



Repetitive Transcranial Magnetic Stimulation for Tinnitus Treatment in Vestibular Schwannoma: A Pilot Study

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Background: Vestibular schwannomas (VS) are brain tumors affecting the vestibulocochlear nerve. Thus, VS patients suffer from tinnitus (TN). While the pathophysiology is mainly unclear, there is an increasing interest in repetitive transcranial magnetic stimulation (rTMS) for TN treatment. However, the results have been divergent. In addition to the methodological aspects, the heterogeneity of the patients might affect the outcome. Yet, there is no study evaluating rTMS exclusively in VS-associated tinnitus. Thus, the present pilot study evaluates low-frequency rTMS to the right dorsolateral pre-frontal cortex (DLPFC) in a VS-associated tinnitus.

Methods: This prospective pilot study enrolled nine patients with a monoaural VS-associated tinnitus ipsilateral to the tumor. Patients were treated with a 10-day rTMS regime (1 Hz, 100% RMT, 1,200 pulses, right DLPFC). The primary endpoint of the study was the reduction of TN distress (according to the Tinnitus Handicap Inventory, THI). The secondary endpoint was a reduction of TN intensity (according to the Tinnitus Matching Test, TMT) and the evaluation of factors predicting tinnitus outcome (i.e., hearing impairment, TN duration, type of tinnitus).

Results: No complications or side effects occurred. There was one drop-out due to a non-responsiveness of the complaint. There was a significant acute effect of rTMS on the THI and TMT. However, there was no significant long-term effect after 4 weeks. While the THI failed to detect any clinically relevant acute effect of rTMS in 56% of the patients, TMT revealed a reduction of TN intensity for more than 20 in 89% and for more than 50 in 56% of the patients. Notably, the acute effect of rTMS was influenced by the TN type and duration. In general, patients with a tonal TN and shorter TN duration showed a better response to the rTMS therapy.

Conclusion: The present pilot study is the first one to exclusively evaluate the effect of low-frequency rTMS to the right DLPFC in a VS-associated tinnitus. Our results prove the

feasibility and the efficacy of rTMS in this patient cohort. There is a significant acute but a limited long-term effect. In addition, there is evidence that patients with a tonal tinnitus and shorter tinnitus duration might have the strongest benefit. A larger, randomized controlled study is necessary to prove these initial findings.

Keywords: repetitive transcranial magnetic stimulation, tinnitus, vestibular schwannoma, neurosurgery, neuromodulation

INTRODUCTION

Brain tumors affect functions related to the affected neuronal structure. Hence, patients with a vestibular schwannoma (VS), a benign tumor of the vestibulocochlear nerve, suffer from audiovestibular symptoms (i.e., hearing loss, tinnitus, or dizziness) (1–4). Tinnitus (TN) is affecting 63–75% of the VS patients (3, 5–7) and significantly impairing patients' quality of life (2, 8, 9). Notably, VS-associated tinnitus, however, is one of the few TN conditions accessible to causal therapy (10, 11). Thus, TN ceases in one third of the patients after a surgical removal of the tumor (4, 12, 13). The pathophysiology of the VS-associated TN has not yet been fully clarified (3, 4, 10). However, it is generally assumed that the pathophysiology might be similar to that of idiopathic TN (3). The current concept hypothesizes spurious auditory signals after partial sensory deafferentation, e.g., after damage to the cochlea (e.g., bang trauma) or cochlear nerve (e.g., vestibular schwannoma), to cause TN onset (1, 14–17). After chronification, however, TN perpetuation is theorized to depend on central maladaptive neuroplasticity because of the disturbed signal-to-noise ratio. These neuroplastic changes are thought to cause a neuronal hyperexcitability for the residual auditory input resulting in the subjective misperception (10, 11, 18, 19). Having a central origin, TN is hardly accessible to therapy (20). In the last years, there is a growing interest in using repetitive transcranial magnetic stimulation (rTMS) in TN therapy (20–24). rTMS is suggested to modify the excitability of relevant neurons and neurotransmitter systems in TN (25). However, the results have been divergent and even contradictory (21, 24, 26–29). First, there are still unsolved methodological issues, e.g., uncertainties concerning appropriate stimulation sites and stimulation intensities (20, 23). Second, there has been a large heterogeneity in the treated patient cohorts (20, 26). Most studies have evaluated the rTMS effects in patients with an idiopathic TN which are characterized by a large variability or ambiguity of the underlying cause. Additionally, the amount of hearing loss, tinnitus duration, and quality of the tinnitus seem to play important roles for the treatment outcome (26, 30, 31). In contrast, patients with anatomical causes of TN, such as VS, are usually excluded from rTMS studies. To our opinion, however, these patients represent a relatively homogenous cohort with a definite TN origin (3, 4). As these patients are presumably seeking

medical advice in an early stage of the disease, the TN duration will be shorter, which is beneficial for rTMS treatment (32, 33). Yet, there is no rTMS study explicitly analyzing patients with a VS-associated TN.

The aim of the present pilot study was to provide the first evidence for the feasibility and effectivity of low-frequency rTMS to the right DLPFC in a VS-associated TN. Here, we describe our first experience in nine patients indicating an acute effect or rTMS on TN perception as measured by questionnaires and TN matching.

METHODS

Patients

This prospective study enrolled nine patients (57.1 ± 10.6 , four female) with a unilateral sporadic VS who were treated at the Neurosurgical Department of the University of Tuebingen, Germany (**Figures 1A,B**). The inclusion criteria covered an age range of 18–80 years old and the presence of a monoaural TN ipsilateral to the tumor. Exclusion criteria were pregnancy, contralesional hearing impairment, and the presence of additional neurological conditions (e.g., epilepsy). Patient characteristics are shown in **Table 1**. Patients gave a written informed consent to their participation. This study was approved by the ethics committee of the Eberhard Karls University Tuebingen and performed in accordance to the Declaration of Helsinki.

Clinical Evaluation

Hearing impairment was classified according to the Gardner & Robertson (GR) scale (34) based on the results of the pure tone audiometry (PTA) and speech discrimination (SDS) resulting in five classes: GR 1 (good, PTA 0–30 dB, and SDS 70–100%), GR 2 (serviceable, PTA 31–50 dB, and SDS 50–69%), GR 3 (non-serviceable, PTA 51–90 dB, and SDS 5–49%), GR 4 (poor, PTA 51–90 dB, and SDS 1–4%), GR 5 (deaf, PTA 0 dB, and SDS 0%). For statistical reasons, GR score was reclassified in (i) preserved hearing (GR 1–4) and (ii) no hearing (GR5). VS tumor size was graded according to the Hannover classification (5) into four classes: T1 (purely intrameatal), T2 (intra- and extrameatal), T3 (filling the cerebellopontine cistern), T4 (compressing the brain stem).

Study Design

The aim of the study was to prove the feasibility and effectivity of repetitive transcranial magnetic stimulation (rTMS) therapy in a VS-associated TN. The study covered a treatment period of 10 consecutive workdays on which rTMS was applied. All

Abbreviations: DHI, Dizziness Handicap inventory; DLPFC, dorsolateral prefrontal cortex; FU, follow-up; GR, Gardner & Robertson scale; HHI, Hearing Handicap Inventory; PTA, pure tone audiometry; RMT, resting motor threshold; rTMS, repetitive transcranial magnetic stimulation; SDS, speech discrimination; THI, Tinnitus Handicap inventory; TMT, tinnitus matching test; TN, tinnitus; VS, vestibular schwannoma.

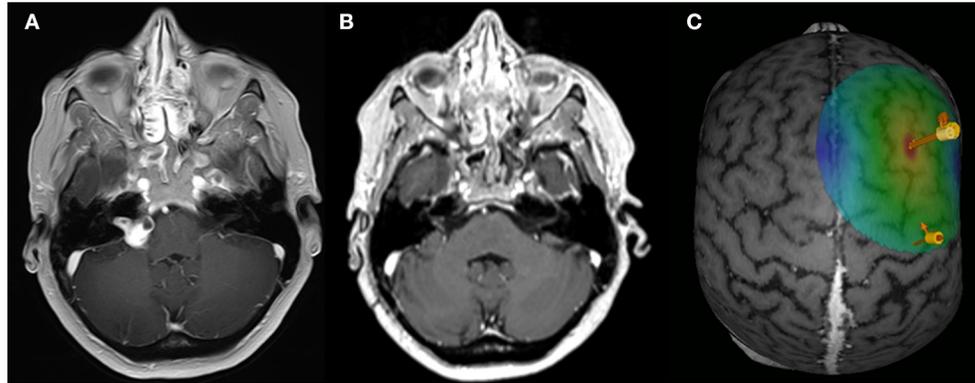


FIGURE 1 | rTMS paradigm. Exemplary axial MRI data (contrast-enhanced T1 sequence) of patient ID1 with a right-sided VS for the preoperative (A) and post-operative (B) situation. (C) Exemplary data of the rTMS application site. Arrows are indicating the APB hotspot and the rTMS on the DLPFC.

TABLE 1 | Data overview.

| ID | 1 | 2 | 3 | 4* | 5 | 6 | 7 | 8 | 9 | Sum |
|--|-------|------|------|-------|------|-------|------|------|------|-------------|
| Age | 60.0 | 51.3 | 67.6 | 71.6 | 44.3 | 33.6 | 60.3 | 47.5 | 67.4 | 57.1 ± 10.6 |
| Gender | F | M | F | M | M | M | f | M | F | 4:5 |
| Tumor | | | | | | | | | | |
| Size | T3 | T3 | T2 | T2 | T3 | T3 | T2 | T2 | T3 | 4:5 |
| Side | Right | Left | Left | Right | Left | Right | Left | Left | Left | 4:5 |
| Hearing | | | | | | | | | | |
| Ipsilateral | 4 | 5 | 4 | 3 | 5 | 1 | 1 | 3 | 5 | 3.4 ± 1.6 |
| Contralateral | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | |
| Tinnitus | | | | | | | | | | |
| Type | T | N | T | N | N | T | N | N | T | 4:5 |
| Side | Right | Left | Left | Right | Left | Right | Left | Left | Left | 4:5 |
| Onset | Pre | Post | Post | Pre | Post | Post | Pre | Pre | Pre | 5:4 |
| Duration (y) | 12.6 | 4.0 | 2.9 | 12.0 | 1.3 | 0.9 | 0.9 | 3.3 | 2.3 | 4.5 ± 4.6 |
| rTMS | | | | | | | | | | |
| Intensity (%) | 38 | 36 | 50 | 30 | 45 | 29 | 32 | 40 | 30 | 37 ± 7 |
| TMT | | | | | | | | | | |
| $f_{\text{int}}^{\text{pre}}$ Freq (kHz) | 7.0 | – | 3.0 | – | – | 5.4 | – | – | 4.0 | 4.8 ± 1.7 |
| $f_{\text{int}}^{\text{post}}$ Int (dB) | 40 | 34 | 64 | 50 | 44 | 35 | 30 | 45 | 33 | 42 ± 11 |
| $f_{\text{int}}^{\text{FU}}$ Freq (kHz) | 5.8 | – | 2.5 | – | – | 1.5 | – | – | 3.6 | 3.3 ± 1.3 |
| $f_{\text{int}}^{\text{FU}}$ Rel. int | 0.39 | 0.67 | 0.1 | 1.0 | 0.43 | 0.05 | 0.25 | 0.53 | 0.20 | |
| THI | | | | | | | | | | |
| Pre | 4 | 44 | 54 | 98 | 52 | 38 | 20 | 34 | 32 | 42.0 ± 26.0 |
| Post | 2 | 36 | 40 | – | 52 | 22 | 18 | 32 | 22 | 28.0 ± 15.3 |
| FU | 2 | 46 | 50 | – | 52 | 34 | 24 | 34 | 30 | 34.5 ± 16.9 |
| HHI | | | | | | | | | | |
| Pre | 8 | 18 | 60 | 18 | 36 | 8 | 10 | 18 | 10 | 20.9 ± 17.1 |
| Post | 8 | 12 | 58 | – | 34 | 24 | 16 | 20 | 12 | 23.0 ± 16.4 |
| FU | 8 | 20 | 60 | – | 34 | 12 | 16 | 16 | 12 | 22.8 ± 17.0 |
| DHI | | | | | | | | | | |
| Pre | 4 | 20 | 38 | 20 | 16 | 46 | 14 | 24 | 18 | 22.2 ± 12.7 |
| Post | 4 | 20 | 40 | – | 18 | 36 | 12 | 20 | 18 | 21.0 ± 11.8 |
| FU | 0 | 20 | 22 | – | 16 | 46 | 14 | 24 | 18 | 20.0 ± 12.8 |

DHI, Dizziness Handicap Inventory; f, female; freq, TN frequency; HHI, Hearing Handicap Inventory; int, TN intensity; m, male; N, non-tonal; pre, pre-operative TN onset; post, post-operative TN onset; T, tonal; THI, Tinnitus Handicap Inventory; * drop out.

patients received a standardized evaluation of VS-associated audiovestibular symptoms (i.e., hearing impairment, tinnitus, dizziness) with questionnaires (i.e., Hearing Handicap Inventory, HHI; Tinnitus Handicap Inventory, THI; Dizziness Handicap Inventory, DHI) at the first day (PRE) and the last day (POST) of the treatment period. Questionnaires were also acquired after 4 weeks (follow-up, FU) to evaluate the long-term effects. In addition, we evaluated the patient's daily TN perception with a Tinnitus Matching Test (TMT) just prior and after the rTMS application. The primary endpoint of the study was a reduction of distress suffered by the TN patient as measured by the THI. Secondary endpoint of the study was the reduction of TN perception as measured by the TMT and the evaluation of factors predicting the rTMS effect (i.e., hearing impairment, tinnitus duration, type of tinnitus.).

Tinnitus Handicap Inventory

The Tinnitus Handicap Inventory (THI) is a self-administered test to determine the degree of distress suffered by the TN patient. The THI has been introduced in 1996 (35). It consists of 25 questions divided into three subgroups: functional, emotional, and catastrophic. Eleven items are included in the functional scale, nine in the emotional scale, and five in the catastrophic scale. A *yes* response yields a score of four points; *sometimes*, two points; and *no*, zero points. The total score ranges from zero (no disability) to 100 (severe disability). Studies have also indicated that the minimum change in the THI score that can be considered clinically relevant is a reduction of 6–7 points (35). It is widely used in medical offices and in clinical trials to determine the effectiveness of a given therapy (36, 37).

Hearing Handicap Inventory and Dizziness Handicap Inventory

The HHI (38) and the DHI (39) are constructed equivalent to the THI and designed as self-administered 25-item questionnaires to determine the degree of disability in relation to hearing impairment and dizziness. A *yes* response yields a score of four points; *sometimes*, two points; and *no*, zero points. The total score ranges from zero (no disability) to 100 (severe disability). The scales consist of a 7-item physical subscale, a 9-item emotional subscale, and a 9-item functional subscale.

Tinnitus Matching Test

The TMT was performed based on pure sinus waves (in tonal TN) or white gaussian noise (wgn, in non-tonal/noise-like TN) provided by custom-written Matlab scripts and presented to both ears of the patient with headphones (HD4.30, Sennheiser, Wennebostel, Germany). In an iterative process, the patient was asked to provide feedback about the individual TN frequency (kHz, in tonal tinnitus) and TN intensity (in dB). Frequency and intensity were adjusted by the experimenter until the patient confirmed that the presented tone/noise matches to his/her individual TN. Frequency and/or intensity were noted for further analysis. The TMT was performed daily immediately prior and after the rTMS application. While TMT is an excellent way to

objectify the subjective tinnitus sensation, it is subject to major problems which have been discussed elsewhere (40).

TMS-Mapping and rTMS Parameter

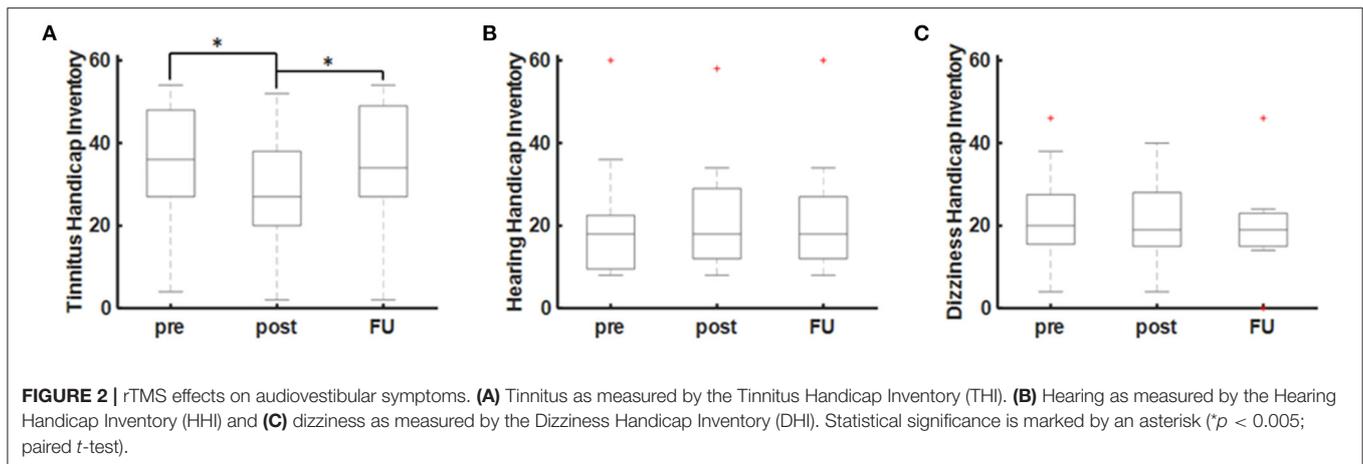
T1-weighted MRI brain scans preceded the experiment to obtain individual anatomical images in combination with an e-field guided neuronavigational rTMS system (NBS, Nexstim, Finland). First, a single standard motor mapping of the right primary motor cortex was performed with a bipulse eight-figure coil (41–44). After determining the “hotspot” yielding the largest motor-evoked potential (MEP) from the left abductor pollicis brevis muscle (APB), the resting motor threshold (RMT), defined as the minimum stimulus intensity to result in at least 5/10 trials a MEP $> 50 \mu\text{V}$, was obtained. The orientation of the induced current in the brain was posterior-anterior for the first phase and anterior-posterior for the second phase of the stimulus. The orientation of the electric field was kept perpendicular to the central sulcus. Subsequently, the cortex was mapped with 110% RMT starting at the primary motor cortex and then extending around this spot to cover the primary motor cortex, somatosensory cortex, and premotor cortex. The TMS coil was localized over the right DLPFC according to a standard algorithm by moving the coil from the APB hotspot 6 cm in the anterior direction (Figure 1C). The coordinates and direction of the e-field were saved and kept constant throughout the experiment. rTMS was applied with a bipulse eight-figure coil as a sequence of 1,200 pulses with a 1 Hz stimulation frequency and an intensity of 110% RMT (45).

Statistical Analysis

All analysis and statistical tests were performed using MATLAB (MathWorks, Inc., Natick, MA, USA) and SPSS (IBM SPSS Statistics for Windows, Version 26.0. Armonk, NY: IBM Corp.). Significance of rTMS related changes in THI, HHI, and DHI were evaluated with paired *t*-test. Changes in the TN frequency and intensity over the course of the therapy were linearly fitted by the Matlab “robustfit.” To evaluate the impact of the hearing status (HEARING), TN duration (DURATION), and the TN type (TYPE) on the acute rTMS effect, an analysis of covariance was applied on the THI and the relative TN intensities. Pearson's regression analysis was performed to evaluate the correlation between the acute effect as measured by the THI and the TMT. Data are shown as the mean \pm standard deviation (SD). $p < 0.05$ were considered significant. Finally, operative complications were evaluated, if detected in the postoperative CT scan.

RESULTS

There were no significant side effects of the rTMS stimulation in any of the patients. One patient (ID4) dropped-out of the study due to a subjective non-response to the treatment (see Table 1). There was a significant acute decrease of the THI scores at the end of the 10-day rTMS therapy (POST) in comparison to the baseline (PRE) values ($T = 3.33$, $p = 0.013$; paired *t*-test). The acute effect of rTMS on the THI values (PRE-POST) was approximated at -7.0 ± 6.0 [–16 0] points ($T = -3.33$, $p = 0.013$; one-sample *t*-test). As a reduction of 6–7 points in the THI are considered clinically relevant, only 4/9 (44.4%) are classified



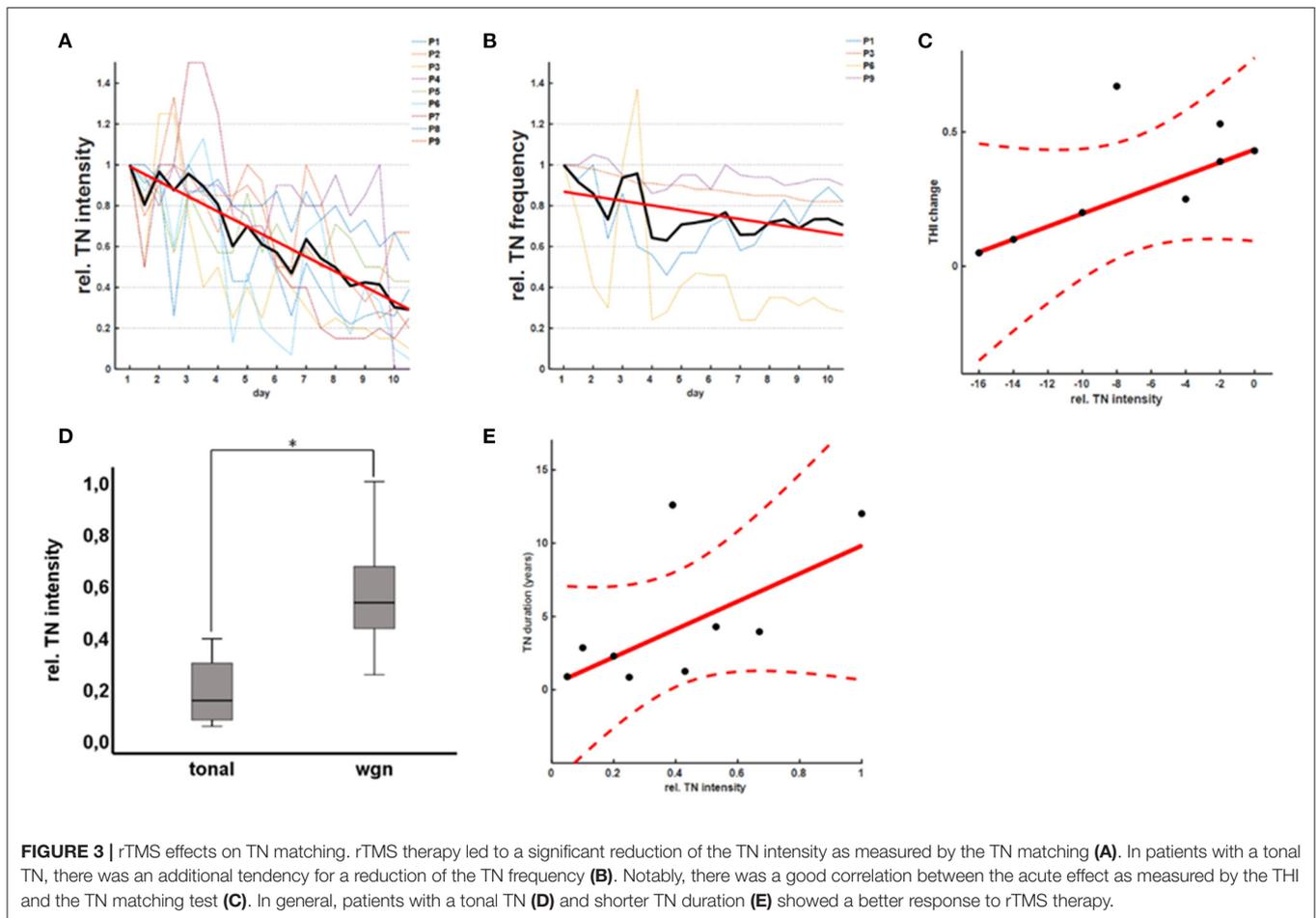
as good responders according to the THI. During the follow-up (FU) after 4 weeks, however, there was no sustained effect of rTMS ($T = 0.683$, $p = 0.516$; paired t -test) on the THI values (Figure 2A). In contrast, there was no short-term or long-term effect of rTMS on the HHI or DHI values (Figures 2B,C).

The acute effect of rTMS on tinnitus perception was confirmed by recordings of the TMT revealing a significant reduction of TN intensity ($b = -0.068$, $p < 0.001$; robust regression) over the course of the 10-day rTMS therapy (Figure 3A). The mean relative TN intensity after rTMS was 0.40 ± 0.30 [0.05–1.00] ($T = -5.95$, $p < 0.001$; one-sample t -test), indicating a reduction of TN intensity of $\sim 60\%$. As a reduction of 20% is considered clinically relevant, 8/9 (89%) of the patients are classified as good responders according to the TMT. Moreover, 6/9 (67%) of the patients showed a reduction of TN intensity for more than 50%. For patients with tonal tinnitus ($n = 4$), there was a tendency for a slight reduction of TN frequency ($b = -0.011$, $p = 0.009$; robust regression) over the course of the 10-day rTMS therapy (Figure 3B). Notably, there was a good correlation ($r = 0.43$; Pearson's) between the acute effect as measured by the THI and the TMT (Figure 3C). To evaluate the effect of the hearing status (HEARING), TN duration (DURATION), and the TN type (TYPE) on the acute rTMS effect, an analysis of covariance was applied on the THI and the relative TN intensities at the end of the 10-day rTMS therapy. In fact, we could not detect any significant main effect of HEARING [$F_{(1, 4)} = 1.56$; $p = 0.782$], TYPE [$F_{(1, 4)} = 4.01$; $p = 0.116$], or DURATION [$F_{(1, 4)} = 4.41$; $p = 0.104$] on the TN perception as measured by the THI questionnaire. Considering the TN matching results, however, we observed a significant effect of TYPE [$F_{(1, 4)} = 10.29$; $p = 0.024$] and DURATION [$F_{(1, 4)} = 17.81$; $p = 0.008$]. Patients with a tonal TN showed a higher benefit from therapy than patients with a noise-like TN (Figure 3D). Additionally, patients with a longer TN duration showed less TN intensity reduction after rTMS (Figure 3E). Basically, patients suffering from TN for < 5 years showed a better response than patients suffering from tinnitus for more than 10 years. In contrast, there was no effect of HEARING [$F_{(1, 4)} = 0.25$; $p = 0.637$].

DISCUSSION

The present pilot study proves a significant acute effect of low-frequency rTMS to the right DLPFC on TN perception (THI and TMT) of nine VS patients. However, there was no significant long-term effect in the follow-up after 4 weeks. In contrast, rTMS had no effect on other audiovestibular complaints such as hearing impairment or dizziness. While the THI failed to detect any clinically relevant acute effect of rTMS in 56% of the patients, TMT revealed a reduction of TN intensity for more than 20 in 89% and for more than 50 in 56% of the patients. Notably, the acute effect of rTMS was influenced by the TN type and duration. In general, patients with a tonal TN and shorter TN duration showed a better response to rTMS therapy.

Considering the hypothesized pathophysiology of TN driven by a central maladaptation, rTMS has been suggested in TN treatment several years ago. However, the results have been divergent and even contradictory (21, 24, 26–29). rTMS applies a train of repetitive magnetic pulses to alter the excitability of the neurons and modulate cortical activity. High-frequency rTMS increases cortical excitability, while low-frequency rTMS is considered to inhibit the neural activity in stimulated regions (46, 47). In general, rTMS has been successfully applied for TN treatment at the primary auditory cortex (36, 37), temporoparietal junction (48), and dorsolateral pre-frontal cortex (DLPFC) (45, 49). Low-frequency rTMS to temporal stimulation sites is supposed to reduce the hyperexcitability of the auditory network (36, 37). However, a recent multicenter randomized controlled trial with a large sample size demonstrated that low-frequency (1 Hz) rTMS over the temporal cortex is not superior to sham rTMS in reducing TN severity (37). To the authors' opinion, the temporal lobe is not an optimal target candidate for rTMS application due to its coverage by the temporal muscle. Depending on the individual's anatomy, the temporal muscle might increase the distance to the cortex and thus, potentially decrease the strength of the magnetic field on the cortex to subthreshold levels. Additionally, involuntary muscle twitches related to the TMS pulses are limiting the applicable stimulation intensity. In contrast, stimulation to the



DLPFC is easily accessible and thought to influence networks involved in auditory attention (50). Interestingly, TN suppression has been shown for either *high*-frequency stimulation of the *left* DLPFC (49) and *low*-frequency stimulation of the *right* DLPFC (45). Furthermore, combined multisite rTMS is hypothesized to improve treatment outcome (48). In a recent meta-analysis, however, concurrent high-frequency stimulation of the *left* DLPFC to the temporal cortex was not found to promote efficacy (23). Considering this evidence, we have decided on the application of *low*-frequency stimulation of the *right* DLPFC (45) for TN treatment. In fact, the present study represents the first study applying *low*-frequency rTMS on the *right* DLPFC in VS-associated TN.

Although being a more homogeneous patient cohort with a shorter TN duration than other published data (26), our response rates were quite comparable to other studies ranging around 50% of the treated patients (51). The application of rTMS in VS patients did not improve the treatment outcome substantially. However, the number of treated patients in this study is too low to draw final conclusions. Additionally, the sensitivity of the THI questionnaire might be—although widely used (21, 36, 37)—too low to detect slight rTMS-related TN improvements (52, 53). In contrast, there was a clear effect of rTMS on the TMT values.

We hypothesize that the treatment duration might be too short to induce a clinically relevant effect measurable by the THI. In depression treatment, rTMS exerts a positive clinical effect after four rather than 2 weeks of treatment (54–56).

Notably, our findings indicate that patients with a tonal TN and shorter TN duration showed a better response to rTMS therapy. These findings are in good accordance with the previous publication indicating an impact of these factors on the treatment outcome (30–33). In particular, tonal TN in comparison to non-tonal/noise-like TN is suggested to benefit from rTMS therapy (32, 33). In contrast to the other studies showing an effect of hearing impairment on the treatment outcome (30, 31), our findings did not reproduce these observations. Due to statistical reasons, we have dichotomized hearing impairment in the present study, which might mask the actual effect. However, the number of patients is too low for more profound statistical evaluation. Finally, although our study indicates an acute rTMS effect on VS-associated TN, there is no evidence for a long-term effect after a period of 4 weeks (21, 24, 26–29). However, independent of the sustained long-term effect, rTMS might be useful for priming the cortex in chronic TN patients in order to increase the susceptibility for further treatment options, e.g., notched-noise therapy, pharmacological intervention, cognitive

behavioral therapy, TN masking, or music therapy (10, 11). Finally, there is an increasing literature indicating that TMS effects depend on the ongoing brain-state (57, 58). Thus, applying TMS in VS treatment in a closed-loop fashion depending on the ongoing brain state might improve the treatment outcome. Comparable observations have been made in the recruitment of additional corticospinal tracts (41, 59) for e.g., stroke therapy. In line with this, a dependency of rTMS-based TN therapy on cortical alpha oscillations has been described recently (60, 61).

Limitations of the Study

There are several limitations to the present study. First, the number of patients is too low to draw final conclusions about the effectivity of rTMS in VS-associated patients. However, our findings are comparable to the known results in literature. Second, there was no control group. Interventional studies should ideally be designed as randomized, double-blinded controlled studies (36, 37). However, considering the low incidence of VS-associated TN in comparison to other types of TN, it will be difficult to achieve an adequate sample size.

CONCLUSION

The present pilot study is the first one exclusively evaluating the effect of rTMS in VS-associated TN. Our results prove the feasibility and the efficacy of low-frequency rTMS to the right DLPFC in this patient cohort. The results were comparable to the available data with a significant acute but limited long-term effect. However, there is evidence that patients with a tonal TN and shorter TN duration might have the strongest benefit.

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A randomized controlled study with a larger sample size is necessary to prove these initial findings.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by Ethics committee of the Eberhard Karls University Tuebingen. The patients/participants provided their written informed consent to participate in this study.

AUTHOR CONTRIBUTIONS

MTL and GN were responsible for data acquisition, data analyses, statistical analysis as well as drafting and reviewing the manuscript. ML, JS, and KM were involved in data acquisition as well as drafting and reviewing the manuscript. MT and AS were involved in drafting and reviewing the manuscript. All authors contributed to the article and approved the submitted version.

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Conflict of Interest: The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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