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Neural activity during attentional conflict predicts reduction in tinnitus perception following rTMS

GA James, J Thostenson, G Brown, G Carter, H Hayes, SP Tripathi, DJ Dobry, RB Govindan, JL Dornhoffer, DK Williams, CD Kilts, and MS Mennemeier

Abstract

Background—Subjective idiopathic tinnitus is an intrusive, distracting, and potentially disabling disorder characterized by phantom perception of sounds. Although tinnitus has no approved pharmacologic treatment, recent evidence supports the use of repetitive transcranial magnetic stimulation (rTMS) to alleviate tinnitus symptoms.

Objective/Hypothesis—Repetitive TMS delivered over the middle superior temporal gyrus (STG) may alter ratings of tinnitus awareness and annoyance more than loudness due to change in attentional processing. STG has reciprocal connections to regions of the prefrontal cortex that mediate attention. To probe the hypothesized influence of STG stimulation on attention, a subset of patients with tinnitus enrolled in an rTMS clinical trial [n=12, 9 male, mean (sd) age = 49 (15) years] underwent an attentional conflict task before and after rTMS treatment in a repeated-measures functional magnetic resonance imaging (fMRI) study.

Methods—The Multi-Source Interference Task (MSIT), a Stroop-based visual attentional conflict fMRI task, was used to map participants' neural processing of attentional conflict prior to rTMS intervention (Baseline) and after three rTMS intervention arms: Sham, 1Hz, and 10Hz (four sessions per arm, 1800 pulses per session, delivered @110% of the motor threshold over the posterior superior temporal gyrus).

Results—All measures of tinnitus severity (awareness, loudness, and annoyance) improved with 1Hz rTMS intervention; however, the greatest and most robust changes were observed for ratings of tinnitus awareness (mean 16% reduction in severity from Baseline, $p<0.01$). The MSIT elicited a similar pattern of neural activation among tinnitus participants at Baseline compared to an independent sample of 43 healthy comparison adults ($r=0.801$, $p=0.001$). Linear regression with bootstrap resampling showed that greater recruitment of bilateral prefrontal and bilateral parietal regions by MSIT at Baseline corresponded with poorer treatment response. Individual regions' activities explained 37–67% variance in participant treatment response, with left dorsolateral prefrontal cortex's MSIT activity at Baseline explaining the greatest reduction in tinnitus awareness following 1 Hz stimulation. Although left dorsolateral prefrontal cortex activity at

Corresponding Author: G. Andrew James, Ph.D., University of Arkansas for Medical Sciences, 4301 W. Markham St #554, Little Rock, AR 72205-7199, Office: (501) 526-8345, GAJames@uams.edu.

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Baseline also predicted reduction in tinnitus loudness and annoyance (~50% variance explained), these symptoms were more strongly predicted by right middle occipital cortex (~70% variance explained) – suggesting that the neural predictors of symptom-specific treatment outcomes may be dissociable.

Conclusion—These candidate neural reactivity markers of treatment response have potential clinical value in identifying tinnitus sufferers who would or would not therapeutically benefit from rTMS intervention.

Graphical abstract

Keywords

Multi-Source Interference Task; working memory; attentional conflict; individual differences; biomarkers; patient selection

Introduction

Subjective idiopathic tinnitus (hereafter tinnitus) refers to phantom perception of sound—such as ringing, buzzing, or hissing—without an identifiable source. Tinnitus is a major health problem that affects 50 million people in the United States and has no known cure.(1) Patients complain that tinnitus is intrusive, obscures sounds in the natural environment, and is difficult or impossible to ignore — which suggests they cannot habituate attention to tinnitus symptoms and become continually aware of and annoyed by their presence. The impact of tinnitus negatively influences broad areas of human health. Twelve million tinnitus patients seek treatment each year for comorbid problems of disturbed sleep, diminished concentration, and depression or anxiety. Two to three million patients are disabled by tinnitus.(2–4) Whereas behavioral and pharmacological interventions can help people cope, such interventions do little to actually reduce tinnitus symptoms.(1)

Repetitive transcranial magnetic stimulation (rTMS) is a well-tolerated, low-risk, noninvasive technique that can reduce tinnitus symptom awareness in a subset of patients. (5–7) TMS is a medical device that uses a stimulating coil to deliver strong, brief magnetic fields (pulses) over the scalp.(8) Magnetic fields pass through the scalp and skull with little impedance and induce electrical currents in the brain that stimulate action potentials in cortical neurons located beneath the coil. The induced neural activity may in turn spread from the stimulation site to widely distributed anatomically connected brain regions.(9) Thus, focal TMS can have widespread effects on neural systems and behavior. Repetitive

TMS (rTMS) uses repeated stimulation to modulate the activity level of neuronal populations, with treatment benefits lasting from minutes to weeks or even months after stimulation. The type, duration, and efficacy of neuromodulation is influenced by TMS parameters such as the intensity, frequency, duration and location of stimulation.(10,11)

Although the precise mechanisms of tinnitus and of the rTMS-induced treatment effect on tinnitus are uncertain and probably multifaceted,(12) both phenomena are thought to influence brain networks that regulate attentional, emotional, and audiological processes. Whereas neurophysiological and neuroimaging studies originally suggested that hyperexcitability and reorganization within the auditory cortex could explain audiological changes in tinnitus,(13) more recent work reveals involvement of two general domain networks:(14) a frontoparietal “working memory” network broadly involved in cognitive control (including the volitional control of attention)(15,16) and a cinguloinsular “saliency” network mediating attentional processing of pain and emotion.(17,18) In a corresponding fashion, rTMS treatments originally targeted temporal cortex to influence auditory processes, i.e. to inhibit hyperexcitability, but the approach expanded to include stimulation of the frontal cortex as a means of influencing attention to tinnitus symptoms.(19,20) However, there is little current evidence to suggest that these rTMS target sites produce mutually exclusive effects on tinnitus. In fact, targeting the temporal cortex alone appears to have as much of an effect on questionnaire surveys of tinnitus symptoms as does a combined approach of temporal and frontal lobe stimulation, although the combined approach may have more durable effects.(21) This outcome might be due to the fact that targeting the superior temporal gyrus, as is common in rTMS studies of tinnitus, can influence attentional processing via its connections with the dorsolateral frontal cortex. The middle and posterior regions of the superior temporal gyrus (STG) project to the lateral (periaruate) prefrontal cortex and to the posterior, dorsolateral premotor cortex, respectively.(22,23) Restricted lesions of the periaruate cortex in monkeys impairs performance on auditory Go/No-go tasks.(24)

The objective of this study was to examine whether and how stimulation of the superior temporal gyrus altered direct ratings of tinnitus awareness and annoyance, which might be more influenced by attentional processes, than ratings of loudness which may reflect auditory processing. To further probe the hypothesized influence of this type of stimulation on attentional mechanisms and to establish a convergent finding, participants also completed task-based, functional neuroimaging sessions before and after rTMS treatment.

An attentional control functional neuroimaging paradigm — the Multi-Source Interference Task (MSIT)(25) was used to monitor changes in attentional processing over the courses of rTMS treatment. The MSIT was developed to explore the behavioral and neural responses to high and low attentional control demands within the functional MRI (fMRI) environment by combining elements of three cognitive interference tasks: the Stroop task,(26) the Eriksen Flanker task,(27) and the Simon effect.(28) Tinnitus patients in this study completed task-based fMRI scans using the MSIT at baseline (prior to rTMS) and following four-day treatment courses of sham and active 1Hz, and 10Hz rTMS. We hypothesized that individual variation in the recruitment of brain regions subserving attentional control may predict post-rTMS treatment response based on self-reported tinnitus awareness.

Materials and Methods

Study Design and Inclusion/Exclusion criteria

Thirteen participants who were part of an ongoing clinical trial to evaluate the efficacy of maintenance rTMS for chronic tinnitus (NCT00926237) also completed MRI scans as part of their participation. The University of Arkansas for Medical Sciences (UAMS) was the site for recruitment and testing. The study was conducted with approval and oversight by the UAMS Internal Review Board (IRB protocol #109033). The clinical trial design was a double-blind, randomized clinical trial with participant crossover. Inclusion criteria for the trial were as follows: 1) age 18–89 years; 2) subjective tinnitus > 6 months duration; 3) passing the Transcranial Magnetic Stimulation Adult Safety Screen (TASS);(29) 4) negative pregnancy test and agreeing to use effective contraception during study participation for females; 5) complying with study procedures; 6) agreeing to be videotaped during rTMS for adverse event monitoring purposes; 7) not consuming alcohol within 72 hours of each test session; and 8) persons taking selective serotonin reuptake inhibitors (SSRIs) or benzodiazepines for tinnitus were required to be on a stable dose for three months prior to enrollment and throughout the entire study. Exclusion criteria were as follows: 1) taking tricyclic antidepressants, bupropion, or any medication other than those allowed under inclusion criteria that could increase risk for seizure; 2) diagnosis of migraine, epilepsy, a first-degree relative with epilepsy, Meniere's Disease, a major neurological or psychiatric disorder (excluding depression or anxiety related to tinnitus); 3) history of head injury with loss of consciousness > 10 minutes, brain aneurysm, stroke, previous cranial neurosurgery, acoustic neuroma or glomus tumors; 4) a condition of profound hearing loss (> 90 dB at 4000 Hz); 5) any contraindications to MRI including ferromagnetic implants or devices, pregnancy (for females, due to unknown influence of high-field MRI upon the developing fetus); and 6) inability to comprehend study instructions or complete questionnaires. Audiometry test results, obtained from existing medical records, indicated the majority of participants had mild to moderate sensory hearing loss associated with their tinnitus.

Participants who remained eligible after screening and baseline assessments were assigned to the following study phases: 1) Baseline assessments occurred over three days before the first treatment arm assignment. 2) An order effect was imposed such that all participants received sham rTMS first (at either 1 or 10 Hz). The order effect prevents the carryover of active treatment into the sham treatment condition which was observed in a previous fully randomized trial.(30) 3) Half of the participants were then block randomized to receive active 1Hz rTMS and half to active 10Hz rTMS. 4) Participants crossed-over to the remaining active treatment arm. Each treatment arm (sham, 1 Hz and 10 Hz) included four days of rTMS completed over a 5-day week. A 21 day washout period followed each treatment arm with assessments performed at day 2, 9 and 16 of the washout period.

All participants completed T1-weighted MRI at baseline so that a structural MRI would be available to guide rTMS placement. Thirteen of these participants also underwent fMRI sessions at baseline and on the final day of rTMS treatment for each rTMS treatment arm (Sham, 1 Hz, 10Hz) as part of a pilot study. The fMRI session consisted of a structural MRI

acquisition and fMRI acquisition during the MSIT task and during wakeful rest (see *Procedures* below).

Participant Demographics

Although thirteen participants underwent fMRI, one participant was excluded from fMRI analysis due to excessive head motion at Baseline and Sham conditions. One of these 12 participants had a familial history of epilepsy and was allowed in the study but not allowed to undergo 10Hz rTMS. Demographics for these 12 participants are provided in Table 1. Table 1 also provides demographics for a comparison sample of $n=43$ healthy adults from the Cognitive Connectome project (31) whom also underwent the MSIT fMRI task at the same site.

Behavioral study measures

The primary outcome measures for this pilot study were the visual analog ratings (VAR) of tinnitus awareness, annoyance and loudness for the ear contralateral to rTMS stimulation. TMS was delivered over temporal cortex opposite the ear with loudest tinnitus (or the left temporal lobe when no difference was reported). As tinnitus is sometimes perceived only in one ear, ratings for the ear ipsilateral to treatment can exhibit a floor effect (i.e., 0) and so were not analyzed. For the VARs, participants were asked to rate tinnitus on a 100 point scale with 0 = “no tinnitus” and 100 = “painfully loud tinnitus”. Ratings were made for each ear for a total of six ratings (right and left ear $\times$ ratings of tinnitus loudness, annoyance, and awareness).

Participants completed VARs of tinnitus symptoms at least once during every study visit. Participants completed VARs two times on each day of treatment — once before and once within five minutes of completing each rTMS session (pre and post session ratings, respectively). Participants also completed neuropsychological tests (Digit Symbol, Finger Tapping, and Three Words at Five Minutes tests) for cognitive safety monitoring. The Tinnitus Handicap Inventory(32) and the Tinnitus Handicap Questionnaire(33) provided baseline assessments of tinnitus severity.

MRI acquisition

Trial participants undergoing fMRI had 4 sessions: a Baseline session prior to rTMS and sessions on the final day of each of three rTMS treatment arms (Sham, 1 Hz, and 10Hz). The primary purpose of the Baseline scan was to acquire a T1-weighted anatomic image to guide placement of the rTMS coil (see *TMS administration*, below). Participants were scanned using a Philips 3T Achieva X-series MRI scanner (Philips Healthcare, USA) and 8-channel head coil. Anatomic images were acquired with a MPRAGE sequence (matrix= 256×256 , 160 sagittal slices, TR/TE/FA= 2600 ms/3.05 ms/8°, final resolution= $1 \times 1 \times 1$ mm³). Functional images were acquired with an echo planar imaging (EPI) sequence [TR/TE/FA= 2000 ms/30 ms/90°, FOV= 240×240 mm, matrix= 80×80 , 37 oblique slices, slice acquisition= “Philips interleaved”, final resolution= $3 \times 3 \times 3$ mm³]. Participants underwent fMRI while performing the Multi-Source Interference Task (MSIT),(25) which was adapted as previously described(31) into a single 8 min scan (240 dynamic images) with alternating 48s blocks of Incongruent and Congruent stimuli (4 blocks each, 8 blocks total). Participants

also underwent a 7.5 min (235 dynamic images) resting-state fMRI scan, for which they were instructed to passively view a fixation cross while relaxing and trying “not to think about anything specific”. As described above, one participant was excluded from the 10Hz treatment arm due to familial history of epilepsy, and a thirteenth participant underwent fMRI scanning but was excluded due to excessive head motion.

TMS administration

The following procedures were completed each day of rTMS treatment. Tinnitus symptom ratings and neuropsychological tests were completed upon arrival to the laboratory. Participants were prepped for TMS motor-evoked potential recording. They were seated in a slightly supine position in an adjustable dental chair. The lower thumb portion of the hand contralateral to stimulation was cleaned. Three disposable, pre-gelled electrodes were placed on the skin above the thenar abductor pollicis brevis (TAPB). Participants were prepped for sham rTMS delivery. Two (6 cm) rubber electrodes coated with electrode gel were placed on the scalp in line with the top of the ear and approximately 2–3 cm anterior and posterior to the ear (these electrodes were only active during the sham stimulation arm). Participants wore form-fitting foam ear plugs for hearing protection. A neuronavigation device (Brainsight Frameless Stereotaxy, Rouge Research, Montreal, Canada) was used to ensure consistent placement of the TMS coil across sessions for motor threshold (MT) testing and rTMS delivery. A study nurse was present to monitor participants during rTMS delivery and to carry out study rescue procedures if required. MT was determined by stimulating motor cortex with an active TMS coil. A Magstim Super Rapid stimulator (Magstim Company, Whitland, Wales, UK) with two visually identical Magstim 70-mm, air-film, figure-of-eight stimulating coils (i.e., sham and active) were used in this study. MT was determined by adjusting the stimulator power to the minimum necessary to observe at least 3 out of 6 motor-evoked potentials (MEP) of at least 50 μ V recorded over the TAPB muscle of the hand contralateral to stimulation. Visible twitching of the thumb could be used as an alternative criterion in the event that a clear MEP response could not be obtained due to electrical noise obscuring the MEP signal (this happened 5 times out of 832 recording sessions). The study nurse escorted the participant out of the laboratory after MT testing was complete and returned after the technician set up equipment for either sham or active rTMS delivery. The center of the TMS coil was positioned over the middle portion of the superior temporal cortex (Brodmann’s area 22) in the hemisphere opposite the ear with the loudest tinnitus or over the left temporal lobe in participants with equivalent, bilateral tinnitus. A sham coil with the stimulator set at 45% of the maximum stimulator output (MSO) was used during sham treatment as per our published method.(34) Additionally, electrical pulses were sent to the two carbon rubber electrodes placed over the temporal muscles using a DS3 Isolated Stimulator (Digitimer Ltd., Welwyn Garden City, Hertfordshire, U.K.) to simulate the sensation of active rTMS. Pulses were triggered by the MagStim unit, so that participants felt scalp muscle twitching each time they heard clicks from the TMS coil. Electrical pulse voltage ranged from 3 to 12 mA. Participants, staff acquiring tinnitus VAR ratings, staff acquiring MRI data, and all statisticians were kept blind to treatment conditions.

TMS behavioral outcome analyses

Using SAS Proc Mixed for mixed effects models, Repeated Measures models were fit to VAR and LM Ratings of Tinnitus Awareness, Annoyance, and Loudness. Since participants received repeated treatments and provided repeated ratings, the pattern of correlation in their responses was examined and an autoregressive covariance structure was selected for the models. Each outcome variable was then predicted by the following two factors: Treatment Phase (Sham, 1Hz active treatment, and 10Hz active treatment) and Stimulation Site (Left hemisphere, Right hemisphere). Differences and confidence intervals between each pair of treatments were estimated by contrasts and tested by two-tailed t-tests.

MRI data preprocessing

MRI structural and functional data preprocessing were performed in AFNI(35) with scripts available upon request. Anatomic MRIs underwent skull stripping and normalization to the icbm452 template brain. Masks of voxels constituting gray matter (GM), white matter (WM), and cerebrospinal fluid (CSF) were generated by automated segmentation with FSL. Functional images underwent despiking, slice-time scan correction, deobliquing, motion correction with registration to the 10th image, co-registration with their native structural scan, alignment with the icbm452-normalized structural scan, regression of 24 motion parameters ($[R \ R^2 \ R_{t-1} \ R_{t-1}^2]$ where R = lateral movement (X, Y, Z) and angular movement (roll, pitch, yaw)),(36) regression of mean WM and CSF timecourses, spatial smoothing to an 8mm FWHM Gaussian kernel, linear and quadratic detrending, and scaling to percent signal change.

Group-level univariate fMRI analyses

General linear modeling (GLM) estimated task-dependent changes in blood-oxygen level-dependent (BOLD) activity between MSIT Incongruent and Congruent conditions for each participant. GLMs included the participant's 24 motion parameters described above as regressors of no interest. Group statistical parametric maps (SPMs) were generated independently for each group using mixed effects meta-analysis (MEMA)(37) of the Incongruent vs. Congruent GLT β -values weighted by GLT t-scores. Group-level SPMs were thresholded by first using AFNI's 3dREMLfit to model residual error of the fMRI task data to the predicted model, then using 3dFWHMx to estimate the spatial smoothness of the residual error, and finally using 3dClustSim to determine clustering parameters. These programs estimated smoothness as a 9mm FWHM Gaussian kernel and estimated that AlphaSim family-wise correction for multiple comparisons ($p_{FW} < 0.05$) could be obtained by thresholding data at an uncorrected $p < 0.001$ with minimum cluster size of 7 voxels with contiguous faces. We used this stringent clustering approach in response to recent evidence that spatial autocorrelation in fMRI data may have a non-Gaussian distribution.(38) Figure 1 (top) depicts regions of significant MSIT-related activity among healthy comparison participants at this clustering threshold. A binary mask derived from this clustering threshold was applied to the tinnitus group's SPM (Figure 1, bottom) so that Spearman's correlation could assess similarity in task-related neuroactivation between groups.

Regressions of baseline MSIT activity with rTMS outcome

Bootstrapped linear regression tested if Baseline MSIT could predict rTMS outcome (i.e. changes in tinnitus awareness, annoyance, or loudness). Bootstrapping was selected for its resiliency against outliers in both predictor and response variables.(39) All analyses were performed using Matlab R2016b with the *bootstrap* and *regress* commands from the Statistics and Machine Learning Toolbox.

To reduce the number of statistical comparisons (and thus control for Type I error without inflating Type II error), analyses were conducted using an *a priori* defined 200 region of interest (ROI) whole-brain atlas previously derived via joint parcellation of resting-state and task-based fMRI data.(40) We calculated the mean MSIT-related changes in brain activity (i.e. GLM betas for the Incongruent vs. Congruent contrast) for each ROI and participant with tinnitus. Since participants' change in tinnitus outcomes were highly correlated across 1Hz and 10Hz stimulation conditions (see Results below) and all 12 participants underwent 1Hz stimulation, our neuroimaging analyses focus upon predictors of treatment response with 1Hz stimulation. Change in tinnitus symptoms (VAR awareness, loudness, and annoyance) was calculated as the difference between mean ratings at Baseline and mean ratings after 1Hz stimulation divided by mean ratings at Baseline; i.e. [mean(Baseline) — mean(1Hz)] / mean(Baseline). With this calculation, positive changes indicate symptom improvement from Baseline.

Linear regression related MSIT-related brain activity for each of the 200 ROIs to participants' change in tinnitus awareness with the equation:

$$\Delta \text{VAR}_{\text{AWARE}} = B_0 + B_1 * \text{ROI}_i + B_2 * \text{AGE}$$

where $\text{VAR}_{\text{AWARE}}$ is percent change in tinnitus awareness from Baseline to post 1Hz stimulation, B_0 is a baseline (constant) variable, ROI_i is task-related GLM betas for the i th ROI for the MSIT contrast Incongruent vs. Congruent at baseline, B_1 is the beta weight relating change in awareness to ROI activity, and B_2 is the beta weight relating change in awareness to participant age. Regressions were performed independently for each ROI. Bootstrapping with replacement generated 10,000 subsamples for estimating mean and standard error of B_1 and B_2 . Two-tailed t-tests evaluated if ROIs' B_1 values significantly differed from 0, with resulting p-values undergoing FDR correction for multiple comparisons ($q < 0.05$) in Matlab.(41) Age did not significantly predict $\text{VAR}_{\text{AWARE}}$ for any ROI_i and was subsequently dropped from analysis. All scripts are available upon request.

Results

Behavioral

Table 2 summarizes group changes in tinnitus symptoms (awareness, annoyance, and loudness) with 1Hz and 10Hz rTMS stimulation relative to Sham stimulation. Participants reported greatest magnitude of change (~16% reduction in symptoms) for tinnitus awareness, which was also the most significantly robust finding ($p < 0.01$ for both 1Hz and 10Hz stimulation). Tinnitus annoyance and loudness had lesser magnitudes of change (~7–

11% reduction in symptoms) which were significantly different from Sham for 1Hz stimulation ($p < 0.05$) but not 10Hz stimulation. Participants' mean change in tinnitus awareness, annoyance, and loudness from Baseline to 1Hz stimulation were strongly correlated with one another (all $\rho = 0.80$, all $p = 0.002$). Among the 11 participants who underwent both 1Hz and 10Hz rTMS stimulation, changes in tinnitus perception from Baseline were highly correlated across 1Hz and 10Hz stimulation for awareness ($\rho = 0.81$), annoyance ($\rho = 0.95$) and loudness ($\rho = 0.82$; all $p = 0.003$).

Neuroimaging

Mapping MSIT-related neural activity in patients with tinnitus—Voxel-wise brain activity for the contrast of Incongruent vs. Congruent MSIT stimuli was strongly correlated between normative participants and patients with tinnitus (Figure 1; $\rho = 0.801$, $p = 0.001$), supporting this paradigm's validity for mapping the neural correlates of attentional conflict in patients with tinnitus. ROIs whose activities significantly differed between Incongruent and Congruent trials (FDR correction $q = 0.05$) are depicted for the tinnitus sample (Table 3). Consistent with prior MSIT findings (Bush et al., 2003), regions with greater task-related activity for Incongruent trials than Congruent trials included midline recruitment of pericingulate cortex and bilateral recruitment of insulae, superior parietal cortices and supramarginal gyri, dorsolateral prefrontal cortices, and primary visual and association cortices. Fewer ROIs survived FDR correction for patients than control participants, possibly owing to the smaller sample size; however, 22 of the 25 ROIs significant for patients were also significant for control participants, including all patients' ROIs with $|t| \geq 5$.

Attentional conflict-related neural activity at Baseline predicts rTMS-related reduction in perceived tinnitus awareness—After FDR correction, Baseline MSIT-related neural activity for 21 different functional ROIs significantly predicted subsequent rTMS-related change in tinnitus awareness (Table 4, Figure 2). These regions broadly encompassed bilateral dorsolateral prefrontal cortex and bilateral inferior parietal cortex. All regressions were negative, with greater Baseline activity for the MSIT contrast (Incongruent vs. Congruent) predicting lesser reduction in tinnitus symptom (i.e. poorer clinical response). The most significant predictor of rTMS-related change in tinnitus awareness was the left superior dorsolateral prefrontal cortex response (ROI #84, Talairach coordinates = $-41, 14, 48$ mm), which explained 66.7% of observed variance in rTMS response (Figure 3, t -score = -4.88 , $df = 11$, $p < 0.0001$). Baseline MSIT-related neural activity for the remaining ROIs each independently explained 39.6%–66.4% of variance in TMS response (see Supplemental Materials for scatterplots).

Attentional conflict-related neural activity at Baseline predicts rTMS-related reduction in perceived tinnitus loudness—After FDR correction, Baseline MSIT-related neural activity of 15 ROIs significantly predicted rTMS-related change in tinnitus loudness (Table S1). Twelve of these ROIs also predicted change in awareness (Table 4), including all ROIs explaining 50% or greater variance in change in loudness. All regressions were again negative, with greater activity at Baseline predicting lesser reduction in loudness. The most significant predictor of change in loudness was the right middle occipital cortex (ROI #184, MNI coordinates = $30, -82, 31$), which explained 66.9% of observed variance in

rTMS response (t -score = -4.90 , $df=11$, $p<0.0001$). Baseline attentional conflict-related activity for the remaining ROIs each explained 41.1%–66.5% variance in TMS response (see Supplemental Materials for scatterplots).

Attentional conflict-related neural activity at Baseline predicts rTMS-related reduction in perceived tinnitus annoyance—After FDR correction, Baseline MSIT-related neural activity of 25 ROIs significantly predicted rTMS-related change in tinnitus annoyance (Table S2). Fifteen of these ROIs also predicted change in awareness (Table 4), including 5 of the 8 ROIs explaining 50% or greater variance in change in annoyance. All regressions were again negative, with greater activity at Baseline for the Incongruent vs. Congruent contrast predicting less reduction in annoyance. As with loudness, the most significant predictor of change in annoyance was the right middle occipital cortex (ROI #184), which explained 73.0% of observed variance in rTMS response (t -score = -5.74 , $df=11$, $p<0.0001$). Baseline attentional conflict-related activity for the remaining ROIs each explained 38.5%–67.4% variance in TMS response (see Supplemental Materials for scatterplots). Note that participant #135 is an outlier with a 172% worsening in annoyance (Baseline VAR=18.3, 1Hz VAR=50.0); however, the scatterplots illustrate that the bootstrap approach is resilient against the effects of this outlier.

Discussion

Our primary finding is that active rTMS treatment (both 1Hz and 10Hz stimulation) led to significant reductions in tinnitus awareness relative to sham rTMS (~16 points on a 100 point VAR scale). Reductions were also observed for tinnitus loudness (~10 points) and annoyance (~11 points) relative to the sham condition, but these reductions were only significant for the 1Hz stimulation condition and not 10Hz stimulation. Studies of tinnitus are consistent in showing that 1 and 10 Hz rTMS delivered over the temporal cortex produce similar effects on tinnitus even though the two frequencies can have opposite effects on cortical excitability. (42,43) In this study, 1 Hz stimulation was associated with less response variability in ratings of tinnitus than 10Hz rTMS which may account for why 1 Hz rTMS produced significant changes in ratings of tinnitus awareness, loudness and annoyance; whereas 10 Hz rTMS only produced a significant change in tinnitus awareness. Overall, changes in tinnitus awareness were larger and more robust than were the changes in tinnitus loudness or annoyance.

Recruitment of the left superior dorsolateral prefrontal cortex during the MSIT task at baseline was the strongest predictor of rTMS-related change in tinnitus awareness; whereas recruitment of the right middle occipital cortex was the strongest predictor of change in tinnitus loudness and annoyance. However, the neural predictors of all three outcomes measures overlapped considerably. For example, middle occipital cortex also predicted change in awareness (10th best predictor, explaining 51% variance), and left superior dorsolateral prefrontal cortex also predicted change in loudness (6th best predictor, 50% variance) and annoyance (5th best predictor, 64% variance). Of the 32 unique regions predicting change in tinnitus awareness, annoyance, or loudness, 11 regions significantly predict change in all three measures; these regions include bilateral dorsolateral prefrontal cortex (ROIs #3, 10, 84, 129), rostral medial prefrontal cortex (#101), left inferior (#14) and

posterior inferior parietal (#76), left posterior caudate (#124), right inferior (#174) and left posterior middle temporal gyrus (#93), and right middle occipital (#184). This pattern of neural predictors may be a global predictor of rTMS treatment response, with the relative ranking of regions (and measure-specific regions) serving as more nuanced predictors of treatment outcome.

The greater magnitude of rTMS-induced change for tinnitus awareness than loudness or annoyance, and the greater role of left superior dorsolateral prefrontal cortex in predicting tinnitus awareness outcome, suggests that tinnitus awareness may be more strongly mediated by attentional mechanisms. Changes in tinnitus loudness and annoyance may be influenced by other mechanisms as well, and fMRI tasks geared toward those aspects of tinnitus (e.g., auditory, pain, or emotion tasks) might result in a better understanding of the involved mechanisms and a better picture of the neural profiles that can predict positive treatment responses from rTMS. But consistent with previous studies, (6) we also report considerable individual differences in treatment response. As shown in Figure 2, seven of twelve participants had clear benefit from 1Hz rTMS (30–60% reductions in tinnitus awareness symptoms from Baseline), but five participants had negligible improvement (reductions < 20%) or non-significant worsening symptoms. A biomarker of treatment response would be valuable for identifying patients whom are likely to have poor rTMS treatment outcomes, thus sparing these patients from the time and moderate risks of rTMS therapy.

Identifying reliable and accurate biomarkers of treatment response is an area of growing interest to the neuroimaging community. (44–47) In addition to their pragmatic value to improving patient selection — and thus facilitating fMRI's translation from a research instrument to a tool which informs clinical decision-making — such biomarkers have heuristic value as a means of elucidating the brain states requisite to optimal treatment outcomes. Since patients typically undergo anatomic MRI scans prior to rTMS treatment to guide consistent TMS coil placement, the MSIT and other fMRI tasks may be added within the initial localizer MRI scanning session as a standardized, cost-effective method for improving patient selection.

The primary limitation of this work is its small sample size. As with many neuroimaging studies, these findings require replication in a larger sample. Nonetheless, we chose several design and analysis features to help mitigate problems associated with a small sample. First, we employed a within-subjects repeated-measures design to facilitate statistical power. Furthermore, our use of bootstrapping reduces the influence of statistical outliers. The issue of whether a representative sample was obtained is partially addressed by showing that MSIT-induced neural activity among this small patient sample is strongly correlated with activity among a larger normative sample ($n=43$) — despite the significant age difference between samples (mean = 27 years, t -score (df) = 4.83 (53), $p < 0.0001$). This marked similarity validates our use of MSIT to map the neural correlates of attention among patients with tinnitus. The small sample size could also be inflating the strong correlation observed among tinnitus patients' reductions in awareness, loudness, and annoyance (all $\rho = 0.80$) — which in turn could be contributing to the overlapping pattern of neural activity predicting change for all three outcome measures.(48) We anticipate that a larger sample

may show greater heterogeneity among outcome measures, and thus potentially greater independence among neural predictors for each outcome.

Our finding that neural responses during the MSIT attentional conflict task at baseline, particularly those in the DLPFC in relation to tinnitus awareness, can predict rTMS treatment outcome supports the view that attentional mechanisms mediate the experience of subjective idiopathic tinnitus. These data provide convergent validity that attentional mechanisms contribute to a treatment response. Further, the region that best predicted change in tinnitus awareness, left dorsolateral prefrontal cortex, is consistent with the findings of primate studies which show reciprocal connections between the middle superior temporal gyrus (our treatment site) and the periarculate cortex.(22,23) Ablative lesions of the periarculate cortex in monkeys impairs performance on both visual and auditory versions of the Go/No-go paradigm, which shares similar features to the Stroop and MSIT tasks. Also noteworthy is that none of the regions predicting change in tinnitus awareness (Table 4) overlapped with regions activated or de-activated by the MSIT task (Table 3). About half of the predictive regions involved the bilateral prefrontal and parietal cortices — regions that have been implicated in broader cognitive functions including working memory(49,50) and executive control of attention.(51,52) Together, these findings suggest that the way in which an individual patient recruits cognitive resources during the MSIT attentional task at baseline can influence the subsequent response to rTMS.

While this finding is intriguing, it is also difficult to interpret at this stage. Such interpretations rely upon reverse inference and are speculative in the absence of additional confirmatory evidence, such as measures of patients' attentional control or working memory capacity. Recruitment of these frontoparietal regions may represent a compensatory mechanism, such as utilizing executive resources to buffer against the distracting influence of tinnitus perception. These alternate hypotheses could be explored through inclusion of additional fMRI tasks measuring executive function. For example, we have established the *n*-back fMRI task as having strong construct validity with neuropsychological measures of working memory.(53) Including alternate paradigms like *n*-back task would allow us to test if these neural predictors of treatment response were specific to selective attention tasks or generalizable to other forms of executive function.

And while these fMRI approaches provide a means for correlating task-based neural responses with change in tinnitus perception, other approaches are need to establish direct connections. For example, our lab is currently using TMS evoked EEG potential (TEPs) to probe the interactions between superior temporal cortex and the prefrontal and premotor cortex during rTMS treatments for tinnitus. These studies have potential to directly measure change in electrical activity of the frontal cortex that results from rTMS of the temporal cortex and they can be used to validate the fMRI findings of this study. Furthermore, TEPs can be correlated with ratings of tinnitus to model how regional brain activity influences tinnitus perception during and across rTMS sessions. The current study provides convergent evidence that rTMS induced change in tinnitus is mediated, in part, by attentional processes. Future studies employing complimentary methodologies like TMS evoked EEG can provide convergent evidence about the brain regions involved.

Conclusions

We found that four-day treatments of either 1Hz or 10 Hz active rTMS (1800 pulses per treatment delivered at 110% of the MT over temporal cortex) significantly reduced tinnitus awareness relative to sham rTMS more than tinnitus loudness or annoyance. Further, we identified potential neural biomarkers of the rTMS-induced tinnitus response. Recruitment of bilateral dorsolateral prefrontal and bilateral parietal cortices during an attentional conflict task — regions not canonically associated with attentional conflict — predicted a poor response to rTMS treatment.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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References

1. Dobie RA. A Review of Randomized Clinical Trials in Tinnitus. *Laryngoscope*. 1999; 109:1202–11. [PubMed: 10443820]
2. Shargorodsky J, Curhan GC, Farwell WR. Prevalence and Characteristics of Tinnitus among US Adults. *Am J Med*. 2010 Aug.123:711–8. [PubMed: 20670725]
3. Schlee W, Dohrmann K, Hartmann T, Lorenz I, Müller N, Elbert T, et al. Assessment and Modification of the Tinnitus-Related Cortical Network. *Semin Hear*. 2008; 29:270–87.
4. Jastreboff PJ, Gray WC, Gold SL. Neurophysiological approach to tinnitus patients. *Am J Otol*. 1996; 17:236–40. [PubMed: 8723954]
5. Langguth B, De Ridder D, Dornhoffer J, Eichhammer P, Folmer RL, Frank E, et al. Controversy: Does repetitive transcranial magnetic stimulation/ transcranial direct current stimulation show efficacy in treating tinnitus patients? *Brain Stimul*. 2008 Jul.1:192–205. [PubMed: 20633385]
6. Lefaucheur JP, Andre-Obadia N, Antal A, Ayache SS, Baeken C, Benninger DH, et al. Evidence-based guidelines on the therapeutic use of repetitive transcranial magnetic stimulation (rTMS). *Clin Neurophysiol*. 2014 Nov.125:2150–206. [PubMed: 25034472]
7. Mennemeier M, George M. The Case for a Definitive Multisite, Randomized Clinical Trial of Repetitive Transcranial Magnetic Stimulation for Tinnitus. *JAMA Otolaryngol Head Neck Surg*. 2017 Jan. [Epub ahead of print]. doi: 10.1001/jamaoto.2016.4055
8. Bohning, DE. Introduction and overview of TMS physics. In: George, MS., Belmaker, RH., editors. *Transcranial magnetic stimulation in neuropsychiatry*. Washington, D.C.: American Psychiatric Press; 2000. p. 13-44.
9. Hampson M, Hoffman RE. Transcranial magnetic stimulation and connectivity mapping: tools for studying the neural bases of brain disorders. *Front Syst Neurosci*. 2010 Aug.4:1–8. [PubMed: 20204156]
10. Rossi S, Hallett M, Rossini PM, Pascual-Leone A. Safety, ethical considerations, and application guidelines for the use of transcranial magnetic stimulation in clinical practice and research. *Clin Neurophysiol*. 2009 Dec.120:2008–39. [PubMed: 19833552]
11. McDonald WM, Durkalski V, Ball ER, Holtzheimer PE, Pavlicova M, Lisanby SH, et al. Improving the antidepressant efficacy of transcranial magnetic stimulation: maximizing the

number of stimulations and treatment location in treatment-resistant depression. *Depress Anxiety*. 2011 Nov;28:973–80. [PubMed: 21898711]

12. De Ridder D, Vanneste S, Weisz N, Londero A, Schlee W, Elgoyhen AB, et al. An integrative model of auditory phantom perception: Tinnitus as a unified percept of interacting separable subnetworks. *Neurosci Biobehav Rev*. 2014 Jul;44:16–32. [PubMed: 23597755]
13. Weisz N, Muller S, Schlee W, Dohrmann K, Hartmann T, Elbert T. The Neural Code of Auditory Phantom Perception. *J Neurosci*. 2007 Feb;27:1479–84. [PubMed: 17287523]
14. Adjamian P, Sereda M, Hall DA. The mechanisms of tinnitus: perspectives from human functional neuroimaging. *Hear Res*. 2009; 253:15–31. [PubMed: 19364527]
15. Smith SM, Fox PT, Miller KL, Glahn DC, Fox PM, Mackay CE, et al. Correspondence of the brain's functional architecture during activation and rest. *PNAS*. 2009 Aug;106:4. 13040–5. [PubMed: 19118193]
16. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: A meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp*. 2005 May;25:46–59. [PubMed: 15846822]
17. Wager TD, Atlas LY, Lindquist MA, Roy M, Woo CW, Kross E. An fMRI-Based Neurologic Signature of Physical Pain. *N Engl J Med*. 2013 Apr;368:1388–97. [PubMed: 23574118]
18. Craggs JG, Price DD, Verne GN, Perlstein WM, Robinson MM. Functional brain interactions that serve cognitive-affective processing during pain and placebo analgesia. *NeuroImage*. 2007 Dec. 38:720–9. [PubMed: 17904390]
19. Langguth B, Landgrebe M, Frank E, Schecklmann M, Sand PG, Vielsmeier V, et al. Efficacy of different protocols of transcranial magnetic stimulation for the treatment of tinnitus: Pooled analysis of two randomized controlled studies. *World J Biol Psychiatry*. 2012 Aug;15:276–85. [PubMed: 22909265]
20. Lehner A, Schecklmann M, Poepl TB, Kreuzer PM, Vielsmeier V, Rupprecht R, et al. Multisite rTMS for the Treatment of Chronic Tinnitus: Stimulation of the Cortical Tinnitus Network: A Pilot Study. *Brain Topogr*. 2013; 26:501–10. [PubMed: 23229756]
21. Noh TS, Kyong JS, Chang MY, Park MK, Lee JH, Oh SH, et al. 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. *Otol Neurotol*. 2017 Feb;38:296–303. [PubMed: 28068305]
22. Romanski LM, Tian B, Fritz J, Mishkin M, Goldman-Rakic PS, Rauschecker JP. Dual streams of auditory afferents target multiple domains in the primate prefrontal cortex. *Nat Neurosci*. 1999 Dec;2:1131–6. [PubMed: 10570492]
23. Petrides M, Pandya DN. Association fiber pathways to the frontal cortex from the superior temporal region in the rhesus monkey. *J Comp Neurol*. 1988 Jul;273:52–66. [PubMed: 2463275]
24. Petrides M. The effect of periarculate lesions in the monkey on the performance of symmetrically and asymmetrically reinforced visual and auditory go, no-go tasks. *J Neurosci*. 1986 Jul;6:2054–63. [PubMed: 3734876]
25. Bush G, Shin LM. The Multi-Source Interference Task: an fMRI task that reliably activates the cingulo-frontal-parietal cognitive/attention network. *Nat Protoc*. 2006; 1:308–13. [PubMed: 17406250]
26. Stroop JR. Studies of interference in serial verbal reactions. *J Exp Psychol*. 1935; 18:643–62.
27. Eriksen BA, Eriksen CW. Effect of noise letters upon identification of a target letter in a non-search task. *Percept Psychophys*. 1974; 16:143–9.
28. Simon JR, Berbaum K. Effect of conflicting cues on information processing: the 'Stroop effect' vs. the 'Simon effect'. *Acta Psychol (Amst)*. 1990 Mar;73:159–70. [PubMed: 2343770]
29. Keel JC, Smith MJ, Wassermann EM. A safety screening questionnaire for transcranial magnetic stimulation. *Clin Neurophysiol*. 2001 Apr;112:720. [PubMed: 11332408]
30. Mennemeier M, Chelette KC, Allen S, Bartel TB, Triggs W, Kimbrell T, et al. Variable changes in PET activity before and after rTMS treatment for tinnitus. *Laryngoscope*. 2011; 121:815–22. [PubMed: 21287564]

31. Gess JL, Fausett JS, Kearney-Ramos TE, Kilts CD, James GA. Task-dependent recruitment of intrinsic brain networks reflects normative variance in cognition. *Brain Behav.* 2014 Sep.4:650–64. [PubMed: 25328842]
32. Newman CW, Jacobson GP, Spitzer JB. Development of the Tinnitus Handicap Inventory. *Arch Otolaryngol Head Neck Surg.* 1996 Feb.122:143–8. [PubMed: 8630207]
33. Kuk FK, Tyler RS, Russell D, Jordan H. The psychometric properties of a tinnitus handicap questionnaire. *Ear Hear.* 1990 Dec.11:434–45. [PubMed: 2073977]
34. Mennemeier M, Triggs W, Chelette KC, Woods AJ, Kimbrell TA, Dornhoffer J. Sham transcranial magnetic stimulation using electrical stimulation of the scalp. *Brain Stimul.* 2009; 2:168–73. [PubMed: 20160893]
35. Cox RW. AFNI: software for analysis and visualization of functional magnetic resonance neuroimages. *Comput Biomed Res.* 1996; 29:162–73. [PubMed: 8812068]
36. Power JD, Schlaggar BL, Petersen SE. Recent progress and outstanding issues in motion correction in resting state fMRI. *Neuroimage.* 2015 Jan.105:536–51. [PubMed: 25462692]
37. Chen G, Saad ZS, Nath AR, Beauchamp MS, Cox RW. FMRI group analysis combining effect estimates and their variances. *Neuroimage.* 2012 Mar.60:747–65. [PubMed: 22245637]
38. Eklund A, Nichols TE, Knutsson H. Cluster failure: Why fMRI inferences for spatial extent have inflated false-positive rates. *Proc Natl Acad Sci U S A.* 2016 Jul.113:7900–5. [PubMed: 27357684]
39. Efron B. Bootstrap Methods: Another Look at the Jackknife. *Ann Stat.* 1979 Jan.7:1–26.
40. James GA, Hazaroglu O, Bush KA. A human brain atlas derived via n-cut parcellation of resting-state and task-based fMRI data. *Magn Reson Imaging.* 2016 Feb.34:209–18. [PubMed: 26523655]
41. Genovese CR, Lazar NA, Nichols T. Thresholding of statistical maps in functional neuroimaging using the false discovery rate. *Neuroimage.* 2002 Apr.15:870–8. [PubMed: 11906227]
42. Khedr EM, Rothwell JC, Ahmed MA, El-Atar A. Effect of daily repetitive transcranial magnetic stimulation for treatment of tinnitus: comparison of different stimulus frequencies. *J Neurol Neurosurg Psychiatry.* 2008 Feb.79:212–5. [PubMed: 18202212]
43. Fitzgerald PB, Fountain S, Daskalakis ZJ. A comprehensive review of the effects of rTMS on motor cortical excitability and inhibition. *Clin Neurophysiol.* 2006 Dec.117:2584–96. [PubMed: 16890483]
44. Abbott CC, Lemke NT, Gopal S, Thoma RJ, Bustillo J, Calhoun VD, et al. Electroconvulsive therapy response in major depressive disorder: a pilot functional network connectivity resting state FMRI investigation. *Front Psychiatry.* 2013; 4:10. [PubMed: 23459749]
45. Castellanos FX, Di Martino A, Craddock RC, Mehta AD, Milham MP. Clinical applications of the functional connectome. *Neuroimage.* 2013 Oct.80:527–40. [PubMed: 23631991]
46. Marhe R, Luijten M, van de Wetering BJ, Smits M, Franken IH. Individual Differences in Anterior Cingulate Activation Associated with Attentional Bias Predict Cocaine Use After Treatment. *Neuropsychopharmacology.* 2013 May.38:1085–93. [PubMed: 23303067]
47. McGrath CL, Kelley ME, Dunlop BW, Holtzheimer PE Iii, Craighead WE, Mayberg HS. Pretreatment Brain States Identify Likely Nonresponse to Standard Treatments for Depression. *Biol Psychiatry.* 2014 Oct.76:527–35. [PubMed: 24462230]
48. Yarkoni T. Big Correlations in Little Studies: Inflated fMRI Correlations Reflect Low Statistical Power-Commentary on Vul et al. *Perspect Psychol Sci.* 2009; 4:294–8. [PubMed: 26158966]
49. Owen AM, McMillan KM, Laird AR, Bullmore E. N-back working memory paradigm: a meta-analysis of normative functional neuroimaging studies. *Hum Brain Mapp.* 2005 May.25:46–59. [PubMed: 15846822]
50. Reineberg AE, Andrews-Hanna JR, Depue BE, Friedman NP, Banich MT. Resting-state networks predict individual differences in common and specific aspects of executive function. *NeuroImage.* 2015 Jan.104:69–78. [PubMed: 25281800]
51. Rossi AF, Pessoa L, Desimone R, Ungerleider LG. The prefrontal cortex and the executive control of attention. *Exp Brain Res.* 2009 Jan.192:489–97. [PubMed: 19030851]
52. Mennemeier MS, Chatterjee A, Watson RT, Wertman E, Carter LP, Heilman KM. Contributions of the parietal and frontal lobes to sustained attention and habituation. *Neuropsychologia.* 1994 Jun. 32:703–16. [PubMed: 8084425]

53. Kearney-Ramos TE, Fausett JS, Gess JL, Reno A, Peraza J, Kilts CD, et al. Merging Clinical Neuropsychology and Functional Neuroimaging to Evaluate the Construct Validity and Neural Network Engagement of the n-Back Task. *J Int Neuropsychol Soc.* 2014 Aug;20:736–50. [PubMed: 24963641]

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Highlights

- + Patients enrolled in an rTMS clinical trial for tinnitus underwent fMRI at baseline
- + Patients underwent the MSIT attentional conflict fMRI task
- + 1 Hz rTMS intervention significantly reduced tinnitus symptoms (i.e. awareness)
- + Prefrontal and parietal recruitment during MSIT negatively predicted rTMS response
- + These regions may be biomarkers for improving patient selection

Figure 1. Comparison of group-level MSIT-related activity between participants with tinnitus and healthy comparison subjects

The contrast of Incongruent vs. Congruent MSIT stimuli elicited similar patterns of activity among samples of healthy normative participants (top) and participants with tinnitus (bottom). Mixed-effects meta-analyses (MEMAs) were conducted for each group. A mask generated from the normative sample FDR-corrected t-score map was applied to the tinnitus sample t-score map. Spearman's correlation indicates strong correlation between the masked t-score maps ($\rho=0.801, p<0.0001$), supporting comparable neural responses to the MSIT task. Images are depicted in neurological convention (left is left).

Figure 2. Localization of attentional conflict-related neural responses at Baseline that significantly predict change in tinnitus awareness after 1 Hz rTMS stimulation

Linear regression with bootstrapping used Baseline MSIT-related activity for the contrast of Incongruent vs. Congruent trials to predict change in tinnitus awareness from Baseline for the 1Hz rTMS condition. Twenty-six ROIs significantly predicted change in tinnitus awareness, with greater activity in these regions at Baseline predicting poorer treatment response. ROIs were primarily located in bilateral prefrontal and parietal cortices. Images are depicted in neurological convention (left is left).

Figure 3. Left dorsolateral prefrontal activity during MSIT at Baseline predicts change in tinnitus awareness after 1 Hz rTMS stimulation

Baseline activity of left dorsolateral prefrontal cortex (ROI #84) was the most significant predictor of change in tinnitus awareness after 1Hz rTMS stimulation ($t = -4.88$) and explained the greatest amount of variance (66.7%). Scatterplot depicts the linear regression between ROI #84 and change in awareness. Data points represent each of the 12 participants.

Table 1

Sample Demographics

Sample	Tinnitus and rTMS Study	Cognitive Connectome Project [28]
n	12	43
Age ¹	mean (sd) = 49.2 (15.3), range 22–66	mean(sd) = 32(10) years, range 18–50
Sex ²	3 female 9 male	26 female 17 male
Ethnicity ³	12 White/Caucasian	27 White/Caucasian* 16 Black/African-American* 1 Hispanic *1 self-reporting as both Cauc and AA
Handedness	11 right 1 left	36 right 4 left 3 did not report
Education	Not formally assessed	2 (5%) did not complete high school/GED 2 (5%) completed high school or GED 15 (35%) partial college/currently enrolled 3 (7%) graduated from 2 year college 7 (16%) graduated from 4 year college 8 (18%) enrolled in graduate/professional 6 (14%) had graduate/professional degree

Significant group differences:

¹t-score, $p < 0.0001$;² χ^2 , $p < 0.04$;³ χ^2 , $p < 0.02$

Changes in visual analog ratings (VAR) of tinnitus awareness, annoyance, and loudness relative to sham for 1Hz and 10Hz rTMS treatment arms.

Table 2

Tinnitus Symptom	Change with 1Hz Stimulation			Change with 10Hz Stimulation		
	Mean (se)	t-score (df)	p	Mean (se)	t-score (df)	p
Awareness	-15.8 (3.84)	-4.13 (21)	0.0005	-15.9 (5.38)	-2.97 (21)	0.0074
Annoyance	-10.8 (4.16)	-2.60 (21)	0.017	-9.90 (5.76)	-1.72 (21)	0.100
Loudness	-9.93 (3.90)	-2.55 (21)	0.019	-6.65 (5.36)	-1.24 (21)	0.228

Table 3Regional activity changes for contrast of Incongruent vs. Congruent MSIT stimuli, Tinnitus sample, FDR $p < 0.05$

ROI	Label	Talairach Coordinates			t-score
		x	y	z	
187 *	Left inferior occipital	-46	-63	-5	6.92
63 *	Left occipital (V3/V4)	-32	-84	1	6.69
62 *	Left posterior dorsolateral prefrontal cortex	-39	7	35	6.33
159 *	Right inferior occipital	44	-68	-4	6.21
58 *	Right occipital (V3/V4)	33	-84	-1	6.14
180 *	Right lateral premotor area (medial)	24	-4	59	5.61
44 *	Left superior primary sensory (S1)	-43	-39	54	5.35
122 *	Right occipital (BA18)	25	-86	15	5.2
61 *	Right dorsolateral prefrontal cortex	53	5	25	5.17
31 *	Left superior parietal lobule (7A)	-29	-54	57	5.09
7 *	Left lateral premotor cortex (medial)	-27	-13	60	4.95
32 *	Left lateral central sulcus	-43	-21	58	4.49
134	Left occipital (BA18)	-25	-86	18	4.49
169 *	Left supramarginal gyrus	-35	-45	40	4.47
150 *	Left middle occipital	-21	-81	38	4.43
116 *	Left superior parietal lobule	-15	-68	53	4.17
53 *	Left dorsolateral prefrontal cortex	-54	6	27	4.15
118 *	Right pre-supplementary motor area (SMA)	8	7	64	4.02
130 *	Right superior anterior insula	34	20	10	3.91
186	Right anterior caudate	12	19	9	-3.84
65 *	Left inferior parietal (PF)	-54	-32	41	3.55
81 *	Left inferior temporal	-45	-46	-14	3.55

ROI	Label	Talairach Coordinates			t-score
		x	y	z	
199	Left lateral occipital	-45	-72	9	3.53
196 *	Left nucleus accumbens	-11	16	-2	-3.41
114 *	Subgenual cingulate	0	7	5	-3.36

* ROI was also significantly active for Healthy Normative Sample

Table 4

Regional activity during Baseline contrast of Incongruent vs. Congruent MSIT stimuli predicting change in tinnitus Awareness, FDR p 0.05

ROI	Label	Talairach Coordinates			t-score	p-value	R ²
		x	y	z			
84	Left superior dorsolateral prefrontal cortex	-41	14	48	-4.84	0.0001	0.667
124	Left posterior caudate	-13	17	12	-5.13	0.0001	0.664
104	Right rostromedial prefrontal cortex	9	58	30	-4.25	0.0001	0.610
166	Right superior frontal gyrus	-11	16	62	-4.23	0.0001	0.604
14	Left inferior parietal (PGa)	-47	-56	41	-4.13	0.0001	0.573
129	Right superior dorsolateral prefrontal cortex	23	30	48	-3.84	0.0001	0.543
2	Right posterior dorsolateral prefrontal cortex	37	6	36	-3.73	0.0002	0.522
3	Left anterior dorsolateral prefrontal cortex	-49	27	21	-3.65	0.0003	0.520
157	Right lateral middle occipital	48	-67	28	-3.63	0.0003	0.515
184	Right middle occipital	30	-82	31	-3.54	0.0004	0.509
174	Right fusiform and inferior temporal gyrus	41	-51	-16	-3.56	0.0004	0.501
76	Left posterior inferior parietal	-31	-66	42	-3.41	0.0007	0.490
93	Left posterior middle temporal gyrus	-55	-36	1	-3.23	0.0013	0.463
10	Right superior dorsolateral prefrontal cortex	39	16	48	-3.19	0.0014	0.443
197	Left anterior caudate	-14	3	21	-3.15	0.0017	0.442
115	Right anterior periculate gyrus	6	33	36	-2.94	0.0034	0.413
73	Left anterior ventrolateral prefrontal cortex	-26	57	16	-2.91	0.0036	0.411
51	Left hippocampus (CA) and amygdala	-25	-10	-16	-2.86	0.0043	0.400
101	Right rostral medial prefrontal cortex	46	24	31	-2.79	0.0053	0.399
149	Right fusiform and parahippocampal gyrus	33	-37	-15	-2.89	0.0040	0.396
160	Left frontal eye fields	-26	6	58	-2.79	0.0053	0.374