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The Effect of Noninvasive Brain Stimulation on Neural Connectivity in Tinnitus: A Randomized Trial

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Objectives/Hypothesis: To explore neural connectivity changes associated with repetitive transcranial magnetic stimulation (rTMS) to the temporoparietal junction for patients with bothersome tinnitus.

Study Design: Randomized, double-blind, controlled clinical trial.

Methods: Thirty patients with subjective, nonpulsatile tinnitus for 6 months duration or longer and a score of 36 or greater on the Tinnitus Handicap Inventory completed the study. Participants were randomized to receive either sham or active treatment with rTMS to the temporoparietal junction for either 2 or 4 weeks of therapy. Participants underwent resting state functional connectivity magnetic resonance imaging before therapy and immediately following treatment. Functional connectivity changes between active and sham treatment groups were compared using regions of interest in auditory, default mode, ventral attention, and executive attention networks.

Results: Sixteen patients received active rTMS treatment; 14 patients received sham treatment. There were no differences between the active and sham groups in baseline functional connectivity. Neither treatment with rTMS nor sham therapy resulted in statistically significant functional connectivity changes in the examined brain networks.

Conclusions: The analysis did not identify any changes in neural connectivity following treatment in patients with bothersome tinnitus. These results are consistent with our findings of lack of symptom changes previously reported in the same group of patients. Measures of neural connectivity may inform future work using rTMS to better understand the possible benefits of neural stimulation for tinnitus.

Key Words: Tinnitus, functional MRI, repetitive transcranial magnetic stimulation.

Level of Evidence: 1b.

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INTRODUCTION

Tinnitus is the perception of sound without an acoustic stimulus. Tinnitus patients often suffer from depression, insomnia, and anxiety—and have difficulty with attention and concentration,[1] which leads to disability. Unfortunately, the pathophysiology of tinnitus is not fully understood, and there is no cure or effective treatment for those who suffer from the disease.

Although most early research in tinnitus focused on the role of peripheral dysfunction in the tinnitus percept, recent focus has shifted to the idea that differential neural connectivity may also explain the amount of bother experienced by tinnitus patients.[2] In this context, it has been suggested that tinnitus is caused by excessive spontaneous activity in the auditory cortex,[3] and that chronic tinnitus may be similar to neuropsychiatric syndromes related to plastic alterations of the brain.[4] Auditory hyperactivity might be evident not only in focal changes in neural activation but in functional connectivity across brain networks.[5] If dysfunctional neural connectivity in auditory processing networks is a source of tinnitus distress, altering this activity may be an effective treatment.

Repetitive transcranial magnetic stimulation (rTMS) is an intervention that might be used to correct dysfunctional cortical networks. It uses a magnetic field to create an electric current within the brain that depolarizes axons and activates neural networks[6]; the repeated application of these pulses has the potential to induce changes in neural connectivity. Outside of tinnitus, functional MRI (fMRI) has identified changes in neural activity following rTMS therapy,[7,8] and rTMS is effective in treating medication-resistant depression.[9]

Despite its promise, the results of studies examining the efficacy of rTMS in tinnitus are mixed.[6] A critical

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decision rests on the site of rTMS stimulation (that is, which brain network to stimulate). Common targets are auditory cortical regions including left temporoparietal junction (TPJ) and auditory cortex in an effort to inhibit auditory hyperactivity. Although some studies suggest symptom improvement following repeated sessions of rTMS to the auditory cortex or TPJ,[10–18] a lack of improvement has been observed in several randomized controlled trials,[19,20] including our own previously published randomized, controlled, crossover trials.[21,22]

Our two previously published studies report symptom outcomes following either active or sham treatment with rTMS to the TPJ. Resting state functional connectivity MRI (rs-fcMRI) was obtained before and after treatment. Tinnitus patients show differences in functional connectivity as compared to healthy controls,[2] and we hypothesize that neural connectivity changes following rTMS will correlate to symptom improvement. The proposed mechanism for intervention is that rTMS results in altered patterns of neural activity in cortical networks, and this altered network activity causes a reduction in symptoms. Under this view, there are at least two explanations for why rTMS to TPJ did not result in symptom improvement. The first is that rTMS did not result in changes to neural connectivity. If symptom improvement indeed follows from changes in brain connectivity, a lack of changes in neural activity would be consistent with a lack of improvement. A second explanation is that rTMS to TPJ effectively alters neural connectivity, but not in a network that is contributing to tinnitus bother. Critically, functional neuroimaging can distinguish between these two possibilities. A mechanistic understanding of the effects of rTMS on the TPJ will help explain the variability of prior results and help guide effective treatments.

The objective of the current study was to systematically evaluate neural network changes in patients with bothersome chronic tinnitus who underwent rTMS treatment targeting the left TPJ, as compared to those who received sham therapy. We targeted the TPJ because it is thought to contribute to secondary and integrative auditory processes. This is the first study to evaluate functional connectivity before and after treatment in a randomized controlled trial of temporoparietal rTMS in tinnitus patients.

MATERIALS AND METHODS

Design

This study was a double-blinded, randomized controlled trial. Participants were considered eligible for this study if they were between 18 and 60 years of age with subjective, nonpulsatile tinnitus for 6 months or longer. All participants were required to score at least a 30 on the Tinnitus Handicap Inventory (THI) assessment[23] and a score of less than 14 on the Beck Depression Inventory.[24] All participants gave informed consent to participate in the study under a protocol approved by the Washington University in Saint Louis Institutional Review Board.

Details of the methods of the study have been previously published.[21,22] Using a block randomization code generated by a statistician, all patients who remained eligible for the study were assigned to receive either sham or active treatment, with both participants and physicians blinded to treatment group. The initial protocol for this study was approved for 2 consecutive weeks of treatment. Midway through the trial, the protocol was revised to allow for 4 consecutive weeks of treatment in order to evaluate increased length of treatment time. Here we collapse these two groups into a single analysis. Prior to initial treatment and immediately following completion of either 2 or 4 weeks of treatment, participants underwent a rs-fcMRI.

This study used a crossover design with a washout period between treatments (sham and active therapy). Following the first arm of treatment, participants underwent a washout period, followed by the second treatment. The focus of this article is the evaluation and comparison of neuroimaging before and after the first arm of treatment.

Measurements

Participants completed multiple assessments including past medical and health information, tinnitus description, hearing history and exposures, audiometric exam, and neurocognitive assessments. Additionally, participants underwent rs-fcMRI prior to and immediately after completion of treatment.

Repetitive Transcranial Magnetic Stimulation Procedure

Participants received five treatment sessions per week for 2 or 4 consecutive weeks. The coil was placed over the left TPJ for all subjects. The sham coil was identical in appearance and sound to the active treatment coil. The delivery stimulus was calculated by placing the coil over the motor cortex and calculating the threshold at which the thumb abductor was stimulated to contract. This was considered the motor threshold. Active treatment was delivered at 1 Hz at 110% of motor threshold. The coil was placed over the TPJ region versus the motor cortex for treatment; therefore, a muscle response was not elicited during treatment and patients would not have been able to differentiate between active and sham treatment. Sessions were conducted with interval stimulation for a total of 42.5 minutes.

Neuroimaging

Resting state functional connectivity MRI was collected prior and immediately after completion of either active or sham treatment on a Siemens 3T Trio scanner (Erlangen, Germany). Participants wore headphones to reduce background noise and remained awake, with their eyes closed, in the scanner. Images were collected using an echo-planar sequence (EPI) (repetition time [TR] = 2,200 ms, echo time [TE] = 27 ms, flip angle = 90°, 4-mm isotropic voxels). Each participant completed three runs of 164 volumes. T1-weighted structural images were also acquired using a Magnetization Prepared Rapid Acquisition with Gradient Echo (MPRAGE) sequence (TR = 2,100 ms, TE = 3.93 ms, flip angle = 7°, $1 \times 1 \times 1.25$ mm voxels).

Analysis

Analysis of behavioral data has been previously described for the 2-week treatment group[21] and the 4-week treatment group[22]; here we report combined statistics for completeness. Pairs of pre- and post treatment intervention MRI scans were available and usable for 30 subjects; participants who did not complete a postintervention scan were not included in any analysis. Magnetic resonance imaging data was processed using SPM8 (Wellcome Trust Centre for Neuroimaging, London, UK) and the Automatic Analysis processing environment (version 4.1; http://www.automaticanalysis.org).[25] The analysis was completed

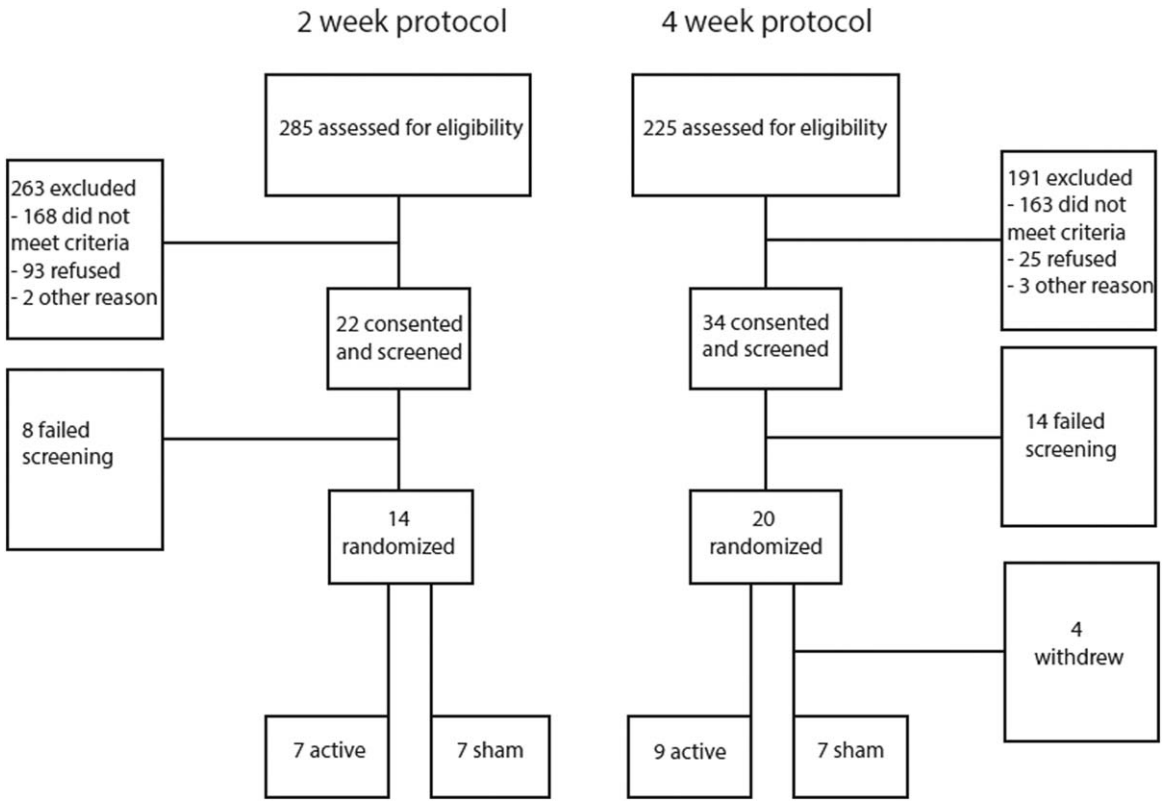

Fig. 1. Flow diagram of participation.

in an identical fashion to our prior study.[26] The variance between successive EPI volumes was computed, and scans were aligned using rigid body transformations. Variance and motion parameters were used to identify scans exceeding any of the following: 0.5-mm translation, 0.3° rotation, or a variance of ≥ 5 standard deviations from the mean scaled variance. These scans were later modeled out to limit the impact of participant motion. Echoplanar sequence images for each participant were coregistered to that participant's structural image, spatially normalized to Montreal Neurological Institute space,[27] and smoothed with a 9-mm full-width half maximum isotropic Gaussian kernel. The statistical model included discrete cosine basis functions to bandpass filter the data from 0.01 to 0.1 Hz, the 6 movement parameters obtained from realignment, and their squares and volterra expansions. Using a singular value decomposition, the number of confounds was decreased to regressors that explained at least 99% of the variance. Estimates for the time series of interest were calculated from the residuals from the model.

For our primary analyses, we chose canonical regions of interest (ROIs)[28] including: primary auditory cortex (left: [−38 –33 17], right: [58 –16 7]), secondary auditory (left TPJ: [−55 –40 14], right TPJ: [52 –33 8]), frontoparietal (left inferior frontal gyrus: [−42 38 21], right inferior frontal gyrus: [48 25 27]), cingulo-opercular (left anterior frontal operculum: [−51 8 –2], right anterior frontal operculum: [36 10 1]), and default (posterior cingulate: [8 –48 31], anterior cingulate: [12 36 20]) networks. The mean time series data was extracted from a 5-mm radius sphere around each coordinate. These data were then entered in a time series model as above to identify regions of the brain in which activity was correlated to that of the seed region. Using a two sample t test, the resulting parameter estimate maps for all participants were then entered into second-level group analyses to look at the activity for the active and sham treatment groups. Additionally, using paired samples t tests, we analyzed the pretreatment scans, posttreatment scans, and their comparison. A cluster-forming voxelwise threshold of $P < 0.001$, corrected for whole-brain significance at the cluster level ($P < 0.05$) using random field theory was utilized.[29] Using Connectome Workbench, the results were displayed on an inflated cortical surface (v0.85; http://www.humanconnectome.org/software/connectome-workbench.html).

Additional exploratory analyses were conducted on a full set of 264 ROIs covering all regions of the brain.[28] These analyses were Bonferroni corrected for multiple comparisons to account for the number of tests conducted.

RESULTS

Patient Characteristics

The flow diagram for patients we recruited is shown in Figure 1. In addition to participants reported in our previous publications,[21,22] two additional patients randomized to receive 4 weeks of sham intervention are included in the current analysis. These patients did not complete the second arm of the study and were not included in previous analyses.

Patient characteristics are shown in Table I. There were no differences in baseline age or hearing between the active and sham groups, as measured by Students t test. Hearing was measured by grading audiogram results based on a 6-level scale: 1) normal, 2) slight, 3) mild, 4) moderate, 5) moderate/severe, or 6) severe hearing loss. Neither active treatment for 2 or 4 weeks was found to be more effective than sham treatment for reduction of

TABLE I.
Demographics.

	Sham	Active
Age (median)	53	50
Gender (% male)	71%	75%
Baseline THI (median)	52	51
Posttreatment THI (median)	43	42
Hearing ranking* (mean)	2.85	2.50

*Hearing was graded as 1) normal, 2) slight hearing loss, 3) mild hearing loss, 4) moderate hearing loss, 5) moderate/severe hearing loss, or 6) severe hearing loss based on patients' audiogram.
THI = Tinnitus Handicap Inventory.

symptoms of chronic bothersome tinnitus according to THI assessments.[21,22] After including the two additional patients, Mann-Whitney U tests revealed no significant differences between baseline, postintervention, or postintervention-baseline THI measurements between the sham and active rTMS groups. There were no serious adverse events reported.[21,22] We do not believe that patients were aware of their randomization assignment because patients' guesses as to which treatment they received were not better than chance.[22]

Neuroimaging Results

Two-sample *t* tests were used to compare baseline functional connectivity of the active and sham groups, including a covariate to control for 2- or 4-week treatment. Although the connectivity with each seed region identified an appropriate resting state network, there were no differences in connectivity between the active and sham groups using any of the seed regions shown in Figure 2. Additionally, analyses were done to compare posttreatment connectivity between the treatment and sham group. As an example, the results for the left auditory ROI are shown in Figure 3. There were no significant differences between active and sham groups, at the pre- or post-time points, using any of these seed regions.

Finally, we conducted exploratory analyses on pairwise connectivity between seed regions covering the whole brain. We first performed paired samples *t* tests comparing pre- and posttreatment for treatment and sham groups to look for connectivity changes following intervention in regions outside the attention networks that were the focus of our hypothesis-driven seed-based analysis above. No significant differences were found. In addition, regardless of group membership, we correlated pairwise functional neural connectivity with baseline THI, change in THI, baseline depression, and change in depression. Again, none of these correlations were statistically significant.

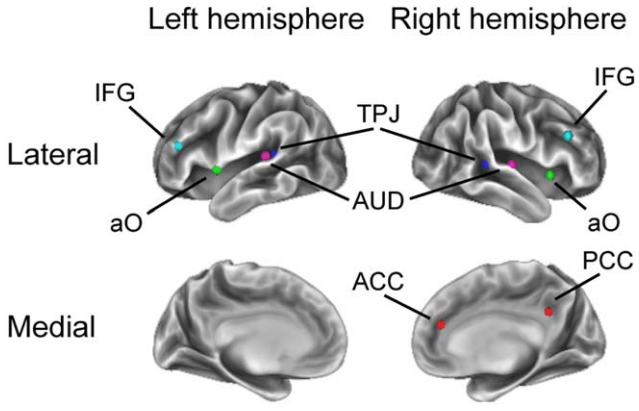

Fig. 2. Regions of Interest used for functional connectivity analysis. ACC = anterior cingulate cortex; aO = anterior operculum; AUD = auditory cortex; IFG = inferior frontal gyrus; PCC = posterior cingulate cortex; TPJ = temporoparietal junction.

DISCUSSION

Here we report the first study to examine changes in neural connectivity following either active rTMS directed toward the TPJ or sham treatment in a group of patients with bothersome tinnitus. Our previous reports suggest the lack of symptom improvement following rTMS therapy to this region,[21,22] and our neuroimaging findings are consistent with these results. Using a seed-based analysis with identified brain regions thought to be affected in tinnitus patients, we did not identify any functional connectivity changes after treatment.

The efficacy of rTMS as an intervention depends on how well it modulates the targeted brain areas, and the degree to which the targeted regions are responsible for symptoms. The use of fcMRI is critical to determine the degree to which neural activity has indeed been modulated. One pilot study used functional connectivity before and after rTMS therapy to the auditory cortex in tinnitus patients to evaluate neural changes; however, the results varied among the small number of tinnitus patients included in the study and are difficult to interpret.[30] There have been mixed results regarding stimulation of the TPJ: some studies support improvement of tinnitus symptoms,[10,11,21] although multiple randomized controlled trials have not verified this finding.[18–20,31]

We propose that the lack of symptom improvement in the current study is due to the lack of neural connectivity changes. The target of rTMS in the current study is the TPJ, which supports secondary and integrative auditory processing. The TPJ is also characterized as part of the ventral attention network, or bottom-up reorienting system. The ventral attention network is likely involved in prioritizing sensory input,[32] which may be important for tinnitus patients who have difficulty ignoring their auditory percept. As compared to healthy controls, patients with bothersome tinnitus have been previously found to have altered activity in attention networks.[3] There are multiple potential explanations for the lack of neural connectivity changes following rTMS in this study. One possibility is that rTMS therapy, although potentially therapeutic for some illnesses, may not modulate neural connectivity to a degree that can be captured using fcMRI. The literature regarding the investigation of imaging in patients with depression receiving rTMS is sparse, and immediate posttreatment effects on fcMRI have not been verified. A second possible explanation is that the specific rTMS protocol used was not sufficient for modulation of the TPJ and

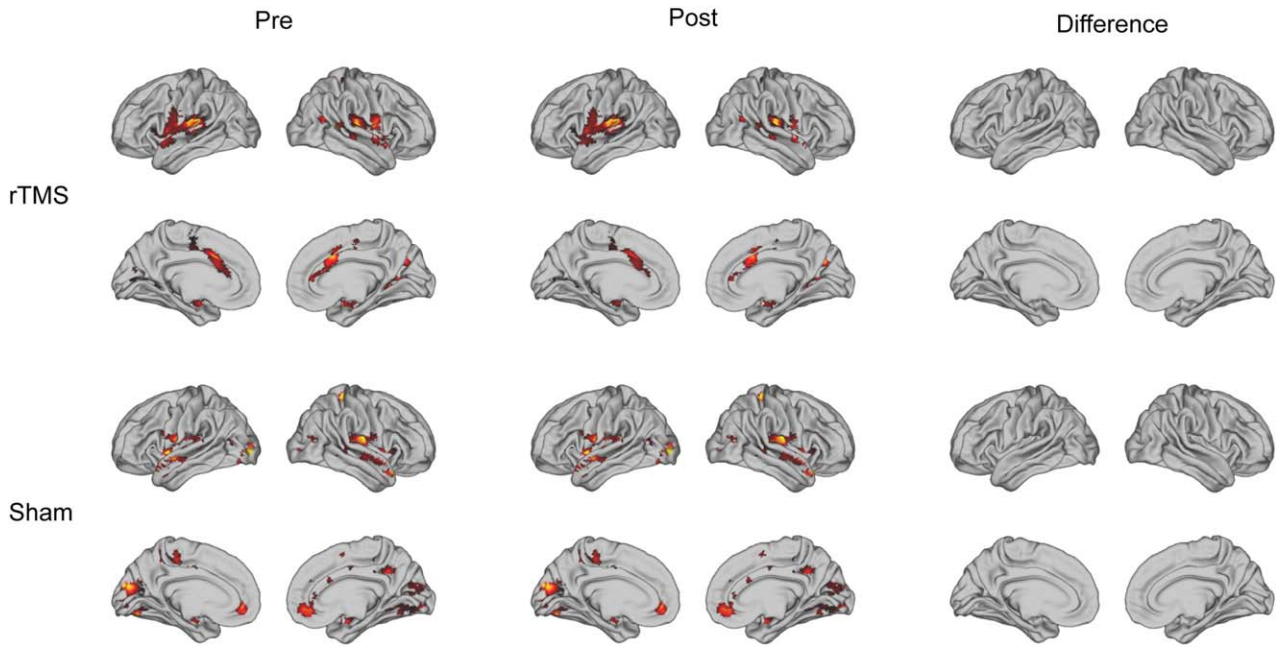

Fig. 3. Left auditory regions of interest: pretreatment, posttreatment, and difference between pre- and posttreatment resting state functional connectivity for active and sham therapy groups.
rTMS = repetitive transcranial magnetic stimulation.

associated networks. Finally, many areas of the brain that contribute to attentional processing may serve as potential targets for rTMS therapy. The TPJ alone may not be the ideal target for rTMS therapy in tinnitus patients. It is possible that there are widespread cortical changes in tinnitus patients, which cannot be treated by a single localized therapy, or that an alternate attention network would serve as a more appropriate target.

Recent work has pointed to the dorsolateral prefrontal cortex (DLPFC), part of the executive attention system, as a potential target for tinnitus therapy. Randomized controlled trials comparing temporal cortex rTMS to combination therapy with temporal and prefrontal rTMS failed to identify statistically significant treatment effects immediately after treatment[20,33] or at 3-month follow-up.[33] However, long-term follow-up of a few pilot studies has suggested that multi-site stimulation of the DLPFC, in addition to the temporal region or TPJ, results in improvement of tinnitus symptoms as compared to single-site stimulation of the temporal cortex.[34,35] The use of rTMS for chronic tinnitus continues to be an area of active research because long-term neuroplastic changes and stable symptom improvements are of interest in this patient population.

Limitations of our study include generalizability; our patient population was screened to exclude patients with active depression. Therefore, our participants may not be truly representative of the tinnitus population. Additionally, we chose to exclude tinnitus patients who are not bothered by their tinnitus because we believe that the bothered tinnitus subgroup is most in need of active research. Again, patient selection may limit generalizability. Finally, although we did not see any significant changes using any of the seed regions included, it is possible that other differences in functional connectivity may exist between patient groups.

In the future, it would be informative to conduct a similar study using a randomized controlled design to evaluate functional connectivity at baseline and following rTMS therapy directed toward multiple attention networks, such as the dorsolateral prefrontal cortex and the TPJ. Effective rTMS therapy may require a multitarget approach in order to target the multiple dysfunctional networks likely responsible for tinnitus. We believe that long-term symptom improvement is a result of changes in one or more neural networks, and that neuroimaging can serve as a biomarker for these changes.

CONCLUSION

Consistent with a lack of symptom improvement following rTMS directed to the left TPJ, we did not find changes in neural connectivity following rTMS therapy. Rather than suggest that rTMS is ineffective for chronic bothersome tinnitus, our results suggest instead that the TPJ alone may not be an ideal target for tinnitus treatment. Further research is necessary to identify better targets for rTMS treatment in patients with bothersome tinnitus in order to create changes to cortical networks associated with symptom improvement.

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