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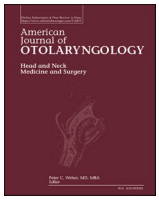

The effectiveness of the combined transcranial direct current stimulation (tDCS) and tailor-made notched music training (TMNMT) on psychoacoustic, psychometric, and cognitive indices of tinnitus patients

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ABSTRACT

Purpose: Tinnitus network(s) consists of pathways in the auditory cortex, frontal cortex, and the limbic system. The cortical hyperactivity caused by tinnitus may be suppressed by neuromodulation techniques. Due to the lack of definitive treatment for tinnitus and limited usefulness of the individual methods, in this study, a combination of transcranial direct current stimulation (tDCS) over the dorsolateral prefrontal cortex (DLPFC) and tailor-made notched music training (TMNMT) was used.

Material and methods: In this descriptive-analytic study, 26 patients with chronic unilateral tinnitus of the right ear were randomly divided into the clinical trial group (CTG) and the control group (CG). In both groups, six sessions of tDCS with 2 mA intensity for 20 min, with anode on F4 and cathode on F3, were conducted. Simultaneous with tDCS sessions, and based on TMNMT, the participant was asked to listen passively for 120 min/day, to a CD containing her/his favorite music with a proper notch applied in its spectrum according to the individual's tinnitus The treatment outcome was measured by, psychoacoustic (loudness-matching), psychometric (awareness, loudness and annoyance Visual Analogue Scale (VAS) scores, and Tinnitus Handicap Inventory (THI)) scores, and cognitive assessments (randomized dichotic digits test (RDDT) and dichotic auditory-verbal memory test (DAVMT)). Repeated measurement test was used for statistical analyses.

Results: In the CTG, the tinnitus loudness and annoyance VAS scores, and THI were reduced significantly ($p = 0.001$). In addition, the DAVMT and RDDT scores were enhanced ($p = 0.001$). Such changes were not observed in the CG ($p > 0.05$).

Conclusion: The combination of tDCS and TMNMT led to a reduction in the loudness, awareness, annoyance, and also disability induced by tinnitus in CTG. Furthermore, this method showed an improvement of cognitive functions (auditory divided attention, selective attention and working memory) in the CTG.

1. Introduction

Subjective tinnitus is the perception of sounds that are absent in the environment, but the auditory system cannot ignore them [3,9]. Estimating the precise prevalence of disorders such as tinnitus, which has no objective manifestation is difficult and may vary depending on the study population [28]. However, according to epidemiologic studies, about 20% of the general population has some form of tinnitus [17], of these; about 90% of patients have some degree of hearing loss [4,10].

Most tinnitus sufferers do not pay attention to it [19], nevertheless, in some cases tinnitus may interfere with sleep and concentration, thus disturbing daily life activities or even cause distress [7]. Despite the extensive studies in recent decades and the growing knowledge in the field of neuroscience, the neural mechanism underlying tinnitus is not completely well-understood yet [28]. Recent perspectives on the pathophysiology of tinnitus are mostly based on the involvement of central mechanisms [20]. It seems that these changes in neural activity are caused by abnormal neuroplasticity activation due to alterations in auditory input, especially auditory deprivation. Such processes can be justified by the homeostasis mechanism; in which neural activity at different levels of the auditory system shows compensatory function and undergoes changes in response to reduced input [20] and induce tinnitus

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in the auditory system.

Perception of tinnitus is not just a simple hearing phenomenon and is not limited to abnormal activities of the auditory cortex (Heschl's gyrus in the superior temporal lobe) [6]; since the mere involvement of the auditory system cannot justify the complications of tinnitus such as distress [5]. The tinnitus network(s) model was introduced to solve this problem. This network(s) consists of pathways in the auditory and, the frontal cortices, and the limbic system and makes the perception and reaction to tinnitus justifiable [6]. Studies using magnetoencephalography (MEG) also indicated some hyperactivities in the auditory cortex and non-auditory structures such as the dorsolateral prefrontal cortex (DLPFC) [24]. Based on the findings, researchers suggested that a change in neural activity and inhibition of hyperactivity in the cortical activity of tinnitus subjects; the perception, distress, and cognitive impairment caused by tinnitus can be modified [24].

Currently, there is no definitive treatment option with the proper long-lasting effect for tinnitus [21], and due to the temporary effects of medical and pharmacological interventions in the management of tinnitus, the tendency to complementary and causal therapies such as sound therapy and neuromodulation has increased [35]. New therapeutic thinking is focused on infrastructure and consequently the conditions that affect onset and continuity of tinnitus. According to a hypothesis by Norena et al. (2011), the reduction of central gain by peripheral stimulation in tinnitus subjects is an alternatives treatment option to conventional methods [29]. In this way, inhibition of tinnitus forming hyperactivity is possible by neuromodulation techniques in forms of physiological with sound stimulation and/or physical with the electrical stimulation.

The transcranial direct current stimulation (tDCS) is one of the most commonly non-invasive neuromodulation methods used over the past decade [23]. The primary mechanism of tDCS is the sub-threshold modulating of resting membrane potential of neurons, which lead to long-term reversible modulation of cortical excitability [14]. The tDCS technique has been widely used for several psychiatric disorders, such as depression, attention deficit hyperactivity disorder (ADHD), tinnitus, etc. Its benefits over the transcranial magnetic stimulation (TMS) are being easier, more cost-effective, better sham control and less acoustic noise [36].

A novel and effective non-invasive neuromodulation technique of the auditory cortex in chronic tinnitus patients is the tailor-made notched music training (TMNMT) [30]. The TMNMT method is based on the hemostasis mechanism and the mechanism of its action is inducing the asynchrony in neural activities by lateral inhibition of neurons coding the notch area of the tinnitus frequency [31], which results in reduction of the auditory cortex hyperactivities [30]. The auditory cortex plays the most important role in the tinnitus network(s) [8]. From this point of view, neuronal hyperactivities of the auditory cortex is assumed to be the probable origin of tinnitus, so it is plausible that modulating the excitatory/inhibitory networks in the auditory cortex and a partial inhibition effect will change the perception of tinnitus [34]. Regarding the tonotopic structure of the auditory cortex neurons, it is logical to reduce the abnormal activity of the affected neurons by stimulation of the auditory system of the sufferers with a piece of tailored music while applying a notch at the tinnitus frequency. In other words, the neurons at the notched region do not receive an excitatory input and thus further receive inhibitory input from the neurons on the edge of the notched area. This may lead to intense suppression of neuronal activity in the notched region [31]. The TMNMT can be used for the chronic tinnitus subjects with tonal tinnitus, hearing thresholds better than 50 dB hearing level (dB HL), 18–60 years range, and the tinnitus frequency less than 8 kHz [33] . Despite the high prevalence of tinnitus, there is no definitive treatment for it. Sound therapy methods, including the music therapy, are generally biological neuromodulation techniques; thus applying it simultaneously with electrical stimulation methods, such as tDCS, may enhance the inhibitory effects. Consequently, this combination may result in more therapeutic effects for tinnitus patients. Gyori (2016) suggested that for the enhancement efficacy of TMNMT, it may be logic to combine it with electrical stimulation techniques, like the tDCS [15]. Due to the lack of definitive treatment for tinnitus and the limited usefulness of the individual methods, in this study, a combination of tDCS over the DLPFC and TMNMT was used in tinnitus patients.

Literature review revealed that tinnitus may have negatively effect on the cognitive functions, in which the auditory divided attention, auditory selective attention and working memory are more affected [27]. In previous studies, psychometric methods have been used mostly to determine the therapeutic outcome. In this study, to explore the probable cognitive impairment of tinnitus subjects, the dichotic auditory-verbal memory test (DAVMT) was implemented to assess the working memory, as well as the randomized dichotic digits test (RDDT) applied to evaluate the auditory divided and selective attention [2,25]. In brief, the aim of this study was to determine the efficacy of the combined bifrontal tDCS and TMNMT on chronic tinnitus, using Persian version of DAVMT and RDDT behavioral tests, Persian version of Tinnitus Handicap Inventory (THI) questionnaire and also the awareness, loudness and annoyance Visual Analogue Scale (VAS), which were conducted pre- and post-intervention in both clinical trial group (CTG) and the control group (CG).

2. Material and methods

In this descriptive-analytic study for enhancement of the quality of treatment, 26 patients with chronic unilateral tinnitus of the right ear that referred to the ear, nose and throat (ENT) and audiology department of Asmaa Rehabilitation Center and Rofeideh Hospital of the University of Social Welfare and Rehabilitation Sciences were enrolled from April 2020 to March 2021. . Participants were randomly divided into the clinical trial group (CTG), including 4 males (30.77%) and 9 females (69.23%), aged 26–56 years with a mean age of 45.77 ± 8.52 years; and the control group (CG), which consists of 8 males (61.54%) and 5 females (38.46%), aged 22–58 years with a mean age of 35.00 ± 11.18 years.

Inclusion criteria were the following: individuals with subjective and idiopathic tinnitus which complaining of it and seeking treatment, chronic tinnitus (six month or more), unilateral tinnitus of the right ear, aged from 18 to 60 years [33], not having obvious cognitive problem based on Persian version of Mini–Mental State Examination (MMSE) [11], hearing threshold less than 50dBHL in 0.25–8 kHz, tonal tinnitus [33], the tinnitus frequency less than 8 kHz [33], right-handed [2], Persian monolinguals [2], Diploma level of education or higher, not using other treatment simultaneously, total score of THI at least 38, the loudness, awareness and annoyance VAS scores 4 or higher, not using the sedatives, no history of cardiovascular disease, no exacerbation of tinnitus in residual inhibition (RI) test, not suffering from fluctuating hearing loss and the active otologic disease(such as Meniere's syndrome), not benefit from existing classic therapies, not having the common cognitive and neurological disorders, like migraine, and, no history of epilepsy and seizures diagnosed by a neurologist and/or psychiatrist.

2.1. Ethical consideration

This study has been approved by the Research Ethics Committee of the University of Social Welfare and Rehabilitation Sciences with code number of IR.USWR.REC.1398.188. Due to ethical considerations, the informed consent, which included a brief explanation of the procedure, was provided to all subjects. The tinnitus subjects who were signed the consent form was enrolled in this study. As the pandemic of coronavirus disease 2019 (COVID-19), during the evaluation and treatment sessions, the face masks and maintaining of social distance were implemented.

2.2. Study design

Participants were enrolled in this study by convenience sampling method. Then, with block randomization, the participants were randomly divided into the CTG (patients with tinnitus receiving active-tDCS and real-TMNMT) and the CG (tinnitus subjects receiving sham-tDCS and placebo-TMNMT). As the usefulness of six sessions of tDCS [32], time consuming and also possible fatigue of participants, in both groups, six sessions of tDCS (twice a week with an interval of three or four days for three consecutive weeks) were conducted. Repeated measurement test was applied for statistical analyses and comparison between the means in different sessions.

2.3. Audiometry test

Pure one audiometry [16] was done using the Interacoustic AC33 two-channel clinical audiometer through the Telephonics Dynamic Headphone (TDH) 39P supra-aural earphones. The hearing threshold of the participants should not exceed 50 dB HL in 0.25–8 kHz.

2.4. Psychoacoustic assessment

For psychoacoustic evaluation of tinnitus patients, the type of tinnitus (tonal vs. noise) has been determined by presenting of the pure tone and the narrow band noise, and asking the patients to indicate which one is the most similar to their tinnitus sounds [18]. Patients with tonal tinnitus were enrolled for this study. Then, pitch matching was done to determine the tinnitus frequency, and it was performed by two-forced choice method in different frequencies. After selecting each one by the patient, the same frequency, and also higher or lower frequency was presented and asked them again. This process continued until the tinnitus frequency was obtained repeatedly. The result was recorded in Hertz (Hz). After determining the tinnitus frequency, to prevent the octave confusion, one octave higher and lower than the specified frequency was presented [18]. Then, loudness matching was performed. For this, at the tinnitus frequency, the intensity increased from the threshold in steps of 1 dB until the patients reported that their tinnitus loudness was the same. The results were recorded in dB sensation level (SL) [18]. In next step, minimum masking level (MML) was assessed, in which at the tinnitus frequency, the narrow band noise (NBN) threshold of patients is determined and at 1-dB steps above the individual threshold; the intensity of the NBN was increased to mask the tinnitus. In RI test, the MML plus 10 dB intensity was presented to the involved ear for 60 s and asked them to report their possible changing tinnitus sound quality. Studies revealed that the tinnitus patients with positive maskability and RI above 30 s may benefit more from sound stimulation methods, such as music therapy [12]. As the possible effects of acoustic reflex stimulus on the tinnitus quality, the acoustic reflex test was performed using the Madsen Zodiac 901 Otometrics at the end of the psychoacoustic evaluation.

2.5. Psychometric assessment

For psychometric evaluation of tinnitus patients, the loudness, awareness and annoyance VAS scores were conducted, in which zero represents no disorder and 10 the worst condition [1,13]. For assessment of disability caused by tinnitus, Persian version of THI was applied [26].

2.6. Behavioral assessment

In this study for assessment of the auditory divided attention, auditory selective attention and working memory in tinnitus patients; Persian version of DAVMT and RDDT was performed [2,25]. The output of laptop and headphones were calibrated using 6 cc coupler, as the tests were performed at the most comfortable level (MCL). To implementation of the DAVMT and RDDT; Audacity software was used through ASUS X452LD laptop and headphones in MCL intensity. The RDDT test was performed in both directed to the right/left ear (i.e., auditory selective attention) and free retrieval (i.e., auditory divided attention).

2.7. tDCS technique

Following initial assessments and eligibility of participants based on inclusion criteria, the intervention phase began. Regarding to the intended stimuli, to apply the tDCS, the Auditory Electrical Stimulation device (AES) of Tanin Pardaz Pasargad was used. In the CTG, one rehabilitation phase was considered, in contrast, in the CG, two phases were considered. The CG received sham-tDCS and placebo-TMNMT stimuli in first phase, and at the end of it, the second phase introduced by combination of active-tDCS and real-TMNMT.

In the CTG, active-tDCS parameters were the direct current (DC) with current intensity of 2 mA, 2 mA plateau, fade in/out 8 s, by two saline-soaked electrodes embedded in sponge (35cm^2). In this study bifrontal montage was used, in which anodal stimulation over the right DLPFC (F4) and cathodal stimulation over the left DLPFC (F3) for 20 min in six sessions (twice a week for three consecutive weeks). In contrast, in the CG, sham-tDCS parameters consists of brief stimuli (110 μA over the 15 ms with peak 3 ms) were delivered by two saline-soaked electrodes embedded in sponge (35cm^2) every 550 ms, which elicited a tingling sensation for the participants to mimic the skin sensation of the active-tDCS. Similar to the CTG, bifrontal montage applied, in which anodal and cathodal stimulation over the F4 and F3, respectively, for 20 min in six sessions (twice a week for three consecutive weeks).

2.8. TMNMT method

With tDCS sessions, and based on TMNMT method, in the CTG, participants were asked to bring a CD containing their favorite music. Regarding to the individual's tinnitus pitch matching, the target frequency was removed from the spectrum of the subject's favorite music by quality (Q-factor) = 0.4 through Audacity software. By comparing the frequency spectrum of music file before and after the notch, it was ensured that if Q factor = 0.4 was selected, exactly the intended frequency would be removed from the music and the adjacent frequencies not be changed. Then, the modified file (with a sampling rate of 44,000 Hz and 24 bits) exported with waveform audio file (WAV) format. The participant was asked to listen passively for 120 min/day, to a CD containing her/his favorite music with a proper notch applied in its spectrum according to the individual's tinnitus in treatment period. In the CG, for the placebo-TMNMT, the participants' favorite music without any notches or modifications were delivered and asked to listen passively for 120 min/day, similar to CTG. Previous studies recommended that for the placebo-TMNMT, the notch may be applied in the octave adjacent to the tinnitus frequency; however, in this study, due to the possibility of octave confusion, this was avoided and music was delivered without notch.

2.9. Outcome measurements and intervention algorithm

Above evaluations were performed before the intervention and after the last treatment session (0 to 48 h after the treatment session) to evaluate the short-lasting effectiveness of the combined tDCS and TMNMT on the psychoacoustic (loudness-matching), the psychometric (awareness, loudness, and annoyance VAS scores, and THI questionnaire) scores as well as the cognitive assessments (RDDT and DAVMT). Also, these assessments were conducted one month after the last treatment session to evaluate the persistency of the mentioned method. In order to ethical considerations and patient rights in the CG, sham stimuli were performed in first phase, in contrast the active-tDCS and real-TMNMT stimuli with the same quality of the CTG were delivered to

these participants in the second phase. The measurements were performed in both phases 1 and 2 of the CG, and therefore within group comparison was obtained. Since this study mainly based on the psychoacoustic, particularly pitch matching, and its importance, at the beginning of intervention, the tinnitus frequency was re-evaluated. The study design algorithm is summarized in Fig. 1.

2.10. Data analysis

The data were analyzed in both descriptive and analytical statistics. In descriptive statistics, data were described using mean and standard deviation and expressed in the form of tables. For the analytical statistics; the normality distribution was checked using the Shapiro-Wilk test. The Levene's test was used to test if the samples had equal variances or not. Then, repeated measurement test was used to compare the means in different times. For this, Mauchly's Test of Sphericity was performed. Greenhouse-Geisser was used whenever the spherecity was not observed. Statistical analyses were performed using SPSS software version 22.0 (IBM, NY, USA), and statistically significance level was considered $p < 0.05$.

3. Results

3.1. Characteristics of tinnitus patients

The mean tinnitus duration in both the CTG and CG were 39.62 ± 25.45 and 29.31 ± 28.82 months, respectively. The mean tinnitus frequency was 4.27 ± 2.16 kHz in the CTG and 4.65 ± 1.86 kHz in the CG.

3.2. The effect of tDCS-TMNMT combination on loudness matching (dB SL) by groups

Repeated measurement analysis was used to compare the findings between different times in the CTG and CG. Based on loudness matching, the results showed a statistically significant difference between groups ($p = 0.004$) (Table 1).

Within-group comparisons were examined and the results showed a statistically significant difference within the CTG ($p < 0.001$), although such a difference was not observed in the CG ($p = 0.51$). In the CTG, there was a statistically significant difference between the mean loudness of tinnitus before and after the intervention ($p < 0.001$). The continuity of the therapeutic effect in the CTG was assessed by comparing the mean loudness of tinnitus after the intervention and one month later. The results indicated that there was no statistically significant difference ($p > 0.05$) which confirmed the persistence of treatment outcome.

Table 1
Comparison of the loudness matching (per dB SL) between groups (repeated measurement test).

Group	n	Pre-treatment	Post-treatment	One month after-treatment	p-value[b]	Partial Eta
Clinical Trial (CTG)	13	8.23 (2.17)	5.23 (2.77)	5.23 (3.22)	0.004	0.298
Control (CG)	13	9.00 (2.77)	9.77 (2.59)	10.08 (3.40)[a]		

[a] Mean (S.D).
[b] Repeated measurement.

3.3. The effect of tDCS-TMNMT combination on the awareness, loudness and annoyance VAS by groups

In Table 2, the awareness VAS, findings showed a statistically significant difference between groups ($p = 0.003$). Within-group comparisons were evaluated and findings revealed a statistically significant difference within the CTG ($p = 0.001$), although the difference was not significant in the CG ($p = 0.37$). In the CTG, there was a statistically significant difference between the mean awareness VAS before and after the intervention ($p = 0.029$). The continuity of the therapeutic effect in the CTG was assessed by comparing the mean loudness of tinnitus after the intervention and one month later. The results demonstrated there was no statistically significant difference ($p > 0.05$) which indicated the stability of treatment outcome.

Repeated measurements of the loudness VAS (Table 2) showed a statistically significant difference between groups ($p = 0.005$). Within-group comparisons were assessed and findings indicated statistically significant difference within the CTG ($p < 0.001$), although the difference was not significant in the CG ($P = 0.53$). Furthermore, in CTG, there was a statistically significant difference between the mean loudness VAS before and after the intervention ($p = 0.029$). The persistency of treatment in the CTG was evaluated and the results showed no statistically significant difference ($p > 0.05$) which indicated the durability of intervention.

From aspect of the annoyance VAS, which showed in Table 2, repeated measurements demonstrated statistically significant difference between groups ($p = 0.046$). Within-group comparisons were assessed and findings indicated statistically significant difference within the CTG ($p < 0.001$), although the difference was not significant in the CG ($p = 0.294$). Furthermore, in the CTG, there was a statistically significant difference between the mean annoyance VAS before and after the intervention ($p = 0.001$). The consistency of treatment in the CTG was evaluated and the results showed no statistically significant difference ($p > 0.05$) which indicated the consistency of intervention.

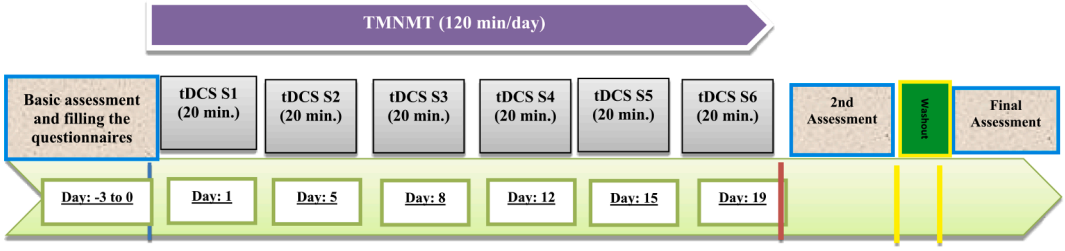

Fig. 1. Study design algorithm
Prior to the intervention, the psychoacoustic, psychometric, and behavioral assessments were performed. The tDCS over the DLPFC (with current intensity of 2 mA for 20 min) and TMNMT (120 min daily) simultaneously were presented for the participants. To evaluate the short and long-lasting findings, the assessment were performed after the last treatment session and one month after the last treatment session, respectively.
For the CG, two phases were designed. The first phase including the sham-tDCS and placebo-TMNMT, at the end of it, the second phase were started including active-tDCS and real-TMNMT similar to the CTG.
(Abbreviations S: Session، tDCS: transcranial Direct Current Stimulation، TMNMT: Tailor-Made Notched Music Training، Min.: Minute).

Table 2
Comparison of the awareness, loudness and annoyance VAS[a] scores between groups (repeated measurement test).

Tests	Group	n	Pre-treatment	Post-treatment	One month after-treatment	*p*-value[c]	Partial Eta
Awareness VAS	Clinical Trial (CTG)	13	6.23 (1.69)	4.69 (2.32)	4.54 (2.07)	0.003	0.319
	Control (CG)	13	7.23 (2.24)	7.38 (1.81)	7.77 (1.42)		
Loudness VAS	Clinical Trial (CTG)	13	5.69 (1.32)	3.23 (2.00)	3.00 (2.24)	0.005	0.283
	Control (CG)	13	5.31 (1.32)	5.62 (1.71)	6.15 (1.28)		
Annoyance VAS	Clinical Trial (CTG)	13	6.77 (1.59)	3.69 (1.75)	3.85 (1.91)	0.046	0.155
	Control (CG)	13	5.69 (1.25)	5.92 (1.66)	6.23 (1.30)[b]		

[a] Visual Analogue Scale.
[b] Mean (S.D).
[c] Repeated Measurement.

3.4. The effect of tDCS-TMNMT combination on the total score of THI by groups

In Table 3, repeated measurements of total score of THI showed a statistically significant difference between groups ($p = 0.016$). Within-group comparisons were assessed and findings demonstrated statistically significant difference within the CTG ($p < 0.001$), but such difference was not observed in the CG ($P = 0.54$). Furthermore, in the CTG, there was a statistically significant difference between total score of THI before and after the intervention ($p < 0.001$). The consistency of treatment in the CTG was evaluated and the results showed no statistically significant difference ($p > 0.05$) which confirmed the consistency of treatment.

3.5. The effect of tDCS-TMNMT combination on the DAVMT scores by groups

In the DAVMT score (Table 4); repeated measurements demonstrated that no statistically significant difference between groups ($p > 0.05$). In contrast, within-group comparisons were assessed and findings showed statistically significant difference within the CTG ($p < 0.001$), but such difference was not observed in the CG ($p = 0.918$). Also, in the CTG, there was a statistically significant difference between the DAVMT score before and after the intervention ($p > 0.001$). The consistency of treatment in the CTG was evaluated and the results showed no statistically significant difference ($p > 0.05$) which indicated the consistency of the combined treatment method.

3.6. The effect of tDCS-TMNMT combination on the RDDT scores in dichotic and selective (right and left ears) subtests by groups

The RDDT score of right ear in dichotic presentation of stimuli demonstrated no statistically significant difference between both groups ($p > 0.05$) (Table 5). Within-group comparisons were assessed and findings showed statistically significant difference within the CTG ($p < 0.001$), but difference was not observed in the CG ($p = 0.277$). Also, in the CTG, there was a statistically significant difference between the RDDT score before and after the intervention ($p = 0.006$). The consistency of treatment in intervention group was evaluated and the findings showed no statistically significant difference ($p > 0.05$) which confirmed the consistency of the combined treatment method.

Repeated measurement test for the RDDT score of left ear in dichotic presentation of stimuli showed a statistically significant difference between groups ($p = 0.049$) (Table 5). Within-group comparisons were assessed and findings showed statistically significant difference within both the CTG ($p < 0.001$) and the CG ($p = 0.019$). Furthermore, in the CTG, there was a statistically significant difference between the RDDT score of left ear in dichotic presentation before and after the intervention ($p = 0.001$). The consistency of treatment in the CTG was evaluated and the findings showed no statistically significant difference ($p > 0.05$) which confirmed the consistency of intervention.

In terms of the RDDT score, auditory selective attention of right ear subtest (Table 4), repeated measurements demonstrated no statistically significant difference between groups ($p > 0.05$). In contrast, within-group comparisons were assessed and findings demonstrated statistically significant difference within both the CTG ($p < 0.001$) and the CG ($p = 0.001$). Furthermore, in the CTG, there was a statistically significant difference before and after the intervention ($p = 0.003$). The consistency of treatment in the CTG showed no statistically significant difference ($p > 0.05$) which indicated the persistency of intervention.

The RDDT score finding, auditory selective attention of left ear subtest, showed no statistically significant difference between groups ($p > 0.05$) (Table 5). In contrast, within-group comparisons were assessed and findings showed statistically significant difference within the CTG ($p < 0.001$), but not observed in the CG ($p = 0.067$). Also, in the CTG, there was a statistically significant difference before and after the intervention ($p = 0.002$). The stability of treatment in the CTG showed no statistically significant difference ($p > 0.05$) which confirmed the consistency of treatment.

Table 3
Comparison of the total score of THI[a] between groups (repeated measurement test).

Group	n	Pre-treatment	Post-treatment	One month after-treatment	*p*-value[c]	Partial Eta
Clinical Trial (CTG)	13	51.08 (10.70)	37.38 (10.91)	36.92 (13.92)	0.016	0.218
Control (CG)	13	54.00 (12.86)	53.08 (14.25)	54.92 (12.35)[b]		

[a] Tinnitus Handicap Inventory.
[b] Mean (S.D).
[c] Repeated Measurement.

4. Discussion

The aim of this paper was to explore the effectiveness of combining the tDCS over the DLPFC and TMNMT on the psychocoustic, psychometric, and cognitive indices of tinnitus patients in both the CTG and CG. In between-group comparisons, the measurements which statistically significant difference included were the following: loudness matching, the awareness, loudness, and annoyance VAS, as well as the total score of THI and RDDT score of left ear in dichotic presentation. In within-group comparisons, all of the psychocoustic, psychometric and behavioral measurements were difference significantly pre- and post-intervention the treatment mere in the CTG. Furthermore, these alterations were consistence over the one month after the last treatment session. Further analysis revealed that in short term in the CTG; the loudness, awareness, and annoyance of the tinnitus, as well as the disability induced by the tinnitus have declined significantly. Also, the

Table 4
Comparison of the DAVMT[a] score between groups (repeated measurement test).

Group	n	Pre-treatment	Post-treatment	One month after-treatment	p-value[c]	Partial Eta	Observed power
Clinical Trial (CTG)	13	3.91 (0.77)	4.47 (0.71)	4.76 (0.75)	0.698	0.006	0.066
Control (CG)	13	4.50 (0.60)	4.46 (0.84)	4.50 (0.78)[b]			

[a] Dichotic auditory verbal memory test.
[b] Mean (S.D).
[c] Repeated measurement.

Table 5
Comparison of the RDDT[a] scores in dichotic (right and left ear) and selective(right and left ear) between groups (repeated measurement test).

Subtests	Group	n	Pre-treatment	Post-treatment	One month after-treatment	*p*-value[c]	Partial Eta	Observed power
Dichotic (right ear)	Clinical Trial (CTG)	13	79.20 (11.57)	86.82 (8.70)	87.61 (8.47)	0.365	0.034	0.144
	Control (CG)	13	87.68 (5.90)	87.47 (5.25)	86.54 (5.42)			
Dichotic (left ear)	Clinical Trial (CTG)	13	69.59 (7.55)	78.35 (10.08)	77.85 (8.43)	0.049	0.151	0.511
	Control (CG)	13	81.12 (10.14)	82.26 (9.37)	84.04 (10.27)			
Selective (right ear)	Clinical Trial (CTG)	13	89.17 (10.95)	94.09 (8.40)	93.87 (8.46)	0.345	0.037	0.152
	Control (CG)	13	96.30 (2.42)	94.44 (1.93)	93.80 (2.40)			
Selective (left ear)	Clinical Trial (CTG)	13	85.18 (11.07)	90.31 (10.36)	90.74 (8.39)	0.176	0.075	0.268
	Control (CG)	13	93.87 (4.01)	92.59 (2.98)	91.67 (4.04)[b]			

[a] Randomized Dichotic Digits Test.
[b] Mean (S.D).
[c] Repeated measurement.

reduction in the CTG was consistence over a month. Such findings were not observed in the CG.

Furthermore, the combined tDCS-TMNMT in the CTG lead to auditory divided attention, auditory selective attention, and working memory improvement in short term. This enhancement in the CTG was persistence over a month later. These findings were not observed in the CG. The findings of this study are in agreement with several previous studies and contradict with others, which mentioned following. Based on the authors' search, in two studies the combination of tDCS with TMNMT was applied to tinnitus subjects [22,34]. For the first time; Teismann et al. (2014) investigated the combined effect of 5-session tDCS over the LTA and TMNMT in tinnitus patient [34]. In another study, Lee et al. (2017) evaluated the combination effect of bifrontal tDCS and TMNMT on chronic tinnitus patients, merely in the CTG, not included the CG [22].

In this study, it was shown that the combination of tDCS and TMNMT may decrease the awareness VAS in the CTG. This finding was an agreement with Lee et al. (2017), in which they showed that the tDCS-TMNMT leads to a significant reduction of awareness VAS [22]. Furthermore, this study demonstrated that the combination of tDCS over the DLPFC with TMNMT may reduce the loudness VAS in the CTG. This finding was in agreement with Lee et al. (2017). Nonetheless, this outcome in contrast to Teismann et al. (2014), in which they showed that the combination of tDCS over the LTA and TMNMT has no significant effect on the loudness VAS [22]. This finding may be probably due to the tDCS electrode montage, in which; it can be suggested that tDCS over the DLPFC may reduce tinnitus loudness [32].

In this study, it was observed that the tDCS-TMNMT combination may reduce the annoyance VAS. This result was in agreement with Lee et al. (2017). Another tool which used in this study was the THI questionnaire. The results of present study indicated that the combination of tDCS and TMNMT may lead to significant reduction in total score of THI in the CTG, which in agreement with Lee et al. (2017). Nevertheless, this outcome in contrast with Teismann et al. (2014), in which they showed that the tDCS-TMNMT had no significant effect on total score of THI [34]. Based on current findings, it can be claimed that the combination of tDCS over the DLPFC and TMNMT may be a proper option for tinnitus management; based on the loudness, awareness, loudness and annoyance VAS, as well as total score of THI. Previous studies did not explore the effect of the combined tDCS-TMNMT method on the behavioral cognition assessments, particularly memory and auditory attention; therefore it is impossible to compare the current study findings with them.

In general, the main hypothesis of this study is based on the dual effect of tDCS and TMNMT on the performance of the cognitive part of the tinnitus network. That is, the tDCS over DLPFC, as its roles in integrating of sensory and emotional aspects of tinnitus and also its important role in interpreting of tinnitus, auditory attention, and memory, and as well as through neural pathways that inhibit the input to the auditory cortex; along with the auditory cortex stimulation by TMNMT, may induce the neuromodulation in the two main networks involved in tinnitus. Consequently, this may lead to a positive change in increasing habituation and improvement of memory and auditory attention. In this way, it can be claimed that the auditory attention and memory of tinnitus sufferers is less involved and as a result, the tinnitus sounds become insignificant for involved subjects.

Since the literature review showed a probable cognitive functions involvement in tinnitus subjects (particularly the auditory divided attention, auditory selective attention, and working memory), in this paper, the DAVMT and RDDT behavioral tests were used to take a broad view from the aspect of effectiveness of the combined tDCS-TMNMT intervention, in addition to psychoacoustic and psychometric assessments. This study may confirm the effectiveness of the combined tDCS over DLPFC with TMNMT on the auditory divided attention, auditory selective attention and working memory in both short term and long-lasting in the CTG.

In this study, the accurate and comprehensive inclusion criteria were applied to reduce the heterogeneity of tinnitus patients. Also, this study was designed in such a way that it was possible to make between-group comparisons of the CTG and CG, in addition to within-group comparison. Another benefit of this study may be the implementing of cognitive assessments, in addition to conventional assessments, with the aim of exploring the effectiveness of the combined tDCS-TMNMT method on the auditory attention and working memory of tinnitus subjects. In

future studies, it is recommended to conduct studies with a larger sample size, as well as applying 6 or 12 month intervals to monitor the maximum duration of therapeutic effects. It is also recommended to combine the TMNMT with other methods such as TMS, in future studies. Furthermore, future works are better to involve the event-related potentials (ERP) and brain mapping assessment to confirm and correlate the behavioral findings.

5. Conclusions

Based on this study, it seems that the combination of tDCS over the DLPFC and TMNMT lead to reduction in the loudness, awareness, annoyance, and also disability induced by tinnitus in the CTG in short term. Also, the findings had been persistent over a month after the treatment sessions. Furthermore, this combined method revealed improvement of cognitive functions (the auditory divided attention, auditory selective attention and working memory) in the CTG.

However, it is recommended to study the effects of combined tDCS and TMNMT, the tDCS, and the TMNMT methods separately on tinnitus patients in larger and different groups to see if the combined modality shows any superior results than either modality alone.

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Declaration of competing interest

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References

[1] Adamchic I, Langguth B, Hauptmann C, Alexander Tass P. Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus. Am J Audiol 2012;21:215–25. https://doi.org/10.1044/1059-0889(2012/12-0010).
[2] Aghamollaei M, Aliakbar Tahaei S, Jafari Z, Toufan R, Keyhani M. Development and evaluation of the persian version of the dichotic auditory-verbal memory test in 18- to 25-year old normal individuals. Audiology 2011;20:86–94.
[3] Baguley D, McFerran D, Hall D 2013;382:1600–7. https://doi.org/10.1016/S0140-6736(13)60142-7.
[4] Barnea G, Attias J, Gold S, Shahar A. Tinnitus with Normal hearing sensitivity: extended high-frequency audiometry and auditory-nerve brain-stem-evoked responses. Int J Audiol 1990;29:36–45. https://doi.org/10.3109/00206099009081644.
[5] De Ridder D, Vanneste S. EEG driven tDCS versus bifrontal tDCS for Tinnitus. Front Psychiatry 2012:3. https://doi.org/10.3389/fpsyt.2012.00084.
[6] De Ridder D, Elgoyhen AB, Romo R, Langguth B. Phantom percepts: tinnitus and pain as persisting aversive memory networks. Proc Natl Acad Sci 2011;108:8075–80. https://doi.org/10.1073/pnas.1018466108.
[7] Dobie RA. Depression and tinnitus. Otolaryngol Clin North Am 2003;36:383–8. https://doi.org/10.1016/S0030-6665(02)00168-8.
[8] Eggermont JJ. Cortical tonotopic map reorganization and its implications for treatment of tinnitus. Acta Otolaryngol 2006;126:9–12. https://doi.org/10.1080/03655230600895259.
[9] Eggermont JJ. The neuroscience of tinnitus. Oxford University Press; 2012. https://doi.org/10.1093/acprof:oso/9780199605606.001.0001.
[10] Emadi M, Rezaei M, Najafi S, Faramarzi A, Farahani F. Comparison of the transient evoked otoacoustic emissions (TEOAEs) and distortion products otoacoustic emissions (DPOAEs) in Normal hearing subjects with and without tinnitus. Indian J Otolaryngol Head Neck Surg 2018;70:115–8. https://doi.org/10.1007/s12070-015-0824-9.
[11] Foroughan M, Jafari Z, Shirin Bayan P, Ghaem Magham Farahani Z, Rahgozar M. Validation of mini-mental state examination (MMSE) in the elderly population of Tehran. Adv Cogn Sci 2008;10:29–37.
[12] Fournier P, Cuvillier A-F, Gallego S, Paolino F, Paolino M, Quemar A, et al. A new method for assessing masking and residual inhibition of tinnitus. Trends Hear 2018;22. https://doi.org/10.1177/2331216518769996. 233121651876999.
[13] Gift AC. Visual analogue scales: measurement of subjective phenomena. Nurs Res 1989;38:286–8. https://doi.org/10.1097/00006199-198909000-00006.
[14] Giordano J, Bikson M, Kappenman ES, Clark VP, Coslett HB, Hamblin MR, et al. Mechanisms and effects of transcranial direct current stimulation. Dose-Response 2017;15. https://doi.org/10.1177/1559325816685467. 155932581668546.
[15] Györi A. Tailor-Made Notched Music Training - a therapy of chronic tinnitus Tailor-Made Notched Music Training - a therapy of chronic tinnitus. Comput. Music Semin. Aachen 2016:0–7.
[16] Katz J. Handbook of clinical audiology, vol. 7. PA: Wolters Kluwer Health Philadelphia; 2014. https://doi.org/10.1097/00003446-198608000-00010.
[17] Kim HJ, Lee HJ, An SY, Sim S, Park B, Kim SW. Analysis of the prevalence and associated risk factors of Tinnitus in adults. PLoS One 2015;10. https://doi.org/10.1371/journal.pone.0127578.
[18] Kostek B, Poremski T. A new method for measuring the psychoacoustical properties of tinnitus. Diagn Pathol 2013;8:209. https://doi.org/10.1186/1746-1596-8-209.
[19] Langguth B, Goodey R, Azevedo A, Bjorne A, Cacace A, Crocetti A. Consensus for tinnitus patient assessment and treatment outcome measurement. In: Tinnitus Research Initiative Meeting, Regensburg, July 2006; 2007. p. 525–36. https://doi.org/10.1016/S0079-6123(07)66050-6.
[20] Langguth B, Kreuzer PM, Kleinjung T, De Ridder D. Tinnitus: causes and clinical management. Lancet Neurol 2013;12:920–30. https://doi.org/10.1016/S1474-4422(13)70160-1.
[21] Langguth B, Elgoyhen AB, Cederroth CR. Therapeutic approaches to the treatment of tinnitus. Annu Rev Pharmacol Toxicol 2019;59:291–313. https://doi.org/10.1146/annurev-pharmtox-010818-021556.
[22] Lee HY, Choi MS, Chang DS, Cho C-S. Combined bifrontal transcranial direct current stimulation and tailor-made notched music training in chronic tinnitus. J Audiol Otol 2017;21:22–7. https://doi.org/10.7874/jao.2017.21.1.22.
[23] Lewis PM, Thomson RH, Rosenfeld JV, Fitzgerald PB 2016;22:406–21. https://doi.org/10.1177/1073858416646707.
[24] van der Loo E, Gais S, Congedo M, Vanneste S, Plazier M, Menovsky T, et al. Tinnitus intensity dependent gamma oscillations of the contralateral auditory cortex. PLoS One 2009;4:e7396. https://doi.org/10.1371/journal.pone.0007396.
[25] Mahdavi ME, Aghazadeh J, Tahaei SAA, Heiran F, Baghban AA. Persian randomized dichotic digits test: development and dichotic listening performance in young adults. Audit Vestib Res 2015;23:99–113.
[26] Mahmoudian S, Shahmiri E, Rouzbahani M, Jafari Z, Keyhani MR, Rahimi F, et al. Persian language version of the "Tinnitus handicap Inventory": translation, standardization, validity and reliability. Int Tinnitus J 2010;16:93–104.
[27] Mohamad N, Hoare DJ, Hall DA. The consequences of tinnitus and tinnitus severity on cognition: a review of the behavioural evidence. Hear Res 2016;332:199–209. https://doi.org/10.1016/j.heares.2015.10.001.
[28] Møller AR, Langguth B, De Ridder D, Kleinjung T. Textbook of tinnitus. New York, NY: Springer New York; 2011. https://doi.org/10.1007/978-1-60761-145-5.
[29] Noreña AJ. An integrative model of tinnitus based on a central gain controlling neural sensitivity. Neurosci Biobehav Rev 2011;35:1089–109. https://doi.org/10.1016/j.neubiorev.2010.11.003.
[30] Pantev C, Okamoto H, Teismann H. Music-induced cortical plasticity and lateral inhibition in the human auditory cortex as foundations for tonal tinnitus treatment. Front Syst Neurosci 2012:6. https://doi.org/10.3389/fnsys.2012.00050.
[31] Pantev C, Rudack C, Stein A, Wunderlich R, Engell A, Lau P, et al. Study protocol: münster tinnitus randomized controlled clinical trial-2013 based on tailor-made notched music training (TMNMT). BMC Neurol 2014;14:40. https://doi.org/10.1186/1471-2377-14-40.
[32] Shekhawat GS, 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. https://doi.org/10.1038/s41598-018-26665-1.
[33] Teismann H, Okamoto H, Pantev C. Short and intense tailor-made notched music training against tinnitus: the tinnitus frequency matters. PLoS One 2011;6:e24685. https://doi.org/10.1371/journal.pone.0024685.
[34] 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. https://doi.org/10.1371/journal.pone.0089904.
[35] Tyler RS, editor. Tinnitus Treatment. Stuttgart: Georg Thieme Verlag; 2006. https://doi.org/10.1055/b-002-59218.
[36] 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;202:779–85. https://doi.org/10.1007/s00221-010-2183-9.