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RESEARCH PAPER

Combined transcranial magnetic stimulation in the treatment of chronic tinnitus

Martin Formánek[1], Petra Migal'ová[2], Petra Krulová[2], Michal Bar[2], Debora Jančatová[1], Hana Zakopčanová-Srovnalová[3], Hana Tomášková[4], Karol Zeleník[1] & Pavel Komínek[1]

[1]Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Ostrava, 17. listopadu 1790, Ostrava 70852, Czech Republic
[2]Department of Neurology, University Hospital Ostrava, 17. listopadu 1790, Ostrava 70852, Czech Republic
[3]Department of Neurology and Psychiatry, Faculty of Medicine, University of Ostrava, Dvořákova 7, Ostrava 70103, Czech Republic
[4]Epidemiological Studies Center, Faculty of Medicine, University of Ostrava, Dvořákova 7, Ostrava 70103, Czech Republic

Correspondence
Martin Formánek, Department of Otorhinolaryngology and Head and Neck Surgery, University Hospital Ostrava, 17 listopadu 1790, 708 52 Ostrava, Czech Republic. Tel: +420 59737 5812; Fax: +420 59737 5805;
E-mail: martin.formanek@fno.cz

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Abstract

Objective: Repetitive transcranial magnetic stimulation (rTMS) is currently being tested for suppressing the symptoms of subjective chronic primary tinnitus, although its effect is controversial. The aim of this randomized double-blinded controlled trial was to determine the effect of rTMS with unique settings for tinnitus treatment. **Methods**: Fifty-three adult patients suffering from chronic subjective unilateral or bilateral nonpulsatile primary tinnitus for at least 6 months were randomly assigned to rTMS (group 1, $n = 20$), sham stimulation (group 2, $n = 12$), or medicament therapy only (group 3, $n = 21$). The dorsolateral prefrontal cortex (frequency 25 Hz, 300 pulses, and 80% resting motor threshold [RMT]) on the left side and primary auditory cortex (1 Hz, 1000 pulses, 110% RMT) were stimulated on both sides in patients in group 1 for 5 consecutive days. The Tinnitus Reaction Questionnaire (TRQ), Tinnitus Handicap Questionnaire (THQ), Tinnitus Handicap Inventory (THI), Beck Depression Inventory (BDI), pure-tone audiometry with Fowler scoring of hearing loss, and tinnitus analysis were used to evaluate tinnitus in all patients. Data were recorded the day the patient was included in the study and at 1- and 6-month follow-up. **Results**: The study groups were homogenous. No significant effect of rTMS was found at 1 or 6 months based on the BDI, THQ, and TRQ scores or tinnitus masking. There was a significant but clinically irrelevant effect on the THI score after 1 and 6 months. **Interpretation**: No significant effect of bilateral low-frequency rTMS of the primary auditory cortex and high-frequency stimulation of the left dorsolateral prefrontal cortex was demonstrated.

Introduction

Tinnitus is defined as hearing a noise or sound without any external acoustic stimulation and is a common symptom experienced by approximately 10–15% of the general population, and 4–5% are severely affected by it.[1–3] The perception of tinnitus causes problems with concentration, falling asleep, anxiety, and feelings of depression. Thus, tinnitus can have severe negative implications on the perceived quality of life.[4]

Concerning etiology, there is a differentiation between objective and subjective tinnitus. Objective tinnitus can be heard by an external observer and is a very rare form of tinnitus that may be caused by a vascular or muscular condition.[5] In contrast, subjective tinnitus cannot be heard by an external observer and no acoustic sound source can be identified. The condition is thought to be the result of plastic changes and reorganization processes in the auditory pathway and brain structures, most likely caused by the deprivation of input.[6] Tinnitus is considered primary if no cause is revealed or secondary if a cause can be determined, and acute if it lasts less than 6 months or chronic if it lasts longer than 6 months.

Therapy for chronic primary subjective tinnitus is challenging. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive method that can modulate the

excitability of the brain cortex and is currently being tested for suppressing the symptoms of tinnitus.[7,8] The use of rTMS in the treatment of tinnitus stems from the development of models of the central generation and maintenance of disabling subjective tinnitus. However, in contrast to the treatment of other brain pathologies, many uncertainties remain regarding the current relevance of the use of rTMS as a treatment for tinnitus, especially in the long term.[9] Tinnitus reduction was mainly referred to in earlier studies, which only reached class III (absence of blinded controlled evaluation), and was generally described as partial and temporary with large interindividual variations.[9] On the other hand, class I studies recently showed nonsignificant changes between active and placebo conditions.[10–12]

In general, studies exhibit considerable variability. Many methodological and practical problems remain to be solved before rTMS therapy can be developed for tinnitus in clinical practice. In particular, these problems concern the method and center(s) of targeting, as well as the side of stimulation.

The side contralateral to the tinnitus was used as a target for stimulation or application in the left hemisphere in most studies.[9] However, the auditory pathway ends in both hemispheres, and no functional changes in the auditory cortex have been found in patients with tinnitus compared to healthy controls when measuring brain metabolism.[4] In addition, no differences have been found in studies comparing the effect of stimulation delivered contralaterally or ipsilaterally to the symptomatic ear.[9,13] Despite this, very few studies have used bilateral stimulation.[11,14] This is also why mostly only patients with unilateral tinnitus were included.

On the other hand, there is nearly agreement regarding stimulation frequency. In general, TMS protocols with <1 Hz frequency are considered inhibitory protocols and used mostly for the treatment of tinnitus.[9] An increasing amount of data also suggest that the efficacy of rTMS therapy in tinnitus can be enhanced by stimulating frontal or prefrontal cortical areas in addition to the temporoparietal cortex.[10,15–19] These results are in line with increased functional connectivity between frontal and temporal cortical areas in tinnitus patients on imaging.[20]

The aim of this prospective study was to determine the effect of rTMS with unique settings on the treatment of primary subjective nonpulsatile tinnitus. Therefore, the study was set up as a parallel double-blinded randomized controlled trial considering that rTMS results from crossover studies must be considered with care because patient blinding may not be adequate (the difference between real and placebo rTMS could be obvious for a subject undergoing both forms) and carryover effects may exist. A group treated by medicament therapy alone was also added to the comparison. There is currently no effective pharmacological treatment for chronic tinnitus. Therefore, this group can be considered another placebo group.

We tried to adjust the study setting according to the most recent data the way we believed rTMS could provide the maximal effect for tinnitus treatment with an awareness of eventual higher risks of side effects. The generally acknowledged inhibitory stimulation (1 Hz frequency) was targeted to the primary auditory cortex bilaterally. In addition, the stimulatory frequency (25 Hz) was targeted to the left dorsolateral prefrontal cortex.

Materials and Methods

This randomized double-blinded controlled trial was approved by the Ethics Committee of the University Hospital Ostrava and performed in accordance with the Declaration of Helsinki and applicable regulatory requirements with good clinical practice. The study was registered at ClinicalTrials.gov under the identifier NCT03425045. Written informed consent was obtained from the patients before initiating any procedure. The study was performed between March 2015 and May 2017 in a tertiary referral hospital. All authors reviewed and approved the final manuscript.

Patients

Adult patients suffering from unilateral or bilateral chronic subjective nonpulsatile primary tinnitus for at least 6 months were included in the study. The definition of tinnitus was based on subjective complaints of noise, ringing, and/or buzzing with no external source. Exclusion criteria were as follows: head injury or brain surgery, epilepsy, organic brain lesion, Meniere's disease or fluctuating hearing loss, cochlear or bone-anchored hearing device implantation, history of attempted suicide, pregnancy, consumption of anticonvulsants or antipsychotic medication, pacemaker, or previous rTMS.

Randomization and blinding

Using random number generation, patients were assigned into the rTMS group, sham stimulation group, or medicament therapy only group. Both the patients and outcome assessor were blinded to the intervention group to which the patients belonged. Stimulation was performed in different hospital building by investigator, who was not in contact with outcome assessor or patients except for the course of stimulation. Patients receiving medicament therapy were not blinded.

Positioning

To achieve optimal coil positioning at the patient's primary auditory cortex, image-guided stereotaxy was performed with the aid of a frameless stereotactic device using structural imaging data to guide TMS coil placement. The location of the patient's primary auditory cortex and dorsolateral prefrontal cortex was determined on

Table 1. Characteristics of the study participants.

	rTMS group (n = 20)			Sham group (n = 12)			Medicament group (n = 21)			P-value
Age (years)	47.9 ± 14.31			51.8 ± 10.34			60.6 ± 15.6			0.156[1]
Male	13			10			10			0.120[2]
Female	7			2			11			0.120[2]
Tinnitus duration (months)	53.4 ± 61.89			76.8 ± 76.85			36.5 ± 30.93			0.436[3]
Hearing loss	9			6			14			0.353[2]
Education level	Prim.	Sec.	Ter.	Prim.	Sec.	Ter.	Prim.	Sec.	Ter.	0.295[4]
	6	8	6	4	5	3	13	5	3	

Data are given as mean ± standard deviation or n. Prim, primary; Sec, secondary; Ter, tertiary.
[1]Kruskal–Wallis test.
[2]Pearson's chi-squared test.
[3]Analysis of variance.
[4]Fisher's exact test.

Table 2. Comparison of improvement in questionnaires' score and tinnitus masking after 1 and 6 months.

		1 month				6 months			
		Not improved		Improved		Not improved		Improved	
		N	%	N	%	N	%	N	%
BDI	rTMS	9	47%	10	53%	10	50%	10	50%
	Sham	8	67%	4	33%	7	58%	5	42%
	Medicament	13	68%	6	32%	11	52%	10	48%
		P = 0.359[1]				P = 0.900[1]			
THI	rTMS	7	37%	12	63%	6	30%	14	70%
	Sham	5	42%	7	58%	4	33%	8	67%
	Medicament	15	75%	5	25%	15	71%	6	29%
		P = 0.039[1]				P = 0.016[1]			
THQ	rTMS	7	37%	12	63%	7	35%	13	65%
	Sham	6	50%	6	50%	5	42%	7	58%
	Medicament	9	45%	11	55%	12	57%	9	43%
		P = 0.754[1]				P = 0.348[1]			
TRQ	rTMS	6	32%	13	68%	6	30%	14	70%
	Sham	5	42%	7	58%	4	33%	8	67%
	Medicament	12	60%	8	40%	10	48%	11	52%
		P = 0.197[1]				P = 0.477[1]			
Tinnitus masking (right)	rTMS	8	67%	4	33%	10	77%	3	23%
	Sham	6	86%	1	14%	3	43%	4	57%
	Medicament	12	92%	1	8%	12	86%	2	14%
		P = 0.269[2]				P = 0.149[2]			
Tinnitus masking (left)	rTMS	14	82%	3	18%	14	82%	3	18%
	Sham	7	70%	3	30%	4	40%	6	60%
	Medicament	13	72%	5	28%	13	68%	6	32%
		P = 0.740[2]				P = 0.083[2]			

BDI, Beck Depression Inventory; rTMS, repetitive transcranial magnetic stimulation; THI, Tinnitus Handicap Inventory; THQ, Tinnitus Handicap Questionnaire; TRQ, Tinnitus Reaction Questionnaire.
[1]Pearson's chi-squared test.
[2]Fisher's exact test.

a structural T1-weighted magnetic resonance image with gadolinium contrast that was performed during the diagnostic stage (Magnetom Avanto Siemens 1.5-Tesla, Siemens Healthcare GmbH, Erlangen, Germany).

The patients were seated in a desk chair with their chin in a jaw support and their forehead secured with a band against a support bar. Using a template, the coil was positioned above the marked location with the handle pointing upwards, perpendicular to the skull. The coil was held in place against the patient's head by a mechanical arm. The location of the targeted cortex was marked with ink on the scalp, and a neurosurgical marker was placed in order to identify the spot in the following days. The patients were provided with ear plugs to minimize the noise dose and possible residual inhibition.

Stimulation

The DuoMAG XT-100 transcranial magnetic stimulator (Deymed, Payette, ID, USA) was used for magnetic stimulation. The rTMS was performed with a 70-mm air-cooled 70BF Butterfly Coil (Deymed). The resting motor threshold (RMT) was determined in every rTMS patient on the first day of treatment using a descending staircase method until the lowest intensity at which 5 of 10 consecutive pulses induced a visible twitch in the contralateral hand was reached. For each hemisphere, the intensity was set according to the motor threshold obtained for that hemisphere. The dorsolateral prefrontal cortex (frequency 25 Hz, 300 pulses, and 80% RMT) on the left side and primary auditory cortex on both sides (1 Hz, 1000 pulses, and 110% RMT) were stimulated in every patient for 5 consecutive days. There was no difference between rTMS group and sham stimulation group. Every patient received 2300 pulses per session (three stimulation sites). A 5–10 min break was used to switch the coil from one position to the other and to allow the patient to relax. All patients were treated by the same investigator.

Placebo treatment was performed with a 70-mm 70BFP Placebo Butterfly Coil (Deymed) replicating the appearance, sound emission, stimulation of superficial tissue (muscles), and operation of the TMS coil without stimulating the cortical tissue. Motor thresholds were not determined in placebo patients to prevent them from perceiving the difference between real and placebo TMS, protecting the blinding. The neuronavigation procedure and treatment schedule were similar.

Medicament therapy

Medicament therapy consisted of ginkgo biloba extract EGb 761 once a day for 6 months. No medicament therapy was given for tinnitus in the rTMS and sham groups.

Data acquisition

The Tinnitus Reaction Questionnaire (TRQ), Tinnitus Handicap Questionnaire (THQ), Tinnitus Handicap Inventory (THI), Beck Depression Inventory (BDI), pure-tone audiometry with Fowler scoring of hearing loss, and tinnitus analysis (loudness matching) were used to evaluate tinnitus in all patients. Audiometry and tinnitus analysis were performed by one audiology assistant trained in tinnitus analysis and blinded to treatment type. Testing was performed in a soundproof cabin using a Madsen Orbiter 922 audiometer (Madsen Ltd., Budapest, Hungary) compliant with ISO 389 standards. Pure-tone audiometry was performed according to international standards (ISO 8253-1).

Follow-up

Data were recorded the day patient was included in the study and during follow-up at 1 and 6 months.

Statistical analysis

Descriptive statistics, such as the arithmetic mean, standard deviation, and absolute and relative frequency tables, were used for data processing. Pearson's chi-squared test, Fisher's exact test, Kruskal–Wallis test, and analysis of variance were used for comparisons among groups. The statistical tests were assessed using a significance level of 5%. The statistical analysis was performed using Stata 13 software (Stata Corp., College Station, TX, USA). Risk groups were identified using SPSS Answer Tree 3.1 (IBM Corp., Armonk, NY, USA).

Results

A total of 56 patients suffering from unilateral or bilateral chronic subjective nonpulsatile primary tinnitus for at least 6 months were included in the study (Table 1). Compliance with follow-up was 94.6%. One patient in the rTMS group and two patients in sham group were lost during follow-up and excluded from the study. Twenty-six patients suffered from unilateral tinnitus and 27 from bilateral tinnitus. Tinnitus was right sided in 34 cases and left sided in 46 cases. No differences were found among the three intervention groups with regards to average age, gender distribution, tinnitus duration, hearing loss, or education level (Table 1).

No significant effect of rTMS was found in the BDI, THQ, and TRQ scores or tinnitus masking at 1 or

6 months compared to the sham coil group and medicament therapy only when number of improved patients was evaluated (Table 2). No significant effect of rTMS was found in the BDI, THQ, TRQ, and THI scores when analysis of variance was performed (Figures 1–4, Table 3).

There was significant effect on THI score at 1 and 6 months. Improvement was found after 1 month in 63% of patients in the rTMS group, 58% of patients in the sham coil group, and 25% of patients in the medicament therapy group ($P = 0.039$). Improvement was also found after 6 months in 70% of patients in the rTMS group, 67% of patients in the sham coil group, and 29% of patients in the medicament therapy group ($P = 0.016$; Table 2). The effect of therapy was not dependent on education level at 6 months (Table 4).

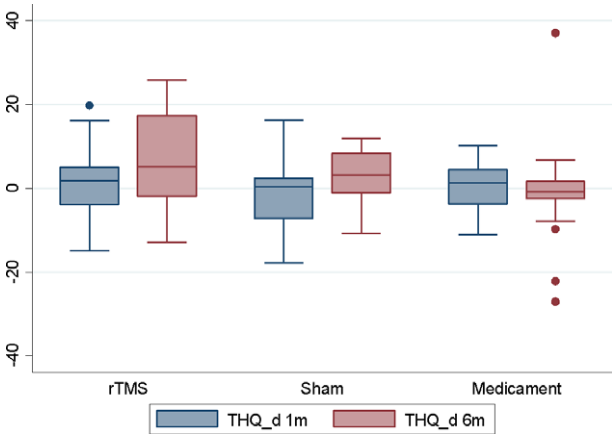

Figure 3. Change in THQ scores after 1 and 6 months (=positive value means improvement).

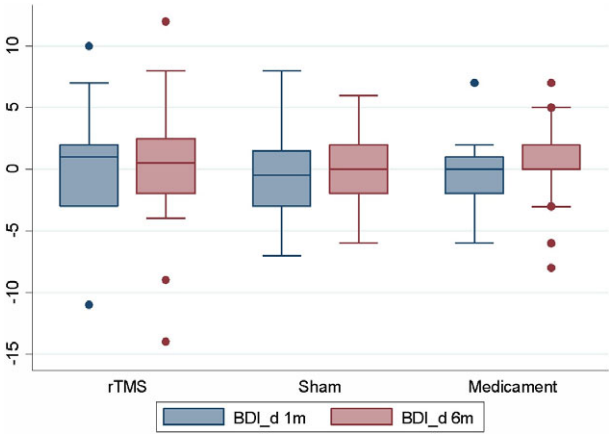

Figure 1. Change in BDI scores after 1 and 6 months (=positive value means improvement).

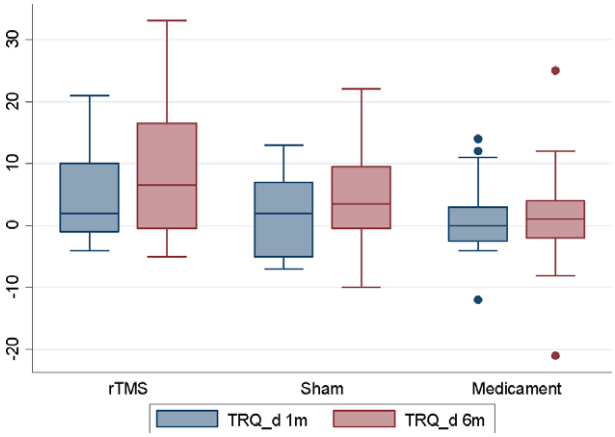

Figure 4. Change in TRQ scores after 1 and 6 months (=positive value means improvement).

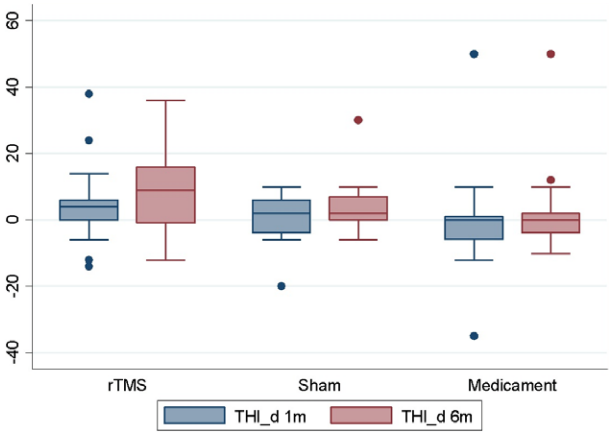

Figure 2. Change in THI scores after 1 and 6 months (=positive value means improvement).

In general, treatment was tolerated well. Three patients experienced temporal side effects from rTMS (all headache) and three patients experienced temporal side effects from placebo (1 headache, 1 dizziness, and 1 blurred vision).

Discussion

The parallel double-blinded randomized controlled study was uniquely set according to the most recent data the way we believed rTMS could provide the maximal effect for tinnitus treatment. Although multiple sites stimulation was performed, a higher risk of side effects was not reported. However, no significant effect of rTMS was found at 1 or 6 months based on the BDI, THQ, and TRQ scores or tinnitus masking in our study. Although a

Table 3. Evaluation of changes in questionnaires' score after 1 and 6 months (=positive value means tinnitus improvement).

		1 month					6 months				
		N	Mean	SD	Min.	Max.	*N*	Mean	SD	Min.	Max.
BDI	rTMS	19	0.5	4.40	−11	10	20	0.1	5.50	−14	12
	Sham	12	−0.6	4.29	−7	8	12	0.0	3.59	−6	6
	Medicament	19	−0.4	2.91	−6	7	21	0.3	3.20	−8	7
		$P = 0.681$[1]					$P = 0.9731$[1]				
THI	rTMS	19	4.5	11.72	−14	38	20	9.1	11.85	−12	36
	Sham	12	0.2	7.98	−20	10	12	4.3	9.41	−6	30
	Medicament	20	−0.7	14.90	−35	50	21	1.4	12.39	−10	50
		$P = 0.3945$[1]					$P = 0.1111$[1]				
THQ	rTMS	19	1.5	8.52	−14.8	19.8	20	6.1	12.55	−12.9	25.9
	Sham	12	−1.1	8.75	−17.8	16.3	12	2.8	6.34	−10.8	11.9
	Medicament	20	0.1	6.23	−11.1	10.3	21	−1.2	11.99	−27	37.1
		$P = 0.6489$[1]					$P = 0.1272$[1]				
TRQ	rTMS	19	4.9	7.04	−4	21	20	9.1	11.55	−5	33
	Sham	12	1.5	6.69	−7	13	12	4.7	8.24	−10	22
	Medicament	20	1.4	6.27	−12	14	21	1.7	8.84	−21	25
		$P = 0.1964$[1]					$P = 0.0641$[1]				

BDI, Beck Depression Inventory; rTMS, repetitive transcranial magnetic stimulation; SD, standard deviation; THI, Tinnitus Handicap Inventory; THQ, Tinnitus Handicap Questionnaire; TRQ, Tinnitus Reaction Questionnaire.
[1]One-way analysis of variance for repeated measures.

Table 4. Education level and effect of therapy after 6 months.

	BDI change		THI change		THQ change		TRQ change	
Education level	NI	I	NI	I	NI	I	NI	I
Primary	13	10	13	10	11	12	8	15
Secondary	10	8	7	11	7	11	6	12
Tertiary	5	7	5	7	6	6	6	6
P-value[1]	0.677		0.485		0.793		0.606	

BDI, Beck Depression Inventory; I, improved; NI, not improved; THI, Tinnitus Handicap Inventory; THQ, Tinnitus Handicap Questionnaire; TRQ, Tinnitus Reaction Questionnaire.
[1]Pearson's chi-squared test.

significant effect of rTMS on THI score was found after 1 and 6 months when number of improved patients was evaluated, but the effect was nearly the same as with the sham coil. There was improvement at 1 month in 63% and 58% of patients in the rTMS and sham groups, respectively, and the difference was even smaller after 6 months. Improvement was noted in 70% patients in the rTMS group and 67% in the sham coil group. Although a positive trend in the THI score may have been in favor of rTMS, the effect was so small that it should be considered clinically irrelevant. The biggest difference in THI score was when both groups were compared to the medicament therapy group, in which only 25% and 29% of patients noted tinnitus improvement, respectively. The THI is a 25-item self-response questionnaire with three possible answers (yes, sometimes, and no) and a score range 0–100. It was developed for busy clinical practice to quickly quantify the impact of tinnitus on daily living.[21] Therefore, it could be less precise in scoring tinnitus severity than the more time-consuming THQ or TRQ and has been evaluated in other studies as only a secondary outcome.[22] In general, questionnaires' scores were very variable at the time of indication. Therefore, evaluation of number of improved patients was preferred as main parameter. However, no significant effect of rTMS was found even if analysis of variance was performed. Results were very variable among patients as shown in box plots.

Some studies have suggested that tinnitus of short duration (<2 years) and normal hearing could be predictors of beneficial treatment outcomes.[23–25] However, this was not confirmed in an analysis of larger samples.[26] In our study, there was no difference between groups in terms of tinnitus duration or hearing loss. The effect of therapy could be also dependent on socioeconomic status. However, the effect of therapy was not dependent on education level at 6 months. Result could be influenced by short treatment phase, which belongs among shorter referred treatment phases. Some authors even recommend treatment for several weeks.[27] However, number of improved patients is regardless the shorter treatment phase relatively high in our study. Therefore, more likely high number of improved patients in sham/medicament group is an issue from the statistical point of view.

Our results are in agreement with recent analogical class I studies in which no significant changes between active and placebo conditions were found.[11,24] Even when additional stimulation targeted left dorsolateral prefrontal cortex after bilateral primary cortex stimulation, no significant changes (except THI score) were found compared to sham stimulation or medicament therapy only. The results could be explained physiologically by recently reported data showing no changes in neural connectivity following rTMS therapy targeting the left temporal junction in resting-state functional connectivity on functional magnetic resonance imaging.[28]

Further research is necessary to identify better targets and better stimulation settings before rTMS therapy could be developed for clinical practice.

Conclusions

This study did not show a significant effect of bilateral low-frequency rTMS of the primary auditory cortex and additional high-frequency stimulation of the left dorsolateral prefrontal cortex compared to parallel placebo sham coil treatment and medicament therapy only. Further research is necessary to identify better targets and settings for rTMS treatment in patients with chronic subjective nonpulsatile primary tinnitus before rTMS therapy can be developed for clinical practice.

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Author Contributions

M.F. – conception and design of the study, acquisition and analysis of data, and drafting a significant portion of the manuscript; P.M. – acquisition of data; P.K. – acquisition of data; M.B. – conception and design of the study and analysis of data; D.J. – acquisition of data; H.Z. – conception and design of the study; H.T. – analysis of data; K.Z. – conception and design of the study and analysis of data; and P.K. – conception and design of the study.

Conflicts of Interest

The authors declare that there are no conflicts of interest.

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