Science Translational Medicine
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# Supplementary Materials for

## Bimodal neuromodulation combining sound and tongue stimulation reduces tinnitus symptoms in a large randomized clinical study

Brendan Conlon, Berthold Langguth, Caroline Hamilton, Stephen Hughes, Emma Meade, Ciara O Connor, Martin Schecklmann, Deborah A. Hall, Sven Vanneste, Sook Ling Leong, Thavakumar Subramaniam, Shona D'Arcy, Hubert H. Lim*

*Corresponding author. Email: hubert.lim@neuromoddevices.com

Published 7 October 2020, *Sci. Transl. Med.* **12**, eabb2830 (2020)
DOI: 10.1126/scitranslmed.abb2830

**The PDF file includes:**

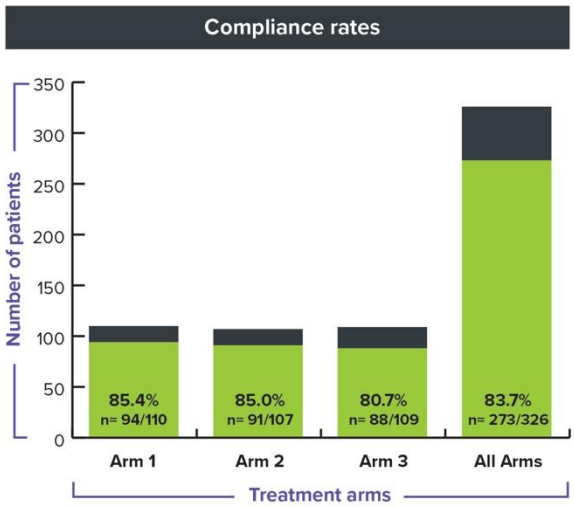
Table S3. Patient referrals for AEs.
Table S4. Stratification category of hyperacusis in Table 1 calculated in units of dB HL.

**Other Supplementary Material for this manuscript includes the following:**

(available at stm.sciencemag.org/cgi/content/full/12/564/eabb2830/DC1)

Data file S1 (Microsoft Word format). CONSORT checklist.

**A**




**B**

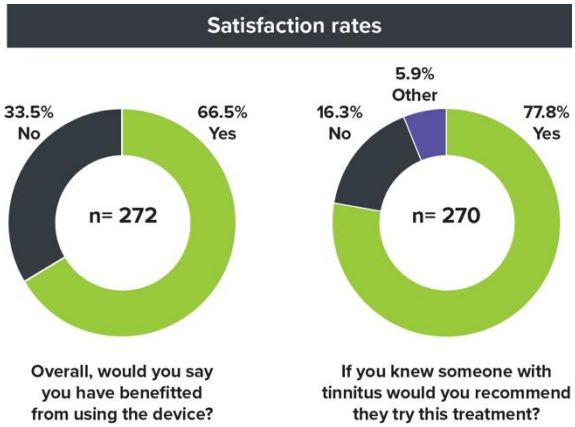



**Fig. S1. Compliance and satisfaction rates in using treatment device. (A)** Number of enrolled participants who achieved the minimum treatment compliance of ≥36 hours over the intended 12-week treatment period *(41)*. The *n* values are larger in this figure compared to the *n* values for the per-protocol analysis in Fig. 2 because Fig. 2 includes treatment-compliant participants who also came to the 12-week visit for THI and TFI assessments. Since the device tracks when it is used by the participants, we were able to determine if participants were compliant to treatment once they returned their device, in which some participants did not attend the 12-week visit but returned the device afterwards. There was no statistically significant differences in compliance rate or number of participants at the final visit between treatment arms ($P > 0.05$; Fisher's exact test). **(B)** Two questions relating to the participant's satisfaction or acceptability of the treatment device were asked at the 12-week visit, in which the percentage of YES or NO responses are shown. The "other" category refers to cases where the participant could not answer YES or NO or did not feel comfortable in committing to an answer.

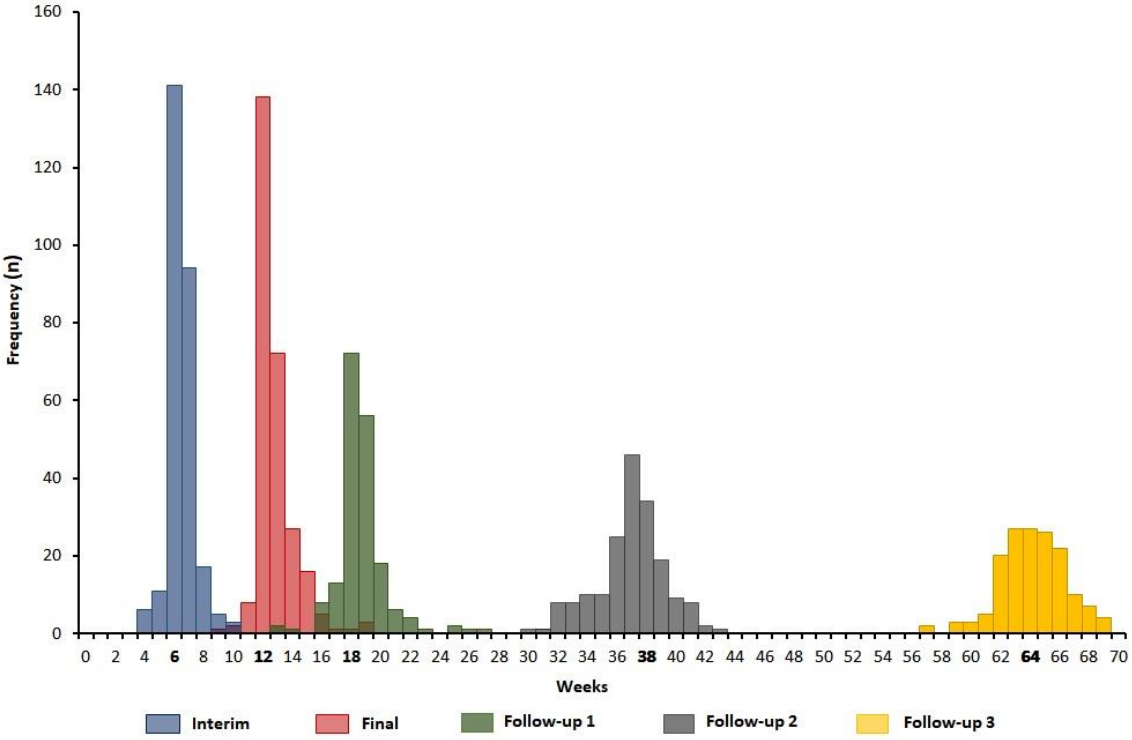



**Fig. S2. Histogram of time (in weeks) when participants attended each visit relative to enrollment.** Treatment began at t = 0 weeks. The participants generally attended each visit at or near the intended time point of 6, 12, 18, 38 and 64 weeks relative to enrollment (see Fig. 1 for study timeline).

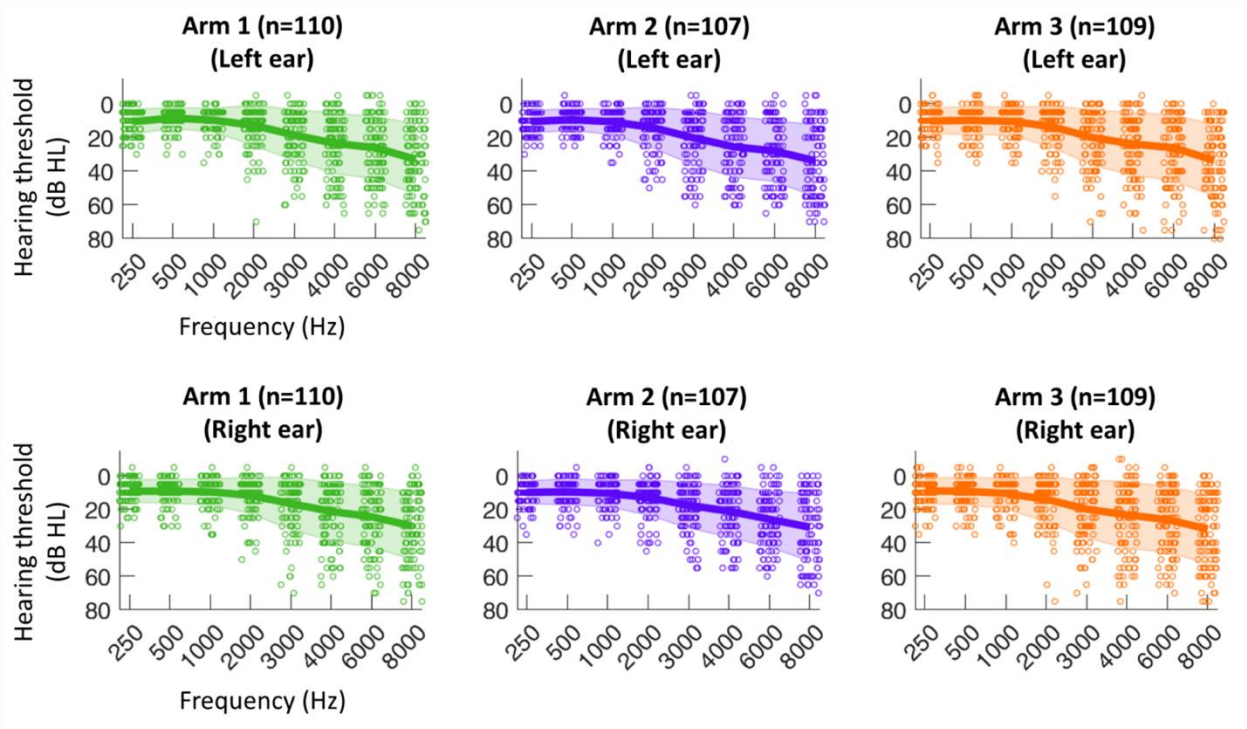



**Fig. S3. Hearing thresholds for enrolled participants.** Data are plotted for each arm and presented for left or right ear. Circle represents threshold value for each frequency and participant, solid line corresponds to mean threshold value for each frequency across participants, and shaded region corresponds to standard deviation of threshold values for each frequency across participants. Data points are jittered for visibility. dB HL: decibels in hearing level.

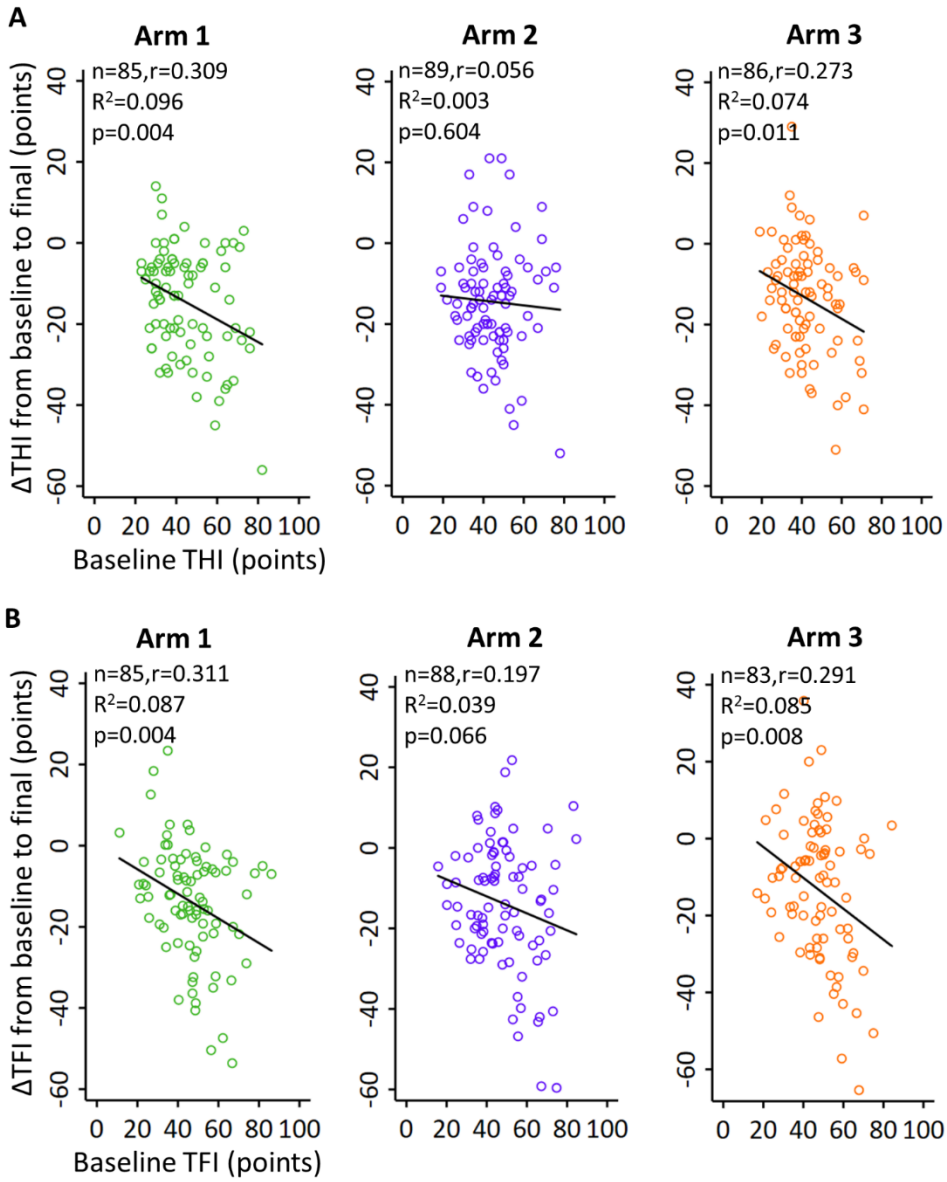



**Fig. S4. Scatterplots for change in THI or TFI score versus baseline score for each arm.** Change measured from baseline to end of 12-week treatment versus baseline (**A**) THI or (**B**) TFI score for each arm. These data correspond to the participants included in Fig. 3. A linear regression was performed for each plot. Data points are jittered for visibility. r is listed as absolute value.

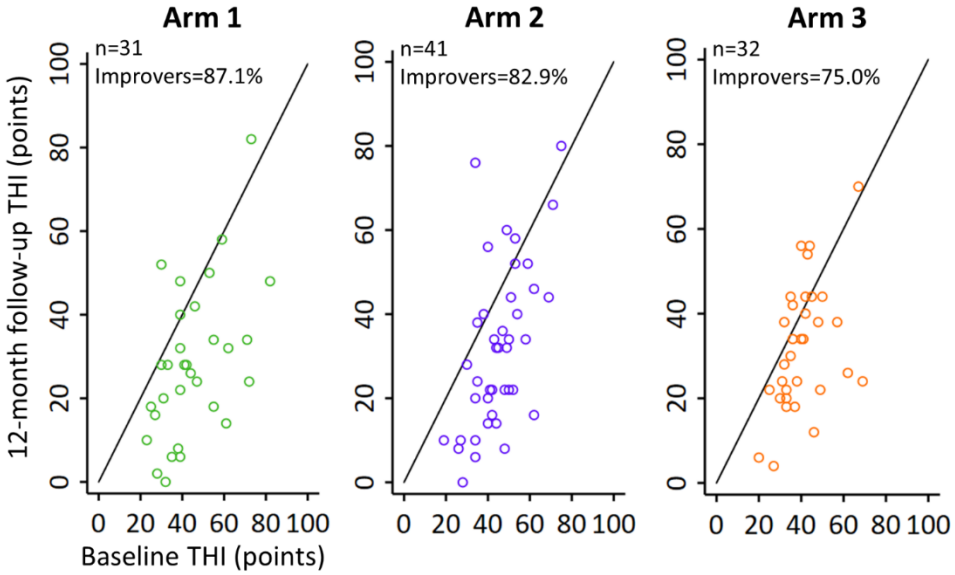



**Fig. S5. Scatterplots for THI scores at baseline versus 12-month posttreatment assessment for each arm.** Figure corresponds to participants included in Fig. 5. Circles below the black diagonal line correspond to "Improvers", which is defined as participants who retained a reduction in THI score relative to baseline. The proportion of participants retaining an improvement in tinnitus symptoms is greater in arm 1 (87%) and arm 2 (83%) compared to arm 3 (75%). Based on the Fisher's exact test, these percentages were not significantly different across arms ($P > 0.05$). Data points are jittered for visibility.

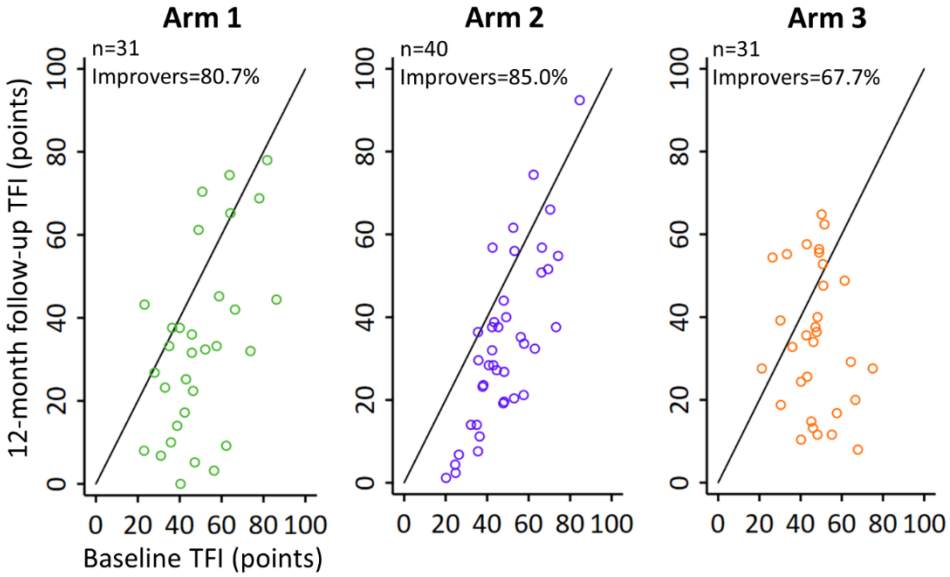



**Fig. S6. Scatterplots for TFI scores at baseline versus 12-month posttreatment assessment for each arm.** Figure corresponds to participants included in Fig. 5. Circles below the black diagonal line correspond to "Improvers", which is defined as participants who retained a reduction in TFI score relative to baseline. The proportion of participants retaining an improvement in tinnitus symptoms is greater in arm 1 (81%) and arm 2 (85%) compared to arm 3 (68%). Based on the Fisher's exact test, these percentages were not significantly different across arms ($P > 0.05$). Data points are jittered for visibility.

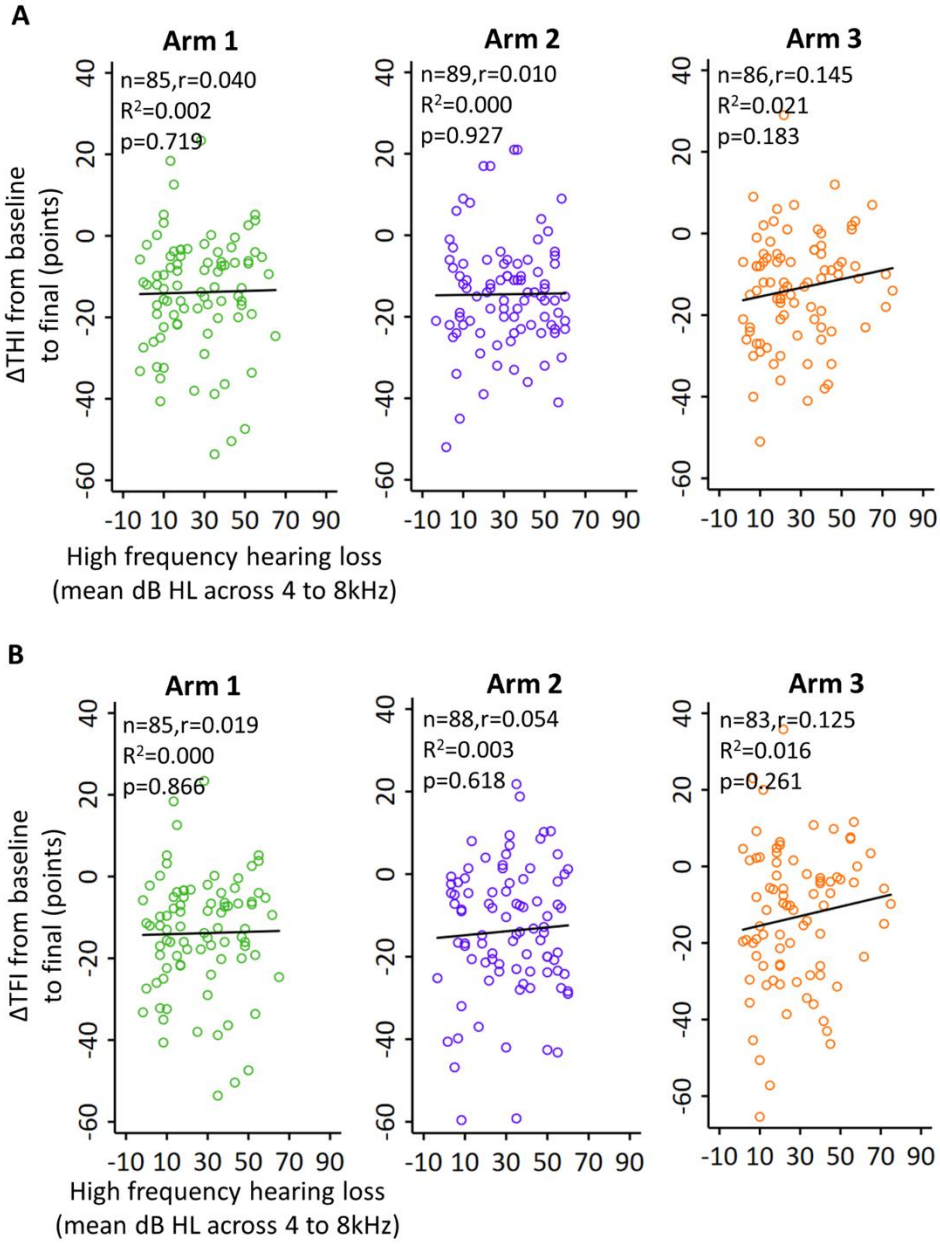



**Fig. S7. Scatterplots for change in THI or TFI score (from baseline to the end of 12-week treatment) versus high-frequency hearing loss (4 to 8 kHz) for each arm.** These data correspond to the participants included in Fig. 3 related to **(A)** THI and **(B)** TFI. A linear regression was performed for each plot. The high frequency hearing loss value is the mean value (dB HL) across several frequencies (4, 6 and 8 kHz; worst ear per frequency) corresponding to the portion of the audiograms in fig. S3 with greater hearing loss values. Data points are jittered for visibility. r is listed as absolute value.

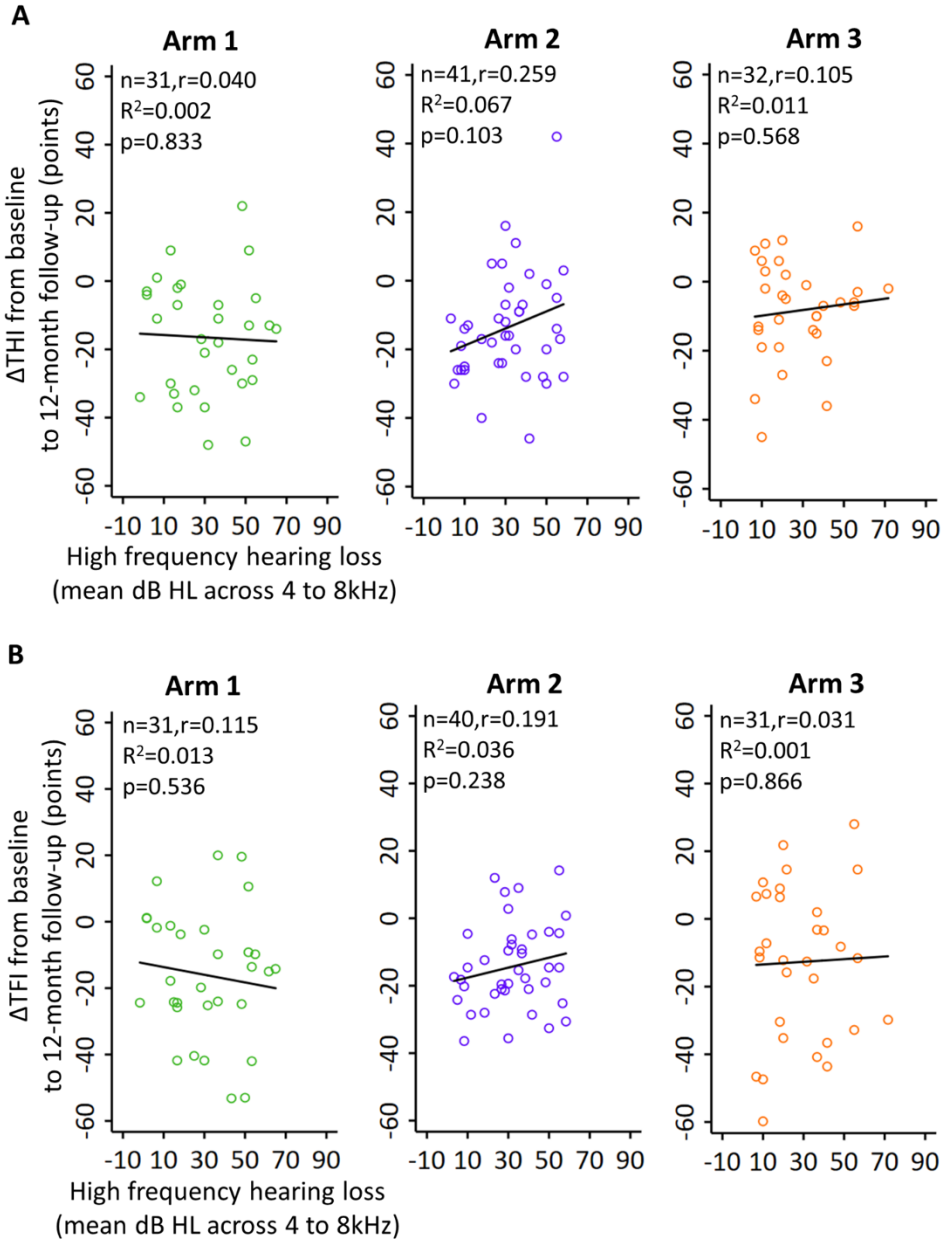



**Fig. S8. Scatterplots for change in THI or TFI score (from baseline to 12-month posttreatment assessment) versus high-frequency hearing loss (4 to 8 kHz) for each arm.** These data correspond to the participants included in Fig. 5 for **(A)** THI and **(B)** TFI. A linear regression was performed for each plot. The high frequency hearing loss value is the mean value (dB HL) across several frequencies (4, 6 and 8 kHz; worst ear per frequency) corresponding to the portion of the audiograms in fig. S3 with greater hearing loss values. Data points are jittered for visibility. r is listed as absolute value.

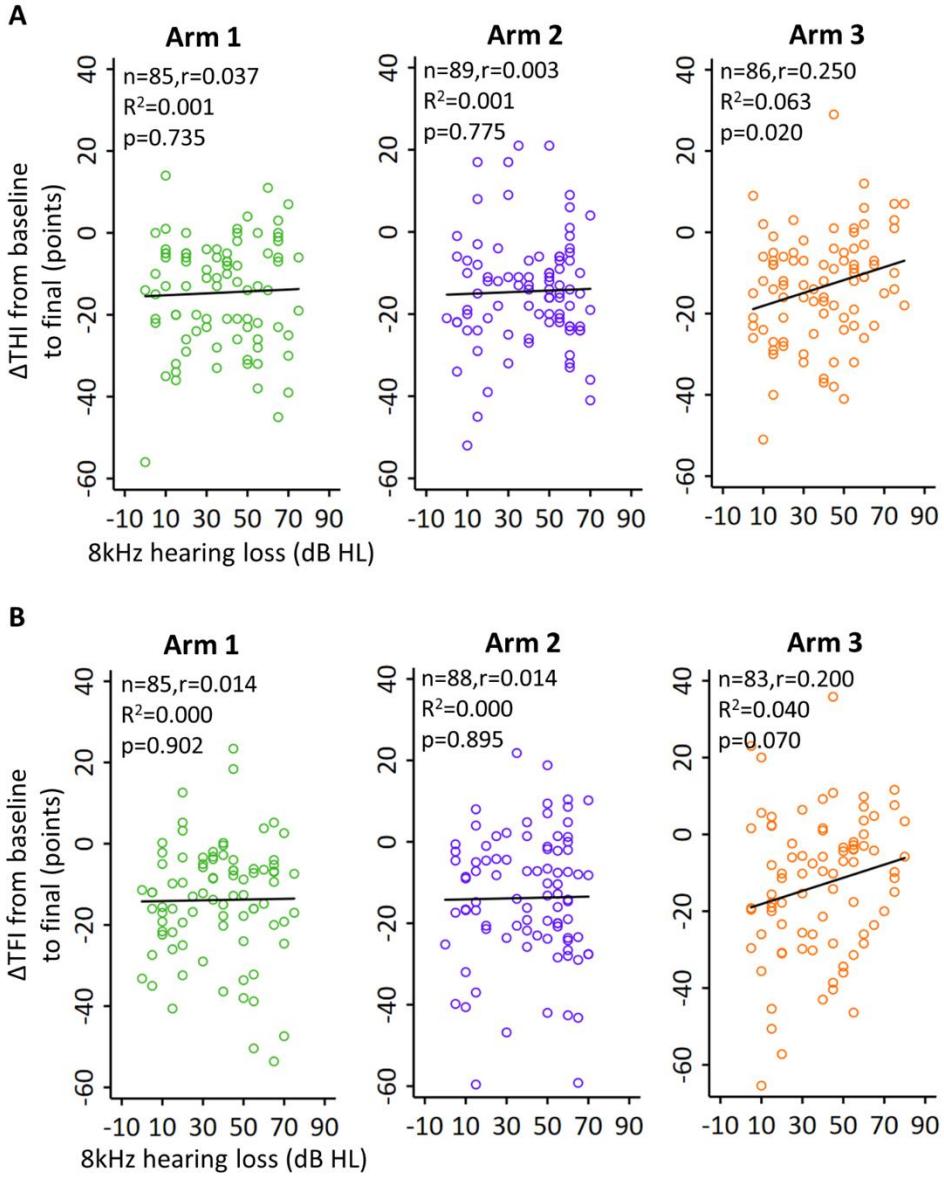



**Fig. S9. Scatterplots for change in THI or TFI score (from baseline to the end of 12-week treatment) versus 8-kHz hearing loss for each arm.** These data correspond to the participants included in Fig. 3 for **(A)** THI and **(B)** TFI. A linear regression was performed for each plot. Only 8 kHz hearing loss (worst ear) is included in these plots to assess the trends for the highest frequency with the greatest hearing loss values assessed in this study (see fig. S3). Data points are jittered for visibility. r is listed as absolute value.

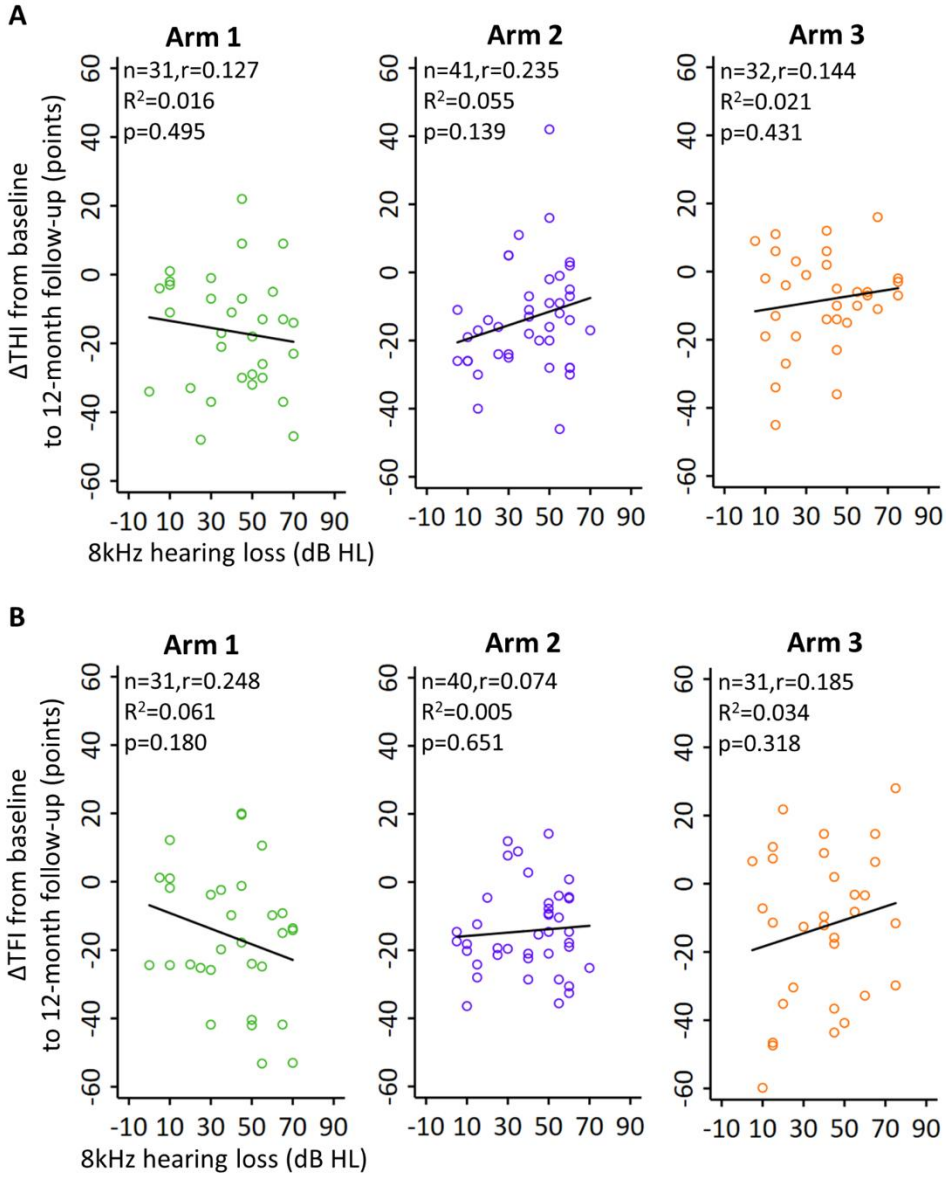



**Fig. S10. Scatterplots for change in THI or TFI score (from baseline to 12-month posttreatment assessment) versus 8-kHz hearing loss for each arm.** These data correspond to the participants included in Fig. 5 for **(A)** THI and **(B)** TFI. A linear regression was performed for each plot. Only 8 kHz hearing loss (worst ear) is included in these plots to assess the trends for the highest frequency with the greatest hearing loss values assessed in this study (see fig. S3). Data points are jittered for visibility. r is listed as absolute value.

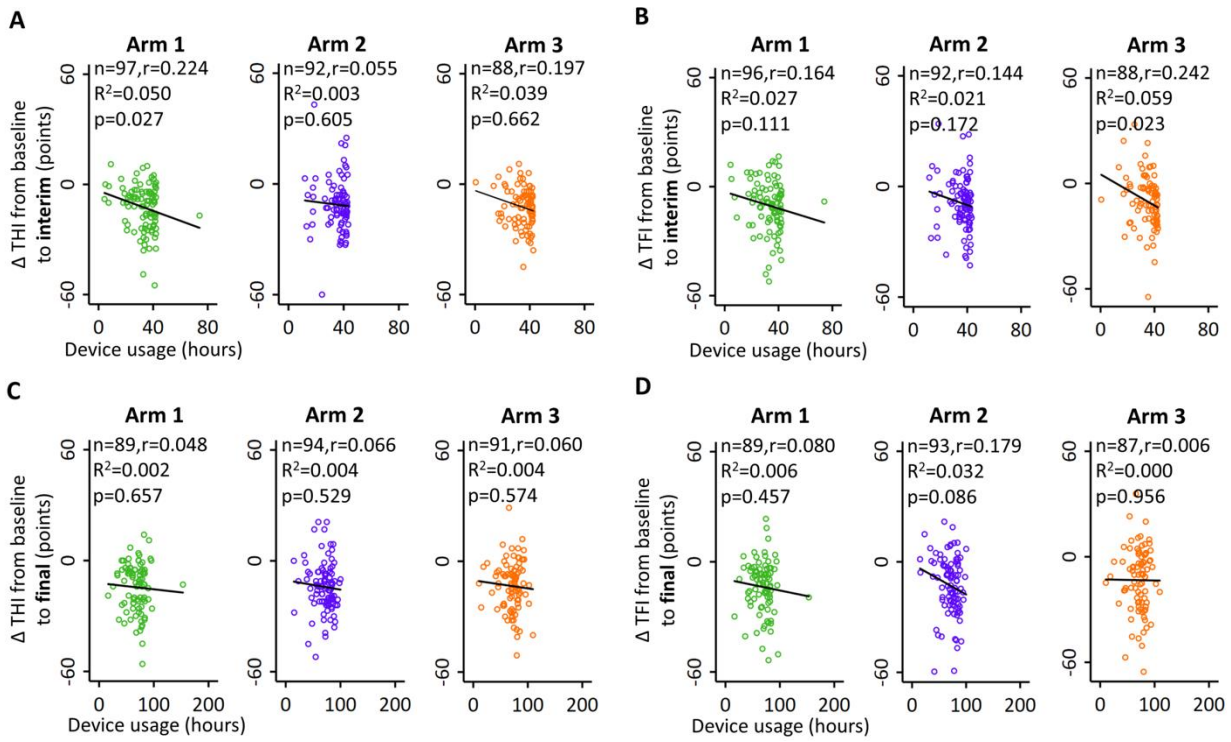



**Fig. S11. Scatterplots for change in THI or TFI score versus duration of device usage.** (**A,B**) Change in THI or TFI score from baseline to interim assessment versus device usage during the first 6-weeks of treatment is plotted for each participant and arm. (**C,D**) Change in THI or TFI score from baseline to final assessment versus device usage during the full 12-week treatment period is plotted for each participant and arm. A linear regression was performed for each plot. These plots include all subjects who received a device and attended interim or final assessment (i.e., even those who used the device less than the minimum compliance of 36 hours by the end of the 12-week treatment period). Data points are jittered for visibility. r is listed as absolute value.

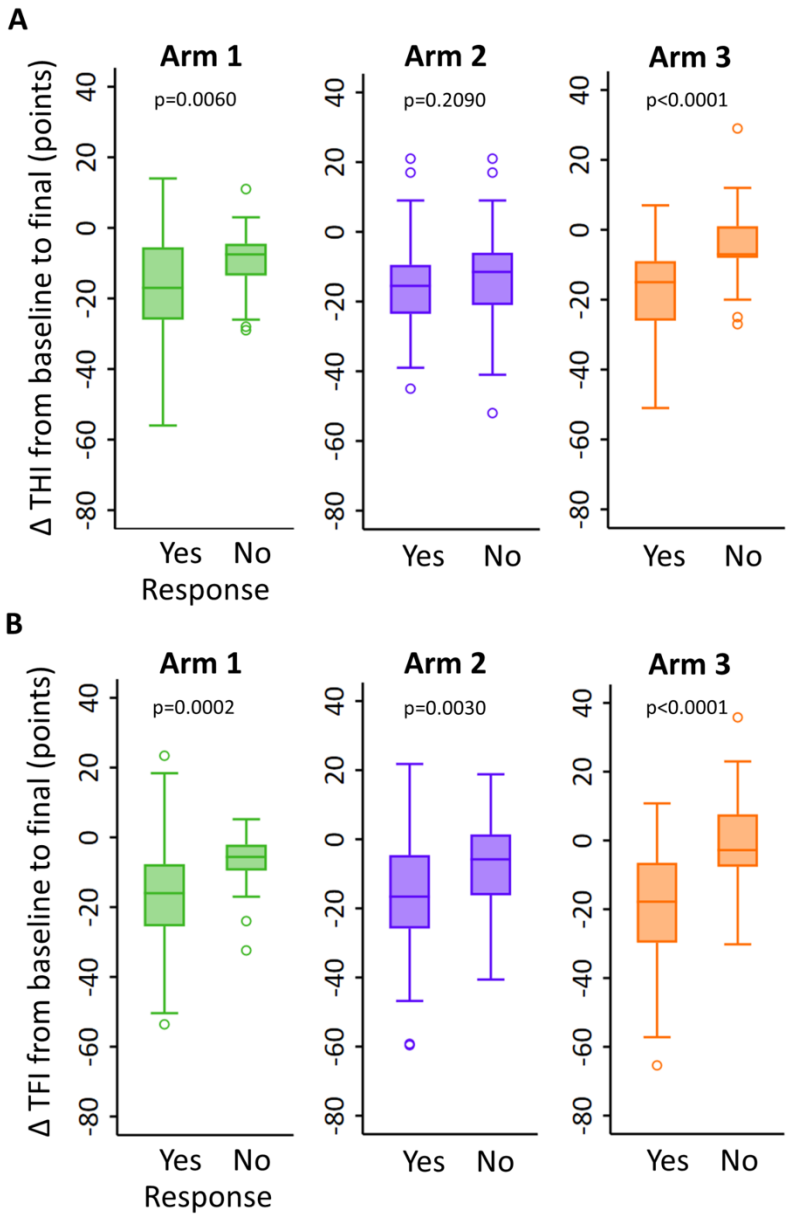



**Fig. S12. Changes in tinnitus symptoms based on responses to first satisfaction question.** Participant were asked at the end of treatment (fig. S1), "overall, would you say you have benefitted from using this device?" Out of 272 responses, 66.5% indicated "Yes". The change in **(A)** THI or **(B)** TFI score from baseline to final assessment for participants who responded "Yes" are plotted next to those who responded "No" for each arm with standard box plots. Statistical significance was determined using an unequal variance two-tailed t-test on ranked data appropriate for this dataset (*76*).

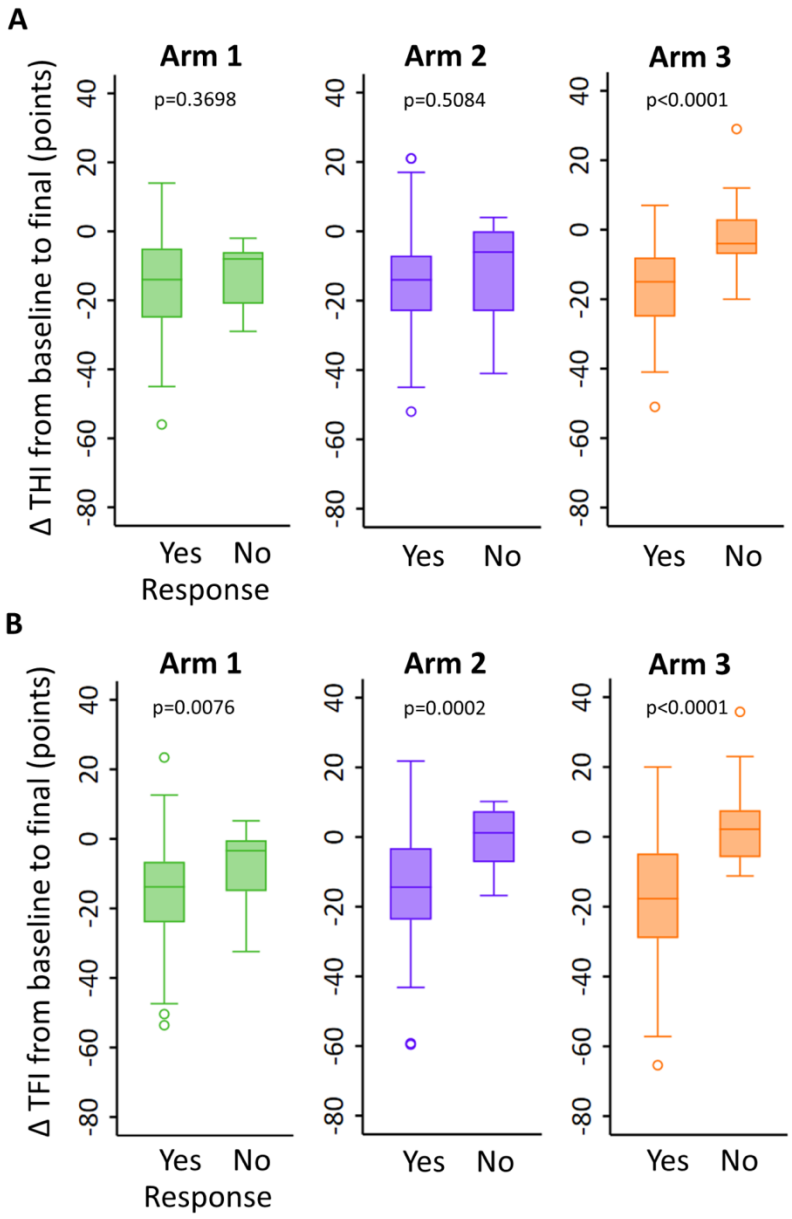



**Fig. S13. Changes in tinnitus symptoms based on responses to second satisfaction question.** Participants were asked at the end of treatment (fig. S1), "if you knew someone with tinnitus would you recommend they try this treatment?" Out of 270 responses, 77.8% indicated "Yes". The change in **(A)** THI or **(B)** TFI score from baseline to final assessment for participants who responded "Yes" are plotted next to those who responded "No" for each arm with standard box plots. Statistical significance was determined using an unequal variance two-tailed t-test on ranked data appropriate for this dataset (*76*).

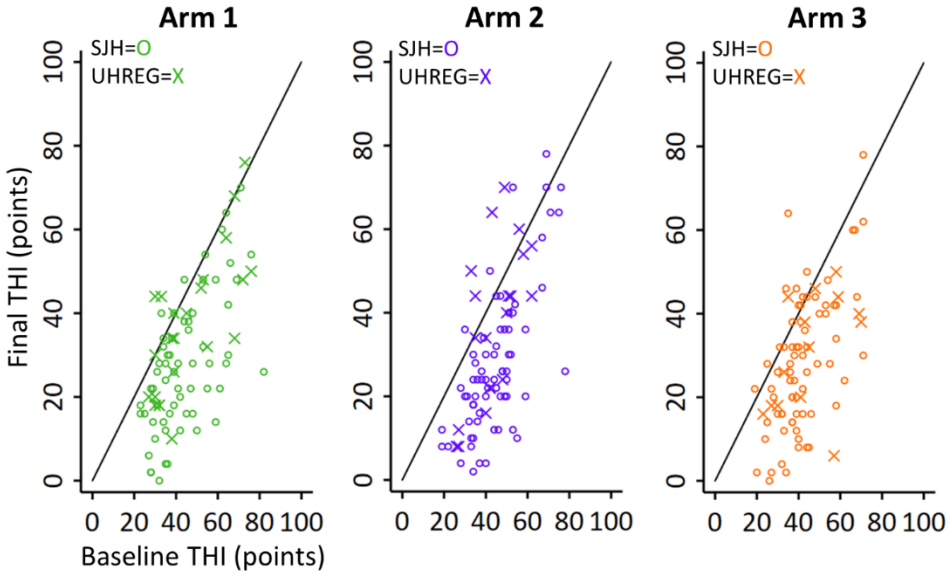



**Fig. S14. Scatterplots for THI scores for each treatment-compliant individual at baseline versus the end of treatment (12-week "final" visit) for each arm.** The points are labeled based on clinical site (SJH: St. James's Hospital; UHREG: University Hospital Regensburg). Data points are jittered for visibility.

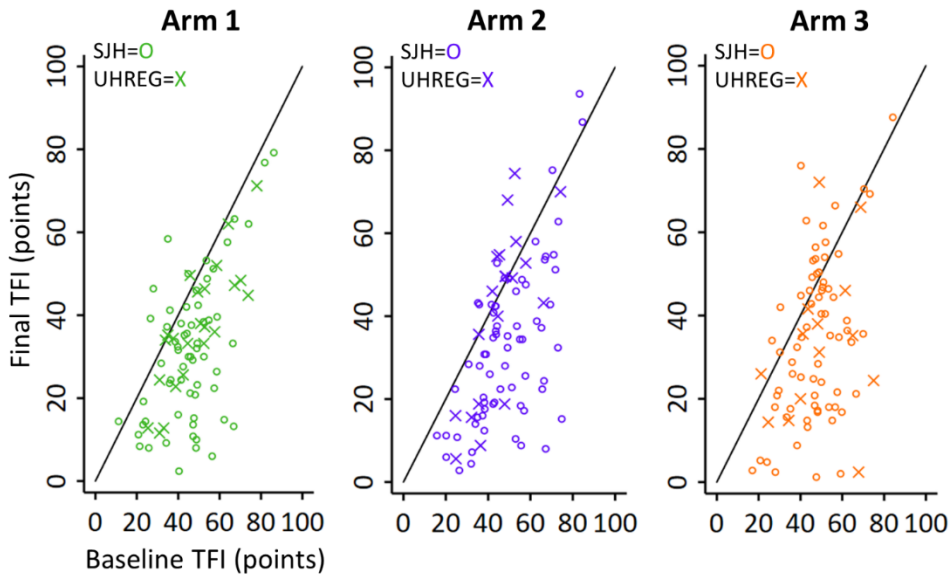
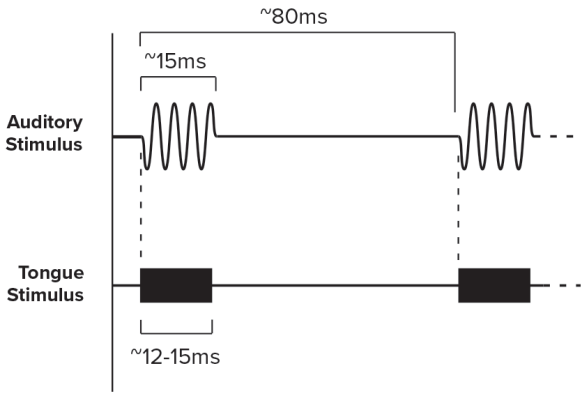
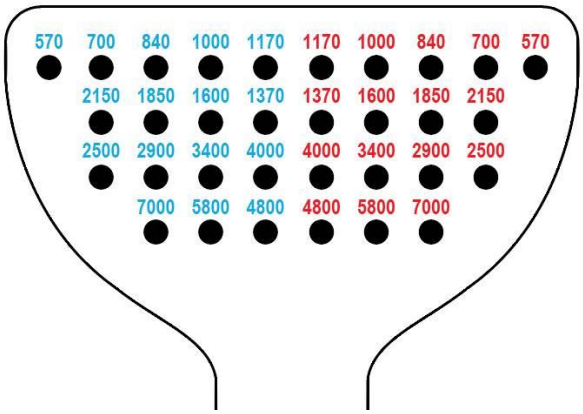



**Fig. S15. Scatterplots for TFI scores for each treatment-compliant individual at baseline versus the end of treatment (12-week final visit) for each arm.** The points are labeled based on clinical site (SJH: St. James's Hospital; UHREG: University Hospital Regensburg). Data points are jittered for visibility.

**Table S1. Schematics and description of stimulation setting used in each arm.**

| Parameter Set (PS) | Description |
|---|---|
| **Arm 1: PS1** | PS1 consisted of broadband noise mixed with frequency tones within a range of 500 to 8000 Hz that were presented every ~80 ms (~12.5 Hz) and each tone stimulus was synchronized in time with a burst of electrical pulses sent to a specific location on the tongue array. The pulse train consisted of 5 or 6 biphasic pulses where each pulse had a constant amplitude but pulse duration was adjusted during the fitting procedure to achieve comfortable sensations on the tongue (5 to 210 μs; inter-pulse period of ~3 ms; ~12-15 ms duration for burst of electrical pulses). The tones spanned the sixteen Bark Scale critical bands of hearing in which the center frequencies of those bands are shown in the tongue schematic below. The tones were presented to both ears simultaneously. Each tone was mapped to a specific location on the tongue array, and both sides of the tongue were stimulated at the same time for each tone stimulus (i.e., two electrodes in symmetric locations on the tongue array corresponding to the same tone).<br>  <br><br>  <br> |

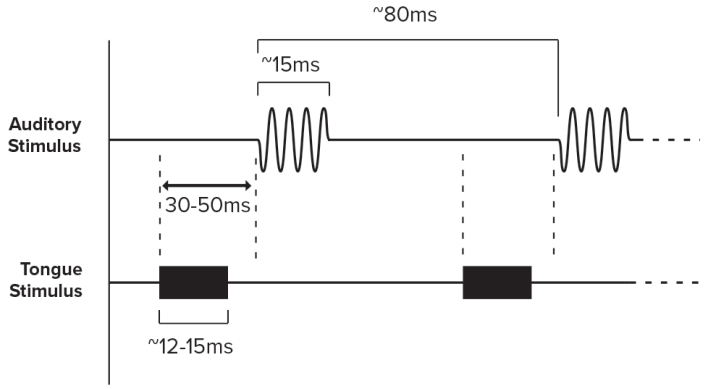
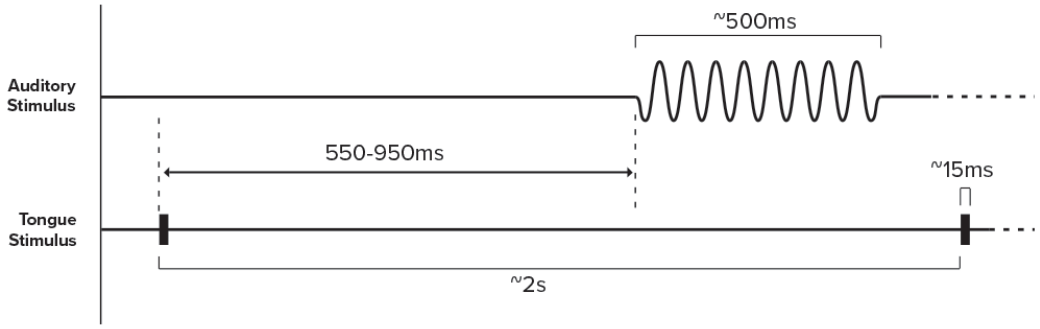
| Parameter Set (PS) | Description |
|---|---|
| **Arm 2: PS2** | PS2 was similar to PS1 (also at ~12.5 Hz rate), except the burst of electrical pulses was presented to the tongue with short varying delays (30-50 ms, uniform distribution) relative to the onset of the tone stimulus and the location of stimulation on the tongue array varied in a random order independent of the tone frequency.<br>  |
| **Arm 3: PS3** | PS3 consisted of a slower repetition rate (~0.5 Hz), lower frequency tones (100-500 Hz) and longer delays (i.e., less synchrony; 550-950 ms, uniform distribution) between auditory and tongue stimulation compared to PS1 and PS2. PS3 also consisted of background noise that contained low frequencies (~100-500 Hz). The location of stimulation on the tongue array varied in a random order independent of the tone frequency. The tongue stimulus consisted of 6 electrical pulses.<br>  |

**Table S2. AEs attributed to patient conditions from Table 2.**

| ***Possibly device related: Negligible*** | ***Possibly device related: Moderate*** |
|---|---|
| • Itchiness on head from headphones but participant reported they have sensitive skin<br>• Temporary stress with increased tinnitus but participant indicated father passed away during that time | • Hearing loss in right ear (30 to 40 dB increase at low frequencies of 250, 500, 1000 Hz) with fullness/pressure in ears, but previous experience with sudden hearing loss possibly attributed to Meniere's disease |
| ***Probably not device related: Negligible*** | ***Probably not device related: Moderate*** |
| • Cold sores but participant had history of cold sores<br>• Pain in ear but also had concurrent ear infection<br>• Five cases of redness of the pharynx/throat but attributed to colds or sore throat as likely cause and these cases were not brought up during treatment<br>• Two cases of small ulcers in the mouth but participants reported biting themselves; these ulcers were not bothersome<br>• Red eyes<br>• Sinus issue<br>• Developed tinnitus in right ear but also had concurrent sinus issue<br>• Bumps at back of patients tongue but participant was not aware of them<br>• Slight dizziness/disorientation but participant was not sure<br>• Forgetfulness but unclear if related to device<br>• Sinusitis but participant has recurring condition<br>• Nausea but concurrently had Norovirus<br>• Common cold<br>• Difficulty in sleeping but participant reported previous issues with sleeping<br>• Participant did not feel as physically fit during treatment but also started a new medication for thyroid gland issue<br>• One participant felt anxious/shaky throughout body temporarily<br>• Heart palpitations for a few seconds | • Uncomfortable ulcer but participant indicated that they bit down on mouth that caused it<br>• Breathing issues but participant has a history of breathing issues and chronic obstructive lung disease, and also concurrently had a pulmonary infection during the treatment period |

**Table S3. Patient referrals for AEs.** Of the adverse events listed in Table 2, there were three cases in which the participants were referred to an otolaryngologist or audiologist as described in the table below.

| ***Adverse event*** | ***Referral description*** |
|---|---|
| Increase in tinnitus listed in Table 2 | Tinnitus symptoms increased in right ear since starting bimodal neuromodulation treatment and was not reduced by the end of the treatment, which further contributed to disruptions in sleeping. The individual reported an ear infection in the right ear in the previous year before treatment that led to being admitted into the hospital. This individual was referred to an otolaryngologist for further assessment with no major clinical concerns reported. At the 6-month follow-up assessment, the adverse event had resolved. |
| Increase in tinnitus listed in Table 2 | Individual returned device after ending treatment and indicated tinnitus had worsened since starting treatment. The individual also reported possible fluctuations in hearing, fluctuations in tinnitus and dizziness. After a final review assessment, the individual was referred to an audiologist to continue monitoring symptoms beyond the study. |
| Recurring sudden hearing loss listed in table S2 associated with patient conditions | Hearing loss in right ear (30 to 40 dB increase at low frequencies of 250, 500, 1000 Hz) with fullness/pressure in ears, but previous experience with sudden hearing loss possibly attributed to Meniere's disease. Individual also reported tinnitus increased with changes in its pitch. The individual was referred to an otolaryngologist who assessed and diagnosed Meniere's disease. |

**Table S4. Stratification category of hyperacusis in Table 1 calculated in units of dB HL.** In Table 1, the hyperacusis category (loudness discomfort level, LDL, at 500 Hz) is calculated in units of dB SL (LDL <60 dB SL). The table below calculates LDL in units of dB HL. Based on the audiogram data plotted in fig. S3, thresholds for 500 Hz can range from about 0 to 20 dB HL. Therefore, the distribution of participants across arms is provided in the table below for three different criteria in units of dB HL that aligns with the original LDL criterion that was in units of dB SL: LDL <60 dB HL, LDL <70 dB HL and LDL <80 dB HL. There is no significant difference between arms for any of these criteria, based on the Fisher's exact test ($P > 0.05$).

| Characteristics | Units | Full cohort | Arm 1 | Arm 2 | Arm 3 | P-value |
|---|---|---|---|---|---|---|
| LDL <60 dB HL at 500 Hz | # participants (% of enrolled) | 7 (2.1%) | 2 (1.8%) | 3 (2.8%) | 2 (1.8%) | 1.000 |
| LDL <70 dB HL at 500 Hz | # participants (% of enrolled) | 36 (11.0%) | 11 (10.0%) | 12 (11.2%) | 13 (11.9%) | 1.000 |
| LDL <80 dB HL at 500 Hz | # participants (% of enrolled) | 110 (33.7%) | 37 (33.6%) | 39 (36.4%) | 34 (31.2%) | 0.928 |