Auditory and Vestibular Research

The Impact of Anodal Prefrontal Transcranial Stimulation on Listening Effort, Working Memory and the expression of N-methyl-D-aspartate receptor blood protein in patients with tinnitus

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ABSTRACT

Background and Aim: Tinnitus has been associated with increased listening effort and reduced working memory (WM) capacity during speech comprehension. A practical approach to enhance cognitive processes is transcranial direct current stimulation (tDCS), a non-invasive neuromodulation technique applying constant low current. Anodal tDCS increases the expression of N-methyl-D-aspartate receptor 1(NR1 and NR2) proteins in blood, which are associated with WM improvement. This study aimed to evaluate the effect of tDCS on listening effort, WM, and N-methyl-D-aspartate (NMDA) receptor subunit protein expression in blood of individuals with tinnitus.

Methods: Thirty-two adults (30–60 years) were randomly assigned to experimental and control groups. The experimental group received anodal tDCS with electrodes on F3 and F4 for 20 minutes at 1.5 mA over 10 sessions, while the control group underwent electrode placement without stimulation. Pre- and post-intervention assessments included audiometry, tympanometry, tinnitus matching, listening effort evaluation (cognitive-behavioral tasks, dual-task, visual analogue scale, and tinnitus functional index), and WM assessment (N-BACK test). Blood samples were analyzed using Western blot to measure NR1 and NR2 protein expression in blood.

Results: Compared to the control group, tDCS significantly reduced listening effort ($p<0.001$) and improved WM ($p<0.001$). After intervention, the experimental group showed a 27% increase in NR1 and a 50% increase in NR2 expression.

Conclusion: tDCS effectively reduced listening effort and enhanced WM in individuals with chronic tinnitus. The upregulation of NR1/NR2 protein expression in blood may contribute to improved auditory-cognitive performance, highlighting the potential role of this technique in tinnitus rehabilitation.

Keywords: Tinnitus, transcranial direct current stimulation,working memory, listening effort, N-methyl-D-aspartate receptor 1,2

Highlights

transcranial direct current stimulation shows potential for tinnitus rehabilitation
tDCS reduced listening effort and improved working memory in tinnitus
NR1/NR2 upregulation may support auditory-cognitive performance

Introduction:

Tinnitus, defined as the perception of sound without an external source, affects approximately 15–20% of the adult population and can negatively influence attention, memory, and overall cognitive function [1].

Neuroimaging and behavioral studies suggest that tinnitus involves abnormal activity in auditory, limbic, attentional, and memory-related networks, as well as the default mode network [2].

These alterations are believed to contribute to tinnitus perception, persistence, and loudness, and they may impair higher-level cognitive processes such as attention control and working memory (WM) [3].

A growing body of evidence indicates that patients with tinnitus often experience elevated listening effort, defined as the attentional and cognitive resources required to extract information from weak or noisy auditory signals. Increased listening effort not only reduces the efficiency of speech comprehension but also leads to mental fatigue and diminished quality of life [4]. (WM), which underpins the temporary storage and manipulation of information, is likewise compromised in tinnitus patients, with studies showing slower reaction times and reduced performance under demanding conditions. Together, heightened listening effort and impaired WM reflect the significant cognitive burden associated with tinnitus [5].

Transcranial direct current stimulation, a non-invasive brain stimulation technique, has recently been investigated as a potential intervention for tinnitus-related cognitive difficulties. Anodal stimulation of the dorsolateral prefrontal cortex has been shown to enhance speech perception, attention, and WM in both healthy individuals and clinical populations [6]. These effects are thought to involve modulation of brain N-methyl-D-aspartate receptor subunits such as N-methyl-D-aspartate receptor1 (NR1) and N-methyl-D-aspartate receptor2 (NR2), which play a central role in synaptic plasticity, long-term potentiation, and the sustained neuronal activity underlying WM [7].

Despite promising preliminary findings, research specifically addressing the influence of prefrontal transcranial direct current stimulation on listening effort, WM, and blood NMDA receptor-related biomarkers in patients with tinnitus remains limited. The present study therefore examined whether anodal prefrontal (tDCS) can reduce listening effort, improve WM, and increase the level of blood NR1 and NR2 expression in patients with chronic tinnitus.

Methods:

Demographic information:

This study was a cross-sectional study, and all procedures were approved by the Ethics Committee Tehran Medical Sciences, Islamic Azad University (Ethic code no: IR.UT.IRICC.REC.1399.007). Following prior research, a cohort of 32 adults [15] males and 17 females; age = 48.88 ± 9.17 years) with chronic tinnitus was recruited. Participants experienced either unilateral or bilateral tinnitus for a minimum of six months, and their condition was validated by an audiologist. The inclusion criteria required the absence of epilepsy, neurological or neuropsychiatric disorders, metal implants, cardiac pacemakers, or cranial infections. All participants were native Persian speakers.

At baseline, prior to the intervention, written informed consent was obtained from all participants, and demographic questionnaires were

Participants then underwent otoscopic and acoustic reflex examinations, pure-tone audiometry (250 Hz–8 kHz), and speech recognition threshold (SRT) and speech recognition score (SRS) tests.

Tinnitus assessments were conducted using a CA86 audiometer (Pejvak Ava Company, Iran) with TDH 39 headphones in an acoustic chamber. Stimuli were presented in 1/3-octave steps with pure tones or narrowband noise. Loudness matching and minimal masking level (MML) were measured following standard procedures [8].

Finally, participants completed the Tinnitus Functional Index (TFI) and Visual Analog Scale (VAS) questionnaires, and blood samples were collected for Western blot analysis. Participants were randomly assigned to the control (n = 14) or experimental (n = 18) group using a random number table. **Fig1**
It should be noted that serum levels of NR1 and NR2 may not directly reflect their expression in the dorsolateral prefrontal cortex (DLPFC); therefore, interpretations regarding cortical mechanisms should be made with caution.

Tinnitus functional index questionnaire:
Tinnitus Functional Index (TFI) is a new questionnaire designed to evaluate tinnitus and measure treatment outcomes. It comprises 25 questions and an 11-point Likert scale from 0 to 10. Questions 1 and 3 are exceptions, and their answers range from 0 to 100%. For calculation, answers should be converted into percentages on a scale of 0-10. The overall TFI score is determined by multiplying the average of all questions by 10. At least 19 questions must be answered to calculate a valid overall TFI.
The overall TFI score ranges from zero to 100, classifying the groups into five levels of tinnitus intensity: no difficulty (0 to 17), low difficulty (18 to 31), moderate difficulty (32 to 53), trouble (54 to 72), a lot of trouble (73 to 100). In addition, the items can be grouped into eight subscales: annoyance (items I: 1-3), decreased sense of control (I: 4-6), cognitive interference (I: 7-9), sleep disturbance (I: 10-12), hearing problems attributed to tinnitus (I: 13-15), interference with relaxation (I: 16-18) decreased quality of life (I: 19-22), and emotional distress (I: 23-25). The method for calculating the subscale score is identical to the total score calculation method, which involves taking the average of the answered questions within a subscale and multiplying it by 10. The score ranges from zero to 100 [9, 10].

Visual analog scale questionnaire:
VAS questionnaire is a self-report simulated eye scale. A simple ruler-like scale with the numbers zero to ten written on it was used in this study [11]. In this scale, the value zero indicates the lowest level of fatigue and the number 10 indicates the highest level of mental fatigue. The subject is asked to determine his level of mental fatigue according to this tool. We measure mental fatigue using a VAS questionnaire, as proposed by Alhabanli et al. [12].

Dual-task:

The dual-task paradigm involved the simultaneous execution of two cognitively demanding auditory tasks. The primary task was a speech recognition test with lists of 5 × 10 two-syllable words recorded in a female voice at 60 dB HL, presented with multitalker noise at 75 dB HL. Noise was delivered 5 seconds before and after word presentation via two loudspeakers at 45° angles, 1 meter from the participant, Signal-to-Noise Ratio -15 dB HL.
The secondary task was an auditory 1-back WM test, in which participants pressed a button whenever a word was repeated in the primary task list. Participants were trained on ten lexical items to ensure auditory acuity and task familiarity. Baseline measurements of the primary and secondary tasks were obtained separately [13], followed by the simultaneous dual-task condition using the AP12 speaker (Pajvak Ava Company, Iran) in the open sound field.

Western blotting test:
At the beginning and end of the brain stimulation intervention, 7 mL of venous blood was collected from each participant. Samples were collected in serum separation tubes containing anticoagulant and gently mixed to prevent clotting. Blood was then diluted 1:1 with phosphate-buffered saline**,** layered over Ficoll, and centrifuged at 1000 rpm for 20–25 minutes to isolate the mononuclear layer. The upper Ficoll layer

was carefully extracted using a plastic pipette, washed three times with serum, centrifuged, and stored at –70°C until analysis [14].
Western blotting was performed to quantify protein levels. Total protein content of 60 µg per sample was determined by the Bradford method using bovine serum albumin as a reference standard. Samples were separated by 12.5% sodium dodecyl sulfate–polyacrylamide gel electrophoresis and transferred to polyvinylidene difluoride membranes. Membranes were blocked with 2% Tris-buffered saline with Tween 20-nonfat dry milk, incubated overnight with specific primary antibodies, and detected using enhanced chemiluminescence. Densitometric analysis was performed using Image software [15].
It should be noted that serum levels of NR1 and NR2 may not directly reflect their expression in the dorsolateral prefrontal cortex; therefore, interpretations regarding cortical mechanisms should be made with caution.

Transcranial direct current stimulation**:**
The experimental and control groups were blinded to the ratio and the method of division. The blinding methodology ensured that both groups remained unaware of their respective groups. The control group had tDCS electrodes placed on their head, but the electric current stopped after just 30 seconds, without the participants' knowledge. In contrast, the tDCS experimental group received electrical stimulation for a total of 20 minutes with a constant current intensity of 1.5 mA throughout of 10 sessions. The Active Dose II device manufactured by Activa Tech with serial number 14070121was utilized to conduct direct tDCS electrical stimulation. The placement of the electrodes within a pair of sponge pads (measuring 35 cm2) effectively facilitated the conduction of current while simultaneously reducing the potential damage incurred by the current passing through normal saline, a solution comprised of 10 grams of salt in 1000 cc of water. Direct current was then transferred through these pads to the head. For all subjects receiving tDCS, the negative electrode, the cathode, was positioned over the right DLPFC. The positive electrode, the anode, was situated over the left DLPFC, as determined by the International Electroencephalogram System 20-10 based on F3 and F4 [16]. The electrical stimulation protocol consisted of a 20-minute session with a current intensity of 1.5 mA and a 20-second current increase gradient in 10 consecutive sessions (with five sessions per week).

Data analysis:

Statistical analyses were conducted using SPSS (v17) at a 0.05 error rate. The following tests were performed: Pearson’s correlation coefficient, repeated measures ANOVA, correlated t-tests, and independent t-tests. Prior to analysis, assumptions of normality and sphericity were checked and confirmed. All analyses were conducted accordingly to evaluate the effects of anodal tDCS on mental fatigue, tinnitus annoyance, listening effort, and WM

Result:
Descriptive psychoacoustic characteristics of tinnitus are summarized as follows: tinnitus loudness was 32 ± 15.8 dB HL, tinnitus pitch was 3925 ± 3027 Hz, and the MML was 28 ± 18 dBSPL.
Analysis of variance with repeated measures indicated that anodal tDCS significantly reduced mental fatigue, tinnitus annoyance, listening effort, and WM impairments in the experimental group compared to controls. Moreover, significant interaction effects across all four outcomes showed that the magnitude of improvement varied between groups, confirming that the impact of tDCS was not uniform but dependent on participant group membership. Table 1 tabulates the mean and standard deviation of the scores for the degree of mental fatigue caused by tinnitus, the amount of annoyance of tinnitus, listening effort, and WM for patients with tinnitus in the two experimental and control groups in the pre-test and post-test phases.

The effect of transcranial direct current stimulation **intervention on the mental fatigue caused by tinnitus**
Repeated measures ANOVA revealed a significant **within-subject effect** of tDCS on mental fatigue in individuals with tinnitus, ($F(1,1)=92.86$, $p=0.001$, $\eta^2=0.75$), indicating a reduction in fatigue scores following active stimulation. A significant between-subject effect of group was also observed, ($F(1, 1)=10.80$, $p=0.003$, $\eta^2=0.26$), reflecting overall differences between experimental and control groups. Importantly, the interaction between tDCS and group was significant, ($F(1, 1)=81.91$, $p=0.001$, $\eta^2=0.73$), demonstrating that reductions in mental fatigue were greater in the experimental group compared to controls.

The effect of transcranial direct current stimulation **intervention on the annoyance caused by tinnitus**
Repeated measures ANOVA revealed a significant within-subject effect of tDCS on tinnitus annoyance, ($F(1, 1)=193.47$, $p=0.001$, $\eta^2=0.86$), indicating a reduction in annoyance scores following active stimulation. A significant between-subject effect of group was also observed, ($F(1, 1)=38.08$, $p=0.001$, $\eta^2=0.55$), reflecting overall differences between experimental and control groups. Importantly, the interaction between tDCS and group was significant, ($F(1, 1)=189.86$, $p=0.001$, $\eta^2=0.86$), demonstrating that reductions in tinnitus annoyance were greater in the experimental group compared to controls.

The effect of transcranial direct current stimulation **intervention on the listening effort of people with tinnitus**
Repeated measures ANOVA revealed a significant within-subject effect of tDCS on listening effort in individuals with tinnitus, ($F(1, 1)=171.73$, $p=0.001$, $\eta^2=0.85$), indicating a reduction in listening effort following active stimulation. A significant between-subject effect of group was also observed, ($F(1, 1)=137.16$, $p=0.001$, $\eta^2=0.82$), reflecting overall differences between experimental and control groups. Importantly, the interaction between tDCS and group was significant, ($F(1, 1)=140.35$, $p=0.001$, $\eta^2=0.82$), demonstrating that reductions in listening effort were greater in the experimental group compared to controls.

The effect of transcranial direct current stimulation **intervention on working memory in people with tinnitus**
Repeated measures ANOVA revealed a significant within-subject effect of tDCS on WM in individuals with tinnitus, ($F (1, 1)=294.86$, $p=0.001$, $\eta^2=0.90$), indicating improvements in WM scores following active stimulation. A significant between-subject effect of group was also observed, ($F (1, 1)=57.10$, $p=0.001$, $\eta^2=0.65$), reflecting overall differences between experimental and control groups. Importantly, the interaction between tDCS and group was significant, ($F (1, 1)=227.42$, $p=0.001$, $\eta^2=0.88$), demonstrating that WM improvements were greater in the experimental group than in controls.

The effect of transcranial direct current stimulation **intervention on the blood level of proteins NR1 and NR2** The effect of tDCS intervention on the levels of NR1 and NR2 in the blood was assessed. In the experimental group, NR1 blood protein expression increased from 1.1 to 1.4 (27%), and NR2 blood protein expression increased from 1.0 to 1.5 (50%) following anodal tDCS. In the control group, no comparable changes were observed. These results describe the observed changes in protein expression after the intervention.

Discussion:
The present study investigated the effects of prefrontal anodal tDCS on listening effort, WM, tinnitus-related annoyance, and blood levels of NR1 and NR2. Our findings indicate that tDCS significantly reduced auditory effort and cognitive load during challenging listening conditions, decreased tinnitus-related annoyance, and improved WM performance. These behavioral improvements were accompanied

by increased NR1 and NR2 blood protein levels, although serum measures may not fully reflect DLPFC expression, necessitating cautious interpretation regarding molecular mechanisms [7].
Anodal tDCS likely enhances cognitive performance by modulating glutamatergic signaling and synaptic plasticity, facilitating NMDA receptor activation, and supporting short-term memory and executive functions within the DLPFC [19]. Modulation of temporal cortex activity may further contribute to improved speech perception and reduced listening effort, given its role in auditory processing and linguistic information encoding [24]. These effects align with long-term potentiation (LTP)-like synaptic potentiation, strengthening neural networks essential for memory, attention, and cognitive control [28].
Despite the overall positive effects observed, some studies have reported null or negative impacts of tDCS on WM and cognitive performance. Such inconsistencies may arise from differences in stimulation parameters (current intensity, duration, electrode placement), task complexity, or individual factors including age, cognitive baseline, and overall health status [30-32].
The present findings reinforce the concept that listening effort is a multidimensional construct, dependent on the interaction of cognitive components and brain networks. In tinnitus patients, elevated listening effort demands additional cognitive resources, potentially causing mental fatigue and impairing daily cognitive function [4, 33]. By reducing listening effort and enhancing cognitive performance, prefrontal tDCS demonstrates potential as a non-invasive intervention for cognitive difficulties associated with tinnitus [23]. Further research is warranted to clarify underlying neural and molecular mechanisms, optimize stimulation protocols, and examine long-term effects in diverse populations.

The current research, like other human-based research, faced many limitations, such as patient non-cooperation in the blood sampling and tDCS stages. Also, due to the situation of the coronavirus pandemic, it was not possible to follow up with all patients.

Conclusion
The present study demonstrates that prefrontal anodal tDCS reduces listening effort and tinnitus-related annoyance while improving working memory performance in challenging listening conditions. These behavioral benefits were accompanied by increased NR1 and NR2 blood protein levels, suggesting potential involvement of glutamatergic mechanisms. These results highlight the potential of prefrontal tDCS as a non-invasive intervention, underscoring the need for future research to refine stimulation protocols and investigate long-term cognitive benefits in broader patient populations.

Disclosure of potential conflicts of interest
The authors declare that they have no conflict of interest. No financial or non-financial incentives were offered.

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Authors' contribution

AI: Study design, acquisition of data, interpretation of the results, statistical analysis, and drafting the manuscript, MN: Study design, interpretation of the results, statistical analysis, HJ: Study design, interpretation of the results, MZ: Study design, interpretation of the results, SKH: Study design, interpretation of the results

Fig.1: The evaluation processes of studied groups

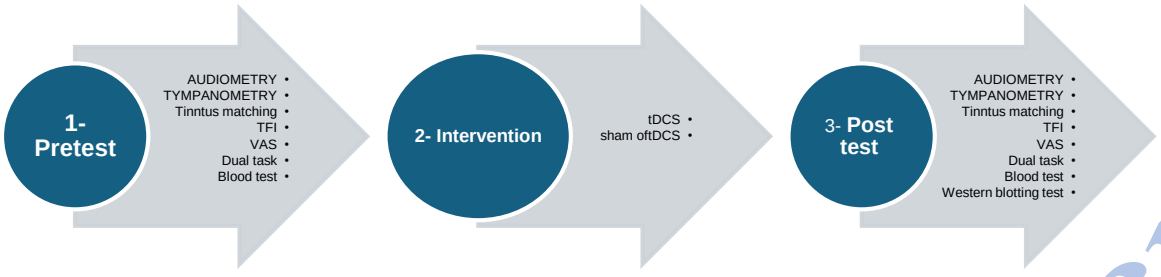

Table 1. Descriptive indicators of research variables in two groups of patients, separated by pre-test and post-test.

Variable	Sessions	Experimental group (n=18)	Control group (n=14)
Assessment		**Mean±SD**	
The degree of mental fatigue caused by tinnitus	**Pre test**	7.66±1.13	7.07±1.32
	Post test	3.11±1.96*	6.92±1.54+
The annoying amount of tinnitus	**Pre test**	0.70±0.13	0.74±0.13
	Post test	0.24±0.12*	0.74±0.13+
Listening effort	**Pre test**	34.72±12.31	37.07±8.80
	Post test	-35.57±13.01*	33.57±10.69+
Working memory	**Pre test**	6.61±1.33	6.42±1.39
	Post test	13.22±0.80*	6.85±1.79+

* Shows a significant difference between pre-test and post-test in the intervention group ($p < 0.001$)
+ shows a significant difference between the post-test of the intervention group and the post-test of the control group ($p < 0.001$). These revisions are highlighted in the manuscript.

Fig.2: The process of blood protein level change of NR1(partA) and NR2(partB) in two groups of tDCS and control group before and after intervention with Tdcs