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Top down prefrontal affective modulation of tinnitus with multiple sessions of tDCS of dorsolateral prefrontal cortex

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Most forms of tinnitus are attributable to reorganization and hyperactivity in the auditory central nervous system with coactivation of nonauditory brain structures. One such nonauditory brain area is the dorsolateral prefrontal cortex (DLPFC), which is important for the integration of sensory and emotional aspects of tinnitus. Based on extensive evidence that transcranial direct current stimulation can induce significant effects on DLPFC-related cognitive function, we aimed to investigate whether left or right anodal DLFPC tDCS is associated with modulation of tinnitus. We conducted a double-blind, placebo-controlled cross-over study in which 15 subjects with tinnitus were randomly assigned to receive active and sham anodal tDCS over left (n = 8) or right DLPFC (n = 7) for six sessions in a counterbalanced order; the cathode electrode was placed in the contralateral DLPFC. The results demonstrate that both active conditions—irrespective of the anodal position—can decrease tinnitus annoyance but it is not associated with improvements in tinnitus intensity when comparing pre-tDCS versus post-tDCS as well as comparing sham-tDCS versus real tDCS. Also, we show that the anode electrode placed over the left DLPFC modulates depression when comparing pre-tDCS versus post-tDCS as well as comparing sham-tDCS versus real tDCS. In addition, we also show that the anode electrode placed over the right DLPFC modulates anxiety when comparing pre-tDCS versus post-tDCS. This latter effect does not remain when we compare sham-tDCS versus real tDCS. This study further supports the involvement of the prefrontal cortex in the neural network associated with tinnitus, and also provides initial evidence for a potential brain stimulation site for tinnitus treatment in association with other treatments that can reduce tinnitus intensity.

Keywords tDCS; depression; anxiety; tinnitus; lateralization; frontal

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Tinnitus is described as ongoing perception of sounds (e.g., a tone, hissing, or buzzing sound, and sometimes combinations of such perceptions) in the absence of any objective physical sound source.[1] In western societies about 5-15% of the population has chronic tinnitus and will seek medical care.[2,3] The constant awareness of this phantom sound often causes a considerable amount of distress; in fact between 6% to 25% of the affected people report symptoms that are severely debilitating.[4,5] Psychologic complications such as lifestyle detriment, emotional difficulties, sleep deprivation, work hindrance, interference with social interaction, and decreased overall health have been attributed to tinnitus.[6-9]

Based on functional imaging studies, it is generally accepted that tinnitus is related to maladaptive plasticity because of damage of the auditory system. Most forms of tinnitus are attributable to reorganization and hyperactivity in the auditory central nervous system[5,10-12] with coactivation of nonauditory brain structures such as the insula,[13,14] anterior cingulate cortex,[14-16] and dorsolateral prefrontal cortex (DLPFC).[14,17]

DLPFC seems to play a significant role in auditory processing. Bilateral DLPFC has a facilitatory effect on auditory memory storage and contains auditory memory cells.[18] This prefrontal area also exerts early inhibitory modulation of input to primary auditory cortex in humans[19] and has been found to be associated with auditory attention[20-22] resulting in top-down modulation of auditory processing.[23] This has been further confirmed by electrophysiologic data indicating that tinnitus might occur as the result of a dysfunction in the top-down inhibitory processes.[24]

In the context of the role of DLPFC for tinnitus modulation, transcranial direct current stimulation (tDCS) is a desirable tool to explore its contribution to tinnitus as it can significantly change neuronal spontaneous firing in a localized cortical area. In tDCS, a weak direct electrical current (1-2 mA) is applied on the scalp, and reaches the brain. This current induces shifts in membrane resting potentials, thereby depolarizing or hyper-polarizing neurons.[25] Depending on the polarity of the stimulation, the technique induces an increase or decrease in cortical excitability in the brain regions to which it is applied.[26,27] Anodal tDCS typically has an excitatory effect on the local cortical excitability by inducing a relative neuronal depolarization, whereas cathode has an opposite effect–it induces a hyperpolarization.[28]

In a recent study, Vanneste and colleagues[29] demonstrated that a single session of tDCS over the DLPFC (anode over right DLPFC) yields a transient improvement in subjects with chronic tinnitus, whereas stimulation with anode over left DLPFC induces no changes in tinnitus. Interestingly, modulation of DLPFC activity with tDCS can lead to a range of behavioral changes in different conditions such as: mood improvement in major depression,[30,31] reduction of impulsiveness,[32] cognitive modulation in Parkinson's disease,[33] and modulation of pain processing.[34,35] However, in recent studies, better results were obtained after multiple sessions of tDCS (i.e., minimum five sessions)[30] and it seems that there was a lateralization effect as anode electrode positioned over the left, but not right DLPFC, induces the most significant effects.[30,31,34]

We conducted a placebo controlled cross-over study to investigate (1) the effects of multiple sessions of tDCS over the DLPFC on symptoms of tinnitus, including tinnitus loudness, tinnitus annoyance, depression, and anxiety; and (2) a potential lateralization effect–in other words, if there is a difference between left and right anodal DLPFC tDCS.

Method

Participants

Fifteen subjects (11 males and four females) with chronic bilateral pure tone tinnitus (> 1 year) participated in this study, with a mean age of 49.43 years (standard deviation [SD] = 14.89). The mean tinnitus duration was 7.44 years (SD = 5.69). To obtain a homogeneous sample and exclude potential variables that would interfere with response to tDCS, we excluded subjects based on the following criteria: individuals with pulsatile tinnitus, a history of epileptic insults, severe organic comorbidity, a pacemaker or defibrillator, a present pregnancy, neurologic disorders such as brain tumors, and individuals being treated for mental disorders. All prospective subjects underwent a complete ENT and neurologic investigation to rule out possible treatable causes for their tinnitus.

Experimental design

We conducted a double-blind, cross-over placebo controlled study to evaluate the suppressing effect of multiple sessions of tDCS over the DLPFC on tinnitus. Subjects were randomized to receive two different types of treatment: anodal left/cathodal right DLPFC or cathodal left/anodal right DLPFC tDCS. In these two conditions they received active and sham conditions (in a counterbalanced order). Therefore, within each study arm each subjects received six sessions (in 2 weeks-3 days of week) of tDCS stimulation (real or sham), followed by a washout of 8 weeks and then the same treatment again with the other condition (sham or real, respectively). Subjects who were first assigned to real tDCS received sham stimulation during the second period and vice versa. To eliminate subjective bias, all subjects and the investigator testing the endpoint measures were blinded to the type of intervention (active or sham/anodal left or anodal right) and were not informed that there was a placebo arm involved until the end of the study.

The study was in accordance with the ethical standards of the Helsinki declaration (1964) and was approved by the institutional ethics committee of the Antwerp University Hospital. All patients singed written informed consents. The study has been registered at the clinical trial registery.

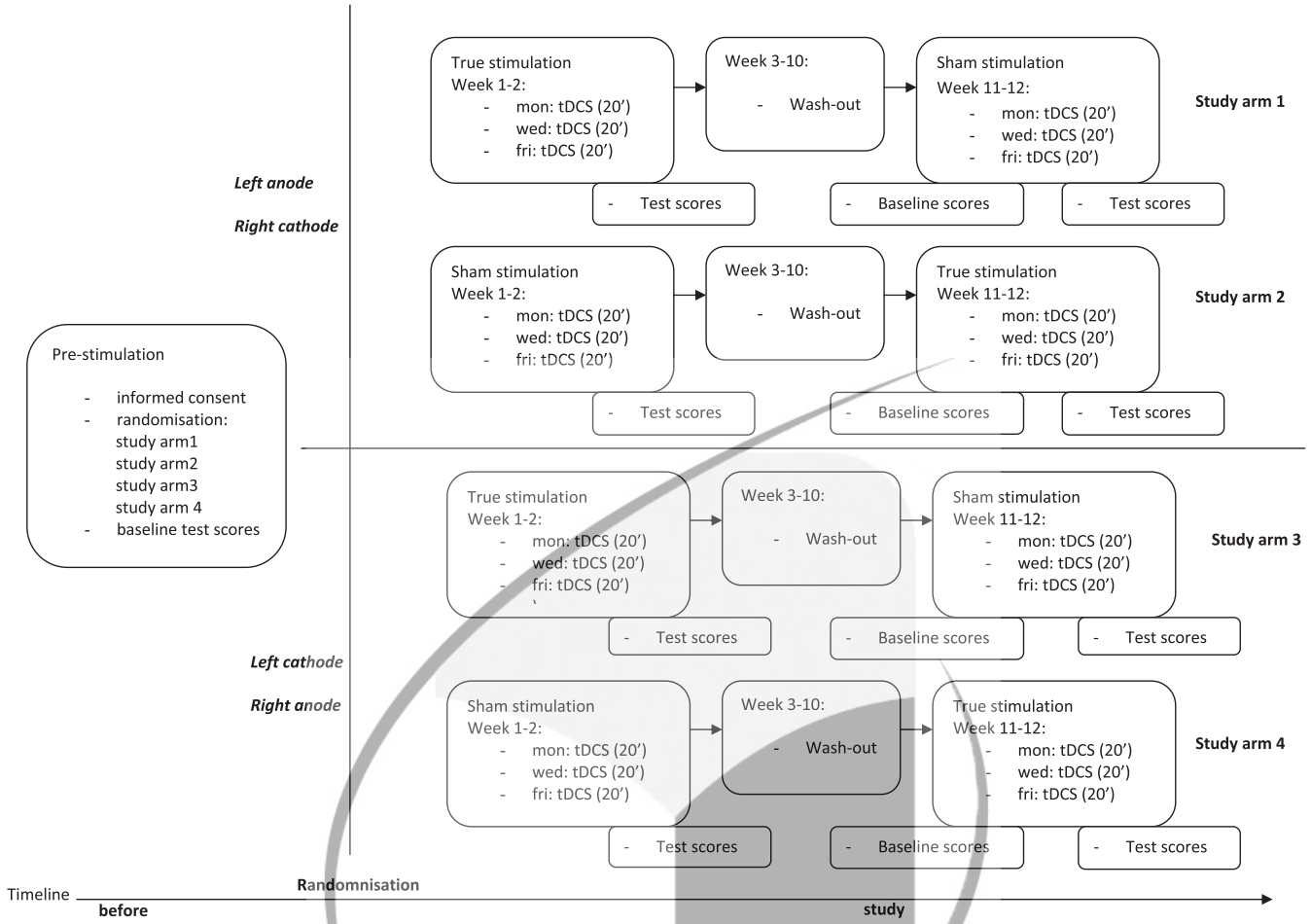

Figure 1 Overview of study design.

Transcranial DCS

Direct current was transmitted by a saline-soaked pair of surface sponges (35 cm^2) and delivered by a battery-driven, constant current stimulator with a maximum output of 10 mA (NeuroConn; http://www.neuroconn.de/). For each subject, we used a bilateral montage over the left and right DLPFC. Half of the subjects received anodal stimulation over right DLPFC (referred in the text as "anodal right"), and the other half received anodal stimulation over the left DLPFC (referred in the text as "anodal left"). For each condition, the cathode electrode was placed on the contralateral DLFPC site. The site for stimulation was determined by the International 10/20 Electroencephalogram System corresponding to F3 and F4, respectively. In both real tDCS and sham, the DC current was initially increased in a ramp-like fashion over several seconds (10 seconds) until reaching 1.5 mA. In active tDCS, stimulation was maintained for a total of 20 minutes; in sham, it was turned off after 30 seconds. These parameters for sham stimulation were chosen based on previous reports that the perceived sensations on the skin, such as tingling, usually fade out in the first 30 seconds of active tDCS.[36,37]

Eight subjects received anodal left and seven subjects received anodal right. Figure 1 is an overview of the study design.

Evaluation

Before and after the experimental procedures, the subjects completed a set of validated self-report inventories and used before in our studies. Primary outcome of treatment was evaluated for the changes of tinnitus annoyance ("How irritating is your tinnitus?') using a Visual Analogue Scale. Secondary outcome parameters were, tinnitus loudness ("How loud is your tinnitus?') using a Visual Analogue Scale, depression and anxiety symptoms as measured by the Hospital Anxiety and Depression Scale (HADS). The HADS is designed as a simple yet reliable tool for use in medical practice[38] and considered to be a measure of general distress.[39-41] This scale consists of 14 questions, seven measuring anxiety (score from 0-21) and seven measuring depression (score from 0-21). Each question was rated on a four-point scale. As this was a cross-over study, data were obtained twice at baseline (at the beginning of the study and after the washout period, before the

Table 1 Comparing before first set of sessions versus before second set of sessions and measures after the washout period for respectively tinnitus loudness, tinnitus annoyance, anxiety, and depression starting with sham group or real tDCS for both anodal right and anodal left DLFPC tDCS separately

	S test
Anode left/Cathode right	
Study arm 1	
Baseline Real tDCS versus Baseline Sham tDCS	
Loudness	−1.41
Annoyance	−1.04
Depression	0
Anxiety	−1.00
Study arm 2	
Baseline Sham tDCS versus Baseline Real tDCS	
Loudness	−1.00
Annoyance	−1.60
Depression	0
Anxiety	−1.00
Anode right/Cathode left	
Study arm 3	
Baseline Real tDCS versus Baseline Sham tDCS	
Loudness	−1.00
Annoyance	−1.63
Depression	−1.00
Anxiety	−1.04
Study arm 3	
Baseline Sham tDCS versus Baseline Real tDCS	
Loudness	−1.00
Annoyance	−1.60
Depression	−1.00
Anxiety	−1.00

second set of stimulation sessions); and posttreatment—twice (at the sixth [after first treatment] and 12th tDCS stimulation [after the second treatment]).

Statistical analyses

Calculations were performed using SPSS software package (version 18.0, Chicago, IL). Nonparametric tests are applied as the measured outcomes were not normally distributed, as a consequence of the small sample size. To verify whether there was a carry-over effect between baseline measures and measures after the washout period, we used a Wilcoxon singled rank test. A Wilcoxon singled rank test was also applied on the data comparing pre- and post-tDCS. A Mann-Whitney *U* test was performed to verify whether there was a difference in tinnitus suppression between anodal left versus anodal right DLPFC tDCS by subtracting post scores from pre scores for tinnitus loudness.

Results

The tDCS sessions were uneventful and no side effects were reported by the patients. There were no significant carry-over effects between baseline measures: when comparing before first set of sessions versus before second set of sessions and measures after the washout period for, respectively, tinnitus loudness, tinnitus annoyance, anxiety, and depression for, respectively, starting with sham group or real tDCS for both anodal right and anodal left DLFPC tDCS separately (Table 1).

Table 2 The effect of repetitive tDCS for tinnitus loudness, tinnitus annoyance

	tDCS		
	Pre	Post	*S* test
Anode left/Cathode right			
Real			
Loudness	5.14 (2.19)	3.71 (1.98)	−1.80
Annoyance	4.57 (2.07)	3.29 (2.13)	−2.04[a]
Depression	10.46 (9.29)	8.00 (8.52)	2.00[a]
Anxiety	6.76 (3.80)	6.29 (4.42)	1.03
Sham			
Loudness	5.57 (2.44)	4.57 (2.15)	−1.41
Annoyance	4.86 (2.41)	4.29 (1.98)	−0.74
Depression	9.77 (9.13)	9.14 (9.19)	0.80
Anxiety	6.29 (4.64)	6.29 (4.75)	0.00
Anode right/Cathode left			
Real			
Loudness	4.25 (2.12)	4.25 (2.71)	0.00
Annoyance	5.13 (2.47)	4.25 (2.60)	−2.12[a]
Depression	8.50 (6.27)	7.61 (4.22)	0.48
Anxiety	6.91 (4.25)	5.50 (4.24)	2.29[a]
Sham			
Loudness	4.71 (1.88)	5.14 (2.19)	0.65
Annoyance	4.86 (2.34)	5.00 (2.16)	0.14
Depression	9.44 (5.57)	8.46 (3.65)	0.46
Anxiety	6.67 (3.93)	5.57 (3.81)	1.34

Wilcoxon singled ranks test.
[a] $P < .05$.

We initially analyzed cross-over results for anodal left. When comparing post- versus pre-tDCS for the real treatment condition, we observed a significant decrease on two domains: the annoyance scale and the depression scale. No significant effect was obtained for the loudness scale and for anxiety. A similar analysis revealed that, for the sham stimulation, there were no significant effects on the annoyance scale, the loudness scale, depression, and anxiety. Table 2 is an overview of results and statistics. In addition, a comparison between sham tDCS versus real tDCS for the obtained suppression effect (pre-tDCS–post-tDCS) for, respectively, annoyance and anxiety revealed a significant effect for both annoyance ($S = -2.06$, $P < 0.05$) as well as for depression ($S = -1.99$, $P < 0.05$). These effects demonstrate that the obtained suppression effect was higher for the real tDCS in comparison to sham tDCS for annoyance and depression.

The same analysis was conducted for anodal right DLPFC tDCS. Similarly, when comparing post-tDCS versus pre-tDCS, the real treatment condition yielded a significant decrease on the annoyance scale; however, in

this case the anxiety, rather than the depression scale, had a significant decrease. Also similarly to anodal left, the loudness scale did not show significant changes (Table 2 for statistics). For the sham condition no effects were demonstrated on the annoyance scale, the loudness scale, depression or anxiety (Table 2 for statistics). When comparing sham tDCS versus real tDCS for the obtained effect (pre-tDCS–post-tDCS) for, respectively, annoyance and anxiety, a significant effect was obtained for annoyance ($S = -2.06$, $P < 0.05$) but not for anxiety ($S = -0.27$, $P < 0.78$) indicating that the obtained suppression effect was significantly higher for the real tDCS in comparison to sham tDCS for annoyance, but not for anxiety.

We then compared left versus right anodal DLPFC treatments for annoyance–as this was significant for both conditions. No significant difference was observed for this comparison ($U = 14$, $P = 0.12$); suggesting that the amount of reduction obtained for tinnitus annoyance for left- or right-sided stimulation is similar. A similar analysis revealed that left anodal DLPFC treatment yielded a significant improvement in depression in comparison right anodal DLPFC treatment ($U = 8$, $P < 0.05$).

Discussion

In this study, 15 subjects with tinnitus were randomly assigned to receive 12 tDCS sessions (six active and six sham tDCS sessions) of either left anodal tDCS or right anodal tDCS. The results indicate that bilateral active, but not sham, tDCS of the DLPFC—irrespective of the place of the anode—can decrease tinnitus annoyance significantly but does not yield any improvement in tinnitus intensity. The results further indicate that there was a lateralization effect for affective scales such as that left anodal induced an improvement of depression symptoms, whereas right anodal induced a decrease in anxiety scores. However, the results obtained for anxiety did not remain when comparing the real tDCS with sham tDCS.

Both strategies of DLPFC stimulation, that is, anodal left and anodal right, resulted in a reduction of tinnitus annoyance. It has been shown that the DLPFC are involved bilaterally in processing aversive auditory stimuli[42]; thus conceivably in tinnitus. In addition, bilateral DLPFC activity correlates with the emotional perception of pain,[43] has a facilitatory effect on auditory memory storage,[20] and contains auditory memory cells.[18] Therefore, it can be hypothesized that excitability-enhancing anodal stimulation of the right DLPFC with excitability-suppression of cathodal stimulation of left the DLPFC or vice versa changes processing in this area and thus likely activates suppressed areas of deactivates enhanced activity in prefrontal areas; thus reducing emotional distress associated with tinnitus processing. Supporting this hypothesis, a previous study showed that left anodal dorsolateral prefrontal cortex tDCS leads to a reduction of pain threshold but not sensory threshold.[35]

Modulation of the DLPFC might also change activity in other functionally connected areas such as the orbitofrontal cortex as well as the striatum and amygdala, integrating the cortical and subcortical processing of tinnitus. In this study, there are two possibilities: a direct effect of tDCS in subcortical networks as recent modeling studies have shown that electrical fields with smaller but still considerable currents can reach some subcortical areas[44] or an indirect network effect as supported by recent data showing that tDCS results in widespread changes in regional brain activity in this same network.[45]

In this context of prefrontal modulation, our results on tinnitus annoyance reduction after tDCS corroborate our preliminary clinical trial with one session of tDCS.[29] It has been stated that the prefrontal cortex is important for the integration of sensory and emotional aspects of tinnitus.[1,14] The DLPFC might regulate structures involved in the emotional perception of tinnitus, including the anterior cingulate cortex, amygdala and insula.[43] TDCS of the DLPFC can reduce tinnitus-annoyance, interfering with the emotional processing of tinnitus (i.e., tinnitus related distress), analogous to tDCS for depression.[30,31] This can also be supported at some extent by frontal lobotomy studies in which it has been shown that by cutting the connections to the prefrontal cortex, the tinnitus loudness does not change but rather the emotional "distress" component of tinnitus.[46,47]

A remarkable result in this study was the lateralized affective result–a finding that was not a priori expected. The study indicates that the anode electrode placed over the left DLPFC modulates depressive symptoms, and a previous study demonstrated that the anode placed over the right DLPFC suppressed distress. It is known that DLPFC plays an important role in anxiety and depression.[30,48] In addition, a previous study has shown that high-frequency excitability enhancing repetitive transcranial magnetic stimulation (rTMS) over the right DLPFC decreases anxiety, whereas similar intervention (high-frequency rTMS) but over left DLPFC improves mood in posttraumatic stress disorders.[49] Our results partially corroborate these findings. Frontal lateralization has been evidenced in depression[50-52] with reduced left-frontal activity. When placing the activating or excitability inducing anodal electrode over the left DLPFC previous research already demonstrated beneficial outcomes in treating major depression.[30,31] In this study, one potential approach to potentialize this treatment is the use of bilateral anodal DLPFC tDCS–using, thus, two anode electrodes over DLPFC cortices and one reference cathodal electrode over the chin (extracephalic reference).

Recent research has shown that repetitive sessions of tDCS stimulation of the temporoparietal area (i.e., auditory cortex) can also produce a reduction of tinnitus loudness, but not tinnitus annoyance.[53,54] In contrast, our study shows that repetitive sessions of frontal stimulation modulates the tinnitus annoyance, but not the tinnitus loudness. Hence, it might be interesting in future research to combine repetitive sessions of tDCS on both the DLPFC combined with

auditory cortex stimulation, as DLFPC stimulation modulates tinnitus annoyance and temporoparietal stimulation modulates the tinnitus loudness.

One limitation of the study is the small sample size. This is partly based on the fact that a cross-over design is a difficult design to apply in repetitive studies as the experiment in total took about 12 weeks (i.e., 2 weeks of real or placebo stimulation, 8 weeks of washout). As some patients receive for six sessions placebo stimulation, followed by 8 weeks of washout (i.e., no treatment) they might not remain motivated to continue the study, if they are not aware of the placebo arm.

In summary, this study encourages further exploration of tDCS for the treatment of tinnitus, offering a novel stimulation target. In addition, this study provides additional insights for the role of DLPFC in tinnitus modulation as well as the intersection between tinnitus and affective processing. Our main result was that bifrontal tDCS modulates tinnitus distress, but not tinnitus intensity. In addition, depending on the location of the anode electrode, tDCS on the left or the right DLPFC modulates depression.

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