

# Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: A randomized, placebo controlled study

Martin Anders<sup>1</sup>, Jana Dvorakova<sup>1</sup>, Lucie Rathova<sup>2</sup>, Petra Havrankova<sup>3</sup>, Petra Pelcova<sup>1</sup>, Manuela Vaneckova<sup>4</sup>, Robert Jech<sup>2</sup>, Martin Holcat<sup>2</sup>, Zdenek Seidl<sup>4</sup>, Jiri Raboch<sup>1</sup>

<sup>1</sup> Charles University in Prague, First Faculty of Medicine, Department of Psychiatry of the First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic

<sup>2</sup> Charles University in Prague, First Faculty of Medicine, Department of Otorhinolaryngology, Head and Neck Surgery of the First Faculty of Medicine and Motol Teaching Hospital, Prague, Czech Republic

<sup>3</sup> Charles University in Prague, First Faculty of Medicine, Department of Neurology of the First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic

<sup>4</sup> Charles University in Prague, First Faculty of Medicine, Department of Radiology of the First Faculty of Medicine and General Teaching Hospital, Prague, Czech Republic

Correspondence to: Martin Anders, MD., PhD.

Charles University in Prague, First Faculty of Medicine, Department of Psychiatry of the First Faculty of Medicine and General Teaching Hospital  
Ke Karlovu 11, Prague 2, 120 00, Czech Republic.

TEL: +420-2-24965220; FAX: +420-2-24923077; E-MAIL: martin.anders@vfn.cz

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## Abstract

**OBJECTIVE:** The pathophysiologic mechanisms of idiopathic tinnitus remain unclear. Low frequency rTMS applied over the auditory cortex has been proposed as a new and causally oriented treatment approach for pathological conditions with abnormal, increased cortical activity including tinnitus with increased activity in the auditory cortex. However available studies are characterized by a positive reports on the therapeutic effects of repetitive transcranial magnetic stimulation (rTMS) for treatment of tinnitus, there are few details about the duration of specific treatment effects.

**DESIGN:** The design of the study was randomized, prospective, placebo-controlled. Right-handed patients were treated with either real or sham 1 Hz frequency rTMS over a period of two weeks. Fifty-two patients with chronic, treatment resistant tinnitus and stable medication were enrolled in the study after giving written informed consent and forty-two patients completed the study and were included in data analysis.

**RESULTS:** The ability to reduce the symptoms of tinnitus appeared in both randomized groups immediately after the 1 Hz rTMS and sham stimulation phase. There was a significant reduction in both groups of the tinnitus total score on the Tinnitus Handicap Inventory (THI) (real rTMS  $p=0.005$ ; sham rTMS  $p=0.049$ ) and Tinnitus Questionnaire (TQ) total score (real rTMS  $p=0.003$ ; sham rTMS  $p=0.049$ ). On the THI evaluation scale, in the real rTMS a mild worsening was noted during week 6 in comparison with the state attained in week 2. During the subsequent course of the study a significant reduction of the total score persisted in the case of THI (real rTMS week 14  $p=0.033$  and borderline week 26  $p=0.058$ ).

The reduction of symptoms as evaluated using the TQ was significant compared to baseline in the real rTMS group at week 2, 6 and 14 ( $p=0.003$ ;  $p=0.024$ ;  $p=0.022$ ). The group treated with sham stimulation reached significant reduction of symptoms only at week 2 ( $p=0.049$ ). A comparison of the difference in the recorded values of the total score during follow-up in relation to baseline expressed as a percentage demonstrates the difference in the effect of rTMS and sham stimulation as evaluated by both the basic scales. Graphical analysis of mean patterns of treatment response according to stimulation type shows a similarity between treatment response patterns evaluated by reduction of the total scores using THI and TQ.

**CONCLUSIONS:** The principal finding of this study is that real 1 Hz rTMS treatment was capable of significantly reducing the total baseline score of basic scales that measure tinnitus severity. This result is important as it proves that significant reduction of symptoms can be achieved even in a group of patients with long-term symptoms resistant to pharmacological treatment.

## INTRODUCTION

Subjective tinnitus has been defined as a frequent auditory sensation experienced in the absence of an external or internal acoustic stimulus e.g. without any corresponding mechanical, vibratory activity within the cochlea (Sala 1997). Tinnitus affects about 10–15% of the adult population (Demeester *et al.* 2007) and in about 5% of cases, it has a significant impact on patient's life, affecting sleep, concentration, emotional balance and social life (Rizzardo *et al.* 1998; Langguth *et al.* 2007). It occurs more frequently in men than in women and it is more frequent among Caucasians. The prevalence of this disorder increases with age. Almost 12% of the population between the age of 65–74 years suffers from chronic tinnitus.

Tinnitus is divided into a pulsatile and non-pulsatile type. The pulsatile type has a mechanical cause, e.g. A-V malformations, otitis media, partial stenosis of the cervical artery, abnormalities of Eustachian tube size or clonic contractions of the tensor veli palatini muscle. As the underlying cause of this type of tinnitus is known, it is usually amenable to treatment. This type is further divided into a subjective and objective form. Objective tinnitus can also be heard externally, while subjective tinnitus is heard only by the patient. The non-pulsatile type of tinnitus is caused by disorders of the peripheral or central auditory nervous system. It is always subjective and is difficult to treat using currently available therapeutic methods (Noell & Meyerhoff 2003). To date, the etiology and pathophysiology of the various types of tinnitus have not been comprehensively clarified.

There is increasing evidence from electrophysiological and functional neuroimaging studies that tinnitus results from increased neuronal activity within central

auditory pathways (Moller 2003). It is presumed that tinnitus may be the acoustic manifestation of pathological neuroplastic processes within the brain that develop as a response to abnormal conditions within the auditory apparatus (Moller 2003). Electrophysiological studies conducted in patients suffering from tinnitus (Muhlnickel *et al.* 1998; Langguth *et al.* 2005) as well as data acquired from animal models (Kaltenbach 2000) demonstrate an impairment of the excitation and inhibition equilibrium within the central auditory cortex, which leads to increased spontaneous activity and structural reorganization.

Data collected to date work with the hypothesis that excessive neuronal activity in both cortical and subcortical auditory regions may cause phantom perception of sound in the central nervous system (Arnold *et al.* 1996; Lockwood *et al.* 1998; Giraud *et al.* 1999; Mirz *et al.* 2000). Additional activation of non-auditory cerebral regions, such as the limbic system, indicates that chronic tinnitus and chronic pain are associated at the neuronal level. This potentially explains why tinnitus causes its sufferers significant emotional discomfort. This is why the investigation of other disorders involving similar neuroplastic changes such as e.g. parallel changes following amputation of a limb or experimental deafferentation is gaining in importance in the treatment of tinnitus (Langguth *et al.* 2005).

Recent neuroimaging studies point to a pathologically over-activated, distributed cortical network involving the interior colliculus (Melcher *et al.* 2000), the thalamus (Reyes *et al.* 2002) and the primary auditory cortex (Arnold *et al.* 1996; Mirz *et al.* 1999; Lockwood *et al.* 1999). The pathophysiological importance of this network has been demonstrated by transient suppression of tinnitus after high frequency rTMS to the temporoparietal cortex (Plewnia *et al.* 2003; De Ridder *et al.* 2005).

Analysis of available clinical studies shows that we currently lack a well-established and fully efficient treatment leading to the long-term reduction of tinnitus. Experience is being sought using various procedures and pharmacological interventions (Dobie 1999; Jalali *et al.* 2009; She *et al.* 2009).

Transcranial magnetic stimulation (TMS) is a noninvasive means of inducing electric current in stimulated brain regions. Repetitive e.g. oscillating transcranial magnetic stimulation (rTMS) can induce alterations of neuronal activity that outlast the actual stimulation period for a considerable amount of time. This method has been experimentally tested in a range of neuropsychiatric disorders, especially in depression alone or associated with a somatic comorbidity (Langguth *et al.* 2005; Langguth *et al.* 2007). A subtype low-frequency ( $\leq 1$  Hz) rTMS is known to reduce neuronal activity in directly stimulated brain regions (Chen *et al.* 1997; Siebner *et al.* 2003) and in structurally connected remote brain regions (May *et al.* 2007). Low frequency rTMS has been proposed as a new and causally oriented

treatment approach for pathological conditions with increased cortical activity (Hoffman & Cavus 2002), including auditory hallucinations in schizophrenia with increased activity in the auditory cortex (review see Zaman *et al.* 2008). Based on the premise that maladaptive cortical reorganization may promote tinnitus, several investigators have studied the effect of slow rTMS on tinnitus (Kleinjung *et al.* 2005; Plewnia *et al.* 2003; De Ridder *et al.* 2005) and they have shown that low frequency rTMS applied over the auditory cortex can ameliorate it, at least temporarily. This suggests that rTMS may inhibit abnormal cortical activity associated tinnitus.

## PATIENT POPULATION AND METHODS

### Patients

Study participants were recruited amongst outpatients seeking treatment at the Department of Otorhinolaryngology, Head and Neck Surgery of the First Faculty of Medicine and Motol Teaching Hospital, Charles University in Prague from June 2006 to December 2008. All participants were enrolled after having signed the study informed consent that had been approved by the Ethics Committee of the General Teaching Hospital Prague (April 2004, registration number of the Ethics Committee of The Office for Human Research Protections at the U.S. Dept. of Health and Human Services IRB00002705 and General Teaching Hospital IORG0002175) in accordance with the Helsinki declaration.

Inclusion criteria were: right handedness as assessed by Annett's questionnaire (Annett 1970), female and male subjects aged 18 to 70 years naïve with regards to rTMS, written informed consent, unilateral or bilateral tinnitus according to the International Classification of Diseases (ICD-10) 10th Revision (H 93.1) of at least 6 months duration, pharmacological treatment for at least 3 months without significant clinical response, identical doses of current pharmacological treatment for at least 6 weeks, age-adjusted normal sensorineural hearing determined by audiogram within the last 6 weeks before start of study, i.e. no more than 5 dB below the 10% percentile (DIN EN ISO 7029) of the appropriate age and gender group in all measured standard frequencies, a normal neurological exam and normal cranial magnetic resonance imaging finding. Normal middle ear status was demonstrated by tympanometry, stapedius reflex tests and otoscopy.

Exclusion criteria were: concurrent other forms of tinnitus treatments, a history of neuropsychiatric disorder (personal or family history of epilepsy, documented abnormal EEG, intracranial hypertension, history of dizziness, significant head injury, stroke, aneurysm, brain malformation, neurodegenerative disorder affecting the brain, previous cranial neurosurgery, presence of acoustic neuroma, glomus tumor, brain tumor, profound hearing loss >90 dB threshold at 4000 Hz or active Menière disease), pacemaker and other metal implants,

implanted medication pump, pregnancy, lactation, presence of other significant medical condition (neuroendocrine, cardiovascular, cerebrovascular, systemic autoimmune diseases), concomitant psychotropic medication or medication that lowers seizure threshold (tricyclic antidepressants or bupropion) or reduces cortical excitation (anticonvulsants, benzodiazepines or other sedatives). All patients also underwent a psychiatric examination by an experienced psychiatrist to exclude patients suffering from clinically relevant concomitant axis I psychiatric disorders according to ICD-10 (especially diagnosis groups F 1–4 according to ICD-10: affective and anxiety disorders, psychoactive substances dependency including alcohol and psychotic disorders). Also excluded were patients unable to fulfill the study requirements and those unable to communicate reliably with the investigators or those unlikely to cope with the trial requirements. Participation in a clinical trial within the last 30 days before starting this trial was also an exclusion criterion.

Amongst the 124 patients who were screened for inclusion in the study, 52 met the selection criteria (see Figure 1). Three patients withdrew consent before beginning treatment. Fifty-two patients were enrolled in the study after giving written informed consent. Patients were randomized (1:1) to receive either active (N=26) or sham stimulation (N=26). In the group of real rTMS, 4 patients withdrew during the course of treatment. Two of these patients experienced a worsening of tinnitus during the initial phase; one woman could not withstand the pain at the site of stimulation and the unpleasant twitching of the masseter muscle; one man withdrew prematurely in the first week of stimulation because of headache. A total of 6 patients withdrew in the group of sham rTMS treatment. The main reason for their withdrawal was a perceived lack of efficacy at the end of the first week of treatment in the case of 3 patients; headache in the case of 2 patients; one patient did not return after two applications for unknown reasons.

Forty-two patients completed the study and were included in data analysis. The real rTMS group (study completed by 22 patients, Table 1) consisted of 10 women/12 men; tinnitus laterality 6right/3left/13bilateral; tinnitus duration 106.8±81.6 months.

The sham rTMS group (study completed by 20 patients, Table 1) consisted of 3women/17men; tinnitus laterality 2right/4left/14bilateral; tinnitus duration 88.4±67.5 months.

### Study design and tinnitus rating: Repetitive TMS procedures and placebo conditions

After screening, written informed consent, baseline assessments and randomization, patients underwent structural magnetic resonance imaging. The Brain-sight-Frameless neuronavigation system (Magstim Company Ltd., Whitland, UK) based on frameless

**Tab. 1.** Descriptive statistics of the age of study completers (N=42) divided into the real treatment group (V) (N=22) and the sham treatment group (S) (N=20).

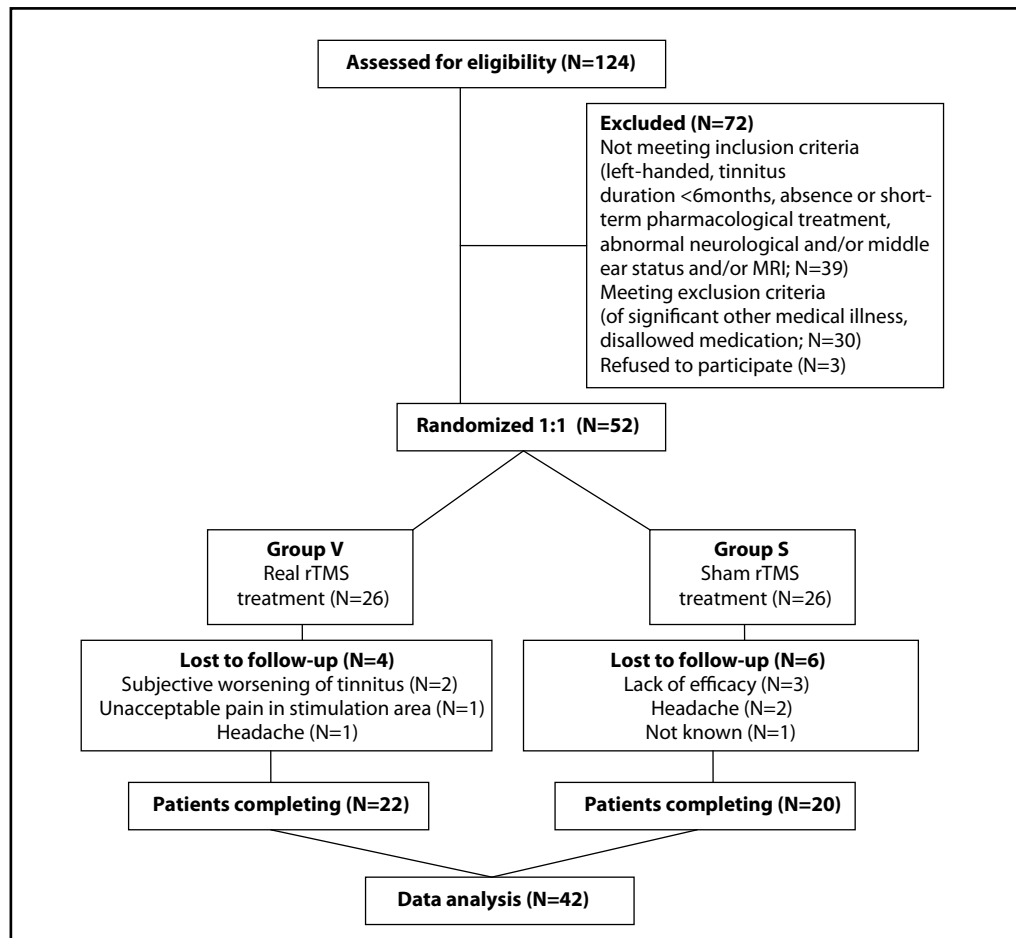
AGE			
V	N	Valid	22
		Missing	0
	Mean		48.09
	Median		51.50
	Mode		58
	Std. Deviation		14.86
	Minimum		20
	Maximum		69
S	N	Valid	20
		Missing	0
	Mean		50.05
	Median		56.00
	Mode		33 <sup>a</sup>
	Std. Deviation		13.97
	Minimum		27
	Maximum		66

<sup>a</sup> Multiple modes exist. The smallest value is shown

stereotaxy allowed navigation of the coil on the surface of the skull over the auditory cortex (Brodmann area 41 and 42) according to individual structural MRI data (T1-weighted, 1.5-T system, Gyroscan NT, Philips Medical Systems, Shelton, CT).

The resting motor threshold was determined at the beginning of the study as the minimal intensity that produced motor-evoked potentials of at least 50  $\mu$ V in the right abductor pollicis brevis muscle in five of ten stimulations. This procedure was taken as the first step of the stimulation process in all randomized patients.

The design of the study was prospective placebo-controlled. Patients were treated with either real or sham low frequency rTMS over a period of two weeks. Repetitive TMS was administered according to current safety guidelines (Wassermann 1998). The Magstim Super Rapid (Magstim Company Ltd., Whitland, UK) stimulator was used for stimulation. Active and sham rTMS was delivered through a figure-eight coil. Sham stimulation was carried out by tilting the coil 45° away from the skull with one wing touching the skull. The treatment group received real stimulation, 2  $\times$  5 sessions, 1 Hz rTMS, stimulation intensity 110% of the individual resting motor threshold, 1500 stimuli per session, coil position over the left primary auditory



**Fig. 1.** Study flow chart.

cortex (Brodmann areas 41 and 42) localized and marked by a water-resistant pen during Brainsight stereotaxy navigation session. Patients were enrolled in the study on Monday and received five sessions of rTMS on five consecutive business days.

The control group received sham stimulation by distortion of the magnetic coil 45° away from the skull with one wing touching the skull. The placement, coil position and stimulation parameters were as in the treatment group. In both groups, low frequency rTMS was administered over the left auditory cortex regardless of tinnitus laterality. During both types of treatments, the coil was held by a mechanical arms and the correct position was periodically adjusted by a physician who was present during the stimulation session.

A blinding design was applied, whereby patients and raters were blind to treatment conditions. All patients were naïve regarding rTMS treatment and were not informed about the technical details of specific rTMS applications. The investigators performing all other assessments were experienced physicians, not involved in the rTMS treatment of the patients and not present during the rTMS procedures. Self-rating instruments were used for assessment.

The aim of the trial was to evaluate the efficacy of 1 Hz rTMS in the treatment of tinnitus. Based on previous findings, we hypothesized that two weeks of active treatment are more efficient for alleviating symptoms than sham treatment. Changes in the Tinnitus Handicap Inventory (Newman *et al.* 1996), the Goebel Hiller tinnitus questionnaire (Goebel & Hiller 1994) and the self rating Visual Analogue Scale (see hereinafter) were used to evaluate the efficacy of real rTMS versus sham rTMS in the treatment of chronic, treatment resistant tinnitus. Another focus of the study was the investigation of the potentially lasting effect of rTMS.

Tinnitus severity was assessed before treatment (baseline), at the end of treatment (week 2) and during the follow-up period of 26 weeks after rTMS treatment (weeks 6, 14, 26) by using the Tinnitus Handicap Inventory and Goebel & Hiller tinnitus questionnaire. Subjects were also asked to rate two Visual Analogue Scales (VAS). The first instruction (VAS1) was “Please, indicate the current severity of your tinnitus. Scale 0 = completely insignificant problem to 10 = currently the most serious problem of my life”.

The second (VAS2) was “How does your tinnitus disrupt your routine daily activities (work, caring for yourself, rest, hobbies, fun)? 0- no disruption at all.....10-disrupts them quite seriously”.

#### Data analysis

SPSS software version 15 was used for statistical analysis. The level of significance was set at 0.05 for all cases. As data collection did not meet the criteria for normal distribution, nonparametric tests were applied for statistical difference assessment and comparison of groups. Groups were created with respect to the type of treat-

ment (active stimulation – STIM(V) versus sham stimulation –SHAM(S)), assessment method and the time of assessment (B-baseline, V1–V4 – follow-up period 26 weeks).

## RESULTS

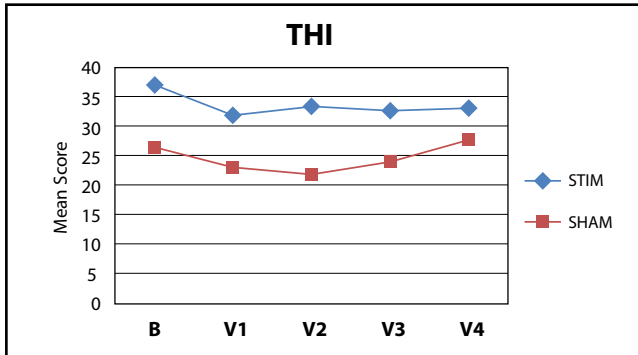
In the group actively treated with 1 Hz rTMS, two patients withdrew during the stimulation phase due to worsening of tinnitus, one patient withdrew due to headache and one woman withdrew due to pain at the site of stimulation and unpleasant, unbearable contractions of the neck muscles on the stimulated side. In the actively treated group, we recorded in completers during the stimulation phase transitory headache, mild tongue paresthesia, transient worsening of tinnitus and changes in quality of sleep. In the group treated with sham stimulation, the spectrum of side effects during the stimulation phase was very similar: two patients withdrew because of headache, but three patients terminated the study after one week because of a perceived lack of efficacy. In those who completed the sham stimulation phase of the study, we noted during the course of the study mild headache (which did not require pharmacological treatment), transient worsening of tinnitus and changes in the quality of sleep. None of the patients developed seizures or other serious side-effects.

The ability to reduce the symptoms of tinnitus appeared in both randomized groups immediately after the 1 Hz rTMS and sham stimulation phase (week 2). There was a significant reduction in both groups of the tinnitus total score on the Tinnitus Handicap Inventory and the 52-items Tinnitus Questionnaire modified by Goebel & Hiller (THI group V  $p=0.005$ ; THI group S  $p=0.049$ ; Goebel Glob group V  $p=0.003$ , Goebel Glob group S  $p=0.049$ ). On the THI evaluation scale, in the real rTMS group, a mild worsening was noted during week 6 in comparison with the state attained in week 2. During the subsequent course of the study, though, a significant reduction of the total score persisted in the case of THI (THI group V, week 14  $p=0.033$  and borderline week 26  $p=0.058$ ). The reduction of symptoms as evaluated using the Tinnitus Questionnaire modified by Goebel & Hiller was significant compared to baseline in the real rTMS group at week 2, 6 and 14 ( $p=0.003$ ;  $p=0.024$ ;  $p=0.022$ ). The group treated with sham stimulation reached significant reduction of symptoms only at week 2 ( $p=0.049$ ) i.e. immediately upon completion of the stimulation phase (Figure 2, Table 2, Figure 5, Table 3). A comparison of the difference in the recorded values of the total score during follow-up in relation to baseline expressed as a percentage demonstrates graphically the difference in the effect of rTMS and sham stimulation as evaluated by both the basic scales (Figure 4, Figure 7). Graphical analysis of mean patterns of treatment response according to stimulation type shows a similarity between treatment response patterns evalu-

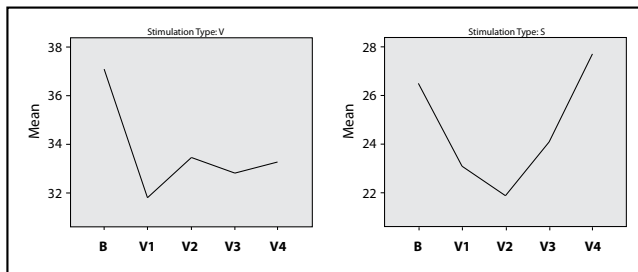
**Tab. 2.** Tinnitus Handicap Inventory total score (mean±standard deviation): comparison of baseline and week 2, week 6, week 14 and week 26 according to stimulation type (V-real stimulation, S-sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

	B	p-value	V1	p-value	V2	p-value	V3	p-value	V4
V									
THI Total	37.09±21.7	0.005	31.82±22.9	0.084	33.45±24.5	0.033	32.82±22.9	0.058	33.27±21.6
S									
THI Total	26.5±20.4	0.049	23.1±19.5	0.074	21.9±19.6	0.125	24.1±22.3	0.293	27.7±23.2

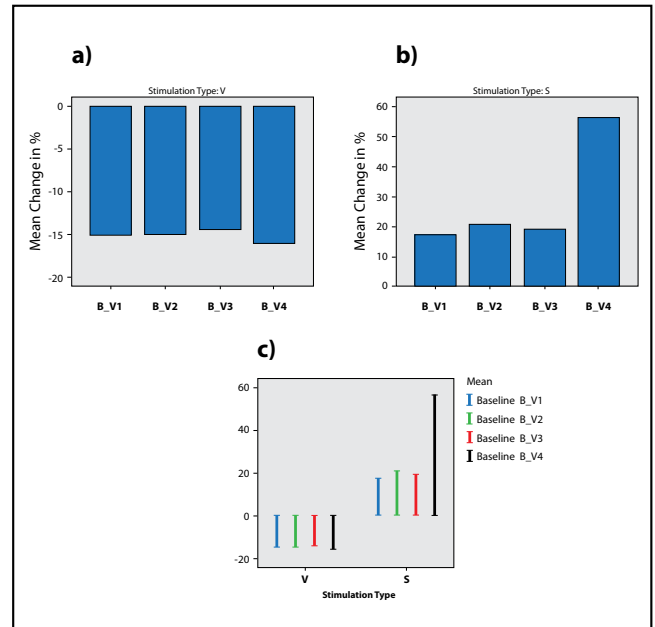
Wilcoxon Signed Ranks Test



**Fig. 2.** Tinnitus Handicap Inventory (THI) mean total score in the 22 patients treated with real stimulation (STIM) and the 20 patients treated with sham stimulation (SHAM) who completed the study (B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).



**Fig. 3.** Tinnitus Handicap Inventory graphical analysis of mean patterns of treatment response according to stimulation type (Stimulation type V – real stimulation; Stimulation type S – sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).



**Fig. 4. a)b):** Mean percentual change according to the Tinnitus Handicap Inventory baseline total score (Stimulation type V – real stimulation; Stimulation type S – sham stimulation; B-baseline, B\_V1- baseline vs. week 2, B\_V2- baseline vs. week 6, B\_V3- baseline vs. week 14, B\_V4-baseline vs. week 26). **c)** A figure showing the calculated upper and lower values (%) for each set of data points, so that two values are displayed graphically for each set. In this case 0% represents the baseline while the other values represent each follow-up change (V1-V4) expressed in percent..

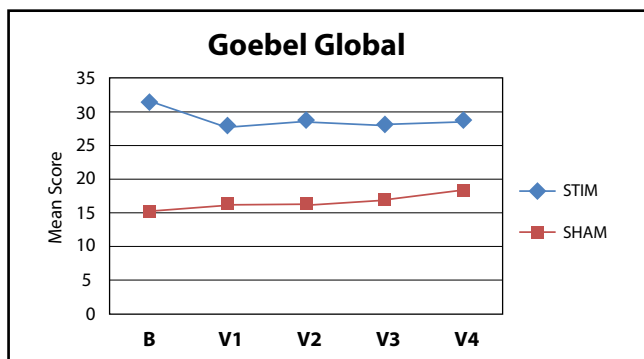
ated by reduction of the total scores using THI and the Tinnitus Questionnaire modified by Goebel & Hiller (Figure 3, Figure 6).

Whereas the total score of the Tinnitus Questionnaire modified by Goebel & Hiller is the sum of items, this instrument also allows the computation of subscales. The most relevant of these include tinnitus associated emotional distress, intrusiveness and audition. Within the emotional distress subscale (Figure 8, Table 4), we observed a reduction of the subscale score in the real rTMS group during follow-up. Active treatment significantly reduced baseline scores at week 2 ( $p=0.013$ ), week

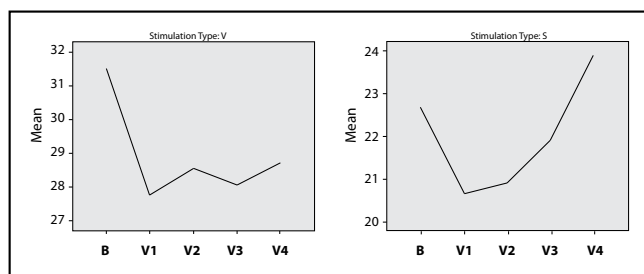
6 ( $p=0.041$ ) and week 14 ( $p=0.036$ ). Sham treatment demonstrated this ability at week 2 ( $p=0.015$ ). These findings are also supported by the graphical analysis of mean patterns of treatment response (Figure 9). Within the intrusiveness subscale (Figure 10), we observed a modest reduction of the subscale score in the real rTMS group during follow-up. This sub score was significantly reduced in the real rTMS group at week 6 ( $p=0.021$ ), week 14 ( $p=0.032$ ) and week 26 ( $p=0.045$ ). Sham treatment significantly reduced this subscale score at week 2 ( $p=0.043$ ), with no significant effect during weeks 6, 14 and 26 (Table 5, Figure 11).

**Tab. 3.** Tinnitus Questionnaire modified by Goebel & Hiller (Goebel Glob) total score (mean±standard deviation): comparison of baseline and week 2, week 6, week 14, week 26 according to stimulation type (V-real stimulation, S-sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

	B	p-value	V1	p-value	V2	p-value	V3	p-value	V4
V									
Goebel Glob	31.50±16.28	0.003	27.77±17.51	0.024	28.55±18.30	0.022	28.05± 17.94	0.096	28.73±18.74
S									
Goebel Glob	22.65±15.13	0.049	20.65±16.28	0.084	20.9±16.23	0.273	21.9±16.87	0.487	23.9±18.41



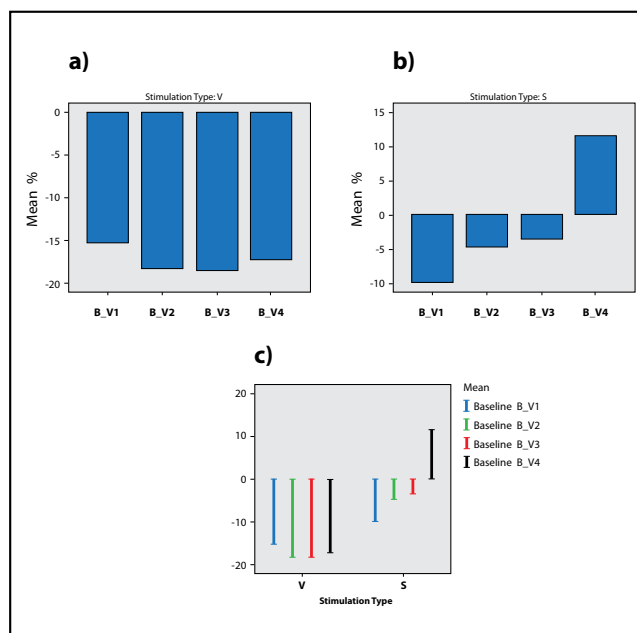
**Fig. 5.** Tinnitus Questionnaire modified by Goebel & Hiller (Goebel Global) total score: mean total score in the 22 patients treated with real stimulation (STIM) and the 20 patients receiving sham stimulation (SHAM) all of whom completed the study (B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26)..



**Fig. 6.** Tinnitus Questionnaire modified by Goebel & Hiller: graphical analysis of mean patterns of treatment response according to stimulation type (Stimulation type V – real stimulation; Stimulation type S – sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

We did not observe any significant reduction for the audition subscale (Figure 12, Table 6) in either the real or sham treatment groups. Graphical analysis of mean patterns of treatment response shows a progressive worsening trend for this subscale in the sham group (Figure 13)

During the study, we did not record any significant changes in the evaluated Visual analogue scale – VAS1 (0–100 points), which studies the perceived severity of tinnitus (Table 7). In the actively treated group, there was a slight decrease in the total VAS1 score, which



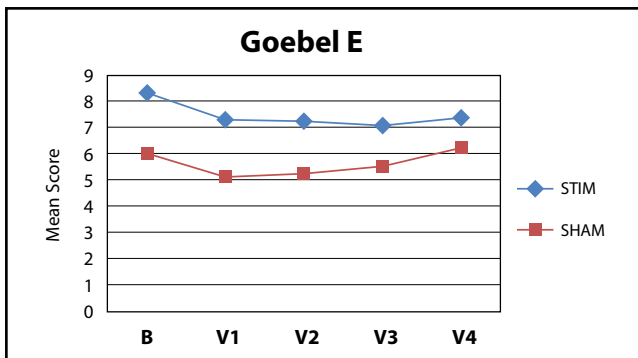
**Fig. 7. a)b)** Mean percent change according to baseline Tinnitus Questionnaire modified by Goebel & Hiller total score (Stimulation type V – real stimulation; Stimulation type S – sham stimulation; B-baseline, B\_V1- baseline vs. week 2, B\_V2- baseline vs. week 6, B\_V3- baseline vs. week 14, B\_V4-baseline vs. week 26). **c)** A figure showing the calculated upper and lower values (%) for each set of data points, so that two values are displayed graphically for each set. In this case 0% represents the baseline while the other values represent each follow-up change (V1-V4) expressed in percent..

continued until week 26, while in the sham treatment group the subjective perception of tinnitus severity rose from week 26.

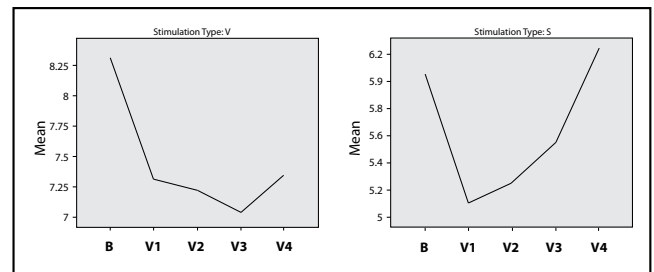
Similarly, no significant changes compared to baseline were recorded in the Visual analogue scale – VAS2 (0–100 points), which studies the disruption of routine daily activities (Table 8). Graphical analysis of mean patterns shows congruency between VAS1 and VAS2 in the real treatment group but incongruence in the sham treatment group.

**Tab. 4.** Tinnitus Questionnaire modified by Goebel & Hiller; emotional distress dimension mean subscore (mean±standard deviation): comparison of baseline and week 2, week 6, week 14, week 26 according to stimulation type (V-real stimulation, S-sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

	B	p-value	V1	p-value	V2	p-value	V3	p-value	V4
V									
Goebel E	8.32±4.92	0.013	7.32±5.0	0.041	7.235±5.12	0.036	7.05±5.21	0.092	7.36±5.70
S									
Goebel E	6.05±4.39	0.015	5.10±4.64	0.128	5.25±4.59	0.168	5.55±4.97	0.45	6.25±5.81



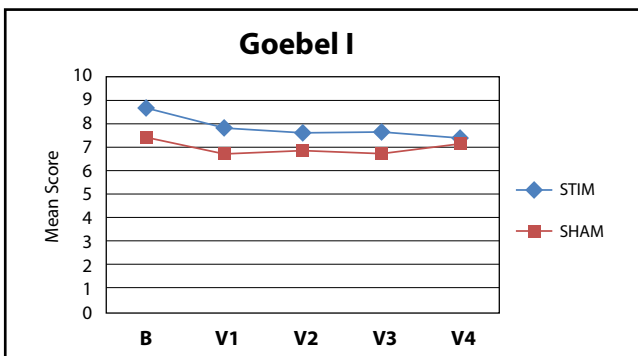
**Fig. 8.** Tinnitus Questionnaire modified by Goebel & Hiller: emotional distress dimension (Goebel E) mean subscore (maximum 24 points) in the 22 patients treated by real stimulation (STIM) and the 20 patients receiving sham stimulation (SHAM) all of whom completed the study (B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).



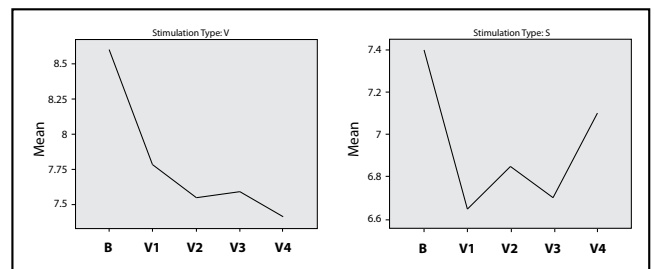
**Fig. 9.** Tinnitus Questionnaire modified by Goebel & Hiller emotional distress dimension: graphical analysis of mean patterns of treatment response according to stimulation type (Stimulation type V – real stimulation; Stimulation type S – sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

**Tab. 5.** Tinnitus Questionnaire modified by Goebel & Hiller; intrusiveness dimension mean subscore (mean±standard deviation): comparison of baseline and week 2, week 6, week 14, week 26 according to stimulation type (V-real stimulation, S-sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

	B	p-value	V1	p-value	V2	p-value	V3	p-value	V4
V									
Goebel I	8.59±4.63	0.084	7.77±4.89	0.021	7.55±5.04	0.032	7.59±4.88	0.045	7.41±4.88
S									
Goebel I	7.40±3.66	0.043	6.65±3.71	0.147	6.85±3.81	0.084	6.70±3.82	0.205	7.10±3.87



**Fig. 10.** Tinnitus Questionnaire modified by Goebel & Hiller: intrusiveness dimension (Goebel I) mean subscore (maximum 16 points) in the 22 patients treated with real stimulation (STIM) and the 20 patients receiving sham stimulation (SHAM) all of whom completed the study (B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).



**Fig. 11.** Tinnitus Questionnaire modified by Goebel & Hiller intrusiveness dimension: graphical analysis of mean patterns of treatment response according to stimulation type (Stimulation type V – real stimulation; Stimulation type S – sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).



## DISCUSSION

The principal finding of this study is that real 1 Hz rTMS treatment was capable of significantly reducing the total baseline score of basic scales that measure tinnitus severity, namely in the case of patients with an average age of 50 suffering from tinnitus for an average duration of nearly nine years and who moreover did not respond to prior pharmacological treatment administered for at least three months before randomization. A similar conclusion applies to some of the subscales dealing with specific dimensions of patient tinnitus symptoms. This result is important as it proves that significant reduction of symptoms can be achieved even in a group of patients with long-term symptoms resistant to pharmacological treatment.

As to duration of the effect following stimulation, we may summarize that the positive effect evaluated using the various scales is chronologically limited and that persistence of significant differences during follow-up visits vs. baseline in our study is limited in the case of the most positively affected parameters up to week 14, including the emotional distress dimension (depression, anger, irritability, anxiety) subscale of the Tinnitus Questionnaire modified by Goebel & Hiller. This long-term improvement cannot be attributed to a placebo response, but rather to the true effect of rTMS on reducing the activity of the stimulated region as well as on neuroplasticity and its effect on other brain structures. The intrusiveness dimension (consisting of symptoms such as continuous focusing on tinnitus, difficulties concentrating) subscale of the Tinnitus Questionnaire modified by Goebel & Hiller remained significantly decreased up to week 26. The intervention, though, practically failed to influence the audition dimension (perceptual difficulties, hearing problems in demanding social situations) subscale of the Tinnitus Questionnaire modified by Goebel & Hiller. It could thus be assumed that the effect of this treatment lies primarily in its impact on items coming under the emotional distress and intrusiveness subscale. Impact on the audition subscale, which already demonstrates low values at baseline, is practically nil during follow-up. Thus, in the actively treated group, there is a significant reduction of emotional distress and intrusiveness, but active treatment fails to impact on the audition subscale.

The situation differs in the sham group, where we observed a significant response in the THI total score, the Tinnitus Questionnaire modified by Goebel & Hiller total score and the intrusiveness dimension subscale of the Tinnitus Questionnaire modified by Goebel & Hiller only immediately after stimulation (week 2) but not during the follow-up phase. Though we recorded a significant reduction of emotional distress at week 2, at the end of the study patients evaluated this parameter as being worse than at baseline. This placebo reaction surely involves factors related to patient selection

for similar studies. These are patients who have been unsuccessfully treated with pharmacotherapy, whose symptoms persist or even worsen in time, patients who have suffered disappointment and often harbor excessive expectations. Treatment motivation and acceptance can be a crucial point in the psychological and also biological intervention for tinnitus sufferers. During stimulation, there is an increase in the feeling of subjective control for 12 days, a sense of “being treated” and of “doing something” with the illness and “fighting it”. At the same time, there is intense contact with the physician and the patient has a tendency to conduct a dialogue regarding his/her complaints (psychotherapy). Within the study, patients receive greater attention than is common under conditions of routine care in outpatient clinics. This may explain the significant reduction of scores at week 2 in our sham group. It may be stated that despite the primarily expected degree of placebo response, we found significant changes only immediately following stimulation.

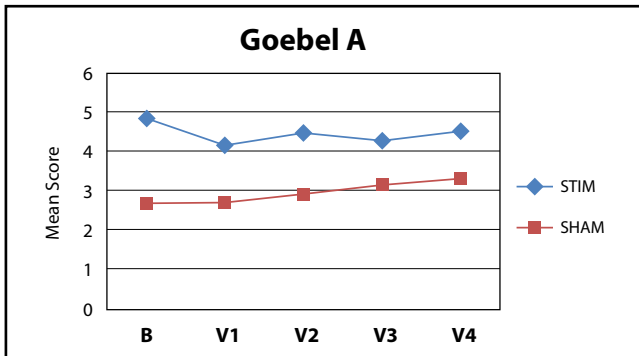
We were unable to demonstrate neither in the real nor in the sham group any changes in the subjective perception of tinnitus using the Visual analogue scale (VAS1) or any influence on daily activities (VAS2). It is probable that these questions are too unspecific, too general and thus we will no longer use them in further studies.

Our results converge with previous studies suggesting that low-frequency rTMS can positively reduce tinnitus perception in some patients, at least temporarily. Some authors demonstrated a positive effect in approximately one half of patients with tinnitus treated with single sessions of rTMS (De Ridder *et al.* 2005). Similarly, further double blind studies (Kleinjung *et al.* 2005; Marcondes *et al.* 2010) have shown that slow frequency rTMS administered for five consecutive days could have a significant effect on tinnitus that persists up to 6 months after treatment. Our results rather correspond to the findings of the Smith *et al.* 2007 study. This study found that a response to active (but not sham) rTMS occurred in all actively treated patients, but tinnitus returned in all patients within four weeks following active treatment. The authors also conclude that there was a significant increase in the reaction time and that it is unclear whether the improved reaction times were caused by tinnitus reduction or a general effect of rTMS. It may thus be presumed, and this is confirmed by our results, that the duration of active treatment efficacy is limited in time and the maximally achieved effect decreases at a certain interval from the study stimulation phase. It will be necessary to consider developing a protocol of maintenance treatment for suitable patients. One case report showed that it is feasible to use maintenance rTMS to manage chronic tinnitus (Mennemeier *et al.* 2008).

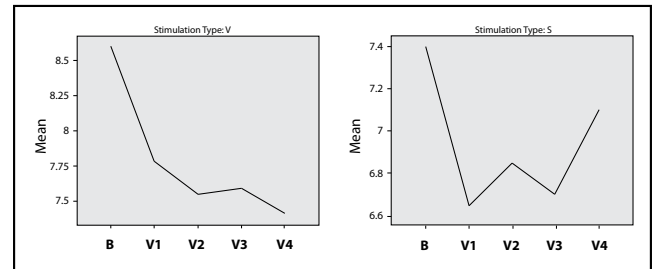
Our study is limited due to many restrictions. We did not use PET imaging (financial aspects and accessibility in the Czech Republic) or functional magnetic

**Tab. 6.** Tinnitus Questionnaire modified by Goebel & Hiller; audition dimension mean subscore (mean±standard deviation): comparison of baseline and week 2, week 6, week 14, week 26 according to stimulation type (V-real stimulation, S-sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

	B	p-value	V1	p-value	V2	p-value	V3	p-value	V4
V									
Goebel I	4.82±3.77	0.067	4.18±3.23	0.129	4.45±3.63	0.105	4.27±3.12	0.325	4.50±3.46
S									
Goebel I	2.70±3.13	0.471	2.70±3.70	0.261	2.90±3.41	0.154	3.15±3.26	0.167	3.30±3.51



**Fig. 12.** Tinnitus Questionnaire modified by Goebel & Hiller: audition dimension (Goebel A) mean subscore (maximum 14 points) in the 22 patients treated by real stimulation (STIM) and the 20 patients receiving sham stimulation (SHAM) all of whom completed the study (B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).



**Fig. 13.** Tinnitus Questionnaire modified by Goebel & Hiller audition dimension: graphical analysis of mean patterns of treatment response according to stimulation type (Stimulation type V – real stimulation; Stimulation type S – sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

**Tab. 7.** Visual analogue scale (0–100 points) (VAS1) mean score (mean±standard deviation): comparison of baseline and week 2, week 6, week 14, week 26 according to stimulation type (V-real stimulation, S-sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

	B	p-value	V1	p-value	V2	p-value	V3	p-value	V4
V									
VAS1	55.73±26.72	0.068	51.45±27.78	0.07	50.95±27.48	0.315	51.95±29.13	0.127	49.55±29.24
S									
VAS1	36.11±23.54	0.237	33.95±21.82	0.504	35.84±17.85	0.422	37.21±19.45	0.255	39.89±20.22

**Tab. 8.** Visual analogue scale (0–100 points) (VAS2) mean score (mean±standard deviation): comparison of baseline and week 2, week 6, week 14, week 26 according to stimulation type (V-real stimulation, S-sham stimulation; B-baseline, V1-week 2, V2-week 6, V3-week 14, V4-week 26).

	B	p-value	V1	p-value	V2	p-value	V3	p-value	V4
V									
VAS2	41.00±25.91	0.28	40.14±25.28	0.195	39.55±27.09	0.347	42.27±29.85	0.382	41.32±31.10
S									
VAS2	26.16±23.06	0.214	26.15±25.02	0.193	27.55±19.48	0.397	28.40±21.40	0.331	28.60±23.45

resonance imaging in order to determine the exact localization of asymmetric metabolic activity. Rather, we localized BA 41 and 42 according to anatomical conditions. It would certainly be interesting to determine the exact localization of metabolic hyperactivity, especially in our sample that included individuals with variously localized tinnitus (left, right and bilateral localized tinnitus).

We used the 1 Hz stimulation protocol at the typical localization of BA 41, 42 in our active treatment. Lately, though, there have been reports regarding the efficacy of combined temporal and prefrontal rTMS (1 Hz over auditory cortex vs. 20 Hz over DLPFC and then 1 Hz over auditory cortex), which confirm that functional abnormalities in tinnitus patients also involve brain structures used for attentional and emotional processing, such as the dorsolateral prefrontal cortex (Kleinjung *et al.* 2008). One recent study (Khedr *et al.* 2009) observed an efficacy of ten days of 1 Hz, 10 Hz, 25 Hz rTMS over the temporoparietal cortex, with some patients showing a lasting benefit at 1 year after 10 days of rTMS treatment.

Although we analyzed the results for the whole groups, we are aware that patient age plays a role and that it would be appropriate to divide the sample into age clusters. Similarly, we could, naturally in the case of a larger sample of probands, analyze the groups according to tinnitus severity or to the average disease duration. Data regarding the extent of response in these subgroups are either few or completely lacking. Some authors recommend that a stable baseline of tinnitus be established before starting a clinical trial. Scoring and rating should also be conducted daily, as relying on pre-experiment and post-experiment measurements may fail to detect real changes that occur during the course of the study. The most likely reason for pretreatment and post-treatment measurements failing to detect change was that tinnitus returned shortly after treatment was concluded (Smith *et al.* 2007).

Another limitation that frequently occurs in similar studies is the control conditions. Although sham stimulation takes place under the same laboratory conditions and the sham positioning of the coil is accompanied by the typical sound of active stimulation, it lacks the somatosensory sensation. Some authors are attempting to verify this original placebo condition (Rossi *et al.* 2007) and have shown that the rTMS effect on tinnitus is not mediated by somatosensory stimulation. We believe that subjects can easily distinguish the difference between real and sham stimulation, especially during stimulation of the temporal region, which strongly biases their judgments regarding eventual clinical benefits. In our study, we did not examine whether patients, who were all naïve for rTMS, identified the active or sham method of treatment.

In summary, our study of rTMS in patients suffering from chronic tinnitus confirms earlier studies by demonstrating tinnitus reduction after active rTMS treat-

ment but not after sham rTMS. An important, clinically significant fact emerging from our study is that the effect of real rTMS treatment persisted for 3 months of follow-up assessment. It is thus necessary to seek a further optimal chronological design of the stimulation protocol, especially in the group of patients with clinical characteristics similar to those of the patients included in our sample.

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