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

Gninenko, Nicolas; Trznadel, Stéphanie; Daskalou, Dimitrios; Gramatica, Luca; Vanoy, Julie; Voruz, François Jean Albert; Robyn, Claudia Lardi; Spadazzi, Anne; Yulzari, Aude; Sitaram, Ranganatha; Van De Ville, Dimitri; Senn, Pascal; Haller, Sven

10.1148/radiol.231143

Appendix S1

Detailed Trial Procedures and Clinical Assessments

Patients were screened by experienced ear-nose-throat (ENT) specialists (D.D., L.G., J.V., F.V., P.S.) at the Geneva University Hospital (Geneva, Switzerland) according to strict inclusion and exclusion criteria (see main manuscript). Prior to enrollment, written informed consent was obtained from all patients, specifying the exclusion of any invasive procedure. After initial screening, all enrolled participants attended a baseline visit at the local hospital, during which the five (one primary and four secondary) clinical questionnaires (Tinnitus Handicap Inventory [THI] (19), Beck's Depression Inventory [BDI] (20), Pittsburgh Sleep Quality Index [PSQI] (21), State-Trait Anxiety Inventory [STAI] (22), and World Health Organization Disability Assessment Schedule 2.0 [WHODAS] (23)) were filled, and audiological tests (audiometry and tinnitometry) were performed. Participants then underwent randomization into one of the 3 experimental arms (cognitive behavioral therapy [CBT], real-time functional magnetic resonance imaging [fMRI] neurofeedback, or electroencephalography [EEG] neurofeedback—see Fig 1). A minimization procedure (40) was used for randomization in a 1:1:1 ratio accounting for age, gender, THI at baseline, tinnitus duration in months, and percentage of hearing loss (calculated according to the Council on Physical Therapy, American Medical Association [CPT-AMA] definition (41), which weights the hearing thresholds at 0.5, 1, 2, and 4 kHz according to their importance for speech understanding). For every new participant assignment, a probabilities vector for all those matching variables was computed for each group using a nonparametric Kruskal-Wallis test. A treatment assignment probability computed using a χ^2 goodness-of-fit test was also added to the probabilities vector. Then, the allocation probability for each group was computed as the minimal probability across the respective vector, normalized by the sum of all minimal probabilities for all groups. The final assignment of the new participant was then performed using a uniformly distributed ($0 \leq P \leq 1$) pseudorandom number (function *rand* in MATLAB R2019b, The MathWorks Inc., USA) generator. Investigators were blinded to the randomization, which was performed by a collaborator external to the study. Due to the COVID-19 pandemic, the acquisition of the EEG neurofeedback data were completed with increased delays and will be published separately. Up to 2 weeks before the first experimental visit, participants were once again asked to fill out the THI questionnaire during the preassessment visit, if more than 4 weeks had elapsed between baseline and planned start of intervention (ie, first visit). The same clinical assessments, as well as audiological tests, were also performed within 1 (early) and 6 (late) months after the end of the last experimental visit. Long-term follow-ups (only the THI questionnaire) were completed online by the participants every 4.5 ± 1.5 month after the late postassessment, up to 5 times, when not lost to follow-up. Participants were able to withdraw from the study at any given time, without providing a valid reason.

Detailed fMRI Neurofeedback Methods

Experimental Procedure and Design

Participants of the real-time fMRI neurofeedback group attended 15 weekly MRI visits spread over 3 to 4 months, each consisting of 6 to 7 fMRI neurofeedback runs. The number of runs per visit was defined during the first visit—participants were able to choose between a fixed amount of 6 or 7 runs per visit, respectively, depending on perceived fatigue. From time to time, up to 2 visits per week were scheduled to conceal with participants' long-term availabilities. Upper time limit between 2 consecutive MRI visits was set to 4 weeks. Details of the fMRI neurofeedback training per participant are summarized in Table S2. All MRI visits began with an anatomic T1 scan to obtain a high-resolution template for subsequent fMRI neurofeedback training. The experimental design of acquisition sequences is illustrated in Figure S2. The experimental procedure and design are also detailed according to the recently adopted CRED-NF checklist ("Consensus on the Reporting and Experimental Design of clinical and cognitive-behavioral NeuroFeedback studies") (18,38).

Data Acquisition

For each participant, high-resolution structural MRI, auditory functional localizers, resting-state fMRI, deformation (b_0) field maps, fMRI neurofeedback, and diffusion-weighted imaging (DWI) data were acquired by N.G. (neuroscientist with 5 years of experience) on a Siemens Prisma 3-T scanner with a 64-channel head and neck coil at the Campus Biotech research facility (Geneva, Switzerland). Anatomic imaging was performed using a T1 magnetization prepared rapid gradient echo (MPRAGE) sequence with a generalized auto-calibrating partially parallel acquisition (GRAPPA, acceleration factor = 2) sequence with repetition time (TR) = 2300 ms, anterior to posterior phase encoding, echo time (TE) = 2.25 ms, inversion time (TI) = 900 ms, resolution (x × y × z) = 208 × 256 × 256, flip angle (FA) = 8°, isotropic voxel size = 1.0 mm^3 (208 volumes, ~ 5 min). Deformation field maps were acquired with TR = 627 ms, anterior to posterior phase encoding, TE_1 = 5.19 ms, TE_2 = 7.65 ms, 106 × 106 × 64 without gap, FA = 60°, isotropic voxel size = 2.0 mm^3 (192 volumes, ~ 3 min). All other functional data (localizers [230 volumes, ~ 5.5 min], resting-state fMRI [320 volumes, 8 min], and fMRI neurofeedback [270 volumes per run, ~ 6.5 min per run]) were acquired using an interleaved multislice echo planar imaging (EPI) sequence (acceleration factor = 4), with TR = 1500 ms, anterior to posterior phase encoding, TE = 31 ms, 108 × 108 × 64 without gap, FA = 64°, isotropic voxel size = 2.0 mm^3. Functional acquisition parameters (eg, in-plane resolution, number of z-slices, TR) were optimized according to the real-time data export and processing capabilities of the real-time computer at the MRI facility, to ensure that no lag would accumulate during visual feedback presentation, balanced with an acceptable coverage of the brain (18). DWI was acquired with an interleaved multislice sequence (acceleration factor = 6) with 30 directions, b_0 = 1000 s/mm^2, TR = 4500 ms, anterior to posterior phase encoding, TE = 60 ms, 150 × 150 × 96 without gap, isotropic voxel size = 1.5 mm^3 (420 volumes, ~ 3.5 min). Physiologic data (breathing belt and photoplethysmography) were additionally acquired during all functional acquisitions using BIOPAC MP150 (RSP100C amplifier, BIOPAC Systems, Inc., Goleta, USA) and the AcqKnowledge 4.4.1 software for further offline preprocessing. During resting-state fMRI, participants were instructed to close their eyes. The latter was monitored with an EyeLink 1000+ eye tracker (SR Research, Canada).

Real-time fMRI Neurofeedback Setup

The real-time fMRI neurofeedback training paradigm was implemented in OpenNFT 1.0, an open-source fMRI neurofeedback training software previously developed in the laboratory (42).

Minimal online preprocessing is described in detail in the referenced manuscript and was not significantly modified. It included motion correction, extraction of the time courses from trained regions of interest (ROIs), and removal of signal drift, spikes, and high frequency noise. Customized scripts (SPM12 (43), www.fil.ion.ucl.ac.uk/spm; MATLAB 2016b, The MathWorks Inc., USA) were written to automatically perform visit-wise anatomic volume reconstruction, previous visit's ROIs remapping, visit-wise functional (EPI) template creation, and OpenNFT parameters' initialization before fMRI neurofeedback training. The new functional (EPI) template was created at each visit using the first 15 exported functional volumes during the preceding resting-state fMRI acquisition. These were realigned, coregistered to the new anatomic template, and the mean volume was then used as the new functional (EPI) template in OpenNFT. ROIs from the preceding visit were then realigned through the remapping of the previous to new functional (EPI) template for visits 2 to 15. The real-time fMRI neurofeedback setup was extensively tested with pilot healthy subjects to ensure that no lag would accumulate in between the real-time export of functional volumes and visual feedback presentation (18). The setup ran on the real-time computer of the MRI facility, a Dell Precision Tower 5810, Intel Xeon E5–1650 v3 (3.5 GHz), with 32 Gb RAM, a NVIDIA Quadro K5200 (8 Gb RAM), on Windows 7.

Auditory Functional Localizers

During auditory functional localizers, participants were instructed to remain still and focus on a white cross presented on a gray background on the MR-compatible screen. Delineation of auditory fMRI neurofeedback target ROIs was adapted from previous studies in the field (14,17): a 1 kHz tone modulated at 6 Hz was delivered bilaterally in the scanner using pneumatic earphones in a 5-blocks auditory stimulation paradigm lasting 30 s each (starting and ending with a rest period; MR Confon Starter f MKII+, Cambridge Research Systems, UK; Fig S1). This paradigm is known to elicit a strong and lasting activation of the auditory cortex (44,45), the target ROIs for subsequent fMRI neurofeedback downregulation. Auditory target ROIs were then manually created using SPM12 in MATLAB, with a statistical threshold on the activation contrast at $P \leq .05$ FWE (family-wise error corrected) and/or a minimal ROI size of at least 200 voxels whenever possible (see Table S2; for a small percentage of participants, P was increased to achieve the minimal ROI size). To maximize consistency, the same individual target ROIs were kept throughout the fMRI neurofeedback training.

Instructions to Participants

Participants were instructed at the beginning of the first MRI visit to attempt to foresee and develop one or several long-term cognitive strategies for defocusing from their tinnitus (and more generally, from noise), and if possible, based on their existing coping habits. The rationale behind this task is that most of severely impacted chronic tinnitus sufferers—in contrast with healthy volunteers—have already developed several coping and habituation strategies in the past. By keeping a balance between an implicit fMRI neurofeedback paradigm and individualized strategy guidance throughout the fMRI neurofeedback training, we hypothesized that such an approach could outperform a more classic and directed fMRI neurofeedback training paradigm (46,47), by enabling participants to test their existing coping cognitive strategies in terms of bilateral auditory cortex downregulation efficacy, as long as these could still be performed within the MRI scanner environment. Individual guidance included the debriefing of the best cognitive strategies used after each visit, the extent to which did these feel relevant for the downregulation success, and the occasional reminding of past strategies (from previous visits) that were

evaluated as successful by the participants. In practice, only specific general keywords (eg, “emotion,” “memories”) were suggested if participants were coming short in exploring new strategies after a few visits. Regarding the visual feedback (see below), participants were instructed to bring and maintain the green bar as high and as long as possible, respectively. They were briefed on the purpose of the regulation (without being aware of the exact mechanism of feedback computation) and on the intrinsic blood-oxygen-level-dependent (BOLD) response delay of 4–5 s on the visual feedback bar and were also instructed to avoid body (especially limbs) and head movements during acquisitions, even if these were monitored through the built-in MRI safety camera. Finally, they were asked not to consume caffeinated or alcoholic drinks prior to each MRI session.

Behavioral Self-reports

At the end of each visit, participants were asked to fill out a participant visit evaluation questionnaire, which consisted of a pre- and a post fMRI neurofeedback training part. Parts of the questionnaire were adapted with permission from a semistructured metacognitive interview questionnaire (48). The first part focused on neurofeedback-related questions, mainly about used cognitive strategies, perceived regulation effort, and pertinence of the displayed visual feedback. It was further completed by customized questions relating to tinnitus perception, motivational aspects, sleep quality, and participant-experimenter interactions. These questionnaires were collected for further analysis relating to cognitive strategies used during fMRI neurofeedback (data not presented in this manuscript).

Visual Feedback Implementation

The feedback signal was presented visually on the MRI-compatible screen in the form of a simple thermometer bar (see Fig 2A in the main manuscript), inspired from previous work in the field (49–51). The display included a red target bar at the top of the screen, a white focus cross at the center, and a moving green regulation bar in between. Differential feedback was implemented to penalize breathing-driven and global BOLD deviation effects on the feedback signal (52):

$$F = \mathrm{mean}\left(\left(\mathrm{ROIs}_{\mathrm{Nf}\ \mathrm{median}((t-2):t)} - \mathrm{ROIs}_{\mathrm{Bs}_{\mathrm{median}(3:(\mathrm{end}-2))}}\right)_{\mathrm{Aud}}\right) - \left(\mathrm{ROI}_{\mathrm{Nf}\ \mathrm{median}((t-2):t)} - \mathrm{ROI}_{\mathrm{Bs}_{\mathrm{median}(3:(\mathrm{end}-2))}}\right)_{\mathrm{Ctrl}},$$

where F is the scaled feedback output signal, Aud denotes auditory ROIs, and Ctrl denotes the chosen control region of the brain. Subscripts Nf and Bs denote neurofeedback and rest (baseline) periods, respectively. While Nf corresponds to the median signal at the current regulation volume at time t, Bs refers to the median signal in the given ROI over the preceding baseline block (30 s), which is truncated by 2 TRs (ie, 3 s) at the beginning and at the end of the block to account for habituation and anticipation effects due to the constant timing of blocks over the whole fMRI neurofeedback training period. The control region was chosen as a larger area involving part of the left primary motor cortex, a region mapped from a previous pilot fMRI neurofeedback finger-tapping imagery experiment (18). No clear consensus exists for the choice of such a region, with earlier experiments also attempting an entire brain slice as control region (53). In our case, the rationale was to pick a region a priori not known to be involved in tinnitus distress, and of larger volume than targeted auditory ROIs, to have a smoother global signal

estimate, and to minimize breathing effects on BOLD variability. Additional to the feedback, intermediate and final downregulation scores were also computed and displayed to the participant for ~ 3 s after each regulation block. The score was computed as the cumulative sum of the feedback bar's value, which was mapped between 1 (minimum value, ie, the green regulation bar almost overlaps with the centered white dot) and 100 (maximum value, ie, the green regulation bar overlaps with the red target bar), so that the minimum score for a given run was always 120 (6 blocks × 20 volumes). The choice of 1 as minimum implied that the participant received a nonzero score even if there was no successful downregulation (or even an upregulation) of auditory regions within a given block. This choice was justified by the lengthy protocol (15 MRI visits), to keep a motivational component, and for discussing previous scores at the debriefing after each fMRI neurofeedback session.

Preprocessing of Real-time fMRI Neurofeedback Data

Real-time fMRI neurofeedback data were preprocessed using SPM12 (43), and with customized code written in MATLAB R2019b (see main manuscript). The first and last 5 volumes of each run were discarded (also in OpenNFT), yielding 260 volumes per run. All runs underwent standard preprocessing steps, including slice timing correction, realignment, coregistration to the anatomic subject-space of the first MRI visit, normalization onto the Montreal Neurologic Institute template (MNI, 91 × 109 × 91, 2.0 mm^3 isotropic voxel size) for group analysis, and spatial smoothing with a 6 mm FWHM Gaussian kernel (in either subject-or MNI space for group analysis). Nuisance regression was performed in subject-space, prior to smoothing, including constant, linear, quadratic trends, 12 motion (3 translational, 3 rotational, and their first order temporal derivatives), 4 white matter (WM) and cerebrospinal fluid (CSF) (average WM and CSF, and their first order temporal derivatives), and 18 physiologic noise (from pulse photoplethysmography and breathing belt recordings) regressors created using the RETROICOR model (54), using the PhysIO TAPAS Toolbox (55). All volumes with frame displacement (FD) ≥ 0.5 mm were also tagged for further processing (fMRI modeling), but not regressed out from the data at this stage. A quality control to exclude artifacts and to ensure proper brain coverage in the preprocessed data were also carried out with additional functional intersect masks for all runs per participant, created with the help of FSL (56).

Detailed CBT Methods

Participants of the CBT group underwent a series of group training visits that encompassed different themes in relation to tinnitus distress management. CBT was proven to be generally well received by patients and is a cost-effective approach for reducing the impact of tinnitus on quality of life. In this study, an adapted protocol with 10 weekly group CBT visits was elaborated by certified clinicians (C.L.R., A.S.). Its contents are summarized in Table S1. In practice, every session began with a guided relaxation period of 15 min. It was followed by a review of previously assigned homework (exercises), involving interparticipant discussion and an oral exchange of previous strategies used to accomplish these exercises. Then, the actual contents of the session's day were discussed in detail, after which new homework was assigned. The session was concluded by another few minutes of exercises depending on the remaining time. During the first session ("Psychoeducation"), the trainer presented themselves, followed by the participants, who outlined their history of tinnitus and its impact on their everyday life, before sharing their expectations from the group therapy. The trainer also briefly explained the Jastreboff neurophysiological model of tinnitus (57,58), to emphasize how a subconscious

conditioned response may arise following tinnitus onset. This model differs from psychologic models by assigning more importance to subconscious processing of auditory information rather than conscious evaluation of the symptom. In the following sessions, all relevant aspects of tinnitus were covered (causes, relaxation, thoughts and emotions, beliefs, defocalization, sleep, hyperacusis, mood and tinnitus, and prevention of relapse). The emphasis was given on methods for increasing acceptance of distressing thoughts, bodily sensations, and emotions related to the distress.

Statistical Analysis

Clinical Data

Clinical data from the five questionnaires (THI, BDI, PSQI, STAI, and WHODAS) were collected from the online reporting platform at the end of the trial. A Levene's quadratic test was performed for the primary (THI) and secondary (other four questionnaires, with STAI split into Y-1 and Y-2) clinical outcomes across all timepoints (baseline, preassessment, early and late postassessments, and late follow-up for THI; and baseline, early, and late postassessments for the other four questionnaires) to assess homoscedasticity. None of the tests were significant, such that the null hypothesis that the variances across different clinical timepoints are equal was not rejected (lowest $P = .056$ for within-CBT group THI at 5 different timepoints). An additional Mann-Whitney *U*-test was performed between fMRI neurofeedback and CBT groups for the five questionnaires at baseline, showing no baseline differences (Bonferroni-corrected for multiple comparisons) between both groups for THI ($P = .56$), BDI ($P = .36$), PSQI ($P = .73$), STAI Y-1 ($P = .75$), STAI Y-2 ($P = .4$), and WHODAS ($P = .15$). To assess the within-group evolution, a repeated measures analysis of variance (rANOVA) model was fit to the 5 timepoints for THI, and to the 3 timepoints for the other questionnaires. Student's *t* tests (left-tailed for THI, according to the prior superiority hypothesis of fMRI neurofeedback over CBT, as per protocol; and two-tailed for the other questionnaires) were performed for baseline against early and late postassessments, as well as for baseline against late follow-up for THI only, with $P < .05$ as statistical threshold, Bonferroni-corrected for multiple comparisons (Figs 3 and 4 in the main manuscript). Additionally, nonparametric Wilcoxon signed-rank tests produced the same statistical outcomes, validating the parametric statistical approach. FMRI neurofeedback was directly compared against CBT for THI reduction at 1 (changes from baseline to early postassessment [additional comparison]) and 6 (changes from baseline to late postassessment [primary outcome as per protocol]) months using a two-sample Student's *t* test (left-tailed with unequal variance) with $P < .05$, Bonferroni-corrected for multiple comparisons.

Additional Analyses for Secondary Outcomes

Although not part of secondary clinical outcomes, we performed additional between-groups (fMRI neurofeedback and CBT) analyses of differences in depression (BDI) and general functioning (WHODAS) scores at 6 months from baseline and of differences in sleep (PSQI) and trait-anxiety (STAI Y-2) at 1 month from baseline using nonparametric Mann-Whitney *U*-tests (Wilcoxon *two-tailed* rank sum tests, because superiority of fMRI neurofeedback over CBT for secondary outcomes was not hypothesized a priori). Nevertheless, fMRI neurofeedback showed superiority over CBT for improved sleep at 1 month (mean score change,-1.7 points ± 2.47 [SD] versus 0 points ± 3.05 [SD]; $P = .03$) after intervention and improved general functioning at 6 months (mean score change,-9.88 points ± 15.88 [SD] versus +4.35 points ± 14.93 [SD]; $P = .02$)

after intervention. Only a superiority trend was found for improved depression (mean score change,-5.53 points ± 8.56 [SD] versus-0.1 points ± 7.34 [SD]; $P = .07$) scores at 6 months following fMRI neurofeedback versus CBT. No difference was found for trait-anxiety (mean score change,-5.18 points ± 7.89 [SD] versus-2.65 points ± 7.04 [SD]; $P = .99$) scores at 1 month after intervention between both groups.

Real-time fMRI Neurofeedback Neuroimaging Data

For post hoc, offline fMRI neurofeedback data analysis, general linear modeling (GLM) was used to delineate brain activity during fMRI neurofeedback downregulation blocks. First-level GLM modeling (run-level) was performed with SPM12 (43) and consisted of an active neurofeedback regressor of interest (neurofeedback task), a constant column (baseline, not modeled), and a variable number of columns loaded from respective FD ≥ 0.5 mm frames (spike regressors of no interest) from the previous preprocessing steps. Default SPM12 parameters were used for the model. After evaluation, positive and negative neurofeedback contrasts and their associated statistical *t*-maps per run were saved for all participants ($P \leq .05$ FWE). Then, a second-level GLM per participant (session- or visit-level) was performed to assess the average levels of activations and deactivations during fMRI neurofeedback throughout the whole training (see Table S2 for the total number of runs per participant). Finally, after assessing individual fMRI neurofeedback regulation performance throughout the course of the training, individual second-level average contrast maps were normalized onto the MNI space, and a third-level (group-level) GLM was run to unveil average group regulation effects across the 1990 fMRI neurofeedback runs across all participants (one-sample *t* test, with standard SPM12 parameters, and with different additional covariates: age, gender, and difference of THI scores from baseline to early postassessment). The analyses were performed using MATLAB R2019b (The MathWorks Inc., USA) and SPM12, with customized code (available on GitHub at *https://github.com/ngs5/neurotin*).

Additional Analyses for Differences in Hearing Loss

In the minimization procedure (40) used for randomization (described above), the averaged percentage of hearing loss was calculated according to the CPT-AMA definition (41), which considers hearing thresholds at frequencies ≤ 4 kHz. However, given the incremental nature of the enrollment in this study over a duration of several years, 3 participants with particularly elevated average (left-right ears) CPT-AMA values (2 above 30% and 1 at 60%) were randomized into the CBT group, creating a close-to-significant imbalance (see pure tone average values in the Table in the main text) between the fMRI neurofeedback and CBT groups. All CPT-AMA values in the fMRI neurofeedback group were below 20%. While differences in hearing loss curves may influence the outcomes of interventions aimed at reducing tinnitus, we show here that these differences were mainly localized to lower frequencies (≤ 4 kHz) on the tested spectrum in the audiograms (Fig S3), and that no differences were significant when correcting for multiple comparisons (Bonferroni correction, $n = 11$ comparisons, with initial $P < .05$) at the level of the individual frequencies tested at baseline and at early (+1 month) and late (+6 months) postassessments. We assessed the associated hearing loss values (in dB hearing level) at measured tinnitus frequencies (separately for left and right ears) during tinnitometry at baseline for both groups ($n = 21$ in fMRI neurofeedback, and $n = 22$ in CBT) with a nonparametric Mann-Whitney *U* test. The hearing loss values are sorted for comparative (visual) purposes in Figure S4 (left). No differences between both distributions were found for both left

(P = .22) and right (P = .6) ears, suggesting that there were no differences in hearing loss specifically at the frequencies of perceived tinnitus between both groups at baseline. Additionally, we evaluated whether perceived tinnitus loudness could differ between both groups at baseline. To that aim, we compared the distributions of perceived tinnitus loudness (as measured during tinnitometry at baseline) in dB SL, with respect to the amount of hearing loss (in dB HL) at the corresponding individual tinnitus frequencies (Fig S4, right). Again, no specific differences were observed between both groups at baseline for the left (P = .91, n = 20 for both groups) and right (P = .75, n = 17 and 19 for fMRI neurofeedback and CBT groups, respectively [see Table in main text for tinnitus laterality characteristics]) ears.

References

40. Taves DR. Minimization: a new method of assigning patients to treatment and control groups. Clin Pharmacol Ther 1974;15(5):443–453.

41. Colucci DA. AMA Hearing Loss/Tinnitus Guidelines. Hear J 2016;69(2):40.

42. Koush Y, Ashburner J, Prilepin E, et al. OpenNFT: An open-source Python/Matlab framework for real-time fMRI neurofeedback training based on activity, connectivity and multivariate pattern analysis. Neuroimage 2017;156:489–503.

43. Ashburner J, Barnes G, Chen CC, et al. SPM12 manual. London, UK: Wellcome Trust Centre for Neuroimaging, 2014; 2426:4.

44. Haller S, Wetzel SG, Radue EW, Bilecen D. Mapping continuous neuronal activation without an ON-OFF paradigm: initial results of BOLD ceiling fMRI. Eur J Neurosci 2006;24(9):2672–2678.

45. Seifritz E, Esposito F, Hennel F, et al. Spatiotemporal pattern of neural processing in the human auditory cortex. Science 2002;297(5587):1706–1708.

46. MacDuffie KE, MacInnes J, Dickerson KC, Eddington KM, Strauman TJ, Adcock RA. Single session real-time fMRI neurofeedback has a lasting impact on cognitive behavioral therapy strategies. Neuroimage Clin 2018;19:868–875.

47. Watanabe T, Sasaki Y, Shibata K, Kawato M. Advances in fMRI Real-Time Neurofeedback. Trends Cogn Sci 2017;21(12):997–1010 [Published correction appears in Trends Cogn Sci 2018;22(8):738.].

48. Gaume A, Vialatte A, Mora-Sánchez A, Ramdani C, Vialatte FB. A psychoengineering paradigm for the neurocognitive mechanisms of biofeedback and neurofeedback. Neurosci Biobehav Rev 2016;68:891–910.

49. Caria A, Veit R, Sitaram R, et al. Regulation of anterior insular cortex activity using real-time fMRI. Neuroimage 2007;35(3):1238–1246.

50. Ninaus M, Kober SE, Witte M, et al. Neural substrates of cognitive control under the belief of getting neurofeedback training. Front Hum Neurosci 2013;7:914.

51. Ruiz S, Lee S, Soekadar SR, et al. Acquired self-control of insula cortex modulates emotion recognition and brain network connectivity in schizophrenia. Hum Brain Mapp 2013;34(1):200–212.

52. Sepulveda P, Sitaram R, Rana M, Montalba C, Tejos C, Ruiz S. How feedback, motor imagery, and reward influence brain self-regulation using real-time fMRI. Hum Brain Mapp 2016;37(9):3153–3171.

53. Sitaram R, Caria A, Veit R, Gaber T, Ruiz S, Birbaumer N. Volitional control of the anterior insula in criminal psychopaths using real-time fMRI neurofeedback: a pilot study. Front Behav Neurosci 2014;8:344.

54. Glover GH, Li T-Q, Ress D. Image-based method for retrospective correction of physiological motion effects in fMRI: RETROICOR. Magn Reson Med 2000;44(1):162–167.

55. Kasper L, Bollmann S, Diaconescu AO, et al. The PhysIO Toolbox for Modeling Physiological Noise in fMRI Data. J Neurosci Methods 2017;276:56–72.

56. BETUserGuide: bet and bet2. https://fsl.fmrib.ox.ac.uk/fsl/fslwiki/BET/UserGuide#bet_and_bet2. Last accessed December 27, 2023.

57. Jastreboff PJ. Phantom auditory perception (tinnitus): mechanisms of generation and perception. Neurosci Res 1990;8(4):221–254.

58. Jastreboff PJ, Hazell JWP. A neurophysiological approach to tinnitus: clinical implications. Br J Audiol 1993;27(1):7–17.

Table S1

Group CBT Training Schedule and Detailed Session Contents

Visit	Theme	Session Contents
1	Psychoeducation	Introduction and presentation of the sessions Anatomy of the ear What causes tinnitus? Hearing loss, noise exposure Hearing loss and tinnitus Mood and tinnitus: depression and anxiety CBT and tinnitus
2	Relaxation	Stress and tinnitus Tips for reducing stress Progressive muscle relaxation (Jacobson) Autogenic training (Schultz) Breathing and relaxation Mindfulness Practical exercise
3	Thoughts and emotions	Changing thoughts about tinnitus Thinking about tinnitus Automatic thoughts Impact of emotions The ABC model (Ellis): activating event, beliefs, consequences
4	Beliefs	Observing beliefs about tinnitus Thinking in a logical manner Challenging illogical thoughts Managing negative thoughts
5	Defocalization	Reducing your attention to the tinnitus Source of defocalization Exercises of defocalization
6	Sleep	Normal sleep States and stages of sleep during a typical night The effects of tinnitus on sleep Managing sleep difficulties

7	Loudness recruitment, hyperacusis, and phonophobia	Loudness recruitment Hyperacusis Phonophobia Sound sensitivity and tinnitus Management of sound sensitivity
8	Concentration	Concentration The effects of tinnitus on concentration Tips to improve concentration
9	Prevention of relapse	How to prevent relapse? Impact of anxiety, depression, and sleep on relapse
10	End and questions	Questions Feedback

Note.—Detailed contents of the 120 min weekly group CBT sessions. The average duration of the CBT training for all participants was 101.2 days ± 46 [SD].

Table S2

FMRI Neurofeedback Participants' Training Details

Participant	Training Duration (Days)	Neurofeedback Runs Total/Transfer	Auditory ROIs Left/Right (Voxels)	Main Cognitive Strategies Used
002	147	103/19	525/514	Picturing favorite sports Best personal achievements Game/play strategies
003	112	90/17	333/460	Auto-hypnosis, relaxation Empty one's mind
004	168	92/18	343/327	Picturing different colors Empty one's mind Positive memories
005	93	91/18	296/315	Focus on different body parts Inner talk, relaxation Interplay tinnitus/feedback bar
008	98	105/19	312/277	Counting, word spelling Positive thoughts Theater recitals, texts
012	149	106/23	275/304	Family, music Alternate focus on tinnitus
013	85	91/19	291/335	Prayers, thought of love
016	96	105/19	316/255	Calculus, visual imagery Empty one's mind Picturing favorite sports
020	146	88/17	367/361	Picturing favorite activities Meditation Recollection of memories
021	138	100/19	223/213	Mind wandering Checklists, positive thoughts Travel memories
023	82	90/18	253/245	Focus on the present moment Alternate focus on tinnitus Positive thoughts
025	105	105/19	224/283	Calculus, word spelling Auditory imagery
026	135	90/20	276/298	Prayers, inner bubble
034	129	90/18	358/361	—
037	191	90/18	298/299	—
041	260	104/19	298/293	Spatial memories Visual imagery
043	159	90/18	291/291	Calculus Visual attention
045	123	90/18	325/322	Calculus Auditory and visual memories
048	97	90/18	303/298	Sophrology Focus on different body parts
054	49	90/18	309/310	Visual imagery, feelings

				Focus on different body parts
056	43	90/19	392/391	Auditory imagery Calculus
Total Mean ± SD	124.1 ± 48.6	1990/391 94.8 ± 6.8/18.6 ± 1.2	314.7 ± 63.9/321.5 ± 68.5	

Note.—Training duration, number of runs, auditory target ROIs' sizes, and main cognitive strategies employed by the participants of the fMRI neurofeedback group.-: missing data, ROI (s): region (s) of interest.

Table S3

Reasons for Withdrawal

Participant	Group	Timeline*	Reason
009	fMRI	after V08	General medical concerns with respect to MRI, unrelated to MRI noise
011	CBT	after V01	Lost to follow-up
014	CBT	after V04	Personal reasons
017	fMRI	after V01	Not convinced by the trial, and no longer interested to commit
018	fMRI	during V08	Back pain, impossible to continue laying on MRI bed
019	CBT	—	Lost to follow-up
031	CBT	after V03	Found a new job and could no longer commit to the trial
032	CBT	after V03	Could no longer commit to the trial
033	fMRI	after V08	Concerns due to the pandemic outbreak
036	CBT	before V01	Training schedules were no longer compatible after randomization
038	CBT	before V01	Not interested to undergo group CBT after randomization
042	fMRI	before V01	Underwent conflicting acupuncture as alternative tinnitus therapy
044	fMRI	after V02	Concerns with respect to MRI noise and tinnitus
045	fMRI	after V06	Personal reasons
046	CBT	before V01	Planned surgery interfered with training schedule
050	fMRI	after V01	Too sensitive to MRI noise and anxious about MRI environment
051		before randomization	Lost to follow-up
055		before randomization	Anxious about MRI environment
058	CBT	after V01	No longer interested in group CBT
074		before randomization	No longer satisfied inclusion criteria

* V is for 'visit', with numbering between 1–15 for fMRI neurofeedback and between 1–10 for CBT.

Table S4

Tinnitus Etiologies (fMRI Neurofeedback Group)

Participant	Etiology
002	Sickness, plane pressure trauma
003	Unknown (possibly AAT)
004	Unknown
005	Long-term noise exposure
008	AAT at the military
012	Unknown
013	Noisy work environment

016	Head trauma
020	AAT
021	AAT from exposure to loud music
023	AAT, noisy work environment
025	Long-term noise exposure (possibly AAT)
026	Unknown
034	Long-term noise exposure
037	AAT
041	Side effect after sickness
043	Side effect after ear infection
045	Unknown
048	Long-term noise exposure
054	Sickness, plane pressure trauma
056	Long-term noise exposure

Note.—Tinnitus etiologies were only recorded in the fMRI neurofeedback group. AAT = Acute acoustic trauma.