Trends in Hearing
Volume 23: 1–14

DOI: 10.1177/2331216518822198
journals.sagepub.com/home/tia
SAGE

Neuronavigated Versus Non-navigated Repetitive Transcranial Magnetic Stimulation for Chronic Tinnitus: A Randomized Study

Hanna Sahlsten[1], Anu Holm[2], Esa Rauhala[2], Mari Takala[2], Eliisa Löyttyniemi[3], Max Karukivi[4,5], Johanna Nikkilä[4,5], Kirsi Ylitalo[6], Janika Paavola[7], Reijo Johansson[8], Tero Taiminen[9], and Satu K. Jääskeläinen[10]

Abstract

Repetitive transcranial magnetic stimulation (rTMS) has shown variable effect on tinnitus. A prospective, randomized 6-month follow-up study on parallel groups was conducted to compare the effects of neuronavigated rTMS to non-navigated rTMS in chronic tinnitus. Forty patients (20 men, 20 women), mean age of 52.9 years (standard deviation [*SD*] = 11.7), with a mean tinnitus duration of 5.8 years (*SD* = 3.2) and a mean tinnitus intensity of 62.2/100 (*SD* = 12.8) on Visual Analog Scale (VAS 0–100) participated. Patients received 10 sessions of 1-Hz rTMS to the left temporal area overlying auditory cortex with or without neuronavigation. The main outcome measures were VAS scores for tinnitus intensity, annoyance, and distress, and Tinnitus Handicap Inventory (THI) immediately and at 1, 3, and 6 months after treatment. The mean tinnitus intensity (hierarchical linear mixed model: $F_3 = 7.34$, $p = .0006$), annoyance ($F_3 = 4.45$, $p = .0093$), distress ($F_3 = 5.04$, $p = .0051$), and THI scores ($F_4 = 17.30$, $p < .0001$) decreased in both groups with non-significant differences between the groups, except for tinnitus intensity ($F_3 = 2.96$, $p = .0451$) favoring the non-navigated rTMS. Reduction in THI scores persisted for up to 6 months in both groups. Cohen's *d* for tinnitus intensity ranged between 0.33 and 0.47 in navigated rTMS and between 0.55 and 1.07 in non-navigated rTMS. The responder rates for VAS or THI ranged between 35% and 85% with no differences between groups ($p = .054$–1.0). In conclusion, rTMS was effective for chronic tinnitus, but the method of coil localization was not a critical factor for the treatment outcome.

Keywords

tinnitus, transcranial magnetic stimulation, TMS, rTMS, neuronavigated

Date received: 17 August 2018; revised: 26 November 2018; accepted: 5 December 2018

Introduction

Tinnitus is the perception of sound in the absence of an external sound source. Its prevalence is 10% to 15% in the general population, increasing with age and after noise exposure (De Ridder et al., 2014). Tinnitus severely impairs the quality of life in 1% to 2% of people and is frequently associated with depression, anxiety, and insomnia (Langguth, Kreuzer, Kleinjung, & De Ridder, 2013; Langguth, Landgrebe, Kleinjung, Sand, & Hajak, 2011).

The exact pathophysiology of tinnitus remains unclear. Neuroplastic changes occurring in the brain following auditory sensory deafferentation alter neural

[1]Faculty of Medicine, University of Turku, Finland
[2]Department of Clinical Neurophysiology, SataDiag, Satakunta Hospital District, Pori, Finland
[3]Department of Biostatistics, University of Turku, Finland
[4]Unit of Adolescent Psychiatry, Satakunta Hospital District, Pori, Finland
[5]Department of Psychiatry, University of Turku and Turku University Hospital, Finland
[6]Department of Ear, Nose and Throat, Satakunta Hospital District, Pori, Finland
[7]Department of Medical Physics, Turku University Hospital, Finland
[8]Department of Ear, Nose and Throat, Turku University Hospital, Finland
[9]Department of Psychiatry, Turku University Hospital, Finland
[10]Department of Clinical Neurophysiology, Division of Medical Imaging, Turku University Hospital and University of Turku, Finland

Corresponding author:
Hanna Sahlsten, Department of Clinical Neurophysiology, Division of Medical Imaging, Turku University Hospital, Postal Box 52, 20521 Turku, Finland.
Email: hanna.sahlsten@hotmail.fi

processing (Adjamian, Sereda, & Hall, 2009; Husain & Schmidt, 2014; Moller, 2007). High-frequency cochlear hearing loss reduces cochlear nerve signaling downregulating the inhibitory cortical processes leading to hyperexcitability within the central auditory structures, especially within the primary auditory cortex (AC; Baguley, McFerran, & Hall, 2013; Leaver et al., 2011). There is also abnormal connectivity and increased activity in non-auditory brain areas, for example, frontal, parietal, and limbic areas, that mediate attention and distress, especially in bothersome tinnitus (Burton et al., 2012; Husain & Schmidt, 2014; Leaver et al., 2011; Maudoux et al., 2012; Roberts, Husain, & Eggermont, 2013). Furthermore, the tinnitus percept does not seem to alter the functional connectivity of the AC or other key cortical regions in patients with non-bothersome tinnitus (Wineland, Burton, & Piccirillo, 2012).

No curative therapy for tinnitus exists, although nearly 60 different treatment modalities have been investigated. Specific tinnitus counseling and cognitive behavioral therapy are usually recommended (Zenner et al., 2017). Possible concurrent depression should be treated, but routine use of antidepressive or other medication should be avoided (Tunkel et al., 2014).

Repetitive transcranial magnetic stimulation (rTMS) is a non-invasive technique that applies magnetic pulses to the scalp and underlying brain causing alterations in neuronal excitability and neurotransmitter systems (Allen, Pasley, Duong, & Freeman, 2007; Lamusuo et al., 2017; Moisset, de Andrade, & Bouhassira, 2016). Cortical excitability can be increased with high-frequency or decreased with low-frequency rTMS via long-term potentiation or long-term depression-like effects in synaptic efficacy (Hoogendam, Ramakers, & Di Lazzaro, 2010). Besides focal alterations, rTMS induces widespread functional changes in the brain networks connected to the stimulated cortical target and also releases dopamine and endogenous opioids (Hoogendam et al., 2010; Lamusuo et al., 2017; Lefaucheur et al., 2014; Moisset et al., 2016). In tinnitus, the AC is thought to be hyperactive (Seidman et al., 2008), and thus, low frequency ($\leqslant$1 Hz) rTMS that reduces cortical excitability has been proposed for the treatment of tinnitus (De Ridder et al., 2006; Plewnia et al., 2007).

Depression and neuropathic pain have been successfully treated with rTMS over the past decade (Cruccu et al., 2016; Lefaucheur et al., 2014; Rossi, Hallett, Rossini, Pascual-Leone, & Safety of TMS Consensus Group, 2009). However, in chronic tinnitus, the evidence is still controversial, although a recent meta-analysis on 720 patients observed moderate efficacy of low-frequency rTMS (Soleimani, Jalali, & Hasandokht, 2016). Several placebo-controlled trials have shown efficacy of rTMS over temporal or temporoparietal regions (Anders et al., 2010; Eichhammer, Langguth, Marienhagen, Kleinjung, & Hajak, 2003; Folmer et al., 2015; Kleinjung et al., 2005; Marcondes et al., 2010; Mennemeier et al., 2011; Plewnia et al., 2007; Rossi et al., 2007), while others have not found significant effects (Hoekstra, Versnel, Neggers, Niesten, & van Zanten, 2013; Landgrebe et al., 2017; Langguth et al., 2014; Piccirillo et al., 2011, 2013; Plewnia et al., 2012; Sahlsten et al., 2017).

The role of neuronavigated rTMS (nrTMS) in tinnitus treatment remains an open question. nrTMS can be targeted over the hypermetabolic or hyperactive cortical regions detected by positron emission tomography or functional magnetic resonance imaging (fMRI) or targeted with structural brain MRI (Langguth, Kleinjung, Landgrebe, de Ridder, & Hajak, 2010). However, nrTMS can be more expensive and time-consuming than non-navigated rTMS. Non-navigated methods are inaccurate (by 1–2 cm) with regard to the anatomical cortical targets actually stimulated (Ahdab, Ayache, Brugieres, Goujon, & Lefaucheur, 2010; Langguth et al., 2006). Currently, the few available studies do not demonstrate superiority of nrTMS for tinnitus treatment (Langguth et al., 2006, 2010, 2014; Noh, Rah, et al., 2017). One reason for this may be uncertainty regarding the optimal target for suppressing tinnitus. Yet, nrTMS has shown better results than non-navigated rTMS for the treatment of depression and pain (Ayache et al., 2016; Fitzgerald et al., 2009).

This study was part of a larger project evaluating rTMS for the treatment of chronic tinnitus (Sahlsten et al., 2017, 2018) and evaluated whether targeting the region overlying the AC with nrTMS based on individual structural head MRI is superior to non-navigated rTMS using the 10–20 electroencephalogram (EEG) electrode location system (Langguth et al., 2006). An additional goal was to evaluate long-term effects of rTMS on tinnitus.

Materials and Methods

This prospective, randomized, single-blind study on parallel groups was approved by the Ethical Committee for the Hospital District of Southwest Finland (73/1800/2013). Patients gave their written informed consent. The trial took place in the Departments of Ear, Nose and Throat Diseases and Clinical Neurophysiology at Satakunta Central Hospital during 2013–2016. The study was registered on ClinicalTrials.gov (ID NCT 01929837).

Patients

All tinnitus patients treated in the Department of Ear, Nose and Throat Diseases in Satakunta Central Hospital

between January 2012 and March 2013 were searched using patient archives. Inclusion criteria were age between 18 and 65 years, chronic (6 months–10 years), unilateral or bilateral tinnitus with an intensity of at least 4/10 on the Numeric Rating Scale (NRS) during a telephone interview. Figure 1 shows the patient recruitment process. Patients were randomized for either navigated or non-navigated rTMS. All patients underwent complete audiological and otological investigations and a three-dimensional (3-D) head MRI to exclude possible treatable causes and provide anatomical guidance for nrTMS. There were no tumor findings in the MRIs, but one patient had a minor benign cyst; another had minor unspecified signal changes in the brain.

Forty patients (20 men and 20 women) of ages 19 to 65 years (mean age of 52.9 years, standard deviation [*SD*] = 11.7) with a mean tinnitus duration of 5.8 years (*SD* = 3.2) and a mean intensity of 62.2/100 (*SD* = 12.8) completed the study and were included in the analyses. There were no drop-outs. All patients were right-handed, except for one in the non-navigated group. Table 1 lists the characteristics of the patients in both groups. The groups did not differ in any of their baseline characteristics ($p = .087–1.0$).

Blinding

Patients were randomized using a random permuted block design for either navigated or non-navigated rTMS. All patients (also in the non-navigated rTMS group) underwent a 3-D head MRI. Measurements of the EEG electrode locations and navigation procedures were done for both groups to avoid patient knowledge of the protocol. In addition, the navigation display was set so that patients could not see it during the sessions. Therefore, the rTMS treatment sessions were conducted exactly in the same manner in both groups from the patients' perspective.

Evaluation Scales

An audiogram (both air and bone thresholds) was measured for decibels (dB) hearing level, and a pure tone average of 500 to 4000 Hz was calculated for both ears

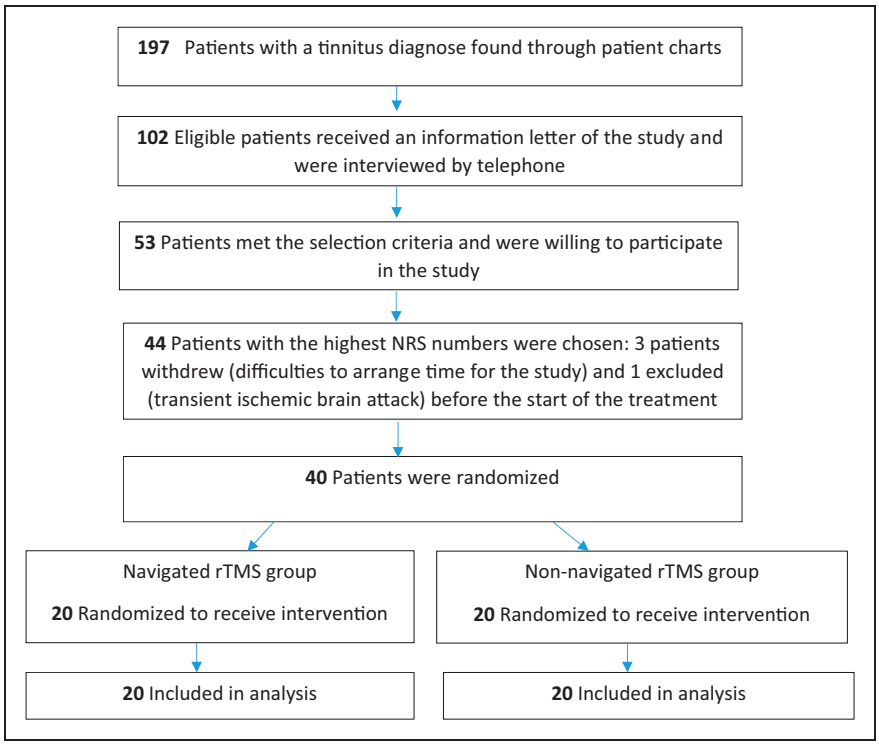

Figure 1. Patient recruitment process. The number of patients are shown, and no patients were lost on follow-up. Pulsatile tinnitus and objective tinnitus were excluded. Other exclusion criteria were magnetically active, metallic intracorporeal appliances (e.g., cochlear implants and cardiac pacemakers); epilepsy, or increased risk of seizure (e.g., brain tumor, stroke, and alcohol abuse); bipolar disorder; severe heart disease; migraine; and pregnancy. Patients were phoned and asked whether they still had intractable tinnitus with an average intensity of at least 4/10 on the NRS from 0 (*no tinnitus*) to 10 (*the worst tinnitus a patient could imagine*). No patients had previously been treated with rTMS.
NRS = Numeric Rating Scale; rTMS = repetitive transcranial magnetic stimulation.

Table 1. The Characteristics of the Patients.

Characteristics	Navigated rTMS group ($n = 20$)	Non-navigated rTMS group ($n = 20$)	p value for between-group comparison
Men, n	11	9	.75
Age, mean (*SD*), years	53.7 (11.3)	52.0 (12.3)	.66
Age-group, no. of patients			
<50 years	6	6	
50–60 years	8	9	1.0
>60 years	6	5	
No. of right-handed patients	20	19	1.0
No. of smoking patients	2	3	1.0
Duration of tinnitus, mean (*SD*), years	4.8 (2.9)	6.8 (3.2)	.087
Tinnitus location, no. of patients			
Right ear	5	3	
Left ear	3	6	.47
Both ears	12	11	
Baseline (first phone contact) NRS tinnitus intensity, mean (*SD*)	5.9 (1.2)	6.5 (1.4)	.17
Baseline VAS tinnitus intensity, mean (*SD*)	59.9 (14.4)	64.7 (10.8)	.24
Baseline VAS tinnitus annoyance, mean (*SD*)	54.7 (18.3)	57.6 (15.1)	.59
Baseline VAS tinnitus distress, mean (*SD*)	52.4 (15.5)	56.9 (16.4)	.38
Baseline Tinnitus Handicap Inventory score, mean (*SD*)	44.3 (20.8)	40.2 (16.9)	.49
Baseline Beck Depression Inventory score, median (quartiles)	6.0 (4.0–9.0)	5.5 (3.0–8.0)	.39
SCID (psychiatric interview), baseline no. of depressed patients	1	1	1.0
Baseline no. of depressed patients with antidepressive medication	2	3	1.0
Baseline Jenkins Sleep Evaluation score, median (quartiles)	14.0 (9.0–18.5)	13.0 (9.0–15.5)	.86
Baseline hearing right ear, PTA (500–4000 Hz), median (quartiles)	19.5 (11.0–29.5)	17.0 (7.0–28.0)	.48
Baseline hearing left ear, PTA (500–4000 Hz), median (quartiles)	19.0 (8.0–27.5)	13.5 (6.0–26.5)	.47
Baseline tinnitus loudness match right ear, median (quartiles), dB sensation level	35.0 (20.0–45.0)	50.0 (30.0–65.0)	.13
Baseline tinnitus loudness match left ear, median (quartiles), dB sensation level	30.0 (20.0–52.5)	37.5 (20.0–50.0)	.92
Baseline tinnitus pitch match right ear, median (quartiles), kHz sensation level	6.0 (3.0–8.0)	8.0 (4.0–8.0)	.38
Baseline tinnitus pitch match left ear, median (quartiles), kHz sensation level	6.0 (4.0–6.0)	6.0 (4.0–8.0)	.97
Baseline tinnitus pitch, no. of patients			
Low pitch	1	2	
High pitch	14	17	.49
Medium pitch	2	0	
Both high and low pitch	3	1	
Resting motor threshold, mean (*SD*), %	62.1 (11.9)	59.6 (9.1)	.58

Note. NRS = Numeric Rating Scale; PTA = pure tone average; rTMS = repetitive transcranial magnetic stimulation; SCID = Structured Clinical Interview for DSM-IV Disorders; VAS = Visual Analog Scale.

at the baseline and after the serial treatment. The loudness (dB) and the pitch (Hz) of tinnitus were psychoacoustically measured with a clinical audiometer at the baseline, after the 2-week treatment, and 1 and 3 months after the rTMS. At these same time points, patients were evaluated using the Tinnitus Handicap Inventory (THI); scores between 0 (*slight tinnitus*) and 100 (*catastrophic tinnitus*; Newman, Jacobson, & Spitzer, 1996) and a Visual Analog Scale (VAS) scores between 0 (no tinnitus) and 100 (*the worst tinnitus the patient could imagine*; Adamchic, Langguth, Hauptmann, & Tass, 2012) for self-ratings of tinnitus intensity, annoyance, and distress in everyday life. In addition, Global Impression of Change (GIC) was given on a scale between −3 (*very much worse than before treatment*) and + 3 (*very much better than before treatment*), 0 meaning no change. The Beck's Depression Inventory (BDI; Steer, Ball, Ranieri, & Beck, 1999) and the Jenkins Sleep

Evaluation Questionnaire (JSEQ; Jenkins, Stanton, Niemcryk, & Rose, 1988) were used to evaluate mood and sleep. The final control was by telephone at 6 months, including NRS (0–10) concerning tinnitus intensity, THI, and GIC. Of the different evaluation scales, VAS and THI were considered as the primary end point measures. Structured diagnostic psychiatric interviews (Structured Clinical Interview for DSM-IV Disorders [SCID] Axis I and II) were performed at the baseline.

rTMS

Navigated rTMS was done with Visor2 navigation system (ANT Neuro, Berlin, Germany) capable of showing in real time the position of the coil and the estimated electric field in relation to the brain. The MagStim Rapid^2 stimulator (Magstim Co., Whitland, Wales, UK) with an air-cooled figure-of-eight coil giving biphasic pulses was used. Prior to treatment, a head MRI was done for all patients with a 1.5 Tesla Siemens Aera scanner (Siemens, Erlangen, Germany) with T1-weighted 3-D sequence. The AC was determined as described in Langguth et al. (2006); details of the nrTMS are noted in Figure 2.

Non-navigated rTMS treatment was based on anatomical landmarks (the International 10–20 EEG electrode location system; Langguth et al., 2006). First, the T3, C3, and Cz EEG electrode sites were defined.

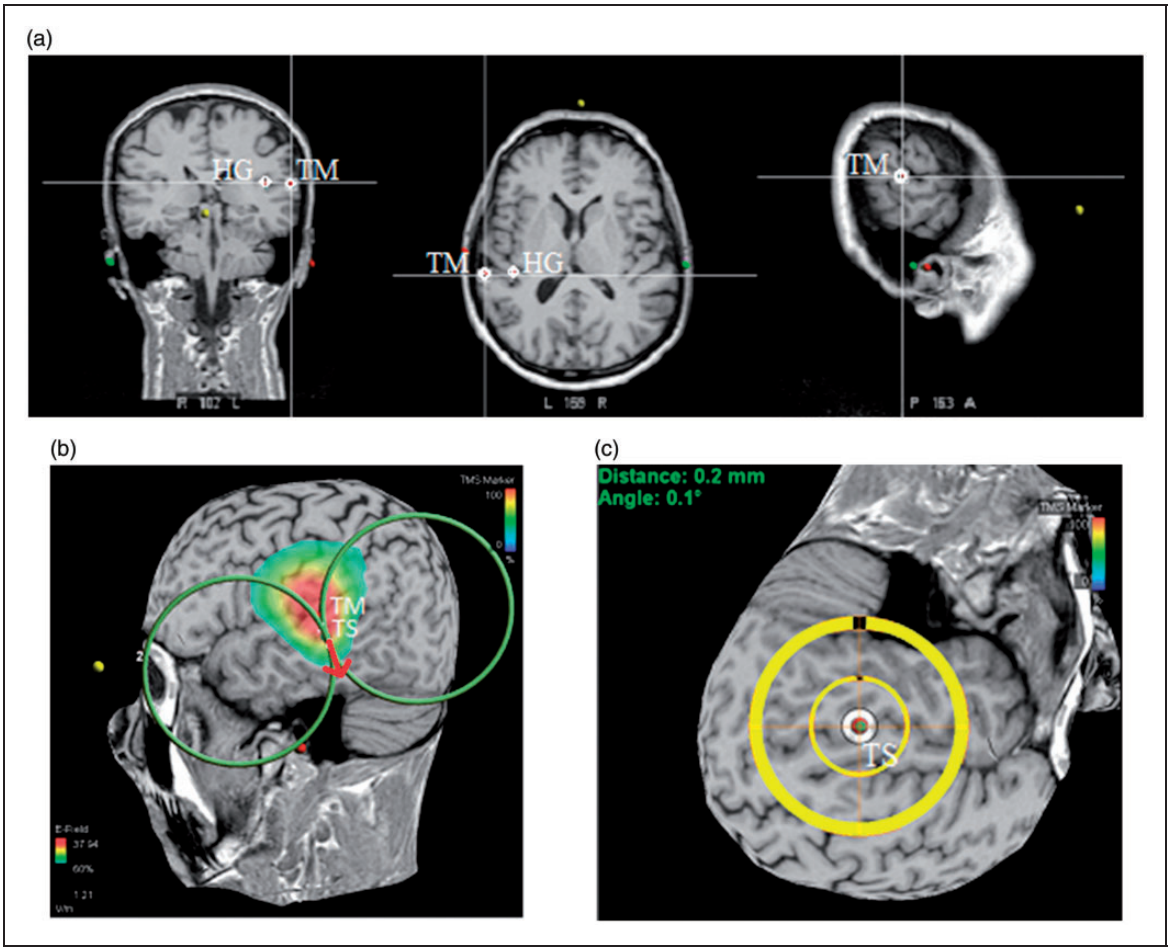

Figure 2. The coil localization with Visor2 navigation system. (a) First, the HG was determined for the individual MRI data set using the anatomical landmarks. Then, the TM was placed perpendicular to the HG on the surface of the 3-D model of the brain. (b) During the first visit to the laboratory, a TS was created. The coil was located so that the centerline of the coil was perpendicular to the superior temporal gyrus, went through to the predefined TM, and the induced electric field best stimulated the auditory cortex. The induced current flow direction of the first quarter cycle of the biphasic pulse pointed downward (the red arrow added in the figure). (c) In each treatment session, the coil was navigated to the position of TS with the help of the reproduce stimuli function in Visor2. The position of the coil was monitored, allowing for a 5-degree and 5-mm shift. If these limits were exceeded, the treatment session was paused, and the coil positioning was corrected.
HG = Heschl's gyrus; TM = target marker; TS = target stimulus.

Then, the coil was positioned over the Heschl's gyrus (HG) by moving the coil 2.5 cm upward from T3 on line T3-Cz and then 1.5 cm in the posterior direction perpendicularly to that line.

Before the serial treatment, the resting motor threshold was determined as recommended by International Federation of Clinical Neurophysiology (Groppa et al., 2012). Motor evoked potentials (MEPs) were recorded from the left hand thenar muscles. An MEP response was defined as an MEP with $> 50\,\mu V$ peak-to-peak amplitude. The maximum-likelihood threshold-tracking algorithm was used to determine TMS intensity yielding a 50% probability of evoking an MEP (Awiszus, 2003). The stimulation was done with the same coil used in the treatment sessions.

Patients were randomly assigned to receive navigated (20 patients) or non-navigated (20 patients) rTMS. Over 2 weeks, 10 treatment sessions were given. Each stimulation session consisted of 4,000 pulses at a continuous 1-Hz rate to the left superior temporal gyrus/AC at 100% of the resting motor threshold. All patients received 10 full sessions, except for 2 patients in the navigated group for whom 1 session was 3,950 or 3,980 pulses, and one patient in the non-navigated group for whom 1 session was only 3,100 pulses (all due to technical problems). In the navigated group, the intensity was lowered to 90%–60% for 13 patients in some sessions, and in the non-navigated group, the intensity was lowered to 90%–70% for 11 patients, because of annoying facial contractions. There were no differences between the treatment groups for the medians of maximal or minimal intensities during rTMS sessions ($p = .17$–$.97$), except for the maximal intensity during the first rTMS session; it was 90% (range 70%–100%) in nrTMS and 100% (range 80%–100%) in non-navigated rTMS ($p = .012$). The left side was chosen because previous studies have shown that stimulation of the left auditory area is efficient, irrespective of tinnitus location (Burger et al., 2011; Lehner et al., 2012), although some contradictory evidence existed (Kim et al., 2014). All patients used ear plugs during the treatment.

Statistical Analysis

All data are presented as a mean with SD or a median with interquartile range (lower and upper quartiles) when describing the data; standard error (SE) is given for the repeated measures analyses. Possible baseline differences were tested using two-sample t test or the Wilcoxon rank sum test as appropriate. Normal distribution of the variables was evaluated from studentized residuals visually and tested using the Shapiro–Wilk test. Logarithmic transformation was performed to THI to fulfill the normality assumption. To study whether the mean change had occurred between the baseline and post-treatment assessment points and whether the mean changes were different between the groups, we used a hierarchical linear mixed model (HLMM) with repeated measures, including one within-factor (time), one between-factor (group) with the interaction added using important clinical background factors (gender, grade of tinnitus, duration of tinnitus, age-group: < 50, 50–60, > 60 years). Compound symmetry covariance structure was used for time. Because of that, we report adjusted mean (SAS least square means) values with 95% confidence interval (CI). If the normality assumption was not met, the treatment groups were compared with the Wilcoxon rank sum test at each visit, and the Friedman's test was used to study the time effect for the entire study population.

Treatment efficacy was calculated using Cohen's d values at follow-up time points against the baseline scores. In addition, the number of responders to rTMS was calculated and defined as patients who showed at least a 30% reduction in tinnitus intensity, annoyance, or distress in the VAS scores at any assessment point (Dworkin et al., 2008). The reduction of 6 points or more in the THI scores was also considered a minimal clinically relevant change (Zeman et al., 2011). The proportion of responders was compared with Fisher's exact test. Confidence interval (95%) was calculated for the absolute difference of proportions between the groups for the excellent responders, the responders based on the reduction of THI scores, and the responders based on the positive GIC. All tests were performed as two sided with a significance level set at .05. The analyses were performed using the SAS System, Version 9.3 for Windows (SAS Institute Inc., Cary, NC, USA).

Results

Primary Outcome Measures

Overall, a decrease over 3 months was observed in mean tinnitus intensity (HLMM: $F_3 = 7.34$, $p = .0006$), annoyance ($F_3 = 4.45$, $p = .0093$), and distress ($F_3 = 5.04$, $p = .0051$) VAS scores for tinnitus in the whole study group. However, the only difference between the navigated and the non-navigated group was in tinnitus intensity ($F_3 = 2.96$, $p = .0451$), favoring the non-navigated rTMS. There were no differences in tinnitus annoyance ($F_3 = 2.04$, $p = .13$) and distress ($F_3 = 1.65$, $p = .19$; Figure 3(a) to (c), Table 2). In both groups, the VAS scores (intensity, annoyance, and distress) improved immediately after treatment and stayed at a lower level for up to the 1- and 3-month time points. The mean tinnitus intensity in NRS units decreased in the non-navigated group from 6.5 ($SD = 1.4$) at the baseline (the first telephone interview) to 5.6 ($SD = 2.3$) at the 6-month control, whereas in the navigated group,

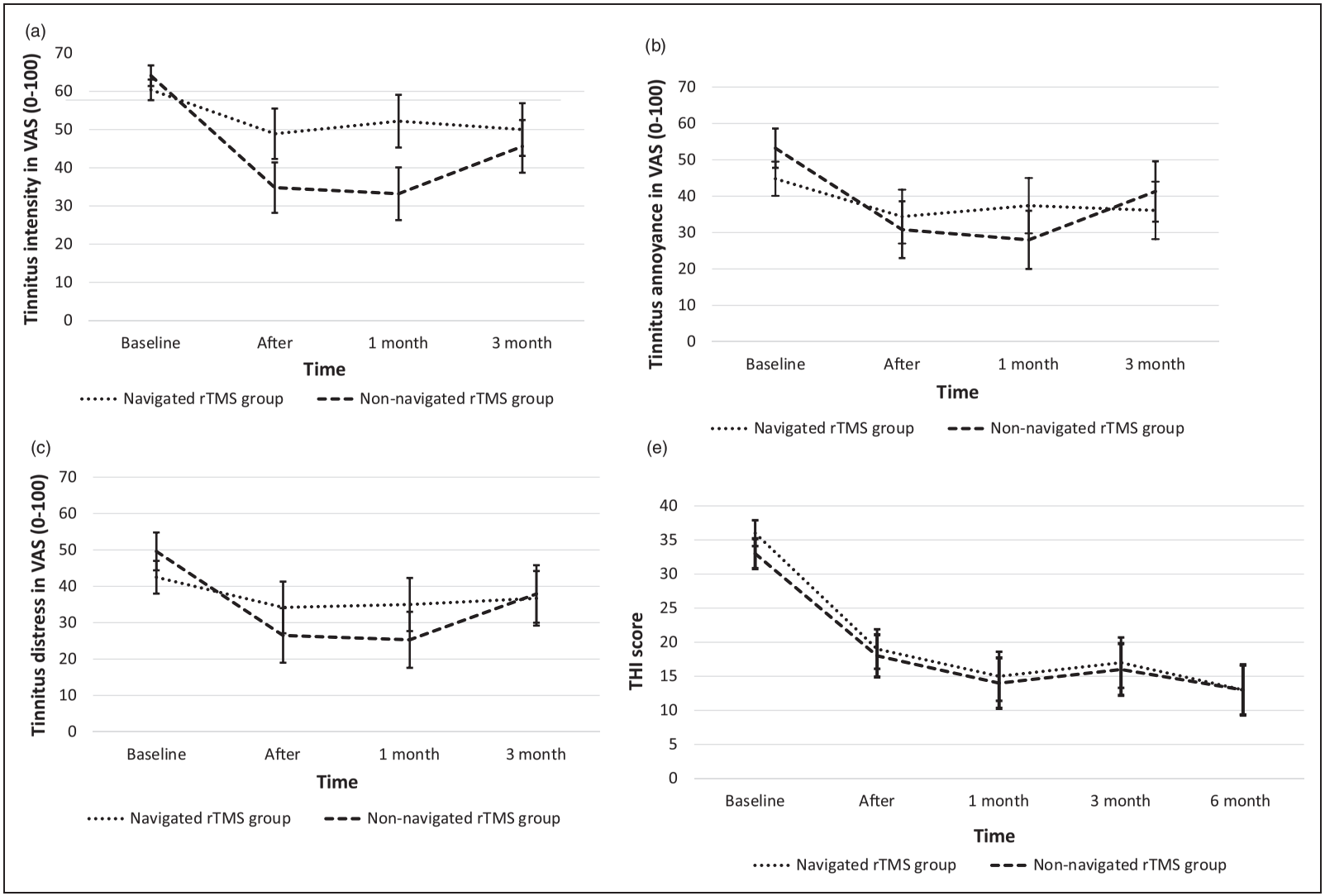

Figure 3. The effect of neuronavigated (based on the structural MRI) and non-navigated (based on the 10–20 EEG electrode location system) serial rTMS treatment on patient's self-rated tinnitus intensity (a), annoyance (b), distress (c) in VAS 0–100, and THI scores (d), in time from the beginning of the treatment, the adjusted means (± SE). The mean tinnitus intensity (HLMM: $F_3 = 7.34$, $p = .0006$); annoyance ($F_3 = 4.45$, $p = .0093$); and distress ($F_3 = 5.04$, $p = .0051$) decreased in both groups over time with no differences between the groups, except for the tinnitus intensity ($F_3 = 2.96$, $p = .0451$) favoring the non-navigated rTMS. There was a reduction ($F_4 = 17.30$, $p < .0001$) in the THI scores in both groups over time with no difference between the two groups ($F_4 = 0.14$, $p = .97$). The reduction in the THI scores was maintained for up to 6 months. See Table 2 for details.
rTMS = repetitive transcranial magnetic stimulation; THI = Tinnitus Handicap Inventory; VAS = Visual Analog Scale.

Table 2. Tinnitus Intensity, Annoyance, and Distress in Visual Analog Scale (0–100) and Tinnitus Handicap Inventory Scores at the Time From the Beginning of the rTMS Treatment, Adjusted Mean, SE.

Time	Total group	*SE*	*p* value	Navigated rTMS group	*SE*	Non-navigated rTMS group	*SE*	*p* value for between-group comparison
(a) Tinnitus intensity								
Baseline	62.2	1.9		60.4	2.7	64.1	2.7	.24
After	41.9	4.7	.0006 over time	48.9	6.6	34.8	6.6	.0451 over time
1 month	42.7	4.9		52.2	6.9	33.2	6.9	
3 months	47.8	4.9		50.0	6.9	45.6	6.9	
(b) Tinnitus annoyance								
Baseline	49.0	3.9		44.8	4.7	53.2	5.4	.59
After	32.6	5.6	.0093 over time	34.4	7.4	30.8	7.8	.13 over time
1 month	32.7	5.7		37.4	7.6	28.0	8.0	
3 months	38.7	5.9		36.1	7.9	41.3	8.3	
(c) Tinnitus distress								
Baseline	46.0	3.7		42.5	4.5	49.6	5.2	.38
After	30.4	5.4	.0051 over time	34.2	7.1	26.5	7.5	.19 over time
1 month	30.1	5.5		35.0	7.3	25.3	7.7	
3 months	37.3	5.6		36.7	7.5	37.9	7.9	
(d) Tinnitus Handicap Inventory scores								
Baseline	34	1.6		36	1.9	33	2.2	.49
After	18	2.2	<.0001 over time	19	2.9	18	3.1	.97 over time
1 month	14	2.7		15	3.6	14	3.7	
3 months	16	2.7		17	3.7	16	3.8	
6 months	13	2.6		13	3.6	13	3.7	

Note. rTMS = repetitive transcranial magnetic stimulation.

it returned to the baseline level from 5.9 ($SD = 1.2$) to 6.1 ($SD = 1.8$). There was a difference between the mean changes over time between the groups ($F_1 = 5.46$, $p = .0253$) favoring the non-navigated rTMS.

There was a reduction ($F_4 = 17.30$, $p < .0001$) in the THI scores for the entire study group over time with no differences between the two treatment groups ($F_4 = 0.14$, $p = .97$; Figure 3(d), Table 2). The reduction in the mean THI scores persisted for up to 6 months.

The background variables of gender, duration of tinnitus, grade of tinnitus (THI grade), and age-group were evaluated in the model. Gender had an effect, as women showed higher tinnitus intensity than did men ($F_1 = 5.8$, $p = .022$). Overall, longer duration and lower THI grade of tinnitus were associated with less annoyance caused by tinnitus ($F_1 = 6.2$, $p = .018$, $F_4 = 4$, $p = .010$), respectively. For distress, the only significant background variable was the grade of tinnitus ($F_4 = 4$, $p = .010$); higher THI grades were associated with more distressing symptoms.

The effect size in Cohen's *d* for tinnitus intensity, calculated between the baseline and the post-treatment time points, ranged between 0.33 and 0.47 after nrTMS and between 0.55 and 1.07 after non-navigated rTMS. Table 4 presents all the Cohen's *d* values for the different variables.

The rate of excellent responders (clinically meaningful reductions in all the VAS and THI scores) did not differ significantly between the navigated and the non-navigated treatment groups, but there were more excellent responders in the non-navigated group at the 1-month control (55% vs. 25%, Fisher's exact test $p = .11$, the absolute difference [navigated rTMS − non-navigated rTMS] of −30, 95% CI [−54.9, 2.6]; Supplement Figure 1, Supplement Table 1). Considering only a 30% reduction in tinnitus intensity after rTMS, there were 65% responders in the non-navigated group and 45% in the navigated group ($p = .34$) and 75% versus 40% ($p = .054$) at the 1-month control. Using a 6-point reduction in the THI scores produced similar responder rates in both groups, namely, 75% responders in the navigated and 80% in the non-navigated group immediately following rTMS ($p = 1.00$, the absolute difference [navigated rTMS − non-navigated rTMS] of −5, 95% CI [−31.3, 21.8]; Supplement Table 1).

Based on the GIC scale, 8/20 (40%) of patients in the navigated group and 3/20 (15%) in the non-navigated group felt they had clearly benefitted (GIC $\geqslant +1$) from the treatment (Supplement Table 2, Supplement Figure 2). The groups did not differ (p values .37–.87) in GIC values (-3 to $+3$) at different evaluation points.

Secondary Outcome Measures and Other Findings

There were no rTMS treatment-induced changes in hearing for the whole group or between the groups for either ear (Supplement Table 3(a)).

There was an improvement in the psycho-acoustically measured loudness of tinnitus (dB) in the left ear for the whole group (mean values; baseline 42.7 [$SD = 21.0$] and the 1-month control 24.4 [$SD = 21.7$], $p = .0023$ over time); otherwise, there were no changes in loudness or the pitch of tinnitus in the whole group or between the groups during follow-up (Supplement Table 3(b) and (c)).

There was a small improvement in the BDI and JSEQ scores after treatment for the whole group and in both treatment groups (HLMM: time effect BDI: $F_2 = 10.9$, $p = .0002$, JSEQ: $F_2 = 55.2$, $p < .0001$) but no significant differences between the groups over time (Table 3). Only two patients were diagnosed with current depression in the baseline structured psychiatric interviews (SCID; Table 1).

There were no major adverse effects, but some patients (approximately two to four patients/each session) reported local inconvenience due to muscle twitching at the stimulation side or mild temporary headache.

Discussion

Chronic tinnitus improved significantly in both rTMS study groups, but nrTMS did not prove to be superior over non-navigated rTMS. In fact, regarding tinnitus intensity, treatment response was even better in the non-navigated group, in both VAS and NRS scores, as well as in Cohen's d values. An improvement in the psycho-acoustically measured loudness of tinnitus in the left ear was observed for the whole group supporting the findings in VAS and THI scores.

Our main findings are in line with another study on tinnitus comparing nrTMS with non-navigated rTMS (Noh, Rah, et al., 2017). Similar to us, they reported significant improvement of THI and VAS scores in both groups but no differences between the groups. Based on improvement of THI scores at least by 7 points, they had somewhat better responder rates, 92% in the navigated group and 89% in the non-navigated group, compared with our rates of 75% and 80% (THI score reduction at least by 6), respectively. Their protocol differed, though, because they treated 22 patients stimulating both the left AC (2,000 pulses/session) and the left prefrontal cortex (1,000 pulses) in only 4 sessions.

Langguth et al. (2014) compared positron emission tomography-guided nrTMS and sham over the left AC, non-navigated rTMS over the left temporal cortex, and non-navigated rTMS combined over the left frontal and the temporal cortices. There was a significant tinnitus reduction for all three active conditions, but as in our study, the comparison between the treatment groups failed to reach significant differences. In another sham-controlled crossover study, eight patients received active nrTMS and eight patients received active non-navigated rTMS (Rossi et al., 2007). Tinnitus improved after active rTMS protocols compared with sham, but the two active rTMS procedures were not systemically compared. In the present study, the rather high number of sessions (10) and possible placebo effect may have had a positive effect on the responder rates.

Table 3. Beck's Depression Inventory and Jenkins Sleep Evaluation Questionnaire Scores at the Time From the Beginning of the rTMS Treatment, Median (Lower and Upper Quartiles).

Time	Navigated rTMS group	Non-navigated rTMS group	p value for between-group comparison	p value for time effect for total group
(a) Beck's Depression Inventory scores				
Baseline	6.0 (4.0–9.0)	5.5 (3.0–8.0)	.39	
After	3.0 (0–8.0)	2.0 (1.0–5.5)	.32 over time	.0002 over time
3 months	1.5 (0–5.5)	2.0 (1.0–5.5)		
(b) Jenkins Sleep Evaluation Questionnaire scores				
Baseline	14.0 (9.0–18.5)	13.0 (9.0–15.5)	.86	
After	4.0 (3.0–5.0)	4.0 (3.5–5.0)	.48 over time	< .0001 over time
3 months	12.0 (8.5–15.0)	11.5 (7.0–15.5)		

Note. rTMS = repetitive transcranial magnetic stimulation.

Table 4. The Effect Size in Cohen's *d* (With 95 % CI) for Tinnitus (a) Intensity, (b) Annoyance, and (c) Distress (Measured in VAS 0–100) Calculated Between the Baseline and Post-treatment Time Points.

Time	Navigated rTMS group	95% CI	Non-navigated rTMS group	95% CI
a. Tinnitus intensity				
After	0.38	[0.19, 0.95]	1.07	[0.44, 1.69]
1 month	0.33	[0.06, 0.73]	1.02	[0.40, 1.65]
3 months	0.47	[0.07, 0.87]	0.55	[0.006, 1.11]
b. Tinnitus annoyance				
After	0.35	[0.15, 0.85]	0.75	[0.14, 1.36]
1 month	0.26	[0.19, 0.71]	0.81	[0.21, 1.42]
3 months	0.31	[0.21, 0.83]	0.37	[0.15, 0.88]
c. Tinnitus distress				
After	0.29	[0.19, 0.77]	0.83	[0.23, 1.42]
1 month	0.31	[0.06, 0.68]	0.78	[0.18, 1.38]
3 months	0.25	[0.16, 0.67]	0.37	[0.16, 0.90]

Note. CI = confidence interval; rTMS = repetitive transcranial magnetic stimulation; VAS = Visual Analog Scale.

In our study, the effect size of Cohen's *d* for tinnitus intensity after nrTMS indicated a modest treatment effect and after non-navigated rTMS good/excellent effect (Table 4). It may be that the target site for non-navigated rTMS was more optimal for tinnitus treatment. Recently, it was demonstrated on 12 participants that the stimulation spot used according to the 10–20 EEG system is on average 10.4 mm superior and 10.8 mm posterior to the scalp location with minimal distance to the primary AC, that is, most probably the optimal target to reach the AC (Theodoroff et al., 2018). Furthermore, in the non-navigated rTMS treatment group, the coil target was not as precise as in nrTMS; therefore, it might have stimulated slightly different cortical targets in a wider brain area in different patients and sessions than in the navigated rTMS group.

Based on our study and the previous literature, it seems that the coil localization method is not a crucial factor in the treatment outcome of rTMS for tinnitus (Langguth et al., 2014; Noh, Rah, et al., 2017) for several reasons. First, the optimal target for rTMS stimulation in tinnitus still remains open (Langguth et al., 2010). The left temporoparietal cortex, overlying the more deeply situated AC, is the most frequently used target. The primary AC is buried deep within this region, so the magnetic field more than likely spreads to the more superficial secondary auditory areas instead of directly influencing the primary AC (Langguth et al., 2010). Hence, the tinnitus suppressing effect is explained by activation of the functional connections that exist between the secondary and the primary AC (De Ridder et al., 2006). In fact, a recent review on non-invasive neuromodulation emphasizes a brain connectivity network perspective for the therapeutic potential rather than just a local effect at the stimulation target (To, De Ridder, Hart, & Vanneste, 2018).

Here, for technical reasons, the coil was placed to induce downward electric currents in the brain (Figure 2), whereas in our previous studies, the currents were in upward direction (Sahlsten et al., 2015, 2017). The effects of posterior–anterior and anterior–posterior currents in the motor cortex may be mediated by different neuronal circuits (Hannah & Rothwell, 2017; Ni et al., 2011), and posterior–anterior current direction is considered more effective than anterior–posterior in inducing MEPs (Andre-Obadia, Mertens, Gueguen, Peyron, & Garcia-Larrea, 2008). The effect of current/field direction should be taken into account in future studies on rTMS for tinnitus, as most previous reports have not stated the direction of the main induced electric field.

In addition to the AC, multisite stimulation, including the dorsolateral prefrontal cortex, may increase efficacy (Lehner, Schecklmann, Greenlee, Rupprecht, & Langguth, 2016; Lehner et al., 2013). Although non-auditory areas participate in tinnitus pathophysiology, rTMS on non-auditory cortical sites alone may be insufficient for tinnitus treatment (Noh, Kyong, et al., 2017).

Second, the cortical area stimulated by rTMS is about 2×3 cm large, and interindividual differences in skull–brain relations vary in the same range (Langguth et al., 2006, 2010). Hence, the precision of neuronavigation may not be needed if the correct target is not more than 1 cm away from the hotspot of the coil. The primary AC may have been within the rTMS coverage in both our treatment groups, at least through the stimulation of the secondary AC.

Third, the heterogeneity of tinnitus etiology, pathophysiology, and its clinical characteristics make it a difficult condition to treat (Baguley et al., 2013). Despite several theoretical hypotheses, the exact pathophysiology of tinnitus is still ambiguous. There is a need for a unified theoretical pathophysiological framework that would cover the different tinnitus models, thereby offer a network for the core pathophysiology of tinnitus and rational rTMS treatment designs (De Ridder et al., 2014).

Generally, tinnitus has been associated with different psychiatric disorders, especially depression (Pinto et al., 2014; Sahlsten et al., 2018). So, theoretically, improvements in the THI scores in this study could be due to the treatment effects on depression. This seems unlikely, though, because we did not stimulate the dorsolateral prefrontal cortex, the main target of rTMS for depression (Lefaucheur et al., 2014). In addition, our patients were not depressed at the baseline (Table 3), and only two patients were diagnosed with a current depression in

the structured psychiatric interview (Table 1). Thus, although there was a small improvement in the BDI scores for the whole group, that change was not clinically significant given the low BDI scores (median 6.0–5.5 suggestive for minimal depressive symptoms) at the baseline. JSEQ scores were rather high (median 14.0–13.0) at the baseline, and they dropped to 4.0 at the first control but returned nearly back to the baseline at the 3-month control (Table 3).

This study has certain limitations. There was no placebo group, so the outcomes may partly be due to a placebo effect. However, our research group has previously conducted a placebo-controlled randomized study on the topic with borderline results (Sahlsten et al., 2017).

The strengths of our study are the elaborate diagnostic evaluation of tinnitus patients by a multidisciplinary research team and a parallel treatment group design to test the study hypothesis. The rTMS treatment was conducted in the same manner at every step in both groups considering the patient's perspective. Follow-up time was also longer than in most rTMS studies.

Conclusions

rTMS was effective for chronic tinnitus for up to 6 months, and the method of coil localization was not a critical factor for treatment outcome. One reason is that the exact optimal target for rTMS stimulation in tinnitus remains uncertain. Structural MRI-based nrTMS and the 10–20 EEG system-based targeting of rTMS showed similar main treatment effects. Indeed, the treatment response was even better in the non-navigated rTMS group but only concerning tinnitus intensity. More research on nrTMS for tinnitus is still needed to finally define the most optimal target site(s) and the coil orientation for the most successful tinnitus treatment.

Acknowledgments

The authors thank all patients for their participation.

Declaration of Conflicting Interests

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Dr. Sahlsten received travel grant from Nexstim for an international congress on rTMS. Dr. Taiminen received lecturer honoraria from AstraZeneca, Bayer, Bristol-Myers Squibb, Efeko, Eisai, GlaxoSmithKline, Lilly, Lundbeck, Nexstim, Orion Pharma, Pfizer, Schering-Plough, and UCB. Professor Jääskeläinen received lecturer honoraria from Nexstim, Orion Pharma, Pfizer, and Ratiopharm. The rest of the authors involved in this study declared no conflicts of interest.

Funding

The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This study was supported by the Finnish Governmental University Hospital grants (EVO), the Finnish Research Foundation of Ear Diseases, and state research funding from the Hospital District of Southwest Finland.

References

Adamchic, I., Langguth, B., Hauptmann, C., & Tass, P. A. (2012). Psychometric evaluation of visual analog scale for the assessment of chronic tinnitus. *American Journal of Audiology*, *21*(2), 215–225. doi:10.1044/1059-0889(2012/12-0010)

Adjamian, P., Sereda, M., & Hall, D. A. (2009). The mechanisms of tinnitus: Perspectives from human functional neuroimaging. *Hearing Research*, *253*(1–2), 15–31. doi:10.1016/j.heares.2009.04.001

Ahdab, R., Ayache, S. S., Brugieres, P., Goujon, C., & Lefaucheur, J. (2010). Comparison of "standard" and "navigated" procedures of TMS coil positioning over motor, premotor and prefrontal targets in patients with chronic pain and depression. *Neurophysiologie Clinique-Clinical Neurophysiology*, *40*(1), 27–36. doi:10.1016/j.neucli.2010.01.001

Allen, E. A., Pasley, B. N., Duong, T., & Freeman, R. D. (2007). Transcranial magnetic stimulation elicits coupled neural and hemodynamic consequences. *Science*, *317*(5846), 1918–1921. doi:10.1126/science.1146426.

Anders, M., Dvorakova, J., Rathova, L., Havrankova, P., Pelcova, P., Vaneckova, M., ... Raboch, J. (2010). Efficacy of repetitive transcranial magnetic stimulation for the treatment of refractory chronic tinnitus: A randomized, placebo controlled study. *Neuroendocrinology Letters*, *31*(2), 238–249.

Andre-Obadia, N., Mertens, P., Gueguen, A., Peyron, R., & Garcia-Larrea, L. (2008). Pain relief by rTMS: Differential effect of current flow but no specific action on pain subtypes. *Neurology*, *71*(11), 833–840. doi:10.1212/01.wnl.0000325481.61471.f0

Awiszus, F. (2003). TMS and threshold hunting. *Transcranial Magnetic Stimulation and Transcranial Direct Current Stimulation*, *56*, 13–23.

Ayache, S. S., Ahdab, R., Chalah, M. A., Farhat, W. H., Mylius, V., Goujon, C., ... Lefaucheur, J. (2016). Analgesic effects of navigated motor cortex rTMS in patients with chronic neuropathic pain. *European Journal of Pain*, *20*(9), 1413–1422. doi:10.1002/ejp.864

Baguley, D., McFerran, D., & Hall, D. (2013). Tinnitus. *Lancet*, *382*(9904), 1600–1607. doi:10.1016/S0140-6736(13)60142-7

Burger, J., Frank, E., Kreuzer, P., Kleinjung, T., Vielsmeier, V., Landgrebe, M., ... Langguth, B. (2011). Transcranial magnetic stimulation for the treatment of tinnitus: 4-Year follow-up in treatment responders – A retrospective analysis. *Brain Stimulation*, *4*(4), 222–227. doi:10.1016/j.brs.2010.11.003

Burton, H., Wineland, A., Bhattacharya, M., Nicklaus, J., Garcia, K. S., & Piccirilo, J. F. (2012). Altered networks in bothersome tinnitus: A functional connectivity study. *BMC Neuroscience*, *13*, 3. doi:10.1186/1471-2202-13-3

Cruccu, G., Garcia Larrea, L., Hansson, P., Keindl, M., Lefaucheur, J., Paulus, W., ... Attal, N. (2016). EAN guidelines on central neurostimulation therapy in chronic pain

conditions. *European Journal of Neurology*, *23*(10), 1489–1499. doi:10.1111/ene.13103

De Ridder, D., De Mulder, G., Verstraeten, E., Van der Kelen, K., Sunaert, S., Smits, M., . . . Moller, A. (2006). Primary and secondary auditory cortex stimulation for intractable tinnitus. *ORL-Journal for Oto-Rhino-Laryngology and its Related Specialties*, *68*(1), 48–54. doi:10.1159/000090491

De Ridder, D., Vanneste, S., Weisz, N., Londero, A., Schlee, W., Belen Elgoyhen, A., & Langguth, B. (2014). An integrative model of auditory phantom perception: Tinnitus as a unified percept of interacting separable subnetworks. *Neuroscience and Biobehavioral Reviews*, *44*, 16–32. doi:10.1016/j.neubiorev.2013.03.021

Dworkin, R. H., Turk, D. C., Wyrwich, K. W., Beaton, D., Cleeland, C. S., Farrar, J. T., . . . Zavislc, S. (2008). Interpreting the clinical importance of treatment outcomes in chronic pain clinical trials: IMMPACT recommendations. *Journal of Pain*, *9*(2), 105–121. doi:10.1016/j.jpain.2007.09.005

Eichhammer, P., Langguth, B., Marienhagen, J., Kleinjung, T., & Hajak, G. (2003). Neuronavigated repetitive transcranial magnetic stimulation in patients with tinnitus: A short case series. *Biological Psychiatry*, *54*(8), 862–865. doi:10.1016/S0006-3223(03)01896-6

Fitzgerald, P. B., Hoy, K., McQueen, S., Maller, J. J., Herring, S., Segrave, R., . . . Daskalakis, Z. J. (2009). A randomized trial of rTMS targeted with MRI based neuro-navigation in treatment-resistant depression. *Neuropsychopharmacology*, *34*(5), 1255–1262. doi:10.1038/npp.2008.233

Folmer, R. L., Theodoroff, S. M., Casiana, L., Shi, Y., Griest, S., & Vachhani, J. (2015). Repetitive transcrania magnetic stimulation treatment for chronic tinnitus: A randomized clinical trial. *JAMA Otolaryngology – Head & Neck Surgery*, *141*(8), 716–722. doi:10.1001/jamaoto.2015.1219

Groppa, S., Oliviero, A., Eisen, A., Quartarone, A., Cohen, L. G., Mall, V., . . . Siebner, H. R. (2012). A practical guide to diagnostic transcranial magnetic stimulation: Report of an IFCN committee. *Clinical Neurophysiology*, *123*(5), 858–882. doi:10.1016/j.clinph.2012.01.010

Hannah, R., & Rothwell, J. (2017). Pulse duration as well as current direction determines the specificity of transcranial magnetic stimulation of motor cortex during contraction. *Brain Stimulation*, *10*(1), 106–115. doi:10.1016/j.brs.2016.09.008

Hoekstra, C. E., Versnel, H., Neggers, S. F., Niesten, M. E., & van Zanten, G. A. (2013). Bilateral low-frequency repetitive transcranial magnetic stimulation of the auditory cortex in tinnitus patients is not effective: A randomised controlled trial. *Audiology & Neuro-Otology*, *18*(6), 362–373. doi:10.1159/000354977

Hoogendam, J. M., Ramakers, G. M. J., & Di Lazzaro, V. (2010). Physiology of repetitive transcranial magnetic stimulation of the human brain. *Brain Stimulation*, *3*(2), 95–118. doi:10.1016/j.brs.2009.10.005

Husain, F. T., & Schmidt, S. A. (2014). Using resting state functional connectivity to unravel networks of tinnitus. *Hearing Research*, *307*, 153–162. doi:10.1016/j.heares.2013.07.010

Jenkins, C. D., Stanton, B. A., Niemcryk, S. J., & Rose, R. M. (1988). A scale for the estimation of sleep problems in clinical research. *Journal of Clinical Epidemiology*, *41*(4), 313–321. doi:10.1016/0895-4356(88)90138-2

Kim, B. G., Kim, D. Y., Kim, S. K., Kim, J. M., Baek, S. H., & Moon, I. S. (2014). Comparison of the outcomes of repetitive transcrania magnetic stimulation to the ipsilateral and contralateral auditory cortex in unilateral tinnitus. *Electromagnetic Biology and Medicine*, *33*(3), 211–215. doi:10.3109/15368378.2013.801353

Kleinjung, T., Eichhammer, P., Langguth, B., Jacob, P., Marienhagen, J., Hajak, G., . . . Strutz, J. (2005). Long-term effects of repetitive transcranial magnetic stimulation (rTMS) in patients with chronic tinnitus. *Otolaryngology-Head and Neck Surgery*, *132*(4), 566–569. doi:10.1016/j.otohns.2004.09.134

Lamusuo, S., Hirvonen, J., Lindholm, P., Martikainen, I. K., Hagelberg, N., Parkkola, R., . . . Jääskeläinen, S. K. (2017). Neurotransmitters behind pain relief with transcranial magnetic stimulation – Positron emission tomography evidence for release of endogenous opioids. *European Journal of Pain*, *21*(9), 1505–1515. doi:10.1002/ejp.1052

Landgrebe, M., Hajak, G., Wolf, S., Padberg, F., Klupp, P., Fallgatter, A. J., . . . Langguth, B. (2017). 1-Hz rTMS in the treatment of tinnitus: A sham-controlled, randomized multicenter trial. *Brain Stimulation*, *10*(6), 1112–1120. doi:10.1016/j.brs.2017.08.001

Langguth, B., Kleinjung, T., Landgrebe, M., de Ridder, D., & Hajak, G. (2010). rTMS for the treatment of tinnitus: The role of neuronavigation for coil positioning. *Neurophysiologie Clinique = Clinical Neurophysiology*, *40*(1), 45–58. doi:10.1016/j.neucli.2009.03.001

Langguth, B., Kreuzer, P. M., Kleinjung, T., & De Ridder, D. (2013). Tinnitus: Causes and clinical management. *Lancet Neurology*, *12*(9), 920–930. doi: 10.1016/S1474-4422(13)70160-1.

Langguth, B., Landgrebe, M., Frank, E., Schecklmann, M., Sand, P. G., Vielsmeier, V., . . . Kleinjung, T. (2014). Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: Pooled analysis of two randomized controlled studies. *World Journal of Biological Psychiatry*, *15*(4), 276–285. doi:10.3109/15622975.2012.708438

Langguth, B., Landgrebe, M., Kleinjung, T., Sand, G. P., & Hajak, G. (2011). Tinnitus and depression. *World Journal of Biological Psychiatry*, *12*(7), 489–500. doi:10.3109/15622975.2011.575178

Langguth, B., Zowe, M., Landgrebe, M., Sand, P., Kleinjung, T., Binder, H., . . . Eichhammer, P. (2006). Transcranial magnetic stimulation for the treatment of tinnitus: A new coil positioning method and first results. *Brain Topography*, *18*(4), 241–247. doi:10.1007/s10548-006-0002-1

Leaver, A. M., Renier, L., Chevillet, M. A., Morgan, S., Kim, H. J., & Rauschecker, J. P. (2011). Dysreguation of limbic and auditory networks in tinnitus. *Neuron*, *69*(1), 33–43. doi:10.1016/j.neuron.2010.12.002

Lefaucheur, J. P., Andre-Obadia, N., Antal, A., Ayache, S. S., Baeken, C., Benninger, D. H., . . . Garcia-Larrea, L. (2014). Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clinical Neurophysiology : Official Journal of the International Federation of Clinical Neurophysiology*, *125*(11), 2150–2206. doi:10.1016/j.clinph.2014.05.021

Lehner, A., Schecklmann, M., Greenlee, M. W., Rupprecht, R., & Langguth, B. (2016). Triple-site rTMS for the treatment of chronic tinnitus: A randomized controlled trial. *Scientific Reports*, *6*, 22302. doi:10.1038/srep22302

Lehner, A., Schecklmann, M., Landgrebe, M., Kreuzer, P. M., Poeppl, T. B., Frank, E., ... Langguth, B. (2012). Predictors for rTMS response in chronic tinnitus. *Frontiers in Systems Neuroscience*, *6*, 11. doi:10.3389/fnsys.2012.00011

Lehner, A., Schecklmann, M., Poeppl, T. B., Kreuzer, P. M., Vielsmeier, V., Rupprecht, R., ... Langguth, B. (2013). Multisite rTMS for the treatment of chronic tinnitus: Stimulation of the cortical tinnitus network – A pilot study. *Brain Topography*, *26*(3), 501–510. doi:10.1007/s10548-012-0268-4

Marcondes, R. A., Sanchez, T. G., Kii, M. A., Ono, C. R., Buchpiguel, C. A., Langguth, B., & Marcolin, M. A. (2010). Repetitive transcranial magnetic stimulation improve tinnitus in normal hearing patients: A double-blind controlled, clinical and neuroimaging outcome study. *European Journal of Neurology*, *17*(1), 38–44. doi:10.1111/j.1468-1331.2009.02730.x

Maudoux, A., Lefebvre, P., Cabay, J., Demertzi, A., Vanhaudenhuyse, A., Laureys, S., & Soddu, A. (2012). Auditory resting-state network connectivity in tinnitus: A functional MRI study. *Plos One*, *7*(5), e36222. doi:10.1371/journal.pone.0036222

Mennemeier, M., Chelette, K. C., Allen, S., Bartel, T. B., Triggs, W., Kimbrell, T., ... Dornhoffer, J. (2011). Variable changes in PET activity before and after rTMS treatment for tinnitus. *Laryngoscope*, *121*(4), 815–822. doi:10.1002/lary.21425

Moisset, X., de Andrade, D. C., & Bouhassira, D. (2016). From pulses to pain relief: An update on the mechanisms of rTMS-induced analgesic effects. *European Journal of Pain*, *20*(5), 689–700. doi:10.1002/ejp.811

Moller, A. R. (2007). The role of neural plasticity in tinnitus. *Tinnitus: Pathophysiology and Treatment*, *166*, 37–46. doi:10.1016/S0079-6123(07)66003-8

Newman, C., Jacobson, G., & Spitzer, J. (1996). Development of the tinnitus handicap inventory. *Archives of Otolaryngology-Head & Neck Surgery*, *122*(2), 143–148.

Ni, Z., Charab, S., Gunraj, C., Nelson, A. J., Udupa, K., Yeh, I., & Chen, R. (2011). Transcranial magnetic stimulation in different current directions activates separate cortical circuits. *Journal of Neurophysiology*, *105*(2), 749–756. doi:10.1152/jn.00640.2010

Noh, T., Kyong, J., Chang, M., Park, M., Lee, J., Oh, S., ... Suh, M. (2017). Comparison of treatment outcomes following either prefrontal cortical-only or dual-site repetitive transcranial magnetic stimulation in chronic tinnitus patients: A double-blind randomized study. *Otology & Neurotology*, *38*(2), 296–303. doi:10.1097/MAO.0000000000001266

Noh, T., Rah, Y., Kyong, J., Kim, J., Park, M., Lee, J., ... Suh, M. (2017). Comparison of treatment outcomes between 10 and 20 EEG electrode location system-guided and neuronavigation-guided repetitive transcranial magnetic stimulation in chronic tinnitus patients and target localization in the Asian brain. *Acta Oto-Laryngologica*, *137*(9), 945–951. doi:10.1080/00016489.2017.1316870

Piccirillo, J. F., Garcia, K. S., Nicklaus, J., Pierce, K., Burton, H., Vlassenko, A. G., ... Spitznagel, E. L. Jr (2011). Low-frequency repetitive transcranial magnetic stimulation to the temporoparietal junction for tinnitus. *Archives of Otolaryngology-Head & Neck Surgery*, *137*(3), 221–228. doi: 10.1001/archoto.2011.3.

Piccirillo, J. F., Kallogjeri, D., Nicklaus, J., Wineland, A., Spitznagel, E. L. Jr, Vlassenko, A. G., ... Garcia, K. S. (2013). Low-frequency repetitive transcranial magnetic stimulation to the temporoparietal junction for tinnitus four-week stimulation trial. *JAMA Otolaryngology-Head & Neck Surgery*, *139*(4), 388–395. doi:10.1001/jamaoto.2013.233

Pinto, P. C. L., Marcelos, C. M., Mezzasalma, M. A., Osterne, F. J. V., de Melo Tavares de Lima, M. A., & Nardi, A. E. (2014). Tinnitus and its association with psychiatric disorders: Systematic review. *Journa of Laryngology and Otology*, *128*(8), 660–664. doi:10.1017/S0022215114001030

Plewnia, C., Reimold, M., Najib, A., Brehm, B., Reischl, G., Plontke, S. K., & Gerloff, C. (2007). Dose-dependent attenuation of auditory phantom perception (tinnitus) by PET-guided repetitive transcranial magnetic stimulation. *Human Brain Mapping*, *28*(3), 238–246. doi:10.1002/hbm.20270

Plewnia, C., Vonthein, R., Wasserka, B., Arfeller, C., Naumann, A., Schraven, S. P., & Plontke, S. K. (2012). Treatment of chronic tinnitus with theta burst stimulation: A randomized controlled trial. *Neurology*, *78*(21), 1628–1634. doi: 10.1212/WNL.0b013e3182574ef9.

Roberts, L. E., Husain, F. T., & Eggermont, J. J. (2013). Role of attention in the generation and modulation of tinnitus. *Neuroscience and Biobehavioral Reviews*, *37*(8), 1754–1773. doi:10.1016/j.neubiorev.2013.07.007

Rossi, S., De Capua, A., Ulivelli, M., Bartalini, S., Falzarano, V., Filippone, G., & Passero, S. (2007). Effects of repetitive transcranial magnetic stimulation on chronic tinnitus: A randomised, crossover, double blind, placebo controlled study. *Journal of Neurology Neurosurgery and Psychiatry*, *78*(8), 857–863. doi:10.1136/jnnp.2006.105007

Rossi, S., Hallett, M., Rossini, P. M., Pascual-Leone, A., & Safety of TMS Consensus Group (2009). Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clinical Neurophysiology*, *120*(12), 2008–2039. doi:10.1016/j.clinph.2009.08.016

Sahlsten, H., Isohanni, J., Haapaniemi, J., Salonen, J., Paavola, J., Loyttyniemi, E., ... Jaaskelainen, S. K. (2015). Electric field navigated transcranial magnetic stimulation for chronic tinnitus: A pilot study. *International Journal of Audiology*, *54*(12), 899–909. doi:10.3109/14992027.2015.1054041

Sahlsten, H., Taiminen, T., Karukivi, M., Sjösten, N., Nikkilä, J., Virtanen, J., ... Jääskeläinen, S. (2018). Psychiatric (axis I) and personality (axis II) disorders and subjective psychiatric symptoms in chronic tinnitus. *International Journal of Audiology*, *57*(4), 302–312. doi:10.1080/14992027.2017.1409440

Sahlsten, H., Virtanen, J., Joutsa, J., Niinivirta-Joutsa, K., Loyttyniemi, E., Johansson, R., ... Jaaskelainen, S. K. (2017). Electric field-navigated transcranial magnetic

stimulation for chronic tinnitus: A randomized, placebo-controlled study. *International Journal of Audiology*, *56*(9), 692–700. doi:10.1080/14992027.2017.1313461

Seidman, M. D., De Ridder, D., Elisevich, K., Bowyer, S. M., Darrat, I., Dria, J., . . . Zhang, J. (2008). Direct electrical stimulation of Heschl's gyrus for tinnitus treatment. *Laryngoscope*, *118*(3), 491–500. doi:10.1097/MLG.0b013e31815daf5a

Soleimani, R., Jalali, M. M., & Hasandokht, T. (2016). Therapeutic impact of repetitive transcranial magnetic stimulation (rTMS) on tinnitus: A systematic review and meta-analysis. *European Archives of Oto-Rhino-Laryngology*, *273*(7), 1663–1675. doi:10.1007/s00405-015-3642-5

Steer, R. A., Ball, R., Ranieri, W. F., & Beck, A. T. (1999). Dimensions of the Beck Depression Inventory-II in clinically depressed outpatients. *Journal of Clinical Psychology*, *55*(1), 117–128. doi:10.1002/(SICI)1097-4679(199901)55:13.0.CO;2-A

Theodoroff, S. M., Stevens, A. A., McMillan, G., Pettersson, D. R., Woodward, W., & Fomer, R. L. (2018). MRI verification of a 10-20 targeting protocol used during transcranial magnetic stimulation sessions for tinnitus. *Brain Topography*, *31*(4), 690–699. doi:10.1007/s10548-018-0636-9

To, W., De Ridder, D., Hart, J., & Vanneste, S. (2018). Changing brain networks through non-invasive neuromodulation. *Frontiers in Human Neuroscience*, *12*, 128–128. doi:10.3389/fnhum.2018.00128

Tunkel, D. E., Bauer, C. A., Sun, G. H., Rosenfeld, R. M., Chandrasekhar, S. S., Cunningham, E. R. J., . . . Whamond, E. J. (2014). Clinical practice guideline: Tinnitus. *Otolaryngology–Head and Neck Surgery: Official Journal of American Academy of Otolaryngology–Head and Neck Surgery*, *151*(2 Suppl), S1–S40. doi:10.1177/0194599814545325

Wineland, A. M., Burton, H., & Piccirillo, J. (2012). Functional connectivity networks in nonbothersome tinnitus. *Otolaryngology–Head and Neck Surgery*, *147*(5), 900–906. doi:10.1177/0194599812451414

Zeman, F., Koller, M., Figueiredo, R., Aazevedo, A., Rates, M., Coelho, C., . . . Landgrebe, M. (2011). Tinnitus handicap inventory for evaluating treatment effects: Which changes are clinically relevant? *Otolaryngology–Head and Neck Surgery*, *145*(2), 282–287. doi:10.1177/0194599811403882

Zenner, H., Delb, W., Kröner Herwig, B., Jäger, B., Peroz, I., Hesse, G., . . . Langguth, B. (2017). A multidisciplinary systematic review of the treatment for chronic idiopathic tinnitus. *European Archives of Oto-Rhino-Laryngology*, *274*(5), 2079–2091. doi:10.1007/s00405-016-4401-y