Transient tinnitus suppression induced by repetitive transcranial magnetic stimulation and transcranial direct current stimulation

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Modulation of activity in the left temporoparietal area (LTA) by 10 Hz repetitive transcranial magnetic stimulation (rTMS) results in a transient reduction of tinnitus. We aimed to replicate these results and test whether transcranial direct current stimulation (tDCS) of LTA could yield similar effect. Patients with tinnitus underwent six different types of stimulation in a random order: 10-Hz rTMS of LTA, 10-Hz rTMS of mesial parietal cortex, sham rTMS, anodal tDCS of LTA, cathodal tDCS of LTA and sham tDCS. A non-parametric analysis of variance showed a significant main effect of type of stimulation ($P = 0.002$) and *post hoc* tests showed that 10-Hz rTMS and anodal tDCS of LTA resulted in a significant reduction of tinnitus. These effects were short lasting. These results replicate the findings of the previous study and, in addition, show preliminary evidence that anodal tDCS of LTA induces a similar transient tinnitus reduction as high-frequency rTMS.

Introduction

Tinnitus is a frequent symptom, occurring in approximately 10–15% of adults and increasing up to 33% in the elderly population [1,2]. In many patients, tinnitus becomes chronic, lasting for several years. Maladaptive plastic brain changes might account for such instances of sustained symptoms, reminiscent of the postulated pathophysiology of phantom pain or visual hallucinations after blindness. Past research has shown that tinnitus is frequently observed with hearing loss [3]. Thus, visual hallucinations after blindness, phantom pain and tinnitus might all represent instances where deafferentation of peripheral input (visual, sensory or cochlear) leads to cortical plastic changes (visual, sensorimotor or auditory cortex) which cause pathologic symptoms.

Consistent with this notion, past neuroimaging studies have shown an overactivation of the left auditory cortex in tinnitus [4,5] and repetitive transcranial magnetic stimulation (rTMS) of this area can induce a tinnitus supression [6–8] – that can be transient or long-lasting, depending on the frequency of stimulation. Furthermore, extradural electrical stimulation of the primary auditory cortex has been shown to suppress tinnitus completely in a patient with tinnitus due to cochlear lesion [9].

We set out to confirm the notion that modulation of cortical activity in temporoparietal cortex can suppress tinnitus and explore whether such effect can also be achieved by transcranial direct current stimulation (tDCS). In tDCS, the cerebral cortex is stimulated through a weak DC current in a non-invasive and painless manner. Several studies have shown that this technique might modulate cortical excitability in the human motor [10] and visual cortex [11]. When compared with extradural electrical stimulation, it has the advantage of being non-invasive. When compared with rTMS, it is easier to apply, has not been associated with seizures, and depending on stimulation polarity provides a reliable control and suitable blinding condition.

Therefore, this controlled, cross-over study aimed to (i) replicate the findings of Plewnia *et al.*[8], investigating the effects of 10-Hz rTMS of left temporoparietal cortex on tinnitus in a different population and compare these results with sham and active-control stimulation; (ii) compare these results with another technique of brain stimulation: anodal and cathodal tDCS of left temporoparietal cortex.

Methods

Subjects

We studied seven patients with chronic tinnitus (four men and three women; mean age of 51.7 ± 8.4 years).

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A complete audiologic examination and medical history was performed by a licensed otolaryngologist (R.M.). The duration of tinnitus was longer than 1 year for all patients (range from 1 to 17 years). All had twice unilateral tinnitus (tinnitus on both ears) and bilateral hearing loss that varied from 10 to 50 dB (see Table 1). Two patients had both high (> 2000 Hz) and low (< 2000 Hz) frequencies affected and the other five patients had only high-frequency hearing loss. The study was performed in accordance with the Declaration of Helsinki (1964). Written informed consent was obtained from all participants prior to inclusion in the study, which was approved by the local ethics committee.

Experimental protocol

The experimental design was based on a previous study that investigated the effects of high-frequency rTMS on tinnitus [8]. Each patient underwent six different types of stimulation: 10-Hz rTMS of left temporoparietal area (LTA), 10-Hz rTMS of mesial parietal (Pz) area, sham rTMS, anodal tDCS of LTA, cathodal tDCS of LTA and sham tDCS. We decided to target LTA for two main reasons: (i) because we aimed to replicate the study of Plewnia *et al*. [8] and this study showed that stimulation of LTA was the only one (amongst 12 stimulation sites) that induced a significant transient reduction in tinnitus and (ii) several neuroimaging studies have indicated a critical involvement of the primary and secondary auditory cortex in tinnitus perception [12–14]. The order of these conditions was counterbalanced and randomized across subjects. Patients were informed that stimulation with either rTMS or tDCS could either transiently improve or worsen their tinnitus; however, further details such as which area and type of stimulation could be expected to yield a greater improvement were not discussed.

Evaluation

We used the same instrument of evaluation – a scale to rate tinnitus reduction – used by Plewnia *et al*. [8]. In this scale, patients were asked to rate tinnitus change from 0 to 4 with 0 indicating no reduction, 1–3 indicating slight, marked and strong reduction and 4 indicating complete suppression of tinnitus immediately after stimulation. Patients were asked to rate tinnitus intensity in the most symptomatic ear, or, in the cases in which its intensity was similar in both ears, tinnitus reduction was rated in the ear contralateral to the stimulation site (right ear). Furthermore, patients were asked about adverse effects, such as headache, neck pain and tinnitus worsening.

Magnetic stimulation

Patients were comfortably seated in a dental chair for the intervention. Focal rTMS was performed using a commercially available figure-of-eight coil (outside diameter of each wing 7 cm) and a Dantec stimulator (1.5 Tesla version; Medtronic, Minneapolis, MN, USA). During the rTMS treatment, we targeted the LTA (halfway between C3/T5) and the Pz cortex [8]. These areas were identified according to the 10/20 EEG international system of electrode placement. For the sham treatment group, stimulation parameters were the same; however, a sham coil (Dantec; Medtronic) was used. Because sham stimulation does not induce the same scalp sensation as active stimulation does, we decided to stimulate Pz (with active rTMS) and considered this area as an active control as Plewnia *et al*. [8] showed no effects on tinnitus reduction associated with stimulation of this area. Stimulation parameters were frequency of 10 Hz and stimulation intensity of 20% above motor threshold (MT). Each patient received nine trains (three for each condition) of 30 stimuli (3-s

Table 1 Demographic and clinical characteristics

Patient	P1	P2	P3	P4	P5	P6	P7	Mean (± SD)
Age (years)	44	45	68	52	46	51	56	51.7 (8.4)
Gender	F	M	F	M	M	M	F	
Duration of tinnitus (years)	15	2.5	15	8	10	1	17	9.8 (6.3)
Laterality of tinnitus[a]	R > L	R = L	R = L	R > L	R > L	R > L	R > L	
Motor threshold	47	45	37	40	37	55	35	42.3 (7.1)
Hearing loss	L > R	Bilateral	Bilateral	Bilateral	R > R	Bilateral	Bilateral	
Hearing threshold (dB) – right	10	15	15	15	25	15	50	
Hearing threshold (dB) – left	15	15	15	15	20	15	20	
Tinnitus reduction (rTMS of LTA)	Yes	Yes	Yes	No	No	No	No	
Tinnitus reduction (A-tDCS of LTA)	Yes	Yes	Yes	No	No	No	No	

rTMS of LTA, repetitive transcranial magnetic stimulation of left temporoparietal area; A-tDCS of LTA, anodal transcranial DC stimulation of left temporoparietal area; F, female; M, male; R, right; L, left.

[a]R = L indicates similar tinnitus intensity (but not pitch) – twice unilateral tinnitus.

duration). There was an interval of 5 min between trains.

Electromyography was used to measure MT. A pair of surface electrodes was placed over the right abductor pollicis brevis muscle. These electrodes were connected to a Dantec Electromyograph (Medtronic). MT was defined as the lowest TMS intensity required to elicit motor-evoked potentials of ≥0.05 mV peak-to-peak amplitude in the contralateral resting abductor pollicis brevis muscle in at least five of the 10 trials with the coil over the optimal scalp position.

Direct current stimulation

Direct current was transferred by a saline-soaked pair of surface sponge electrodes (35 cm^2) and delivered by a specially developed, battery-driven, constant current stimulator (Schneider Electronic, Gleichen, Germany) with a maximum output of 10 mA. Each patient received anodal and cathodal stimulation of LTA and sham stimulation. For anodal stimulation, the anode electrode was placed over LTA (between C_3K_5-EEG 10/20 system) and the cathode electrode over the contralateral supraorbital area. For cathodal stimulation, the electrodes were reversed: the cathode was placed over LTA and the anode over the contralateral supraorbital area. A constant current of 1 mA intensity was applied for 3 min. This duration of stimulation was chosen because this is the minimum stimulation duration to induce stimulation after-effect and the maximum to induce a short after-effect of 1 min only [15]. Six stimulation sessions (two of each condition – anode, cathode and sham) were delivered for each subject. There was an interval of 6 min between the sessions. Subjects felt the current as an itching sensation at both electrodes in the beginning of the stimulation. For sham stimulation, the electrodes were placed in the same position; however, the stimulator was turned off after 5 s as previously described [16]. Therefore, the subjects felt the initial itching sensation in the beginning of stimulation, but received no current for the rest of the stimulation period.

Data analysis

Analyses were done with SAS statistical software (version 8.0; SAS Institute, Cary, NC, USA). We initially evaluated data distribution using the Shapiro–Wilk test. This test revealed that tinnitus reduction scores were not normally distributed ($W = 0.84$, $P < 0.0001$). Therefore, we applied non-parametric tests. To test if there was an overall effect of stimulation (10-Hz rTMS of LTA, 10-Hz rTMS of Pz, sham rTMS, anodal tDCS of LTA, cathodal tDCS of LTA and sham tDCS) on tinnitus reduction immediately after stimulation, the Kruskal–Wallis test using correction for ties was applied. If appropriate, *post hoc* comparisons were carried out using the Wilcoxon signed-rank test and Bonferroni correction for multiple comparisons. We also report the number of responders as defined by tinnitus reduction (rated as 1 or more in the evaluation scale for at least two trials). Statistical significance refers to a two-tailed P-value < 0.05.

Results

Demographic and clinical characteristics are summarized in (Table 1). There were no side effects related to the application of rTMS and tDCS.

There was an overall significant main effect of type of stimulation ($\chi^2 = 18.48$, d.f. $= 5$, $P = 0.0024$). *Post hoc* analysis showed that there was a significant effect on tinnitus reduction after rTMS of LTA ($P = 0.015$) and anodal tDCS of LTA ($P = 0.014$). Three patients (42%) had a significant reduction in tinnitus (tinnitus reduction of at least one in more than one trial) after rTMS of LTA and anodal tDCS of LTA. There were no responders after sham rTMS, active rTMS of Pz, sham tDCS and cathodal tDCS (Fig. 1).

The same patients responded to rTMS and tDCS, therefore, in an exploratory manner, we analyzed whether these three patients differed from the four non-responder patients regarding clinical features. This analysis disclosed that responders had less hearing loss compared with non-responders – the mean hearing threshold for responders was 14.2 ± 2.0 dB (range 10–15) and for non-responders was 21.9 ± 11.9 dB (range 15–50).

As this protocol was designed to investigate the immediate effects of brain stimulation on tinnitus, we tested and confirmed that the effects of either rTMS or tDCS on tinnitus reduction were short lasting: when present, they washed-out after few minutes (< 5 min for rTMS and < 6 min for tDCS), therefore, not contaminating the following session.

Discussion

This study shows that 10-Hz rTMS and anodal tDCS of the LTA result in a transient reduction of tinnitus. There were no adverse effects associated with these two types of stimulation and the effects were short lasting.

Our findings replicate and extend the findings of Plewnia *et al.* [8]. We confirm that high-frequency rTMS can exert a location-specific beneficial effect on tinnitus and show that anodal stimulation of LTA results in a similar transient tinnitus reduction. We showed that three of seven patients (42%) responded to high-frequency rTMS of LTA, whereas, in Plewnia's

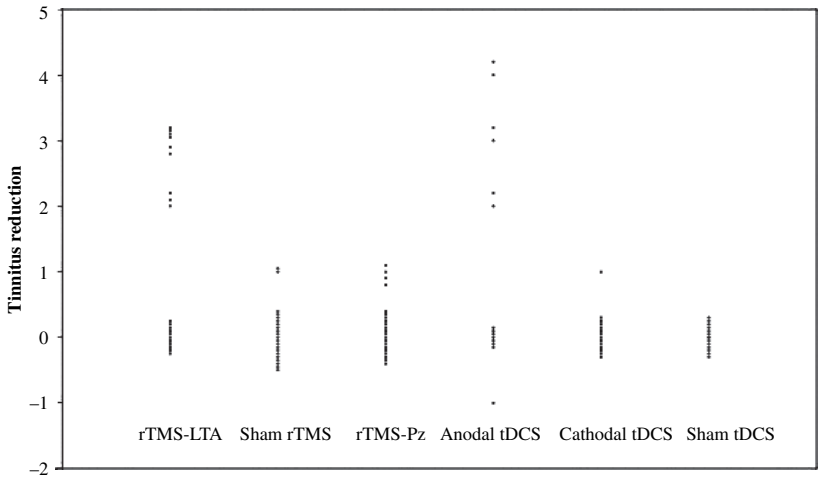

Figure 1 Tinnitus reduction immediately after each type of stimulation: repetitive transcranial magnetic stimulation (rTMS) of left temporoparietal area (LTA), sham rTMS, rTMS of mesial parietal, anodal tDCS of LTA, cathodal tDCS of LTA, sham tDCS (LTA indicates left temporoparietal cortex). Tinnitus reduction was evaluated by a scale in which 0 indicates no reduction, 1 slight, 2 marked, 3 strong reduction and 4 complete suppression of tinnitus immediately after stimulation. Each dot represents the score of each evaluation, therefore, each area stimulated by rTMS has three dots per patient (total of 21 dots) and by tDCS has two dots per patient (total of 14 dots). This plot shows that, only after rTMS of LTA and anodal tDCS of LTA, there are scores of 2 and 3, indicating a tinnitus reduction after these two paradigms of stimulation.

study, eight of 14 patients (57%) had a significant tinnitus reduction immediately after this type stimulation. This small difference (42% vs. 57%) might be a result of the small sample sizes of these studies (i.e. due to a wide confidence interval), or, alternatively, because of patient's selection. For instance, patients in Plewnia's study had less hearing deficits compared with our study – whereas, three patients had normal hearing in Plewnia's study; in our study, all patients had hearing deficits. Indeed, hearing loss might indicate a more severe disease and therefore less responsive to any type of intervention, especially short-lasting ones. This might be observed analyzing the characteristics of the group of responders versus non-responders. In Plewnia's study, two of the eight responders (25%) and five of the six non-responders (83%) had bilateral hearing loss. In our study, we found that responders had less hearing loss compared with non-responders as well. This might indicate that plastic changes are different or more profound in patients with greater hearing loss and that in them, higher doses of rTMS or tDCS (duration and intensity) might have to be used to induce beneficial effect on tinnitus.

An important finding of our study is that anodal stimulation yielded a similar benefit compared with 10-Hz rTMS. Although both techniques modulate brain activity, they have different mechanisms of action. High-frequency rTMS disrupts brain activity in the targeted brain region (through neuronal depolarization) during the period of stimulation and hence creates a temporary 'virtual lesion' [17]. tDCS as applied here only causes a slight change in the resting potential of the stimulated cells [18]. Therefore, whilst it is intuitive that high-frequency rTMS suppresses tinnitus, it is less intuitive that anodal, but not cathodal, tDCS has the same effect, especially because anodal tDCS is associated with an increase of cortical excitability (i.e. the effects of anodal stimulation might be at first glance paradoxical to the proposed pathophysiology of tinnitus – an overactivation of the temporoparietal cortex). Although not much is known about the behavioral effects of tDCS, some recent studies give some evidence that might be applied to our study.

A possible explanation is based on the focality of tDCS. As we used an electrode of 35 cm^2, it is conceivable to assume that a large area of the temporoparietal cortex has been stimulated. In such circumstance, an excitability enhancement induced by anodal tDCS possibly activates additional surrounding cortical areas that might, by competition or inhibitory connections, decrease the pathologically increased activity of some areas related to tinnitus pathophysiology. This would be in accordance with a defocusing effect of anodal tDCS on network activity, which has been demonstrated in other studies before [19,20].

An alternative explanation for the effect of anodal tDCS is that cortical stimulation with tDCS affects not only the targeted brain region, but also distant cortical and subcortical structures. Such remote impact might

account for (or at least contribute to) the behavioral effects. Indeed, a recent PET study showed that anodal tDCS of the motor cortex compared with cathodal tDCS induced a more widespread increase of regional cerebral blood flow [21]. Therefore, one can assume that the network cortical effects induced by anodal tDCS are different from that of cathodal tDCS, which could explain the different behavioral effects.

Finally, if tinnitus is associated with a decrease of intracortical inhibition and increase of spontaneous activity [3], it remains to be explained why cathodal stimulation that is associated with an increase of intracortical inhibition [22] did not alleviate tinnitus in our experiment. As cathodal tDCS is too weak to disrupt ongoing activity – it only modulates it; for us, it seems plausible that a bottom-effect occurred and thus, the tDCS-induced activity-modulation was not sufficient to suppress tinnitus. One of the reasons for that is because our protocol intended to study the online/immediate, but not the after-effects of tDCS. Therefore, an extended cathodal tDCS protocol might induce a longer and stronger modulation of the cortical excitability [23] and result in a significant tinnitus reduction by an increased degree of cortical inhibition or de-activation. Therefore, future experiments should encompass tDCS for several minutes (and sessions). This would parallel the results obtained with rTMS: whereas a short session of high-frequency rTMS induces an immediate change in the tinnitus perception [8], several sessions of low-frequency rTMS induce prolonged diminution of tinnitus perception that can last up to several months [6,7,24].

Our study shows that a short stimulation with either rTMS or tDCS has a short-lasting effect on tinnitus reduction. This finding is in accordance with a recent large study with 114 patients by De Ridder *et al.*[25]. This investigation showed that tinnitus could be suppressed by rTMS for very short time. Furthermore, this study showed that the tinnitus reduction is correlated to tinnitus duration and thus might also indicate a correlation with tinnitus severity. Finally, this study demonstrated that tinnitus could be reduced (good and partial effect) in 53% of the patients – similarly to our results (42% of patients) [25].

In contrast with a previous study, our study showed a low incidence of tinnitus reduction after sham interventions (sham rTMS, parietal rTMS and sham tDCS). For instance, De Ridder *et al.*[25] found a placebo effect in 63% of patients. Several reasons might account for these differences. The population sample might be an important difference as the degree and duration of tinnitus symptoms may be correlated to a placebo effect. Another difference might lie on the experimental design as our study consisted of less sessions of stimulation compared with De Ridder's study. Therefore, the duration of stimulation might have a direct impact on the placebo effect as more sessions of stimulation might reinforce the placebo effect. Indeed, Plewnia *et al.*'s[8] study that has a similar design when compared with ours also showed a low incidence of placebo effect. Moreover, patients of our study were told that stimulation (with either rTMS or tDCS) would not result in any clinical long-lasting benefit and therefore, this might have decreased a potential placebo effect. Finally, because patients of De Ridder's study knew that a good response to rTMS treatment might result in a neurostimulator implantation that could lead to a definite cure, it might have increased the placebo response in that study [25].

This study has some limitations. First, the interval between each train of stimulation might have not been long enough to wash out the effect of the previous stimulation. However, we used longer intervals than those applied by Plewnia *et al.*[8] (30-s interval in Plewnia's study versus 5 min in our study). Furthermore, we randomized and counterbalanced the order, therefore, controlling for an order effect. Regarding the tDCS, 3 min of anodal tDCS affects motor cortical excitability for no more than 1 min [15]. Consistent with this, patients reported no long-lasting effects of this technique on tinnitus reduction.

The small sample size of our study might also be viewed as a limitation. However, we showed a significant effect of 10-Hz rTMS and anodal tDCS that was consistent across stimulation conditions: the same patients responded to the same active conditions and did not respond to the two sham (sham tDCS and sham rTMS) and two active (rTMS of Pz and cathodal tDCS of LTA) conditions.

In summary, this study encourages further exploration of both techniques of non-invasive brain stimulation – rTMS and tDCS – for the study of the pathophysiology and perhaps the treatment of tinnitus. Studies investigating the effects of consecutive and longer stimulation sessions of non-invasive brain stimulation on tinnitus reduction might find greater and long-lasting behavioural effects.

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