Radiology

ORIGINAL RESEARCH • HEAD AND NECK IMAGING

Functional MRI Neurofeedback Outperforms Cognitive Behavioral Therapy for Reducing Tinnitus Distress: A Prospective Randomized Clinical Trial

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Conflicts of interest are listed at the end of this article.

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Background: Cognitive behavioral therapy (CBT) is the current standard treatment for chronic severe tinnitus; however, preliminary evidence suggests that real-time functional MRI (fMRI) neurofeedback therapy may be more effective.

Purpose: To compare the efficacy of real-time fMRI neurofeedback against CBT for reducing chronic tinnitus distress.

Materials and Methods: In this prospective controlled trial, participants with chronic severe tinnitus were randomized from December 2017 to December 2021 to receive either CBT (CBT group) for 10 weekly group sessions or real-time fMRI neurofeedback (fMRI group) individually during 15 weekly sessions. Change in the Tinnitus Handicap Inventory (THI) score (range, 0–100) from baseline to 6 or 12 months was assessed. Secondary outcomes included four quality-of-life questionnaires (Beck Depression Inventory, Pittsburgh Sleep Quality Index, State-Trait Anxiety Inventory, and World Health Organization Disability Assessment Schedule). Questionnaire scores between treatment groups and between time points were assessed using repeated measures analysis of variance and the nonparametric Wilcoxon signed rank test.

Results: The fMRI group included 21 participants (mean age, 49 years ± 11.4 [SD]; 16 male participants) and the CBT group included 22 participants (mean age, 53.6 years ± 8.8; 16 male participants). The fMRI group showed a greater reduction in THI scores compared with the CBT group at both 6 months (mean score change, −28.21 points ± 18.66 vs −12.09 points ± 18.86; $P = .005$) and 12 months (mean score change, −30 points ± 25.44 vs −4 points ± 17.2; $P = .01$). Compared with baseline, the fMRI group showed improved sleep (mean score, 8.62 points ± 4.59 vs 7.25 points ± 3.61; $P = .006$) and trait anxiety (mean score, 44 points ± 11.5 vs 39.84 points ± 10.5; $P = .02$) at 1 month and improved depression (mean score, 13.71 points ± 9.27 vs 6.53 points ± 5.17; $P = .01$) and general functioning (mean score, 24.91 points ± 17.05 vs 13.06 points ± 10.1; $P = .01$) at 6 months. No difference in these metrics over time was observed for the CBT group (P value range, .14 to >.99).

Conclusion: Real-time fMRI neurofeedback therapy led to a greater reduction in tinnitus distress than the current standard treatment of CBT.

ClinicalTrials.gov registration no.: NCT05737888; Swiss Ethics registration no.: BASEC2017–00813

Supplemental material is available for this article.

Tinnitus is commonly defined as a phantom auditory perception (often described as "ringing in the ear") in the absence of a corresponding external sound stimulus (1). In Western industrialized countries, up to 10%–15% of the general population are affected (2) and 1%–2% experience severe forms of tinnitus with substantial reduction of quality of life (1). Alongside recent efforts to define a clear consensus for the proper definition of tinnitus (3), the heterogeneity of this condition has also become more widely recognized (4). Several types of tinnitus have been clinically distinguished, the most common descriptors being objective versus subjective, acute versus chronic, primary versus secondary, and pulsatile versus nonpulsatile (5).

Subjective continuous chronic tinnitus without evident underlying structural abnormality is the most common type of tinnitus (6). Despite the high prevalence of chronic tinnitus and the significant associated morbidity, no evidence-based universal cure exists, and currently available therapeutic options are of limited efficacy or inconsistent benefit (7). Cognitive behavioral therapy (CBT) is recognized, to some degree, as the current standard treatment for tinnitus. CBT for tinnitus aims to reduce the distress

Abbreviations

CBT = cognitive behavioral therapy, fMRI = functional MRI, THI = Tinnitus Handicap Inventory

Summary

Patients with severe chronic tinnitus who underwent real-time functional MRI neurofeedback therapy showed reduced tinnitus burden 6 months after intervention compared with patients who received group cognitive behavioral therapy.

Key Results

- In this prospective trial of 43 participants with chronic severe tinnitus, real-time functional MRI (fMRI) neurofeedback therapy led to a greater reduction in Tinnitus Handicap Inventory scores compared with cognitive behavioral therapy 6 months after intervention (mean score change, −28.21 points ± 18.66 [SD] vs −12.09 points ± 18.86; $P = .005$).
- Only participants who underwent real-time fMRI neurofeedback showed improvement in depression and general functioning questionnaire scores 6 months after intervention (mean score range, 13.71 points ± 9.27 to 24.91 points ± 17.05 at baseline vs 6.53 points ± 5.17 to 13.06 points ± 10.1 at 6 months; P value range, .011–.014).

and debilitating impact of the condition by having patients focus on more positive and realistic thoughts but does not directly influence the auditory percept itself (8). In a large randomized controlled clinical trial ($n = 492$) in the Netherlands, a significant improvement in quality of life was reported in patients with tinnitus who underwent CBT compared with those who underwent the usual standard of care, which consisted of audiologic diagnostics and intervention and, if necessary, a maximum of 10 1-hour consultations with a social worker (9).

Previous studies indicate that chronic tinnitus may be associated with excessive activation in the auditory cortex (10–12). Real-time functional MRI (fMRI) neurofeedback is an emerging noninvasive neuroimaging technique that allows patients to learn volitional control over distinct brain areas (13). Taken together, these observations suggest that patients can learn voluntary downregulation of auditory cortex activation by means of fMRI neurofeedback and that this might improve chronic tinnitus, as demonstrated in a previous pilot study (14).

Subsequent studies have been carried out to better understand and optimize the underlying mechanisms and setup of fMRI neurofeedback (15–17), but these studies did not directly compare the efficacy of fMRI neurofeedback against a standard clinical group of patients with chronic tinnitus receiving CBT. Thus, the aim of the current study was to compare the efficacy of fMRI neurofeedback against CBT to reduce chronic tinnitus distress, with the hypothesis that fMRI neurofeedback would outperform CBT.

Materials and Methods

Study Design and Participants

NeuroTin was a prospective, randomized, unblinded controlled clinical trial conducted at the Campus Biotech research center, with participants recruited at Geneva University Hospitals (Geneva, Switzerland). The trial was independently overseen and sponsored by the Wyss Center for Bio and Neuroengineering (Geneva, Switzerland). The sponsor was not involved in data collection and analysis, and the authors had control over the data and the information submitted for publication. The protocol was approved by the Swiss cantonal scientific ethics committee in Geneva (registration no. BASEC2017–00813) and registered with ClinicalTrials.gov (registration no. NCT05737888). The trial was performed in accordance with principles of the Declaration of Helsinki. All participants provided written informed consent prior to enrollment.

Patients aged 18–80 years with continuous, persistent, moderate to severe (Tinnitus Handicap Inventory [THI] score ≥48 [range, 0–100] at baseline) nonpulsatile chronic tinnitus, with a duration of at least 6 months, and functional hearing with normal inner ear structure and normal tympanic membrane mobility were eligible for enrollment. Patients presenting with contraindications to MRI (eg, noncompatible cochlear implant, pacemaker, implanted deep brain stimulation device); conductive hearing loss exceeding 20 dB at two or more frequencies; known systemic disease (eg, vestibular schwannoma, endolymphatic hydrops); lesion in the central nervous system; history of several craniocerebral trauma; acute ear canal or middle ear inflammation or effusion; significant neurologic or psychiatric disease; substance abuse or acute allergic disease; ongoing medication known to treat, influence, or cause tinnitus (eg, high-dose aspirin, quinidine, aminoglycosides); ongoing or recent (<4 weeks) alternative tinnitus therapy (eg, tinnitus maskers, acupuncture); participation in another pharmacologic study; or pregnancy were excluded from participation. Eligible patients were asked to be willing, able, and available to participate in the entire research study. Enrolled participants were able to withdraw from the study at any time without providing a specific reason. The fMRI neuroimaging data from this cohort and the trial protocol have been previously described (18), but clinical outcomes have not been reported.

Participants were randomized into the CBT, fMRI, or electroencephalographic neurofeedback groups according to a minimization procedure based on a minimal probability score (detailed in Appendix S1) in a 1:1:1 ratio accounting for age, sex, THI score at baseline, tinnitus duration in months, and percentage of hearing loss (Fig 1). The trial timeline is summarized in Figure 2. The entire trial lasted from July 2017 to December 2022. The electroencephalographic neurofeedback data collection encountered delays due to the pandemic outbreak and will be published separately.

All groups underwent clinical assessment at baseline (within 1 month after enrollment), and postintervention assessments were conducted within 1 month after intervention (early time point) and within 6 months after intervention (late time point). During postintervention assessments, all questionnaires were administered (THI [19], Beck Depression Inventory [20], Pittsburgh Sleep Quality Index [21], State-Trait Anxiety Inventory [22], and World Health Organization Disability Assessment Schedule 2.0 [23]) and full examinations with audiometry and tinnitometry were performed. For the THI, a preassessment evaluation was also performed if more than 4 weeks had elapsed between baseline and the planned start

of intervention. Additionally, long-term THI follow-up assessments (within 12 months after intervention) were collected using an online reporting platform. Enrollment and clinical evaluations were performed by trained ear, nose, and throat specialists from Geneva University Hospitals (D.D., L.G., J.V., F.V., P.S.).

Real-time fMRI Neurofeedback

Real-time fMRI neurofeedback was performed in individual participants with a Siemens MAGNETOM Prisma 3-T MRI scanner (N.G., a neuroscientist with 5 years of experience). Double acoustic protection (in and over ear) was provided. During the first session, an auditory functional localizer (Fig S1) was used to delineate the bilateral auditory cortex regions of interest for each participant, which is needed for subsequent fMRI neurofeedback therapy (14,17). During the therapy, the average activity of the individual bilateral auditory cortex was visually presented to the participants as a thermometer bar on an MRI-compatible screen through a mirror mounted on the head coil (Fig 2A). During each of the 15 weekly sessions, six to seven fMRI neurofeedback runs of 6.5 minutes were performed, each consisting of six downregulation and seven rest blocks of 30 seconds, respectively. The fMRI neurofeedback training schedule is shown in Figure S2, and additional details of the procedure are available in Appendix S1.

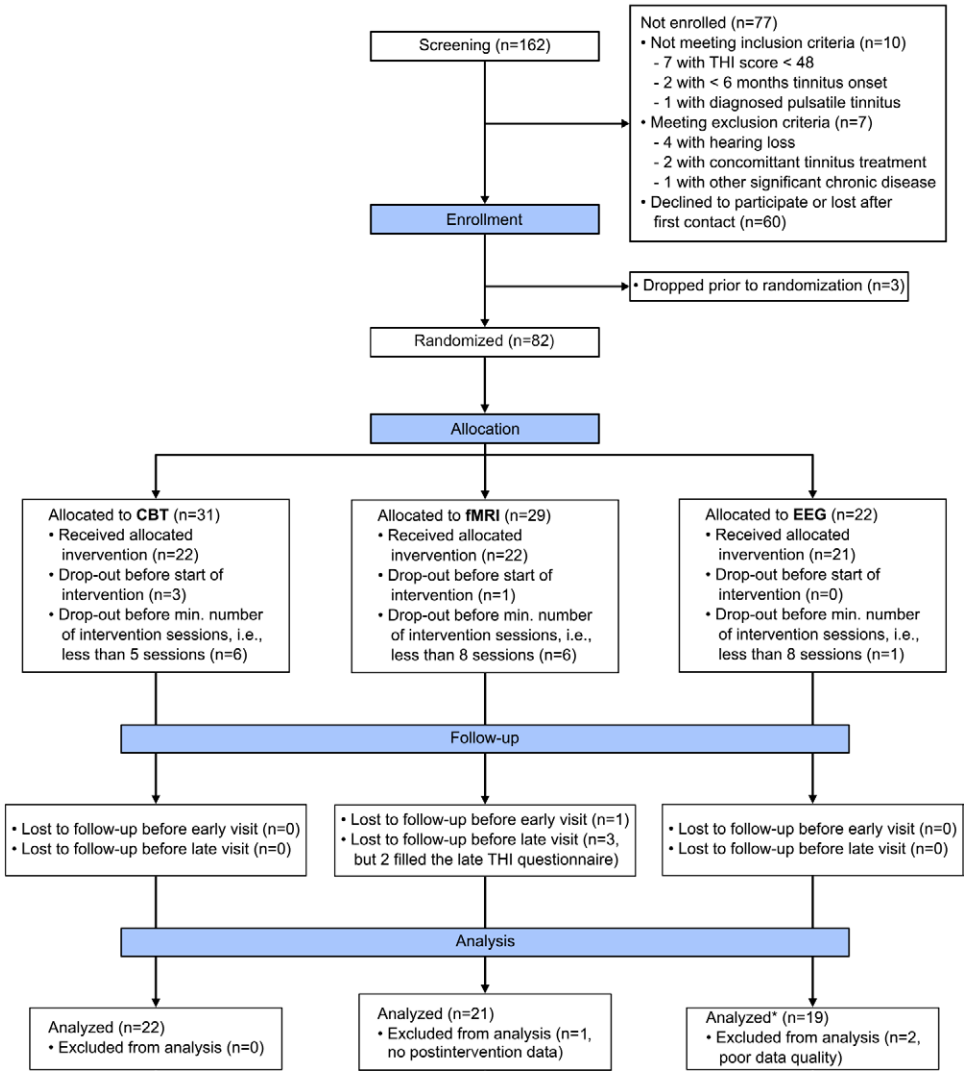

Figure 1: Flowchart shows participant inclusion and exclusion in the NeuroTin clinical trial (ClinicalTrials.gov no. NCT05737888, Swiss Ethics no. BASEC2017–00813). CBT = cognitive behavioral therapy, EEG = electroencephalography, fMRI = functional MRI, min. = minimum, THI = Tinnitus Handicap Inventory. * = Electroencephalographic neurofeedback data are not presented in this report and will be published separately.

Cognitive Behavioral Therapy

CBT was carried out in a group setting by two experienced board-certified psychologists (C.L.R., A.S.) at Geneva University Hospitals, following standard clinical routine (24). Groups of three to four participants were treated over 10 weekly sessions that lasted 120 minutes each. An important part of the intervention consisted of sharing experiences and discussing individual coping strategies. Tinnitus-related topics covered in these sessions are reported in Figure 2E. Participants were encouraged to complete homework assignments to facilitate understanding and practice. Additional details of the CBT procedure are available in Appendix S1.

Outcomes

The primary outcome was the change in THI score from baseline to 6 months after intervention. The THI score ranges from 0 to 100, with higher scores indicating more severe tinnitus burden and a seven-point change representing a minimal clinically important difference (19). Secondary outcomes were changes from baseline to 6 months in the Beck Depression Inventory score (range: 0–63, with higher scores indicating more severe depression and a five-point change representing a minimal clinically important difference [20]), Pittsburgh Sleep Quality Index score (range: 0–21, with higher scores indicating worse sleep quality [21]), State-Trait Anxiety Inventory score (range: 20–80, with higher scores indicating elevated anxiety [22]), and World Health Organization Disability Assessment Schedule score (range: 0–100, with higher scores indicating worse overall functioning [23]). Additional secondary outcomes included changes in audiometric results before and after intervention and, in participants in the fMRI neurofeedback group, auditory

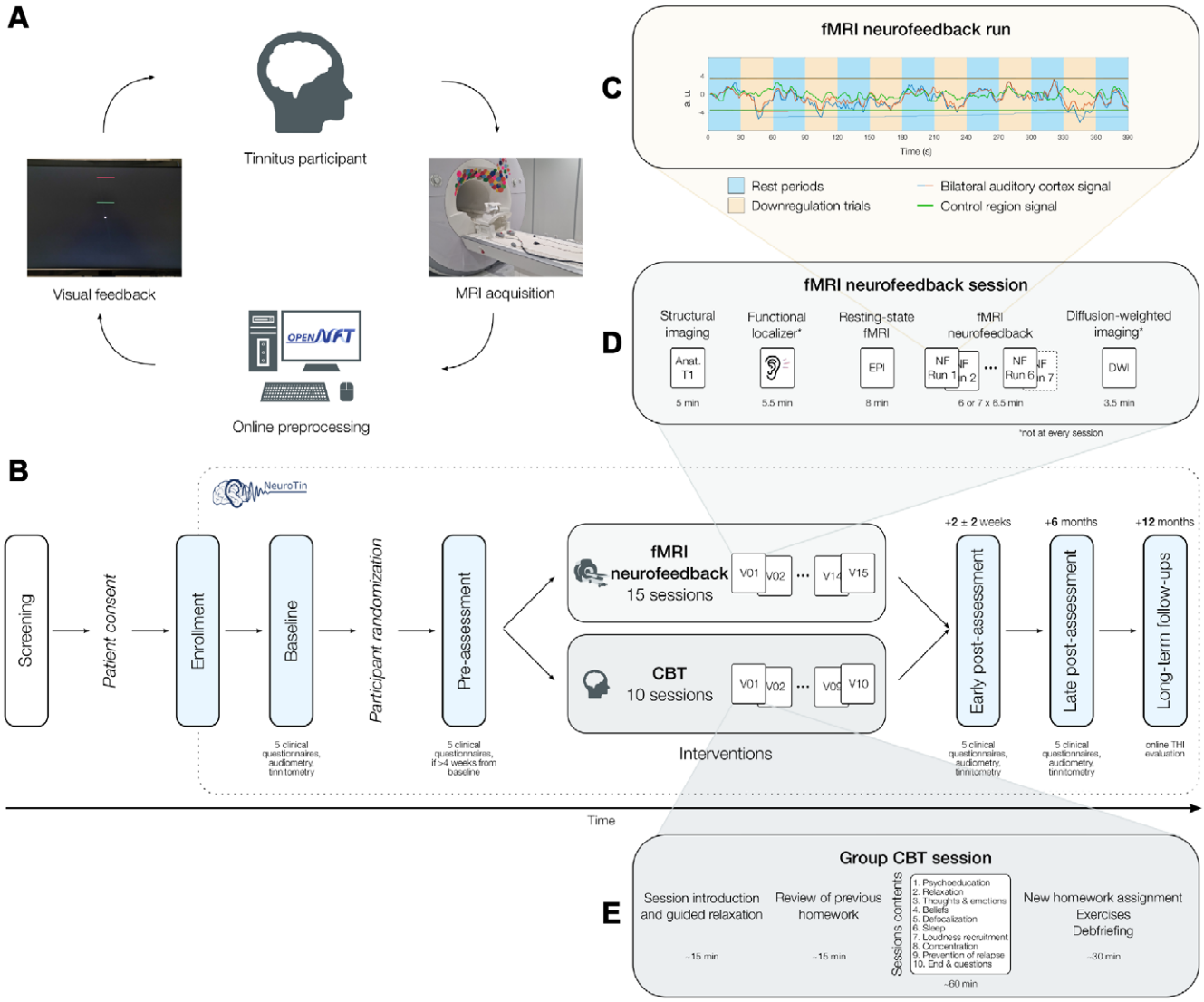

Figure 2: Clinical trial procedural components. **(A)** Schematic shows the closed-loop real-time functional MRI (fMRI) neurofeedback training in which individual participants received real-time visual feedback while lying in the MRI scanner. **(B)** Schematic shows the full clinical trial timeline. **(C)** Graph shows the structure of a single fMRI neurofeedback run. Participants were asked to downregulate bilateral auditory cortex during six 30-second trials per run, interleaved with seven 30-second rest periods. **(D)** Schematic shows the structure of a single fMRI neurofeedback session. Structural imaging, resting-state fMRI, and fMRI neurofeedback were performed at every session. * = Auditory functional localizers and diffusion-weighted imaging were performed at sessions 1 and 15. **(E)** Schematic shows the structure of the group cognitive behavioral therapy (CBT) sessions, including the main topic (session contents) covered in each of the 10 sessions. Anat. = anatomic, a.u. = arbitrary units, EPI = echo-planar imaging.

cortex activity throughout the intervention. To evaluate auditory cortex deactivation after fMRI neurofeedback, standard fMRI data preprocessing steps were performed and are described in Appendix S1. Adverse effects, including tinnitus perception after MRI, as well as general acceptance of intensive neurofeedback sessions by the participants, were monitored throughout the intervention through clinical surveillance and individual debriefing after each session.

Statistical Analysis

The sample size was determined based on the previous literature (13) and using the estimated dropout rate of 20%–30% from our previous studies (14–17). Given the duration of the planned interventions, a total of 90 participants were set as the enrollment goal, considering the dropout margin. Superiority of fMRI neurofeedback compared with CBT was defined as a significant difference in THI scores from baseline to 6 months between the two groups ($P < .05$, Bonferroni-corrected for multiple comparisons). The Levene test was used to assess homogeneity of variances between groups, and repeated measures analysis of variance and the nonparametric Wilcoxon signed rank test (all Bonferroni-corrected for multiple comparisons) were conducted to assess the reduction in symptoms over time based on questionnaire scores. All statistical and neuroimaging data analyses were performed by an author (N.G.) using customized code written in MATLAB (version R2019b; MathWorks) and with the Statistical Parameter Mapping toolbox (version 12; Wellcome Centre for Human Neuroimaging). The code repository is available on GitHub *(https://github.com/ngs5/neurotin)*. Additional details of the statistical analyses are described in Appendix S1.

Results

Participant Characteristics

Of 162 patients screened, 10 were excluded due to not meeting the inclusion criteria (seven with a THI score <48 at baseline, two with symptoms for <6 months, and one with diagnosed pulsatile tinnitus), seven were excluded for meeting exclusion criteria (four with significant hearing loss, two with concomitant tinnitus treatment, and one with another significant chronic disease), and 60 declined to participate in the study or were lost after first contact (Fig 1). After enrollment, three participants dropped out. A total of 82 participants underwent randomization; however, four participants dropped out before the start of intervention and 13 dropped out before completing the minimum number of intervention sessions. Thus, the fMRI neurofeedback group included 21 participants (mean age, 49 years ± 11.4 [SD]; 16 male and five female participants), the CBT group included 22 participants (mean age, 53.6 years ± 8.8; 16 male and six female participants), and the remaining participants were part of the electroencephalographic neurofeedback group, which will be reported in a future article. The mean therapy time per participant per group did not significantly differ between the CBT (101.2 days ± 46) (Table S1) and fMRI neurofeedback (124.1 days ± 48.6; P = .12) (Table S2) groups. In the fMRI neurofeedback group, one participant was lost to follow-up before the early postintervention assessment and three participants were lost to follow-up before the late postintervention assessment (although two of them completed the THI). All participants were naive to fMRI neurofeedback (no overlap with the previous pilot study [14]). Participant characteristics at baseline are summarized in the Table. For the fMRI neurofeedback group, reasons for withdrawal are shown in Table S3, average audiometric profiles per group are shown in Figure S3, results

Baseline Demographic and Clinical Characteristics of Participants

Characteristic	fMRI Group (n = 21)	CBT Group (n = 22)	P Value
Age (y)	49 ± 11.4	53.6 ± 8.8	.15
Sex			.99
F	5 (24)	6 (27)	
M	16 (76)	16 (73)	
Quality-of-life assessment			
THI score*	67.8 ± 12.6	65.5 ± 12.8	.56
BDI score†	13.7 ± 9.3	12 ± 9.9	.57
PSQI score‡	8.6 ± 4.6	8.1 ± 4.1	.71
STAI score§			
Form Y1	40.5 ± 12.7	40.8 ± 10.3	.93
Form Y2	44 ± 11.5	40.5 ± 9	.28
WHODAS score‖	24.9 ± 17.1	16.8 ± 12	.08
Tinnitus			
Duration (y)	8.8 ± 11.6	9.7 ± 12.4	.81
Frequency (kHz)			
Left	5.9 ± 2.1	5.7 ± 2.4	.77
Right	6.2 ± 2	5.6 ± 2.8	.42
Intensity (dB HL)			
Left	44.9 ± 26.2	50.6 ± 23.5	.46
Right	45.5 ± 18.2	44.1 ± 26.2	.84
Intensity score#			
Left	6.5 ± 1.4	6.9 ± 2.3	.49
Right	5.9 ± 2	6.7 ± 2.2	.22
Laterality			.96
Left	4 (19)	3 (14)	
Right	1 (5)	2 (9)	
Bilateral	16 (76)	17 (77)	
Pure tone average (dB)			
Left	13 ± 9.5	20.4 ± 13.2	.05
Right	10.6 ± 6.6	17.3 ± 12.5	.07

Note.—Categorical data are reported as numbers of participants, with percentages in parentheses, and continuous data are reported as means ± SDs. Categorical data were compared between groups using the Fisher exact test, and continuous data were compared between groups using the Student t test or nonparametric Mann-Whitney U test. BDI = Beck Depression Inventory, CBT = cognitive behavioral therapy, fMRI = functional MRI, PSQI = Pittsburgh Sleep Quality Index, STAI = State-Trait Anxiety Inventory, THI = Tinnitus Handicap Inventory, WHODAS = World Health Organization Disability Assessment Schedule.

* Scores on the 25-item THI range from 0 to 100, with higher scores indicating more distress experienced because of tinnitus, as follows: 0–16, slight or no handicap (grade 1); 18–36, mild handicap (grade 2); 38–56, moderate handicap (grade 3); 58–76, severe handicap (grade 4); and 78–100, catastrophic handicap (grade 5; minimal clinically significant difference, seven points).

† BDI scores range from 0 to 63, with higher scores indicating more severe depression (minimal clinically significant difference, five points).

‡ PSQI scores range from 0 to 21, with higher scores indicating worsened sleep quality.

§ Scores on both subscales of the STAI range from 20 to 80, with higher scores indicating an increased state anxiety (situation-based anxiety, form Y1) or trait anxiety (long-term anxiety, form Y2).

‖ WHODAS 2.0 scores range from 0 to 100, with higher scores indicating a worsened general functioning in six different domains of life (cognition, mobility, self-care, interaction with others, life activities, and community participation).

Intensity refers to subjective tinnitus loudness rated on a scale from 0 to 10, with higher scores indicating louder tinnitus perception.

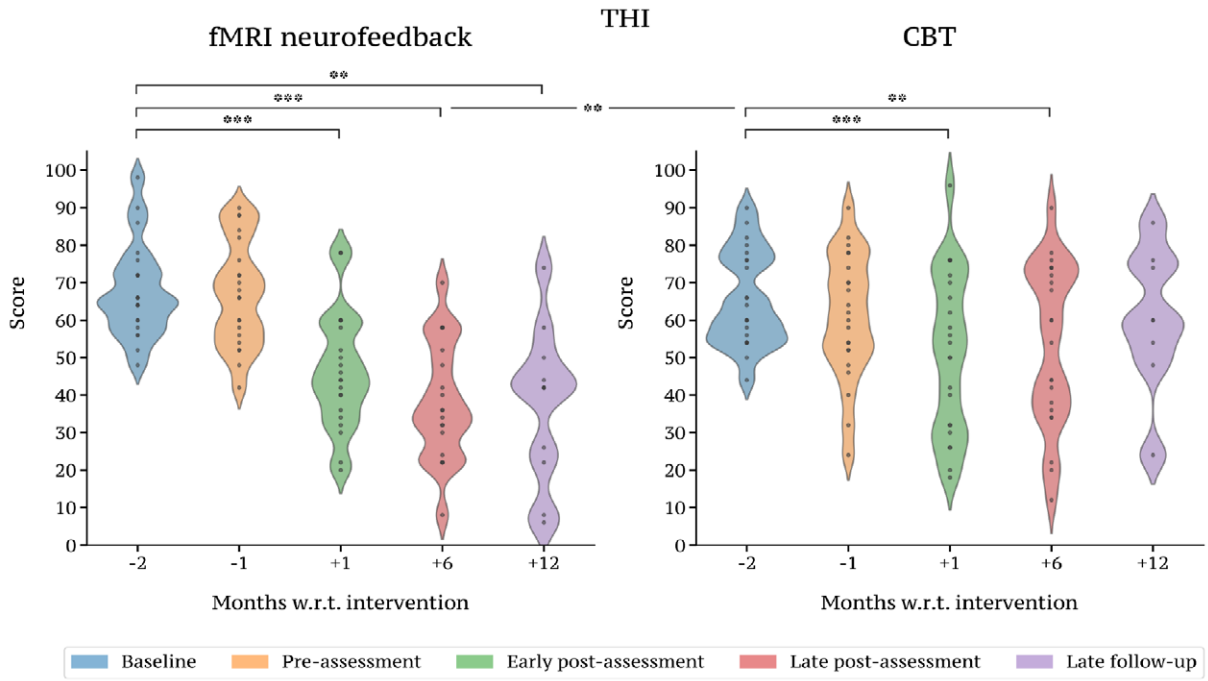

Figure 3: Changes in tinnitus distress over time. Violin plots show the Tinnitus Handicap Inventory (THI) scores (primary outcome) for participants in the real-time functional MRI (fMRI) neurofeedback group (n = 21) and cognitive behavioral therapy (CBT) group (n = 22) from baseline (2 months before intervention) to late follow-up (12 months after intervention). Compared with baseline, THI scores were reduced after fMRI neurofeedback at assessments 1 month (P < .001), 6 months (P < .001), and 12 months (P = .002, n = 11) after intervention. THI scores were also reduced at assessments 1 month (P < .001) and 6 months (P = .004) after CBT, but no difference was observed at 12 months (P = .28, n = 8). Compared with participants treated with CBT, those treated with fMRI neurofeedback showed a greater reduction in THI scores at the primary end point (6 months after intervention, P = .005), but not directly after cessation of intervention (1 month after intervention, P = .1). A wide or narrow section of the plot indicates a higher or lower density of individual data points. Note that limited follow-up data are available at 12 months after intervention. ** = .001 ≤ P ≤ .01, *** = P < .001 (Bonferroni-corrected for multiple comparisons). w.r.t. = with respect to.

of hearing loss comparative analyses are shown in Figure S4, and tinnitus etiologies are shown in Table S4.

Primary Outcome and Follow-up Assessment

From baseline to 1 and 6 months after intervention, the mean THI score decreased by −21.43 points ± 18.39 (P < .001) and −28.21 points ± 18.66 (P < .001), respectively, in the fMRI neurofeedback group and −14.27 points ± 16.7 (P < .001) and −12.09 points ± 18.86 (P = .004) in the CBT group (Fig 3). While the change in THI score over time for both groups exceeded the minimal clinically important difference, participants in the fMRI neurofeedback group achieved comparable and greater improvement than those in the CBT group at 1 (P = .1) and 6 (P = .005) months after intervention. At 12 months, the THI score of participants in the fMRI neurofeedback group (mean score, 37.64 points ± 20.61) remained lower compared with baseline (mean score, 67.81 points ± 12.55; P = .002, n = 11) (Fig 3), whereas no difference in THI scores was observed for participants in the CBT group between baseline (mean score, 65.55 points ± 12.77) and 12 months (mean score, 60.25 points ± 19.29; P = .28, n = 8). Additionally, the greater improvement for participants in the fMRI neurofeedback group (mean score change, −30 points ± 25.44) than for those in the CBT group (mean score change, −4 points ± 17.2) lasted at 12 months compared with baseline (P = .02), albeit with a lower available sample size.

Secondary Outcomes

Compared with baseline, participants in the fMRI neurofeedback group showed lower Pittsburgh Sleep Quality Index (mean score, 8.62 points ± 4.59 vs 7.25 points ± 3.61; P = .006, n = 20) and State-Trait Anxiety Inventory (mean score, 44 points ± 11.5 vs 39.84 points ± 10.5; P = .02, n = 19) scores within 1 month after intervention and lower Beck Depression Inventory (mean score, 13.71 points ± 9.27 vs 6.53 points ± 5.17; P = .01, n = 19) and World Health Organization Disability Assessment Schedule 2.0 (mean score, 24.91 points ± 17.05 vs 13.06 points ± 10.1; P = .01, n = 20) scores at 6 months after intervention (Fig 4). For participants in the CBT group, no difference in any questionnaire scores was observed between baseline and follow-up (P value range, .14 to >.99). The average activity of the left and right auditory cortex (mean t score across all overlapping individual masks, −0.83 ± 1.74 and −2.02 ± 1.6, respectively) was downregulated in the fMRI neurofeedback group (Fig 5).

Safety

No adverse effects related to tinnitus distress were reported in the fMRI neurofeedback group after intervention. All participants who completed fMRI neurofeedback therapy tolerated the MRI environment. Only two of eight participants from the fMRI neurofeedback group who dropped out of the study (Table S3) reported possible concerns about MRI-related noise.

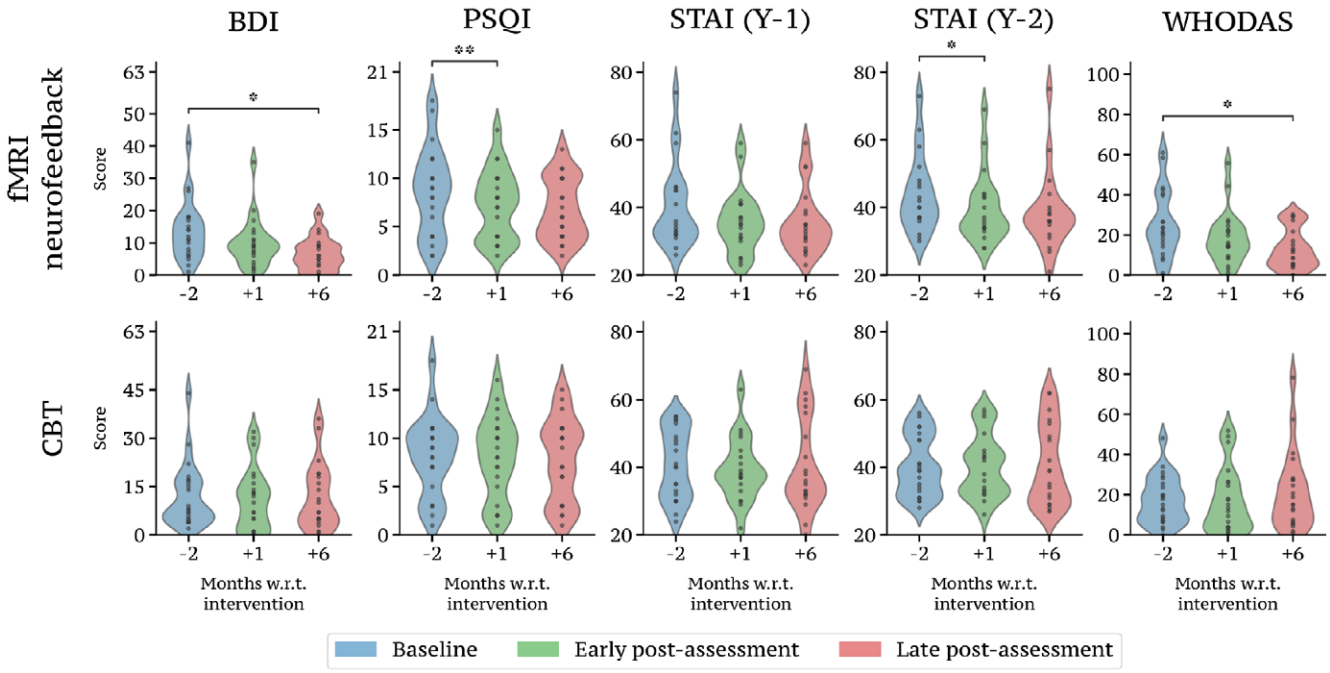

Figure 4: Changes in quality of life over time. Left to right: Violin plots show the depression, sleep, state and trait anxiety, and general functioning scores (secondary outcomes) for participants in the real-time functional MRI (fMRI) neurofeedback group (n = 21) and cognitive behavioral therapy (CBT) group (n = 22) from baseline (2 months before intervention) to late postassessment (6 months after intervention) time points. Compared with baseline, participants who underwent fMRI neurofeedback showed improvement in depression (measured using the Beck Depression Inventory [BDI]; P = .01, n = 19) and general functioning (measured using the World Health Organization Disability Assessment Schedule 2.0 [WHODAS]; P = .01, n = 20) at 6 months. Between baseline and 1 month after intervention, participants who underwent fMRI neurofeedback also showed improvement in trait anxiety (measured using the State-Trait Anxiety Inventory [STAI] form Y2; P = .02, n = 19) and sleep (measured using the Pittsburgh Sleep Quality Index [PSQI]; P = .006, n = 20). No differences in questionnaire scores were observed for the CBT group (P value range, .06–.96). A wide or narrow section of the plot indicates a higher or lower density of individual data points. For a few incomplete questionnaires, scores could not be computed. * = P < .05, ** = .001 ≤ P ≤ .01 (Bonferroni-corrected for multiple comparisons). w.r.t. = with respect to.

Discussion

Previous studies (14–17) suggested that real-time functional MRI (fMRI) neurofeedback could be used as an efficient noninvasive therapy for patients with chronic tinnitus to downregulate excessive neuronal activity in the auditory cortex (10–12). In the current study, we investigated whether prolonged treatment of 15 fMRI neurofeedback sessions could yield a better clinical benefit in longer-term alleviation of tinnitus distress, compared with the more established treatment of cognitive behavioral therapy (CBT). In this prospective controlled trial, fMRI neurofeedback administered in individuals outperformed CBT administered in a group setting, with significant and persisting reduction of tinnitus burden as measured using the Tinnitus Handicap Inventory (THI) questionnaire at 6 months (P = .005) and 12 months (P = .01) after intervention. Although appreciated by most participants, CBT received in small groups was effective in the short term, but clinical benefit did not last at 12 months. General functioning (World Health Organization Disability Assessment Schedule mean score, 24.91 points ± 17.05 at baseline vs 13.06 points ± 10.1 at 6 months; P = .01) and depression (Beck Depression Inventory mean score, 13.71 points ± 9.27 at baseline vs 6.53 points ± 5.17 at 6 months; P = .01) were also improved in the fMRI neurofeedback group 6 months after intervention.

Despite the widespread use of CBT to treat tinnitus, our results are in line with recent literature (24) in which the efficacy of CBT is established immediately after intervention (25), but with overall low certainty of evidence for efficacy at 6 months or later (9,24). In our study, the THI score remained significantly decreased compared with baseline in the CBT group at 6 months (mean score, 65.55 points ± 12.77 vs 53.45 points ± 21.89; P = .004), but this benefit did not last at 12 months (P = .28), albeit with a smaller sample size.

The improvements observed in participants with tinnitus who underwent fMRI neurofeedback therapy in this study are highly encouraging, especially given that the most widely accepted drug treatment against tinnitus, ginkgo biloba, was not found to have a clear beneficial effect in a recent systematic review (26). Similarly, meta-analyses on other treatment methods, such as ozone therapy (27), intratympanic dexamethasone treatment (28), or transcranial direct current stimulation (29), have also not shown conclusive results. Some therapy forms, such as tinnitus retraining therapy (30) or yoga and meditation (31), showed a mild benefit; however, the studies were limited by a high risk of nonresponse bias. The beneficial effects observed with tinnitus retraining therapy or yoga and meditation are, however, in line with the fMRI neurofeedback results as the underlying strategies contain similar approaches of active mental downregulation of tinnitus. It seems that repeated visual feedback after successful downregulation of the auditory cortex, as observed in our study, is particularly helpful for affected individuals. Other auditory treatments, either

alone or in combination with sensory stimulation and counseling, have been evaluated to alleviate tinnitus. Proposed interventions include hearing aids, sound generators, and devices that combine both. By amplifying external sounds, hearing aids improve communication and may reduce tinnitus awareness, refocus attention, and lead to auditory cortex reorganization. Sound generators may reduce tinnitus audibility, inducing immediate relief and relaxation. However, there is currently insufficient evidence to support these treatments over waiting list comparison, placebo, or education (32,33). Cochlear implantation, particularly for patients with tinnitus and severe hearing loss, led to reduction or complete suppression of tinnitus in 50% and 25%, respectively. A meta-analysis of 11 studies demonstrated a mean THI reduction of 23.2 points at an average follow-up of 8.1 months after implantation (34). Bimodal neuromodulation, which combines sound with electrical stimulation of somatosensory pathways, has been proposed to enhance brain plasticity, thus improving tinnitus (35). Tongue stimulation combined with sound stimulation resulted in a mean THI reduction of 14.2 points within 6–12 weeks of self-administered treatment, sustained at 12.7 points at 12 months (36). Currently, none of these treatments are unanimously recommended by clinical practice guidelines (37).

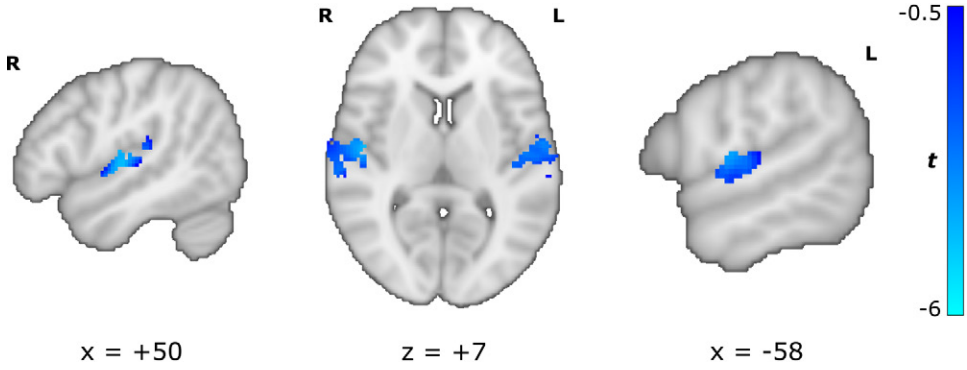

Figure 5: Downregulation of bilateral auditory cortex in the real-time functional MRI (fMRI) neurofeedback group. Activation contrast images (overlaid on a standard Montreal Neurological Institute brain template) show the *t* score of average downregulation of targeted bilateral auditory cortex activity for 21 participants in the fMRI neurofeedback group, across 1990 runs, at indicated coordinates in the Montreal Neurological Institute space. L = left, R = right, x = sagittal plane, z = axial plane.

The current study had several limitations. First, the lack of standardization across both interventions, notably a different number of sessions and an individualized (fMRI) versus group (CBT) setting, could represent systematic bias. Second, the fMRI neurofeedback protocol was determined based on previous experience and limited available literature in the field (13–17), and with no existing consensus at the time (38). The successful choice of parameters may still be improved in future larger-scale studies, including an optimized number and duration of sessions, as well as intersession time interval, and the potential for silent fMRI sequences that would not interact with the tinnitus percept. Finally, some differences in hearing loss (pure tone average values in the Table) between both groups, albeit in lower frequencies than the tinnitus percepts, may have also introduced a bias in favor of the fMRI neurofeedback group. On the other hand, CBT was offered in quiet group sessions, in contrast to the noise associated with an MRI environment. Improved clinical protocols, including those for electroencephalographic neurofeedback (39), may help to increase the scalability and decrease the cost of neurofeedback interventions for chronic tinnitus by further incorporating combined fMRI and electroencephalographic recordings.

In conclusion, participants with chronic tinnitus who underwent functional MRI (fMRI) neurofeedback therapy, individually, showed reduced tinnitus burden and improvement in quality of life up to 12 months after treatment, while such improvements were less for participants who underwent cognitive behavioral therapy in small groups. Despite the promising results of this study, fMRI neurofeedback is limited by its technical complexity and associated costs. However, given the significant morbidity of severe chronic tinnitus and the absence of efficient therapeutic options today, there may be a place for fMRI neurofeedback therapy for highly affected patients.

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