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High-definition transcranial direct current stimulation of the dorsolateral prefrontal cortex for tinnitus modulation: a preliminary trial

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Abstract Tinnitus is the perception of sound in the absence of its external source. Non-invasive neuromodulation techniques have been used in the past decade to investigate the impact of stimulation on tinnitus perception. The objective is to invest the impact of high-definition transcranial direct current stimulation (HD-tDCS) of dorsolateral prefrontal cortex (DLPFC) stimulation on tinnitus loudness and annoyance. Thirteen participants underwent two sessions of HD-tDCS (real and sham) in a double blind, sham controlled, randomized trial. The washout period between the real and sham stimulation session was 1 week. Tinnitus loudness and annoyance was measured using a ten-point tinnitus loudness/annoyance numeric rating scale at the baseline, after 5, 10, 15 and 20 min of stimulation. There was a significant reduction in the tinnitus loudness after the HD-tDCS of DLPFC. A comparison of the different time points (5, 10, 15 and 20 min) with the baseline measurement for tinnitus loudness showed a statistically significant reduction after 15 min ($t = 1.82$, $p = 0.047$) and 20 min ($t = 1.82$, $p = 0.047$) of stimulation using the real HD-tDCS; this effect was not observed for tinnitus annoyance. HD-tDCS of DLPFC is a safe technique for tinnitus modulation. The most common transient sensations experienced during HD-tDCS were tingling, sleepiness and scalp pain. HD-tDCS of DLPFC resulted in transient tinnitus loudness suppression after 15 min of stimulation. We propose the optimum stimulation duration for HD-tDCS of DLPFC for tinnitus suppression to be 15 min instead of 20 min.

Keywords Tinnitus · Neuromodulation · Dorsolateral prefrontal cortex (DLPFC) · Non-invasive brain stimulation · High-definition transcranial direct current stimulation (HD-tDCS) · Treatment

Introduction

Tinnitus is the perception of a sound in the absence of its external auditory source. It impedes the quality of life by potentially causing anger, frustration, tension, poor communication and lack of sleep (Lockwood et al. 2002). Tinnitus is a prevalent condition and approximately 10% of the US adult population has experienced significant tinnitus, and around 16 million Americans experience tinnitus frequently (Shargorodsky et al. 2010). However, because of the multifactorial mechanisms that lead to tinnitus, effective treatment targeting tinnitus remains elusive.

In the past decade, several novel tinnitus research management options have been explored. The use of non-invasive neuromodulation techniques such as: transcranial direct current stimulation (tDCS) (Garin et al. 2011; Vanneste et al. 2010; Fregni et al. 2006) is one of them and has shown promising results but is transient in nature (Shekhawat et al.

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2012, 2013). Neuromodulation techniques are hypothesized to work by inducing neural plasticity and disturbing the pathological neural networks responsible for tinnitus (Langguth and De Ridder 2011). This stimulation is polarity dependent, with anodal stimulation causing neuronal depolarization leading to increased excitability, and cathodal stimulation causing neuronal hyperpolarization leading to decreased excitability (Nitsche and Paulus 2000; Bindman et al. 1962; Iyer et al. 2005). Thus, when an anode or cathode is positioned over a target area of the cortex, it can facilitate or suppress cortical activity (Nitsche and Paulus 2000).

High-definition transcranial direct current stimulation (HD-tDCS) is a non-invasive and painless technique to stimulate the various cortical and sub-cortical brain structures (Minhas et al. 2010; Edwards et al. 2013; Kuo et al. 2012; Dmochowski et al. 2013; Borckardt et al. 2012; Villamar et al. 2013b). Its action is highly focal and can specifically modulate cortical activity within the region confined by its 4 × 1 ring of electrodes, such that the targeted region becomes more amenable to neuroplastic change. In HD-tDCS the conventional large rubber electrodes used during tDCS are replaced with an array of small microelectrodes. Current is applied to selected microelectrodes to optimize current flow to the target. Recently, HD-tDCS has been used to achieve a more precise current delivery to the brain (Villamar et al. 2013a). Specific areas of the brain are targeted utilizing a central ring electrode over the cortical region of interest, circumscribed by a four-electrode ring configuration (Villamar et al. 2013a, b). The constraint of brain current flow created by the 4 × 1 ring allows for focal stimulation, sparing the surrounding anatomical areas (Datta et al. 2008, 2009; Kuo et al. 2012). The most commonly encountered transient sensations while undergoing HD-tDCS are tingling, sleepiness and sensation of scalp pain (Shekhawat et al. 2015b).

The two most popular stimulation locations for tinnitus management have been the left temporoparietal area (LTA) and dorsolateral prefrontal cortex (DLPFC) (Shekhawat et al. 2015a). Shekhawat et al. (2012) conducted a pilot study to explore tDCS intensity and duration effects on tinnitus suppression with LTA stimulation. This pilot study demonstrated that anodal tDCS of the LTA using a 2 mA current intensity delivered for 20 min was most effective in transiently suppressing tinnitus. Further, an optimization trial for HD-tDCS showed that 2 mA current intensity for 20 min was optimum for tinnitus suppression (Shekhawat et al. 2015b). Furthermore, both LTA and DLPFC revealed to be an effective site of stimulation for tinnitus suppression. Connected to the LTA is a neural network that appears to play a significant role in tinnitus perception: primary auditory cortex and auditory association areas, as well as the amygdala and hippocampus (Mühlnickel et al. 1998; Mirz et al. 2000; Giraud et al. 1999). There are several studies supporting the stimulation of LTA for tinnitus suppression (Fregni et al. 2006; Garin et al. 2011; Joos et al. 2014; Teismann et al. 2014; Shekhawat et al. 2013, 2015b). DLPFC is actively involved in modulating tinnitus loudness and annoyance (Vanneste et al. 2010; Faber et al. 2012). DLPFC contains auditory memory cells and has been associated with auditory attention, early inhibitory modulation of input to primary auditory cortex and a facilitatory effect on auditory memory storage (Lukman et al. 2010; De Ridder et al. 2015; Ashton et al. 2007; Moazami-Goudarzi et al. 2010; Jastreboff 1990).

A study using HD-tDCS revealed a positive response rate of 77% (Shekhawat et al. 2015b), which is superior to conventional tDCS (56%) (Shekhawat et al. 2012). However, both of these studies (Shekhawat et al. 2012, 2015b) were dose–response trials and not sham controlled design. In HD-tDCS, trial duration settings used were 10 and 20; 5 and 15 min duration settings were not used in that trial. It is important to conduct sham controlled trails to investigate if similar results can be replicated about the optimization parameters for tinnitus suppression. The aim of the present study was to conduct a preliminary trial with a superior research design (double blind, sham controlled, randomized trial) investigating the impact of DLPFC stimulation on tinnitus suppression to inform the need for future randomized controlled trials. Since the DLPFC is a non-auditory brain area which integrates sensory and emotional aspects of tinnitus (Faber et al. 2012), we hypothesize that HD-tDCS of the DLPFC will result in tinnitus suppression compared to a sham session. This potential clinical effect of promising new treatments can give important information about the effect size of the treatment and may help to identify subgroups of patients being more likely to respond to the tested intervention. This information is necessary to design larger prospective placebo-controlled clinical trials, which are more costly and time consuming (Dobie 2004). As such, we installed an explorative pilot study on the effect of HD-tDCS targeting the DLPFC on tinnitus.

Methods

Participants

Thirteen participants with continuous chronic tinnitus for more than 2 years were recruited through the University of Auckland Hearing and Tinnitus Clinic, and Centre for Brain Research participant databases. Participants were excluded if they had any contraindications to undergoing HD-tDCS (personal or family history of seizures, metal or electronic implants, pregnancy, heart conditions, brain surgery and others) as screened by a neurologist. This study was approved by the University of Auckland Human Participants Ethics

Committee. Written informed consent was provided by all participants as per the Declaration of Helsinki.

Research protocol and questionnaires

This preliminary trial was a double blind, sham controlled, randomized study. Experimental procedures and data analysis were performed before being unblinded. Each participant underwent two sessions (one sham and one real HD-tDCS) with a 1-week washout period. Research participants were randomized to either a sham or true HD-tDCS stimulation for their first session. Seven participants received sham stimulation first followed by real stimulation after 1 week and six participants received real stimulation first followed by sham stimulation after 1 week. Real stimulation was 20 min long and included a 30 s fade in/out period. Sham stimulation included 30 s fade in/out period and there was no stimulation in between the fade in and fade out period.

Tinnitus Functional Index (TFI) (Meikle et al. 2012) and Tinnitus Sample Case History Questionnaire (TSCHQ) (Langguth et al. 2007) were conducted at the time of recruitment. During each session, six numeric rating scales (Axelsson et al. 1993) were filled to assess the loudness and annoyance of the participants' tinnitus at the following time points: immediately upon arrival (first baseline), immediately prior to stimulation (second baseline), during stimulation (5, 10, 15 and 20 min, respectively) of the real/sham session. Two baseline ratings were performed prior to the stimulation to document the change in environment from day-to-day environmental settings to sound treated rooms where the stimulation was performed. Using the second baseline as the comparison for post-stimulation ratings accounts for time to adjust from the day-to-day environment to a sound treated room. Tinnitus suppression was defined as a minimum one-point decrease in a ten-point loudness and annoyance numeric rating scale. Participants were monitored for adverse events and their perceptions of sensations experienced during the stimulation were documented.

Hearing assessment

A hearing assessment was conducted in a sound treated room (ISO 8253–1:2010). Pure tone audiometry (0.25–16 kHz) was undertaken using a 2-channel audiometer (either GSI-61, Grason Stadler, Eden Prairie, MN; or AC40, Interacoustics, Assens, Denmark). Measurements (0.25–8 kHz) were made using standard earphones (TDH-50P; Telephonics) or insert headphones (E.A.RTONE 3A) and high-frequency (8–16 kHz) headphones (Sennheiser HDA 200). Audiometry was obtained using the modified Hughson–Westlake procedure (Carhart and Jerger 1959).

High-definition transcranial direct current stimulation (HD-tDCS)

HD-tDCS was applied for 20 min in accordance with the recommendations of international guidelines for tDCS (Norris et al. 2010; Loo et al. 2011; DaSilva et al. 2011). A NeuroConn DC stimulator (Germany) was used for all procedures. A 4 × 1 HD-tDCS was placed on the scalp with the central electrode (the anode) placed on the right dorsolateral prefrontal cortex. High-definition gel-based electrodes have been shown to increase focality as compared to standard electrode pads (Nitsche et al. 2007). Stimulation location was determined using the international 10–20 system (Reilly 1993) by first calculating the Cz and from that the DLPFC (20% the distance to the nasion forward and 20% the distance to the right tragus laterally). The anode was placed at F4 and four adjoining cathodes were placed at F2, FC4, F6 and AF4, respectively. Cathodes were approximately 3.5 cm away from the anode. Impedance and voltage were monitored and maintained < 6 kΩ and < 6 V, respectively, across all the stimulation settings.

Sensitivity and statistical analysis

Based on a sensitivity analysis for we enrolled 13 participants, the study is designed to give us adequate power (80%) to detect meaningful differences (two-paired *t* test) between active and sham between each condition with a Cohen's *dz* estimation of effect size (0.7).'

To normalize the data at baseline, we calculate the percentage of change in comparison to baseline. This allows us to have a better idea of the improvement over time and avoid difference at baseline (see Table 1). Two-paired *t* test was used to compare the different time points (baseline, 5, 10, 15, 20 min) as well as between the real and sham stimulation for the outcome measures tinnitus loudness and annoyance, respectively.

Results

Baseline characteristics

Thirteen participants with mean age of 53.6 years completed the trial. Demographic details of participants included in the

Table 1 Average baseline scores (and standard deviations) for tinnitus loudness and annoyance for the real and the sham HD-tDCS

	Loudness	Annoyance
Real HD-tDCS	4.46 (1.42)	4.38 (1.73)
Sham HD-tDCS	5.23 (1.28)	3.38 (1.33)

study are depicted in Table 2. Hearing status of the participants included in this study is shown in Fig. 1. There was a mild sensorineural hearing loss up to 8 kHz among all the participants. Hearing loss reached up to a severe degree at extended high frequencies (up to 16 kHz). No significance difference was obtained for the loudness ($t = 2.01$, n.s.) and annoyance between the sham and real stimulation condition ($t = 1.87$, n.s.) (see Table 1).

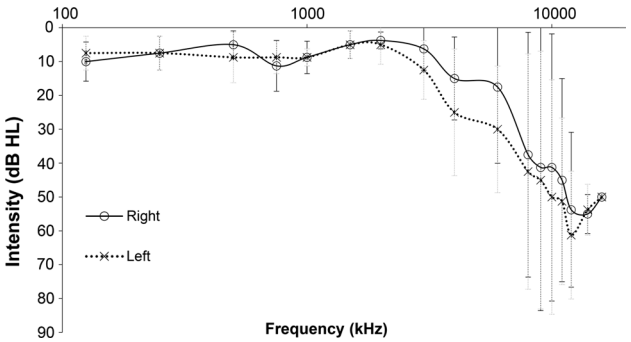

Fig. 1 Mean hearing thresholds of right (circles) and left ear (crosses) for thirteen participants in the study. The error bars represent ± 1 standard error of the mean

Stimulation

Overall, HD-tDCS of DLPFC was safe and without any adverse event. Some participants experienced sensations such as tingling, sleepiness and scalp pain (Table 3). All these sensations were transient and did not persist after the completion of HD-tDCS stimulation.

During each session of stimulation (real or sham), participants rated their loudness and annoyance on a ten-point rating scale at six time points (twice at the baselines and after every 5 min of stimulation during the 20 min session). A comparison of the different time points (5, 10, 15 and 20 min) with the baseline measurement for tinnitus loudness showed a significant effect after 15 min ($t = 1.82$, $p = 0.047$) and 20 min ($t = 1.82$, $p = 0.047$) of stimulation using the real HD-tDCS targeting DLPFC. For both, 15 and 20 min of stimulation, we see an average improvement of 13.57% (SD 26.88) and 13.57% (SD 26.88) in comparison to baseline, respectively. No effect was obtained after 5 min ($t = 0.73$, $p = 0.23$) or 10 min ($t = 0.77$, $p = 0.23$). In addition, no effect was obtained at 5 ($t = -0.82$, $p = 0.21$), 10 ($t = -0.82$, $p = 0.21$), 15 ($t = -0.31$, $p = 0.38$) and 20 ($t = -0.31$, $p = 0.38$) min of HD-tDCS sham stimulation targeting the DLPFC. A similar analysis for comparing the different time points with the baseline for tinnitus annoyance revealed no significant effect for the real ($t = -0.91$ to -1.68, $p = 0.06$ to 0.19), and sham ($t = -0.41$ to 0.60, $p = 0.27$ to 0.34) HD-tDCS stimulation targeting DLPFC. See Fig. 2 for an overview.

A comparison between the real and sham HD-tDCS conditions for tinnitus loudness revealed a significant effect at 15 and 20 min, but not for 5 and 10 min (see Table 4). A comparison between the real and sham HD-tDCS conditions for tinnitus annoyance revealed no significant effects at 5, 10, 15 and 20 min (see Table 4). An overview of the outcome can be found in Table 4 and Fig. 3.

To find the critical duration of stimulation that generates an effect on tinnitus loudness we compared the different time points during real HD-tDCS targeting the DLPFC. Table 4 demonstrates a significant effect was obtained after 15 and 20 min of real HD-tDCS stimulation in comparison to baseline, 5 and 10 min. No significant effect was obtained between 15 and 20 min of stimulation. No effect

Table 2 Demographic details of participants included in the study

S. no	Tinnitus						
	Age	Sex	TFI score	Quality	Laterality	Duration	Pitch
1	60	M	27.20	Noise	R < L	> 30	Medium frequency
2	68	M	24.58	Crickets	R > L	> 30	High frequency
3	67	M	8.80	Tone	R > L	10	High frequency
4	52	M	27.20	Noise	L	10	High frequency
5	63	M	34.00	Noise	R < L, Inside the head	35	Very high frequency
6	49	M	29.60	Crickets	R = L	13	High frequency
7	43	M	42.80	Tone	R = L	18	High frequency
8	50	M	22.00	Tone	R > L	17	High frequency
9	53	M	5.60	Tone	R < L	> 30	High frequency
10	29	M	3.20	noise	L > R	10	High frequency
11	63	M	34.00	noise	R > L	43	Very high frequency
12	36	M	24.80	Noise	R = L, inside the head	5	Very high frequency
13	64	M	45.20	Crickets	L > R, inside the head	44	Medium frequency

'R' represents 'right ear' and 'L' represents 'left ear'. 'M' is male, age and duration is in years

Table 3 Sensations experienced during sham and real HD-tDCS of DLPFC ($n = 13$ participants)

Symptoms or side effects	Sham stimulation *n* strength of sensation: if related to HD-tDCS	Real stimulation	Significant
Headache	0	2 mild: not related	n.s.
Neck pain	0	2 mild: 1 not related, 1 possibly related	n.s
Scalp pain	3 mild: 1 possible, 2 definite	3 moderate: 1 probable, 2 definite 1 mild: definite	n.s
Scalp burns	1 severe: probable 1 moderate: definite 1 mild: definite	2 moderate: 1 not related, 1 definite 3 mild: 3 definite	n.s.
Tingling	6 mild: 1 not related, 1 possible, 4 definite 1 moderate: definite	7 mild: 1 possible, 1 probable, 5 definite	n.s.
Sleepiness	4 mild: 2 not related, 1 remote, 1 probable 1 moderate: possible	6 mild: 2 not related, 2 remote, 2 possible 1 moderate: remote	n.s.
Trouble concentrating	0	1 mild: possible	n.s.
Acute mood change	1 mild: not related	0	
Other	1 wave like sensation: not related	0	n.s.

"*n*" represents the number of participants experiencing a symptom or side effects, "strength of sensation" refers to the strength (mild/moderate/severe) of the symptom and if that sensation has been related to HD-tDCS is mentioned (not related/remote/possible/probably/definite). 'Scalp burn' is the sensation of burning instead of real burn n.s.: not significant based on a χ^2 test

HD-tDCS high-definition transcranial direct current stimulation, *DLPFC* dorsolateral prefrontal cortex

was obtained for sham HD-tDCS stimulation on tinnitus loudness, nor was there an effect for both real and sham HD-tDCS stimulation on tinnitus annoyance (see Table 4).

Discussion

Thirteen participants underwent two sessions of HD-tDCS of DLPFC (real and sham) with 1-week washout period. Most commonly perceived sensations while undergoing HD-tDCS were tingling, sleepiness and scalp pain. These sensations were experienced at the onset of the stimulation and were transient; they did not last after the stimulation. Similar results were reported in a dose–response trial of HD-tDCS conducted by Shekhawat et al. (2015b), and most commonly experienced sensations were: tingling, scalp pain, scalp burn and sleepiness. These sensations were experienced irrespective of the site of stimulation (both LTA and DLPFC). Overall HD-tDCS is a safe technique, which was well-tolerated by research participants and no adverse event was observed during the present study and the past trial by Shekhawat et al. (2015b).

HD-tDCS of DLPFC resulted in significant suppression of tinnitus loudness after 15 min of stimulation. However, no statistically significant suppression was observed for tinnitus annoyance. These findings are contrary to the findings of the dose–response study by Shekhawat et al. (2015b) where both, tinnitus loudness and annoyance, were suppressed by stimulation of both DLPFC and LTA. However, there are few differences in these two trials. The previous trial conducted was a dose–response design that was not sham controlled; however, the present preliminary trial was superior in its design being a double blind, sham controlled randomized in nature. The aim of the present study was to investigate the impact of HD-tDCS of DLPFC on tinnitus loudness and annoyance; however, the study conducted by Shekhawat et al. (2015b) was aimed at optimization of current intensity, duration and location for tinnitus suppression. There were differences in terms of sample size (27 participants compared to 13 in the present study) and gender (both males and females in the past study, however, the present study was limited to only males). Frank et al. (2012) reported the effect of gender on the responsiveness towards the tDCS stimulation. Females tend to respond more positively compared to males. Considering our study did not have any female research participants, it would be difficult to rule out the impact of gender towards the responsiveness to HD-tDCS. The optimization trial by Shekhawat et al. (2015b) revealed current intensity of 2 mA and duration of 20 min to be the optimal setting for tinnitus suppression. However, the present study reveals that 2 mA current intensity for 15 min is not statistically different to 2 mA stimulation for 20 min. It is interesting, that there was no difference between 15 and 20 min of real stimulation targeting the DLPFC using HD-tDCS in the outcome for loudness and annoyance. This latter finding could suggest that there is a plateau effect after 15 min, which remains after 20 min. Hence, we recommend that for HD-tDCS of DLPFC, 15 min stimulation to be optimum instead of 20 min.

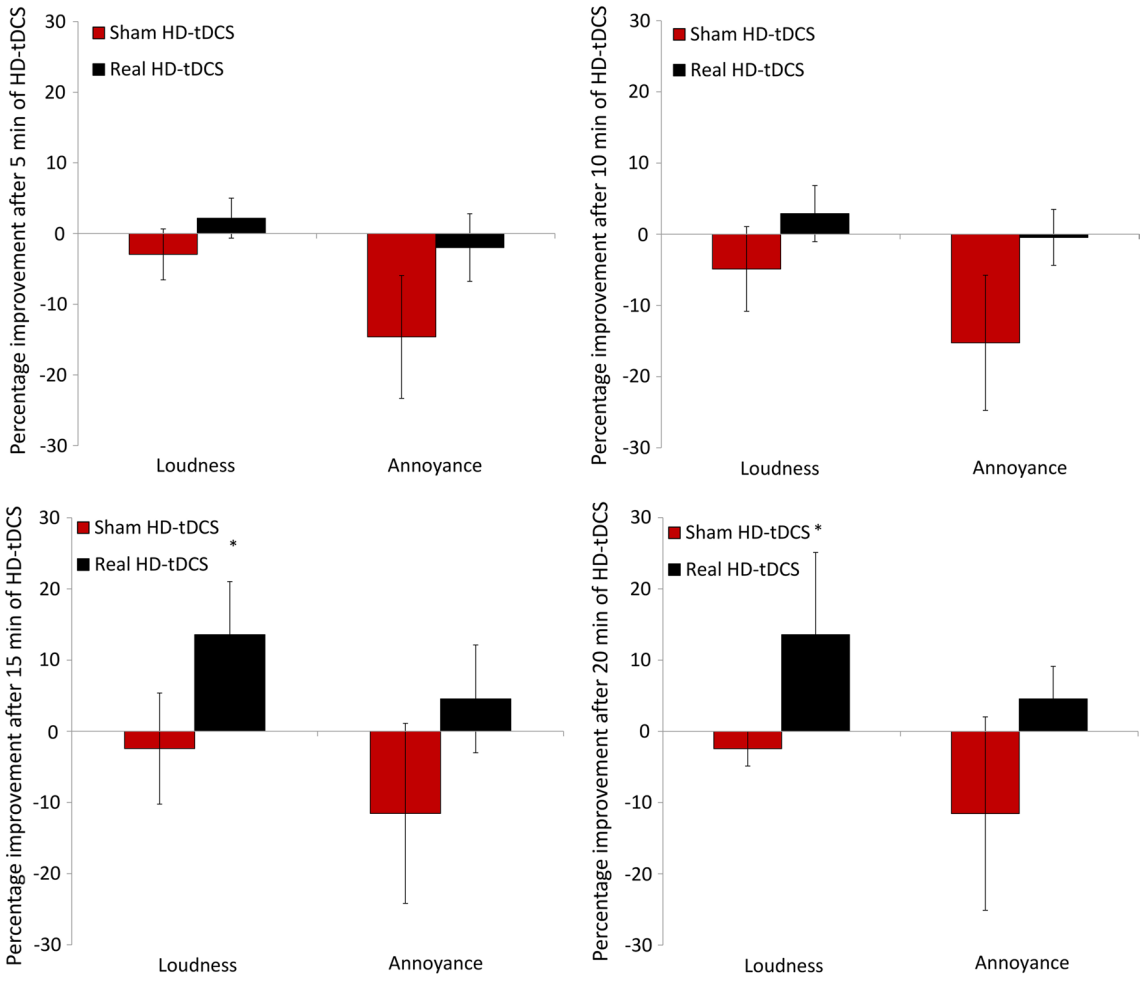

Fig. 2 A comparison between the real and sham HD-tDCS conditions for tinnitus loudness and annoyance at 5, 10, 15 and 20 min

Table 4 A comparison between the real and sham HD-tDCS conditions for tinnitus loudness and annoyance at 5, 10, 15 and 20 min

	Sham HD-tDCS		Real HD-tDCS		Comparison	
	M	SD	*M*	SD	*t* value	*p* value
Loudness						
Baseline	–	–	–	–		
5 min	− 2.95	12.98	2.18	10.17	− 1.33	0.103
10 min	− 2.44	28.13	2.89	14.21	− 0.79	0.224
15 min	− 2.44	28.13	13.57	26.89	− 1.90	**0.041**
20 min	− 2.44	28.13	13.57	26.89	− 1.90	**0.041**
Annoyance						
Baseline	–	–	–	–		
5 min	− 14.62	31.32	− 1.98	17.22	− 1.38	0.097
10 min	− 15.26	34.23	− 0.44	14.16	− 1.71	0.057
15 min	− 11.54	45.59	4.56	27.31	− 1.17	0.133
20 min	− 11.54	45.59	4.56	27.31	− 1.17	0.133

p value in bold show a significant effect

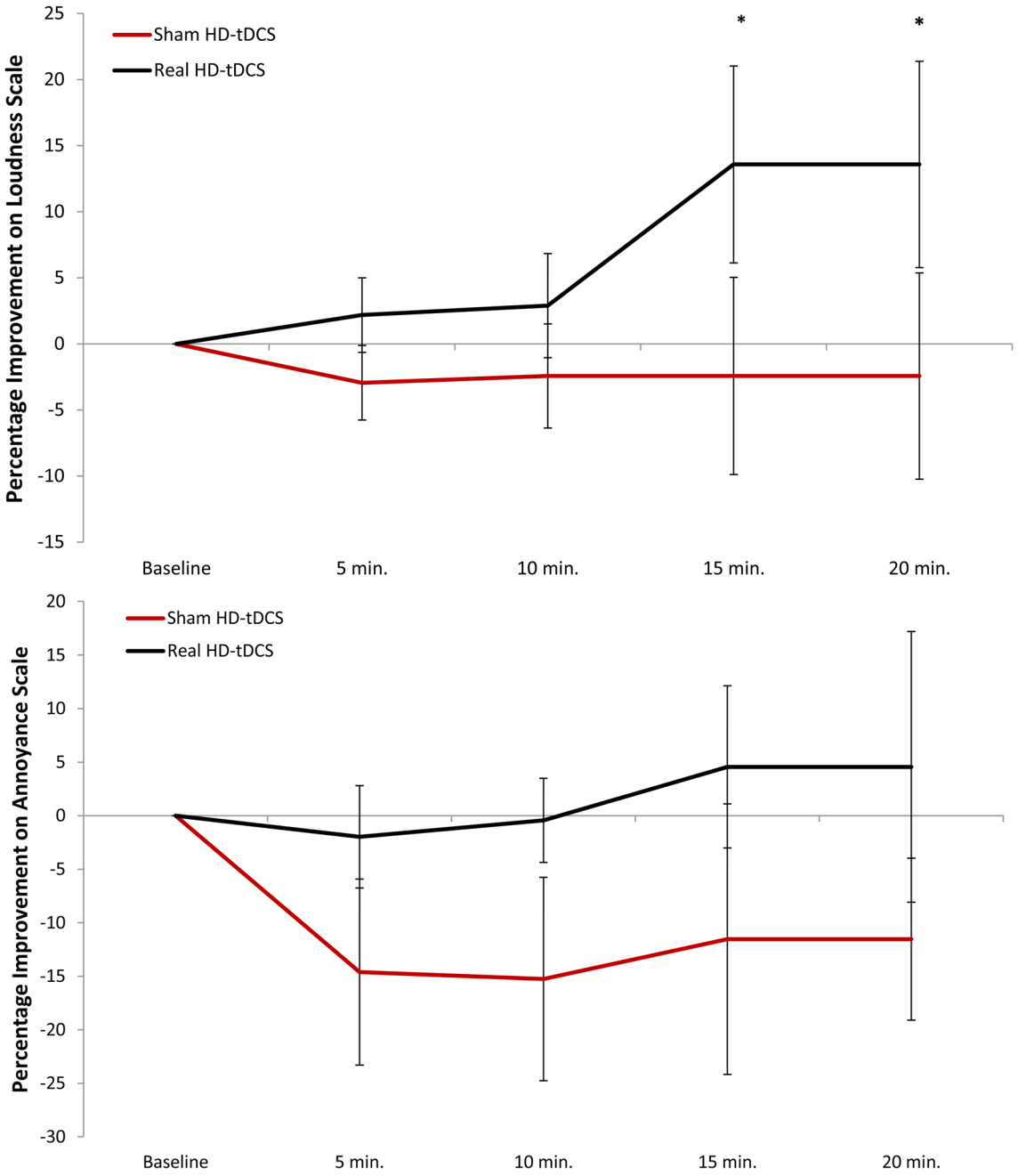

Fig. 3 A comparison between the effect of real and sham HD-tDCS over time (baseline 5, 10, 15 and 20 min) for tinnitus loudness and annoyance

There are some early trends that stimulation of DLPFC results in suppression of tinnitus annoyance more than tinnitus loudness and the stimulation of LTA results in suppression of tinnitus loudness more than tinnitus annoyance (Shekhawat et al. 2015a). The study by Shekhawat et al. (2015b) also reported a similar trend where both, LTA and DLPFC, were effective in suppressing tinnitus annoyance and loudness. However, DLPFC resulted in slightly more annoyance suppression (compared to LTA stimulation) and LTA stimulation led to more loudness suppression (compared with DLPFC stimulation) but the differences in the loudness and annoyance suppression between the two sites of stimulation was not statistically significant. Faber et al. (2012) proposed tDCS of the DLPFC modulated tinnitus annoyance but had no impact on tinnitus loudness (Faber et al. 2012). However, the hypothesis of difference in loudness and annoyance has been contradicted by other studies (Vanneste and De Ridder 2011; Vanneste et al. 2011, 2013;

De Ridder and Vanneste 2012). Most of these evidence comes from tDCS studies and it is impossible to rule out the slightly different impact HD-tDCS might have on the underlying cortical areas compared to conventional tDCS.

DLPFC is important for integration of sensory and emotional aspects of tinnitus and has a bilateral facilitator effect on memory storage; it contains auditory memory cells, early inhibitory modulation to primary auditory cortex in humans (Lukman et al. 2010; De Ridder et al. 2015; Ashton et al. 2007; Moazami-Goudarzi et al. 2010; Jastreboff 1990). DLPFC may affect tinnitus intensity by an inhibitory modulation of the auditory cortex, "top-down" inhibitory mechanism via anterior cingulate.

Future implications

The present preliminary trial was of superior research design (sham controlled, double blind and randomized); however, it was limited by its sample size (thirteen) and all the research participants included in this trial were males. For future research, we recommend to conduct clinical trials with both genders and a larger sample size. We recommend registering the clinical trials in a clinical trial repository. Sham controlled trials should also have the provision of asking the participants about placebo effects by asking them about their perception of the real and sham session towards the end of the clinical trial. It would also be helpful to include long-term follow up visits to investigate the long-term impact of HD-tDCS on tinnitus perception. This study was confined to DLPFC stimulation; however, it would be interesting to investigate the stimulation of multiple locations on tinnitus perception.

Conclusion

HD-tDCS is a safe and well-tolerated non-invasive stimulation technique for tinnitus modulation. HD-tDCS of DLPFC resulted in significant suppression of tinnitus loudness after a session of 15 min of stimulation. We propose the optimum stimulation duration for HD-tDCS of DLPFC for tinnitus suppression to be 15 min instead of 20 min. In the present study, we did not find statistically significant suppression of tinnitus annoyance as a result of DLPFC stimulation. Although the research design of the present trial was superior because it was double blind, sham controlled and randomized, results need to be interpreted with caution considering the small sample size and the preliminary nature of the study.

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