1 to 7 where 4 is no change; 5 is minimally worse; 6 is much worse; 7 is very much worse; 3 is minimally better; 2 is much better and 1 is very much better. CGI score was rated after each session, after completion of treatment and 2 weeks after last session of treatment. Patients with CGI score of 3 or less were considered as responders.

Visual analogue scales were used to evaluate tinnitus loudness and distress [9].

Tinnitus loudness was rated using a 10-point Visual Analogue Scale (VAS), where 0 is no tinnitus and 10 is tinnitus as loud as possible. Loudness of tinnitus was rated in the more symptomatic ear and in the cases with similar intensity in both ears; it was rated in right ear (contralateral to the stimulation site).

Tinnitus-related distress was rated using a 10-point VAS, where 0 is no distress and 10 is suicidal quality of distress.

The Persian version of tinnitus handicap inventory (THI) was used to evaluate the patients before initiation of treatment, immediately after and 2 weeks after completion of intervention [10].

Statistical analysis

Analysis was performed using SPSS22 software. Baseline characteristics of patients were compared between two groups using independent samples *t* test for continuous variables and Chi square test for qualitative variables.

Loudness and distress VAS scores, before and immediately after each session were compared to evaluate the immediate effects of anodal tDCS. Paired samples *t* test and independent *t* test were, respectively, used for within-subject and between-subject analyses of VAS score changes.

To investigate the long-term effect of tDCS on VAS and THI scores, a repeated measures analysis of variances (ANOVA) was carried out across three time points; at baseline, after completion of intervention (day 5) and at 2 weeks follow-up session.

Mann–Whitney *U* test was performed to compare CGI scores between groups after completion of intervention and at follow-up session.

Results

Twenty-two patients with chronic tinnitus (14 males and 8 females) were recruited in this study with a mean age of 48.22 ranging 26–80 years. Two patients discontinued participation in the study; one patient in active treatment group due to worsening of tinnitus after the first session and one patient in sham treatment group due to personal reasons. 20 patients completed the study.

Comparison of baseline clinical and demographic characteristics of patients revealed no statistically significant difference between two groups at the time of enrollment. Tinnitus characteristics and demographics of patients are summarized in Table 1.

Within group analysis of loudness and distress VAS scores using paired samples *t* test revealed no statistically significant reduction in VAS scores immediately after each session in neither group. Likewise, the results of independent samples *t* test failed to show any significant difference between two groups following each single treatment session (Tables 2, 3).

A repeated measures ANOVA was conducted with tinnitus loudness VAS scores across three time points (at baseline, immediately after fifth session and 2 weeks after fifth session) as within-subject variable and stimulation type (sham versus anodal) as between-subject variable. The

same analysis was performed for tinnitus-related distress VAS scores and THI scores. As the results of Mauchly's sphericity test showed that the sphericity assumption is violated, the degree of freedom of the *F* distribution was adjusted using the Greenhouse-Geisser correction. The results of repeated measures ANOVA did not prove any significant interaction between time and stimulation type, regarding tinnitus loudness ($F_{(1.5,27.3)} = 0.4$, $P = 0.585$); tinnitus-related distress ($F_{(1.2,22.8)} = 1.2$, $P = 0.297$) and THI scores ($F_{(1.2,22.2)} = 0.1$, $P = 0.807$), indicating that anodal tDCS was no more effective than sham stimulation. The main effects of time and stimulation type were also nonsignificant (Table 4).

The results of Mann–Whitney *U* test elicited a borderline, still nonsignificant difference between two groups after fifth session ($P = 0.054$). However, the difference did not persist at 2 weeks follow-up ($P > 0.9999$). Table 5 provides the details of CGI scale scores.

There were five responders in anodal tDCS group as compared to two responders in sham stimulation group after completion of intervention (day 5). Three patients in anodal tDCS group and one patient in sham tDCS group reported improvement of symptoms at 2 weeks follow-up. Most responders reported a CGI score of 3 (minimally better). One participant reported a CGI score of 2 (much better) after completion of treatment with anodal stimulation; even in this case no improvement were seen at follow-up session (Table 5).

Of note there were reports of tinnitus worsening in both active and sham treatment groups: 4 out of 11 patients experienced worsening of symptoms following application of active anodal tDCS. One patient discontinued the intervention after the first session. Three patients experienced worsening of tinnitus within few days after completion of the intervention; in one patient the severity of tinnitus returned to baseline within 5 weeks, however, in two patients, mild deterioration of symptoms was persistent at least 19 weeks after the intervention.

Two patients experienced changes in the quality of their tinnitus following active tDCS. One patient reported that her tinnitus was “more obvious” than usual. Another patient developed a new tinnitus perception superimposed on his previous tinnitus. Two patients in sham treatment group also mentioned mild worsening of their tinnitus at follow-up session.

Discussion

The purpose of this pilot study was to investigate whether repeated application of tDCS over left temporoparietal area could induce long-lasting relief in patients with chronic tinnitus. Therefore, the effect of multisession tDCS on

Table 1 Clinical and demographic characteristics of patients

Variable	Anodal tDCS group	Sham tDCS group	<i>P</i> value
Age	49.81 ± 4.14	46.63 ± 5.26	0.640
Gender			>0.999
Male	7 (63.6 %)	7 (63.6 %)	
Female	4 (36.4 %)	4 (36.4 %)	
Duration of symptoms (years)	9 ± 3.67	6.54 ± 1.44	0.539
Tinnitus laterality			
Right	3 (27.3 %)	0 (0 %)	0.131
Left	1 (9.1 %)	3 (27.3 %)	
Bilateral	7 (63.6 %)	8 (72.7 %)	
Hearing threshold			
Right ear	25.3 ± 5.3	35.3 ± 9.16	0.357
Left ear	21.4 ± 5.2	41.5 ± 10.8	0.107

Data are presented as mean ± standard deviation for continuous variables and number (%) for qualitative variables

Table 2 Immediate changes in tinnitus loudness VAS score following each session

	Condition	Pretreatment VAS scores	Posttreatment VAS scores	<i>P</i> value of paired <i>t</i> test	<i>P</i> value of independent <i>t</i> test
Session1	Sham	5.2 ± 2.5	4.7 ± 3.1	0.215	0.703
	Anodal	5.3 ± 2.6	4.9 ± 2.6	0.172	
Session2	Sham	5.0 ± 2.7	4.9 ± 2.6	0.563	0.284
	Anodal	4.9 ± 2.6	5.2 ± 2.2	0.382	
Session3	Sham	5.1 ± 2.3	5.1 ± 2.4	0.758	0.773
	Anodal	4.9 ± 2.1	4.8 ± 2.1	0.168	
Session4	Sham	5.1 ± 2.4	5.1 ± 2.5	>0.999	0.177
	Anodal	5.1 ± 2.2	4.9 ± 2.2	0.081	
Session5	Sham	5.0 ± 2.4	5.0 ± 2.4	Error ^a	0.193
	Anodal	4.9 ± 2.3	4.8 ± 2.2	0.193	

Data are presented as mean ± standard deviation

^a Error because the standard error of the difference is 0

Table 3 Immediate changes in tinnitus-related distress VAS score following each session

	Condition	Pretreatment VAS scores	Posttreatment VAS scores	<i>P</i> value of paired <i>t</i> test	<i>P</i> value of independent <i>t</i> test
Session 1	Sham	4.7 ± 2.3	4.3 ± 2.4	0.104	0.223
	Anodal	5.6 ± 2.5	5.5 ± 2.4	0.167	
Session 2	Sham	4.5 ± 2.4	4.5 ± 2.4	Error ^a	0.343
	Anodal	5.5 ± 2.4	5.4 ± 2.6	0.343	
Session 3	Sham	4.4 ± 2.0	4.3 ± 2.2	0.343	0.660
	Anodal	5.1 ± 2.4	5.1 ± 2.3	0.343	
Session 4	Sham	4.5 ± 2.0	4.5 ± 2.1	0.343	0.343
	Anodal	5.1 ± 2.2	5.1 ± 2.2	Error ^a	
Session 5	Sham	4.5 ± 1.9	4.5 ± 1.9	Error ^a	0.193
	Anodal	5.2 ± 2.2	5.0 ± 2.1	0.193	

Data are presented as mean ± standard deviation

^a Error because the standard error of the difference is 0

Table 4 Changes of tinnitus loudness VAS score, tinnitus-related distress score and THI score from baseline to the end of intervention course and follow-up session

Variable	Tinnitus loudness VAS score		Tinnitus-related distress VAS score		THI score	
	Anodal	Sham	Anodal	Sham	Anodal	Sham
Baseline	5.3 ± 2.6	5.2 ± 2.5	5.6 ± 2.5	4.7 ± 2.3	58.6 ± 28.1	53.7 ± 20.0
After fifth session	4.8 ± 2.2	5.0 ± 2.4	5.0 ± 2.1	4.5 ± 1.9	58.6 ± 28.1	54.1 ± 24.9
2 weeks follow up	5.1 ± 2.5	4.8 ± 2.8	5.0 ± 2.2	4.2 ± 2.4	55.8 ± 23.2	53.4 ± 30.9
<i>P</i> value (time-stimulation interaction)	$F(1.5,27.3) = 0.4$ $P = 0.585$		$F(1.2,22.8) = 1.2$ $P = 0.297$		$F(1.2,22.2) = 0.1$ $P = 0.807$	
<i>P</i> value (main effect of time)	$F(1.5,27.3) = 0.6$ $P = 0.475$		$F(1.2,22.8) = 0.7$ $P = 0.431$		$F(1.2,22.2) = 0.2$ $P = 0.708$	
<i>P</i> value (main affect of stimulation)	$F(1,18) = 0.002$ $P = 0.964$		$F(1,18) = 0.9$ $P = 0.339$		$F(1,18) = 0.12$ $P = 0.729$	

Data are presented as mean ± standard deviation

Table 5 CGI scores of patients

Condition	Sham										Anodal											
	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22
Patient	P1	P2	P3	P4	P5	P6	P7	P8	P9	P10	P11	P12	P13	P14	P15	P16	P17	P18	P19	P20	P21	P22
CGI score	4	4	5	3	5	3	4	4	4	5	^a	4	4	3	3	4	4	3	2	3	4	^b
5 days follow up	5	4	5	1	4	4	4	4	4	4		4	4	6	3	5	3	3	4	6	4	

^a Dropped out after second session; she was minimally better at the end of first session but reported no change after the second session

^b Dropped out after first session; the patient reported no change immediately after completion of first session; however, she experienced worsening of tinnitus within few hours from stimulation

severity of tinnitus was compared between active anodal and sham stimulation. The current intensity of 2 mA for 20 min was chosen according to the results of the study by Shekhawat et al. [11].

The early controlled trials that investigated the tinnitus-suppressing potential of tDCS mostly focused on immediate effects. Anodal stimulation of LTA resulted in a significant reduction in tinnitus compared to sham stimulation, while cathodal tDCS did not; an observation seemingly contradictory to the excitatory properties of anodal tDCS [2, 3]. This finding was explained, to some extent, based on focality of tDCS. Since rubber electrodes as large as 35 cm² were used for applying tDCS, a large area of neural network involved in tinnitus perception has possibly been stimulated; therefore, excitation of surrounding cortical areas might decrease abnormal spontaneous activity of involved areas through inhibitory connections [3]. Joos et al. [12] conducted a study investigating the polarity specific effect of tDCS on tinnitus loudness and annoyance. There was significant reduction in tinnitus loudness following both anodal and cathodal stimulation of left auditory cortex. However, anodal

stimulation was significantly more effective for tinnitus annoyance. It was hypothesized that tDCS of auditory cortex, irrespective of the polarity of stimulation, may disrupt ongoing neural hyperactivity and lead to the suppression of tinnitus loudness.

Another study by Vanneste et al. [13] did not show any significant reduction in tinnitus symptoms following a single session of tDCS over bilateral auditory cortices. This trial was not sham controlled, however.

There are also trials that provide auditory stimulation along with tDCS [14–16]. A study by Shekhawat et al., investigating the additive effect of auditory residual inhibition and tDCS of LTA, showed nonsignificant beneficial effects from simultaneous application of acoustic and electrical stimulation [14].

Two sham-controlled multisession studies have evaluated the long-term tinnitus-suppressing effect of tDCS in combination with some forms of sound therapy [15, 16].

An uncontrolled study by Frank et al. investigating the effectiveness of prefrontal tDCS in the treatment of tinnitus reported some positive long-term results [17].

A multisession controlled trial using cathodal stimulation of auditory cortex with anode over prefrontal cortex found no beneficial effect of tDCS on tinnitus. [18].

This research is the first, to this date, to investigate the long-term tinnitus-relieving potentials of anodal stimulation of left temporoparietal area without combination of other concurrent interventions that may interact with neuromodulating properties of tDCS. The results of this study revealed a slight reduction in tinnitus severity following anodal tDCS that never reached the level of statistical significance and was not clinically significant as well. Our findings, especially regarding immediate effects, seem rather inconsistent with the results of early studies [2, 3]. This difference might be due to small sample size as well as different study designs. The results of multisession studies are in more accordance with our findings. Teismann et al. [15] evaluated the efficacy of repeated sessions of transcranial stimulation of left auditory cortex in combination with Tailor-Made Notched Music Training; a novel treatment option for chronic tinnitus, considered as an acoustic neuromodulation technique. The results of their study did not prove any significant difference between anodal, cathodal or sham stimulation. The study of Shekhawat et al. [16] investigated the ability of repeatedly applied anodal tDCS of left temporoparietal area to enhance the efficacy of treatment with hearing aids. The results of their study elicited a positive effect of anodal tDCS on minimum masking level. However, the reduction in tinnitus functional index questionnaire did not significantly differ in anodal and sham stimulations. Considering the fact that tinnitus is a subjective perception, it is not surprising that our measurements of tinnitus severity are almost quite subjective. Indeed, mild subclinical changes may occur following tDCS of left temporoparietal area that might not be detected using subjective outcome measures. The susceptibility of such subjective measures to missing small changes probably accounts for disparity between the results of minimum masking level and questionnaire responses in the study of Shekhawat et al. [16].

The results of the present research are discussible from two standpoints. The first is clinical usefulness of the stimulation parameters used in the study. As mentioned, the reduction in severity of tinnitus was not only statistically nonsignificant, but also clinically negligible. Indeed, for those who positively responded to tDCS, the reported improvements were almost always minimal. Lack of considerable clinical importance is probably the most noticeable finding that questions the clinical usage of this stimulation protocol.

The second question arises as to whether transcranial direct current stimulation of brain areas involved in tinnitus network can facilitate neural plasticity. As mentioned previously, persistent worsening and altered quality of

tinnitus were reported by some patients following real tDCS even months after the treatment. It should be noted that the follow-up period of the study was 2 weeks and not all patients were followed for that long. Tinnitus worsening was spontaneously reported by patients as a possible adverse effect and it is not clear whether ameliorations reported by responders also lasted for such a long time span. In fact, the follow up period may not be long enough to detect all positive outcomes. Tinnitus worsening following tDCS is per se not an unexpected finding and several studies have already reported aggravation of tinnitus after tDCS of left temporoparietal area [2, 11, 14]. However, such a long-lasting deterioration cannot be attributed to the application of tDCS with certainty. Furthermore, even if worsening of symptoms is assumed to be caused by intervention, it is not against the usefulness of tDCS in tinnitus management; if tDCS has induced such neuroplastic changes that resulted in that prolonged adverse effects, there might be much hope to achieve long-term beneficial effects by optimizing the stimulation parameters. Although the results are somewhat disappointing when it comes to clinical usefulness of the stimulation parameters used in this study, yet our observations support the ability of tDCS in triggering synaptic plasticity in patients with tinnitus. Long-lasting worsening of tinnitus symptoms, development of new tinnitus perception, as well as altered quality of tinnitus following anodal tDCS are consistent with the potential neuromodulating effects of tDCS in tinnitus patients suggested by previous researches.

Considering the fact that this area of tinnitus research is still in its infancy, it is too early to benefit from tDCS as a treatment option for tinnitus in routine practice. Further research is needed to achieve clinically significant effects through optimizing stimulation parameters and also to determine whether responsiveness to tDCS is predictable according to baseline characteristics of tinnitus.

Conclusions

The results of the present study did not show significant long-term beneficial effects from multi-session anodal tDCS of the left temporoparietal area. However, the findings support the ability of tDCS to induce neuromodulation in tinnitus patients. Therefore, it is recommended for future trials to consider modifications in research protocols including longer follow-up periods, looking at baseline characteristics of patients, different stimulation sites, tDCS polarity, duration and intervals of treatment. Furthermore, considering more objective outcome measures, for instance, neuroimaging methods will be of benefit in detection of subclinical changes in cortical excitability.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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