Repetitive transcranial magnetic stimulation frequency dependent tinnitus improvement by double cone coil prefrontal stimulation

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ABSTRACT

Background A double cone coil (DCC) with large angled windings has been developed to modulate deeper brain areas such as the dorsal and subcallosal anterior cingulate cortex.

Methods Seventy-eight tinnitus patients received transcranial magnetic stimulation (TMS) using a DCC placed over the dorsal frontal cortex. Treatment effects were assessed with visual analogue scale for intensity and distress.

Results The results showed that 1 and 3 Hz of DCC frontal TMS can improve both tinnitus intensity and tinnitus distress, 5 Hz is equal to sham and 20 Hz is significantly worse than sham. Of the 78 tinnitus patients, 52 had no control response. Of these 52 placebo negative participants, 21 showed no suppressive response to stimulation and 31 patients were TMS responders. For this latter group, mean transient tinnitus suppression was obtained in 34.38% for tinnitus intensity and in 26% for tinnitus related distress.

Conclusion Frontal TMS using a DCC is capable of suppressing tinnitus transiently dependent on the repetitive TMS frequency used. These data further support the idea that non-auditory areas are involved in tinnitus intensity and tinnitus distress modulation.

INTRODUCTION

At some point in life most people experience a sound in their ears or head although no external sound is present. This might be caused by listening to loud music, fever, sudden sensorineural hearing loss, use of medication, trauma or other causes. Typically, this sensation is reversible and subsides a few seconds to a few days later. This phantom sound is also called tinnitus. In an adult population, 10–15% of the population perceives tinnitus chronically and about 6–25% of affected people report interference with their daily living as tinnitus can cause a considerable amount of distress, involving sleep deprivation, annoyance, concentration problems and work impairment.[1–5]

Functional neuroimaging and electrophysiological studies in humans indicate reorganisation[6] and abnormal spontaneous γ band activity[7] of the auditory CNS as the possible neurobiological basis of tinnitus. In addition, one study revealed that the amount of auditory cortex reorganisation correlates with the severity of tinnitus,[6] and another study demonstrated that the intensity of the perceived phantom sound correlates with the amount of auditory cortex γ band activity.[8] However, recent tinnitus research has shown that non-auditory brain structures are also involved in tinnitus.[9–12] In particular, the involvement of the anterior cingulate cortex (ACC) seems to play a specific role in tinnitus, as well as the dorsolateral prefrontal cortex, amygdala, hippocampus and ventral striatum.[9 13–17] The ACC may be responsible for integration of cognitive and emotional processing for tinnitus.[15] A recent study reported that the degree of phase locked coupling between ACC and the right frontal lobe correlates negatively with tinnitus intrusiveness (ie, how bothersome and obtrusive tinnitus is perceived).[11] Also, it was hypothesised that the ACC is critically involved in attentional control of auditory processing[18] and in the generation of tinnitus.[19]

The dorsolateral prefrontal cortex (DLPFC) is also involved in auditory processing. The DLPFC has a bilateral facilitatory effect on auditory memory storage and contains auditory memory cells.[20] The DLPFC also exerts early inhibitory modulation of input to primary auditory cortex in humans[21] and has been found to be associated with auditory attention,[22–24] resulting in top down modulation of auditory processing.[25] Based on electrophysiological data, it is hypothesised that tinnitus might occur as the result of a dysfunction in the top down inhibitory processes.[19 26]

Over the past decade, transcranial magnetic stimulation (TMS) has received increasing attention as a potential therapeutic tool for the treatment of tinnitus. TMS is non-invasive, provoking a strong impulse of magnetic field that induces an electrical current to a specific region of the brain through an intact scalp. An increasing number of clinical studies have demonstrated that TMS on the temporal lobe can alter tinnitus.[27–31] Typically, TMS in tinnitus is applied with a figure of eight coil. TMS modulates the superficial cortical areas directly but has an indirect effect on remote areas functionally connected to the stimulated area, such as the auditory thalamus.[32] A recent study using positron emission tomography revealed that frontal TMS using a double cone coil (DCC) can modulate both the dorsal and subcallosal ACC as well as a number of more distal cortical areas.[33]

As the ACC might be involved in attentional control both in auditory processing and in tinnitus,[19] prefrontal TMS using a DCC could modulate tinnitus perception. Furthermore, as the two leaves of the coils extend over the DLPFC, the local effect may also interfere with tinnitus perception. Furthermore, a preliminary study by the Regensburg team has demonstrated that adding

frontal cortex magnetic stimulation to auditory cortex repetitive TMS (rTMS) yields better long term results.[13]

Hence based on the fact that the DCC might modulate the ACC as well as the underlying frontal cortex, the aim of this study was to determine the extent to which frontal TMS using a DCC can modulate tinnitus.

METHODS

Seventy-eight tinnitus patients (63 men, 15 women) participated in this experiment at the multidisciplinary TRI tinnitus clinic, Antwerp University Hospital, Belgium. Mean age was 53.45 years (SD 11.87; range 22–81). Forty-nine patients had narrow band noise and 29 patients presented with pure tone tinnitus, while 55 patients had bilateral tinnitus and 23 unilateral tinnitus. Mean tinnitus duration was 7.84 years (SD 8.40; range 1–38). All prospective participants underwent a complete audiological, ENT and neurological investigation to rule out possible treatable causes for their tinnitus. Tinnitus matching is performed by presenting sounds to the ear in which the tinnitus is not perceived in unilateral tinnitus and bilaterally in bilateral tinnitus patients. Technical investigations include MRI of the brain and posterior fossa, pure tone and speech audiometry, and tympanometry.

The study was approved by the Antwerp University Hospital IRB ('Comité voor medische ethiek').

Before the TMS session, patients graded their tinnitus perception ("How loud is your tinnitus? 0=no tinnitus and 10=as loud as imaginable") and tinnitus distress ("How stressful is your tinnitus? 0=no distress and 10=suicidal distress") on a numeric rating scale from 0 to 10. TMS is performed using a super rapid stimulator (Magstim Inc, Wales, UK) with a DCC (P/N 9902-00; Magstim Co Ltd) placed over the medial frontal cortex (1.5 cm anterior to one-third of the distance from the nasion inion).[33] The intensity of the stimulation is fixed at 50% machine output for all patients. We opted to use a fixed machine output as with the DCC the motor threshold is difficult to obtain due to the shape of the coil. Patients perceived repeated stimulation in random order at 1, 3, 5, 10 and 20 Hz, each stimulation session consisting of 200 pulses. When tinnitus suppression was noted, the amount of improvement in tinnitus perception ("How much in percentage is your tinnitus perception reduced?") as well as the amount of improvement on tinnitus related distress ("How much in percentage is your distress reduced?"). When tinnitus perception was back to its initial score, the next TMS frequency was applied. The presence of a control procedure (ie, placebo effect) was tested by placing the coil perpendicular to the frontal area at the frequencies that yielded maximal tinnitus suppression rates. The sham effect was performed after the TMS procedure using the frequency that yielded maximal suppression. All patients were wearing earplugs during the TMS session.

Calculations were performed using SPSS software package. A repeated measures ANOVA was conducted with, as the dependent variable, the different stimulation protocols (1, 3, 5, 10 and 20 Hz as well as the sham treatment) and order of the stimulation protocols as a covariate. Next, for each patient, the frequency that yielded maximal tinnitus suppression was included in the analyses. A linear regression analysis was conducted with tinnitus type, tinnitus laterality and tinnitus duration as independent variables with, respectively, tinnitus perception and tinnitus related distress as dependent variables for the stimulation parameters (1, 3, 5, 10 and 20 Hz) that were significant in previous analyses. The dependent variables were computed by making the subtraction between 'tinnitus loudness for the respective stimulation parameter' minus sham scores. This subtraction was also calculated for tinnitus related distress. These scores give an indication of the net effect of stimulation. The independent variables tinnitus type and tinnitus laterality were recorded in contrast variables, tinnitus type (narrow band noise 1 and pure tone −1) and tinnitus laterality (bilateral 1 and unilateral −1). We corrected the regression analysis for multiple comparisons using the Bonferroni method.

The Pearson correlation coefficient was calculated between tinnitus loudness and tinnitus related distress for the respective stimulation parameters that were significant.

Responders were defined as patients whose improvement to TMS treatment was higher than 0 (amount of tinnitus perception or tinnitus distress) while non-responders were defined as patients whose improvement to TMS treatment = 0 (amount of improvement on tinnitus perception or tinnitus distress).

RESULTS

Patients reported a mean tinnitus perception of 6.93/10 and a mean tinnitus distress of 6.78/10 on a visual analogue scale before the TMS treatment.

Repeated measures ANOVA revealed a significant effect for tinnitus intensity ($F=8.89$, $p<0.001$) and tinnitus distress ($F=5.28$, $p<0.001$) (see table 1). Multiple comparisons with Bonferroni correction further revealed that for tinnitus intensity, 1 Hz and 3 Hz TMS obtained the best suppression effects which significantly differed from the sham treatment. However, 5 Hz and 10 Hz TMS did not differ significantly from the sham treatment. Furthermore, 20 Hz stimulation had a worse suppression effect than the sham treatment. For tinnitus distress, similar results were obtained. Multiple comparisons with Bonferroni correction revealed that 1 Hz and 3 Hz TMS exerted a significantly higher suppression effect than sham treatment, and that 5 Hz did not significant differ from sham treatment. For 10 Hz and 20 Hz, the results were even worse than for the sham treatment. For both analyses, the covariate order of the stimulation protocols did not become significant ($F=0.99$, $p>0.45$ for tinnitus perception and $F=1.13$, $p>0.45$ for tinnitus distress). Also, there was no significant effect obtained for the interaction between stimulation protocols and the covariate order for tinnitus perception ($F=0.62$, $p>0.65$ and for tinnitus distress $F=1.47$, $p>0.20$).

A linear regression analysis revealed that the amount of tinnitus intensity improvement depended on tinnitus laterality, and was independent of tinnitus type and tinnitus duration (see table 2). A linear regression analysis demonstrated that the amount of suppression for tinnitus intensity and tinnitus related distress was independent of tinnitus laterality, tinnitus type and tinnitus duration for both 1 and 3 Hz (see table 2).

Furthermore, a positive significant correlation was shown between the amount of reduction on tinnitus loudness and tinnitus related distress for 1 Hz ($r=0.58$, $p<0.01$) and 3 Hz ($r=0.78$, $p<0.01$) stimulation, indicating the more suppression

Table 1 Amount of suppression (% reduction) for tinnitus perception and tinnitus distress in comparison with baseline

	Sham	1 Hz	3 Hz	5 Hz	10 Hz	20 Hz
Tinnitus intensity	3.53	10.77*	10.19*	5.64†	6.22†	0.45‡
Tinnitus distress	3.49	11.67*	11.73*	1.54†	0.25‡	0.45‡

Multiple comparisons with Bonferroni correction, $p<0.05$:
*Significantly better than sham;
†No significant difference compared with sham;
‡Significantly worse than sham.

Table 2 Regression model: predicting the amount of response (difference real−sham) from tinnitus type, tinnitus laterality and tinnitus duration

Linear regression model	Amount of suppression					
	Tinnitus perception			Tinnitus distress		
	B	SE B	β	B	SE B	β
1 Hz						
Tinnitus type	1.95	2.64	0.09	−4.16	2.83	−0.18
Tinnitus laterality	−1.34	2.87	−0.09	3.21	3.06	0.13
Tinnitus duration	−0.17	0.31	−0.07	−0.16	0.33	−0.06
R^2		0.02			0.05	
3 Hz						
Tinnitus type	1.25	2.41	0.06	−3.88	2.83	−0.17
Tinnitus laterality	2.91	2.62	0.14	−0.42	3.07	−0.02
Tinnitus duration	−0.21	0.28	−0.09	−0.15	0.33	−0.06
R^2		0.03			0.03	

B, unstandardised beta coefficient; β, standardised beta coefficient.

the patient had on tinnitus loudness, the more suppression the patient had on tinnitus related distress.

Of the 78 tinnitus patients, 52 (66.67%) had no response to the sham treatment and were further analysed. Exclusion of responders to the sham procedure was performed to exclude the possible influence of sound from the TMS masking the tinnitus as TMS equipment generates a clicking sound on each magnitude pulse delivery. For each patient, the frequency that yielded maximal tinnitus suppression was included in the analyses. A significant suppression effect was obtained for both tinnitus perception ($t=6.80$, $p<0.001$) and tinnitus distress ($t=6.65$, $p<0.001$), indicating a suppression effect of 20.47% for tinnitus perception and 15.48% for tinnitus distress.

However, of these 52 participants who did not respond to the sham procedure, 21 (40.39%) showed no suppressive response to stimulation and 31 patients (59.61%) were TMS responders. For this latter group, mean transient tinnitus suppression was 34.38% for tinnitus perception ($t=8.85$, $p<0.001$) and 26% for tinnitus related distress ($t=7.80$, $p<0.001$). For the sham free responders, the highest suppression effects for tinnitus perception were obtained with 1 Hz and 3 Hz stimulations and for tinnitus related-distress using 1 Hz stimuli.

DISCUSSION

This is the first study to describe the effect of frontal TMS on tinnitus using a DCC with large angled windings. Our results show that bifrontal stimulation can modulate tinnitus intensity and tinnitus distress. This fits with a previous bifrontal transcranial direct current stimulation study demonstrating a transient improvement in both tinnitus related distress as well as tinnitus intensity.[34] This study however shows that low frequency frontal rTMS with the DCC improves both tinnitus perception and tinnitus distress transiently, but not 5 Hz, and that high frequency rTMS improves tinnitus perception less than sham, 10 Hz improves tinnitus distress less than sham and 20 Hz improves both intensity and distress less than sham. The amount of suppression on tinnitus loudness and tinnitus related distress was independent of tinnitus laterality, tinnitus type and tinnitus duration for both 1 Hz and 3 Hz. Furthermore, a correlation was found between tinnitus loudness and tinnitus related distress for both 1 Hz and 3 Hz.

Our study shows that low and high frequency bifrontal rTMS has opposing effects on tinnitus perception, both for tinnitus intensity and tinnitus distress. This could be based on an inhibitory effect of low frequency rTMS in contrast with high frequency rTMS, as low and high frequency frontal rTMS exert a differential effect on the frontal cortex, with low frequency rTMS decreasing metabolism and high frequency rTMS increasing metabolism.[35 36] Based on these data it can be hypothesised that 1 and 3 Hz inhibit the ACC[33] or frontal areas, thereby reducing tinnitus. Perhaps 10 and 20 Hz TMS excite the ACC or frontal areas, thereby not improving tinnitus.

The fact that both tinnitus intensity and tinnitus distress suppression are related should be further explored, however, a hypothesis can be introduced. The dorsal part of the anterior cingulate (alternating with the VMPFC) generates frontal midline θ.[37] Frontal midline θ oscillations are involved in attentional processes,[38] and both sympathetic and parasympathetic indices are increased during the appearance of frontal midline θ.[39] The function of the ACC might be to integrate motivationally important information with appropriate bodily responses[40] related to the survival needs of the body.[41] Based on this concept the hypothesis can be proposed that a possible function of the ACC in tinnitus could be related to the fact that the internally generated phantom sound is considered as motivationally important information and that the ACC responds with an appropriate bodily response—that is, it keeps the tinnitus in the focus of attention which ultimately can lead to tinnitus related distress. The subgenual ACC (sgACC) is characterised by an anticorrelated activity with the dorsal ACC,[42] and voxel based morphometry has shown that the sgACC is involved in tinnitus,[9 43] possibly controlling a noise cancelling mechanism[43] via the reticular nucleus of the thalamus, thereby modulating pathological thalamocortical activity implicated in tinnitus.[44] This suggests that the ACC is involved in tinnitus intensity modulation. It was further shown that the amount of tinnitus distress suppression obtained by temporal TMS is related to metabolism in the ACC,[45] further demonstrating the importance of this area in tinnitus distress. Thus targeting the dorsal ACC and sgACC by DCC rTMS[33] can potentially modulate both tinnitus intensity and distress. Functional imaging studies will have to elucidate this hypothetical ACC mediated working mechanism.

A second hypothetical working mechanism of DCC frontal TMS is by top down modulation of the auditory cortex. As mentioned, based on electrophysiological data it has been suggested that tinnitus might occur as the result of a dysfunction in the top down inhibitory processes,[19 26] and a preliminary study has demonstrated that modulating the frontal cortex in addition to auditory cortex rTMS yields better long term results.[13] In a positron emission tomography study, increased neural activity for tinnitus sufferers was shown in the right hemisphere, on the middle frontal and middle temporal regions as well as in lateral mesial posterior sites.[10] In magnetoencephalography studies, more reduction in α (8-12 Hz) and an increase in δ (1.5–4 Hz) was found in temporal regions, left frontal and right parietal areas[46] as well as functional connectivity in the right frontal lobe and ACC.[11] A combination of both mechanisms is also possible, or an as yet unknown mechanism.

It is important to note however that Marcondes *et al* reported two cases who experienced a recurrence or worsening of their tinnitus using 10 Hz repetitive TMS with a classic eight coil.[47] However, Kleinjung *et al* preceded each session of 1 Hz TMS of the temporal cortex with 20 Hz TMS on the left DLPFC and reported an improvement for tinnitus related distress.[13] Our group showed that transcranial direct current stimulation of the bifrontal DLPFC can suppress both tinnitus related distress as well as tinnitus perception.[34] These latter data corroborate with our present results.

One limitation of this study relates to coil positioning. These were not performed under neuronavigated control and were only defined by anatomical landmarks. Yet, recent studies for TMS demonstrated that consistent results can be obtained with a probabilistic approach (ie, non-neuronavigated).[48] Nevertheless, even if functional MRI guided stimulation is accurate within the range of millimetres for targeting purposes, the area of modulation might still be as large as 3 cm,[49] questioning the value of functional MRI guided TMS of the auditory cortex.[27] Another limitation might be the sham condition. As the sham coil only mimics the sound of active TMS but lacks the somatosensory sensation, it is not an optimal sham condition. However, it has already been shown that TMS effect on tinnitus is not mediated by somatosensory stimulation.[50 51] Moreover, as patients in this study were naive for TMS, they may not have been able to identify whether they were stimulated with active or sham TMS. In addition, no patient had worsening of their tinnitus. Yet this might be due to the questions asked. For tinnitus intensity and tinnitus distress we asked: "How much in percentage is your tinnitus perception reduced?" and "How much in percentage is your distress reduced?" after each stimulation protocol. Based on these questions, it is possible that patients only reported improvement or non-improvement, but not worsening. Lastly, it is possible that due to the different stimulation protocols there is a carryover effect from the previous to the next stimulation, even though the stimulation was only continued when the tinnitus was back to the initial level. Previous research has revealed that preconditioning of cortical excitability exerts an influence on subsequent TMS.[52] The order of stimulations was randomised over the patients, preventing an order effect, but not excluding a preconditioning effect. This has to be taken into account as a potential weakness when interpreting the data.

In conclusion, frontal TMS using a DCC might be considered clinically relevant in the suppression of tinnitus. Our findings give further support to the fact that non-auditory areas are involved in tinnitus intensity and tinnitus distress. Combining this stimulation method with functional imaging will refine our knowledge of the neural circuits involved in auditory phantom perceptions such as chronic tinnitus.

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