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A Randomized Double-Blind Crossover Study of Phase-Shift Sound Therapy for Tinnitus

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

Abstract

Objective. The purpose of this study was to compare the efficacy of the treatment of tinnitus with a phase-shifting pure tone to that of the same tone treatment without phase shifting.

Study Design. A double-blind crossover randomized controlled trial.

Setting. This study was conducted at the University Medical Center Groningen.

Subjects and Methods. Twenty-two patients with predominantly tonal tinnitus underwent both intervention and control treatments. Each treatment consisted of three 30-minute sessions in 1 week. The control treatment was identical to the intervention treatment, except that the stimulus was a pure tone without phase shifting. Questionnaires, tinnitus loudness match, and annoyance and loudness ratings were used to measure treatment effects.

Results. Pure-tone treatment and phase-shift treatment had no significant effect on tinnitus according to questionnaires (Tinnitus Handicap Index, Tinnitus Reaction Questionnaire, Hospital Anxiety and Depression Scale, and Maastricht Questionnaire), audiological matching procedures, and loudness and annoyance ratings of tinnitus. Furthermore, phase-shift treatment showed no additional significant improvement in comparison with pure-tone treatment. Changes in questionnaire scores due to pure-tone and the phase-shift treatment were correlated.

Conclusion. On average across the group, both treatments failed to demonstrate a significant effect. Both treatments were beneficial for some patients. However, a positive effect was not demonstrated that could be attributed to the periodic shifting of the phase of the stimulus tone.

Keywords

tinnitus, therapy, residual inhibition, phase shift, RCT

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Tinnitus is a sound percept in the absence of a sound source external to the body. Estimates of patients with chronic tinnitus range from 5% to 15% in a normal population.[1,2] The available treatments for the management of patients with tinnitus are diverse, just like their outcomes. Some treatments are efficient only for a small group of patients but have no to little effect for most tinnitus sufferers. One way of attenuating tinnitus is by trying to restore the sound input from the cochlea to the brain. This may be done by commonly used devices such as hearing aids or cochlear implants[3] or with a specific tinnitus masker. Other tinnitus treatments are removal of earwax, middle-ear drug application, oral medication, brain surgery, brain stimulation, and counseling therapies.[4-7] The range of treatment shows that there is no universal treatment for tinnitus at this moment. Therefore, tinnitus management often focuses on how the patient handles his or her tinnitus.

Tinnitus can be masked with a sound.[8-11] When this masker sound stops, the tinnitus may temporarily reduce or even temporarily become absent. This phenomenon is referred to as ''residual inhibition'' and lasts seconds to minutes.[12] Tinnitus Care (London, UK) produces a pure-tone phase-shift device that tries to elongate the residual inhibition effect by shifting the phase of a pure-tone stimulus. It is a noninvasive tinnitus therapy aimed at inhibiting the tinnitus by presenting a specially synthesized sound for 30 minutes by headphones. The theory behind this device is based upon sound cancellation. In sound cancellation, a sound wave is generated with the same amplitude and frequency, however with an inverted phase to the original sound, so the original sound and the generated sounds cancel each other out. Tinnitus is a patient's endogenous

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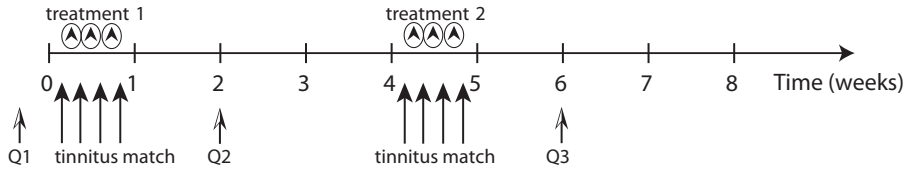

Figure 1. Timeline of the double-blind crossover treatment design for each subject. Treatments 1 and 2 were separated by 1 month; each treatment consisted of 3 sessions. Questionnaires were filled out 3 times (Q). Tinnitus loudness and pitch match was performed 8 times (arrows). Tinnitus loudness and annoyance was rated daily for 4 weeks.

wave and may be cancelled by negating the cortical perception of tinnitus. The theory thus assumes that the tinnitus is perceived as a sound wave with a constant phase and that optimal suppression occurs with a tone with a phase shift of 180 degrees relative to the ''endogenous wave.'' However, the sound-wave phase of the tinnitus, if any, is not known, and therefore the device is equipped with a 6-degree phase shift every 30 seconds. This phase-shift sound therapy essentially aims to elongate the period of residual inhibition.[13] In the United States and Belgium, pilot studies with the phase-shift device (also: phase-out device) have been performed with mixed results.[13-15] Lipman and Lipman[13] compared a sound generated by the audiometer with a phase-shift sound generated with the phase-shift device in a single-blind study. They showed an improvement of at least 1 grade in the Tinnitus Handicap Inventory (THI) questionnaire in 42% of the subjects and a mean reduction of 9.2 dB in the tinnitus loudness match. Vermeire et al[15] evaluated the phase-shift treatment for a week. If a positive effect was noticed, the device was given to the patient for 6 weeks. In contrast, Meeus et al[14] found no effect of the phase-shift therapy, comparing patients with tinnitus resembling a pure-tone noise and with tinnitus resembling narrow-band noise.

Because of these mostly promising results, we performed a randomized double-blind crossover study to evaluate this new treatment according to consort statements.[16] We compared the effect of the phase-shift therapy with that of a nonshifting pure-tone control therapy. To achieve well-controlled results and to keep the burden for a subject acceptable, we chose to give each treatment throughout 1 week, taking into account that in a previous study,[15] effects were already noticeable after 1 week of treatment in patients with pure-tone tinnitus. To evaluate the effect of the phase shift, a tinnitus-matched pure tone without phase shifts was presented as control treatment. With this design, we specifically test the effect of the phase shifts in the tone stimulus.

Material and Methods

We performed a randomized double-blind crossover efficacy study, in which each participant underwent a phase-shift treatment and a control treatment. The treatments started 1 month apart. This study was approved by the Medical Research Ethics Committee of the University Medical Center Groningen.

Sample Size

To determine the sample size, the 1.5-decrease in tinnitus loudness (from 6.4 to 4.9, standard deviation 2.2) on a 10-point visual analog scale was used, which was described by Vermeire et al.[15] While testing 2-sided with $\alpha = .05$ and 80% power, it was found that 19 patients would be needed to obtain significance, in a crossover randomized control study design.

Randomization and Blinding

The order of the treatments was randomized across the subjects: 13 subjects received phase shift as their first treatment, and 12 started with the control treatment. Before the study started, an independent audiologist randomized the subject numbers by a select allotment. Stratification was not applied in the randomization. The treatment settings were identical in every way, except for 2 identical laptops, 1 delivering a phase-shifted signal and the other a non-phase-shifted control tone. The treatment and control laptops were marked by letters *A* and *B* on the bottom, respectively. This indication was blind to the subject and to the examiner. The laptop was placed in the audiometric room by an independent audiologist, prior to the entry of the subject and the examiner.

Participants

Twenty-five patients were recruited, all having tinnitus that was continuously present and resembled a pure tone. Their hearing thresholds at the standard audiometric frequencies (250-8000 Hz) were all $\leqslant$60 dB hearing level (HL). Pregnant subjects or subjects with acousticus neurinoma, aortic tract stenosis, or pulsatile tinnitus were excluded. All subjects consulted our clinic for tinnitus as their primary complaint.

Intervention

The intervention treatment consisted of 3 sessions (**Figure 1**). The sessions took place within 1 week on Monday morning, Wednesday morning, and Friday morning, in a large sound-isolated room that is normally used for audiometric testing. Each session started with a tinnitus-matching procedure, in which the subject matched an external pure tone in frequency and loudness to his or her tonal tinnitus for at least 3 times. The median values were used as the best tinnitus match. The matched frequency and intensity were used to generate the treatment tone. The frequency-matched and loudness-matched

tone was presented on the tinnitus ear for 30 minutes, while the phase of this pure-tone stimulus was shifted by 6 degrees every 30 seconds. During the treatment, the subject was free to do some reading.

All stimuli were controlled via an IBM Thinkpad Lenovo R60e laptop using the Tinnitus Control, Inc (London, UK) software. The frequency could be set from 100 to 13,000 Hz in 10-Hz steps for 100 to 1000 Hz and 100-Hz steps for 1000 to 13,000 Hz. The intensity could range from 0 to 110 dB HL with 1-dB increments. The laptop was connected to a phase-shift sound generator (Tinnitus Care), which delivered its stimuli through Sony MDR-V600 headphones. All equipment was provided by Tinnitus Control, Inc.

Control

The control treatment was identical to the intervention treatment, except that the stimulus consisted of a pure tone without phase shifting. A separate laptop was used, with an appearance that was identical to that of the intervention laptop. The sound generator used for the control treatment was the same as that of the intervention. The software for the control treatment was developed by the manufacturer of the phase-shift sound generator (Tinnitus Care). The appearance and user interface of this program was identical to that of the computer program used for the intervention. Thus, the investigator and the patient could not distinguish the hardware and software used for the investigational and control treatments, respectively.

Evaluation

The treatments were evaluated by an audiometric tinnitus pitch and loudness match, subjective ratings of the tinnitus loudness and annoyance, and questionnaires.

The tinnitus matching was performed before and after each treatment with the same equipment that was used for the treatments: a pure tone was matched in frequency and loudness to the subject's tinnitus.

Subjects kept a tinnitus diary in which they filled out a daily rating for tinnitus loudness and tinnitus annoyance for 4 weeks. Subjects were instructed to rate their mean daytime tinnitus in the evening. The score ranged from 0.0, which represents the worst possible condition (unbearable tinnitus), to 10.0, which corresponds to the best possible situation (no tinnitus). In addition to this daily rating, we also asked them to provide ratings before the first treatment session and immediately after each treatment session.

The evaluating questionnaires were the THI,[17] the Tinnitus Reaction Questionnaire (TRQ),[18] the Hospital Anxiety and the Depression Scale (HADS),[19] and the Maastricht Questionnaire (MQ) for vital exhaustion.[20] The questionnaires were filled out before the first treatment and 1 week after the end of each treatment (**Figure 1**).

The THI consists of 25 items to quantify the impact of tinnitus on daily living. The responses to each of the 25 items are assessed by a 3-point scale (0 = no, 2 = sometimes, 4 = yes) and are summed to get the total score. The score is interpreted in terms of handicap severity. Scores ranging from 0 to 16 indicate no or slight handicap, 18 to 36 indicate mild handicap, 38 to 56 indicate moderate handicap, 58 to 76 indicate severe handicap, and 78 to 100 indicate catastrophic handicap.

The TRQ consists of 26 items and assesses tinnitus-related distress. The responses to each of the 26 items are evaluated by a 5-point Likert scale (0-4; 0 = *not at all* to 4 = *almost all of the time*) and are summed into a total score.

The HADS includes 2 subscales: anxiety and depression. Both subscales consist of 7 items each. Subjects answer on a 4-point Likert scale (0-3; 0 = *not at all* to 3 = *most of the time*). Thus, scores could range from 0 to 21 for anxiety as well as for depression. A subscale score >11 is considered an indication of depression or anxiety. The combined score of 16 or more is suggestive of depression and anxiety.

The MQ consists of 21 questions that assess the vital exhaustion of individuals. Each question is rated from 0 to 2, which gives a total score ranging from 0 to 42.

Statistical Analyses

Statistical analyses were performed with PASW Statistics 18 (SPSS, Inc, an IBM Company, Chicago, Illinois). The paired Wilcoxon signed ranks test was performed to evaluate the effect of both treatments separately and the effect of the phase-shift treatment over the control treatment. Pearson correlation was performed to compare the individual effect of both treatments.

Results

Patient distribution is shown in **Figure 2**. Of the 25 patients who started the study, 3 did not complete the study. In 1 case, the tinnitus had stopped before the first treatment. In the second case, the tinnitus loudness increased during the treatment, which led the patient to withdraw from the study. The third patient decided not to complete the study because it was too time-consuming. The median age of the remaining 22 participants was 53 years (range, 41-68 years). There were 19 men and 3 women. The median tinnitus duration was 3 years and 6 months, ranging from 8 months to 52 years. The tinnitus was reported to be on the right side in 6 cases, on the left side in 1 case, in both ears in 7 cases, and centrally localized in 8 cases. The average tinnitus frequency match was 6.6 kHz, ranging from 1.3 to 12.5 kHz. None of the participants used hearing aids or had equilibrium problems. Seven participants had noise exposure prior to the onset of their tinnitus. The hearing thresholds were 60 dB HL or better. **Figure 3** displays the audiometric characteristics of the subject group.

Figure 4 shows spectra of the control and treatment stimuli, respectively. The spectrum of the phase-shift treatment stimulus is broader than that of the control treatment stimulus, which is consistent with the presence of phase shifts in the treatment stimulus.

To investigate the separate treatment effects, the differences between pretreatment and posttreatment measurements were analyzed (**Table 1**). The only significant effect was a reduction of the intensity of the tinnitus matching tone in the case of the control treatment, from a median

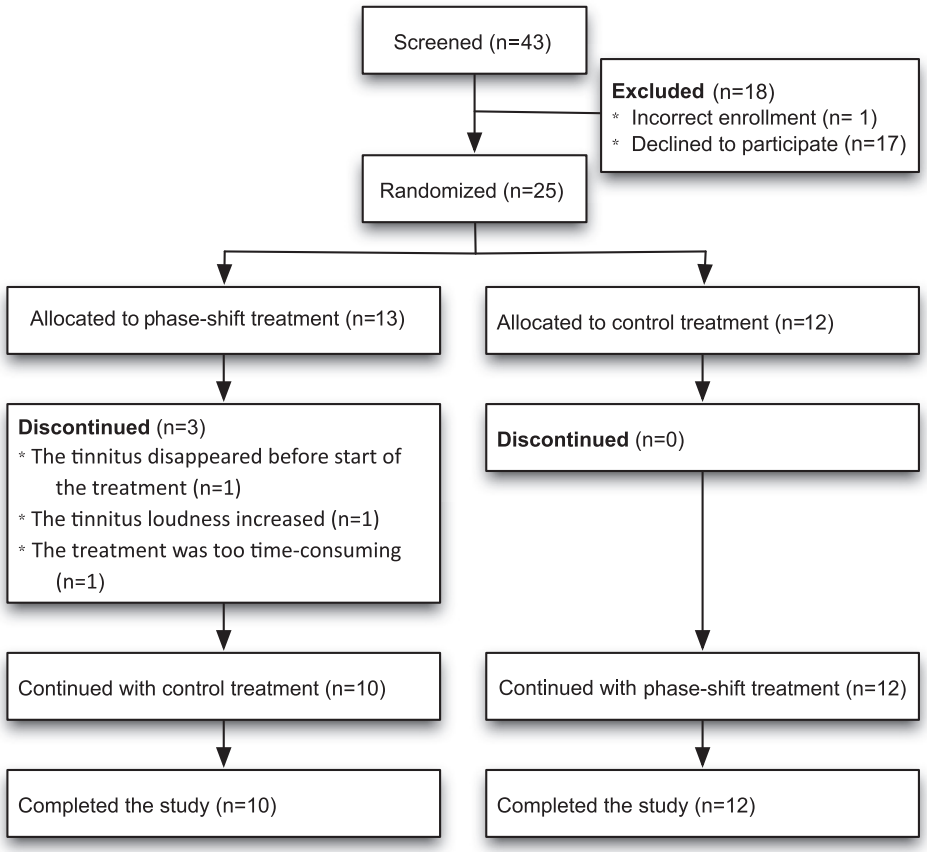

Figure 2. Flowchart of patient inclusion. Forty-three patients were screened; of the 25 who were enrolled, 3 dropped out and 22 (= 10 + 12) completed the study.

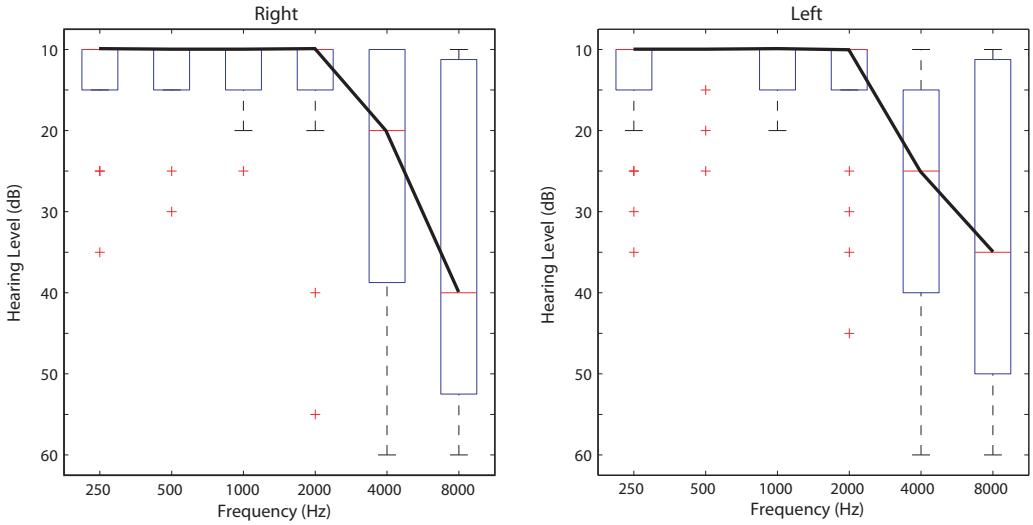

Figure 3. Box and whisker plots of the hearing thresholds on the audiometric frequencies. The boxes have lines at the lower quartile, median, and upper quartile values; whiskers are at the extreme data values (within 1.5 times the interquartile range); outliers are denoted by a "+". The bold lines connect the median values.

value of 65.5 dB to 57 dB (paired Wilcoxon signed ranks test [pWSRT], $P = .002$; **Figure 5**).

Consequently, the differences between the paired treatment results were calculated (**Table 2**). The immediate effect of the treatment on the perceptual characteristics of the tinnitus was assessed by 3 measures: (1) a subjective rating of the perceived loudness, (2) a subjective rating of the tinnitus annoyance, and (3) the intensity of a tone that

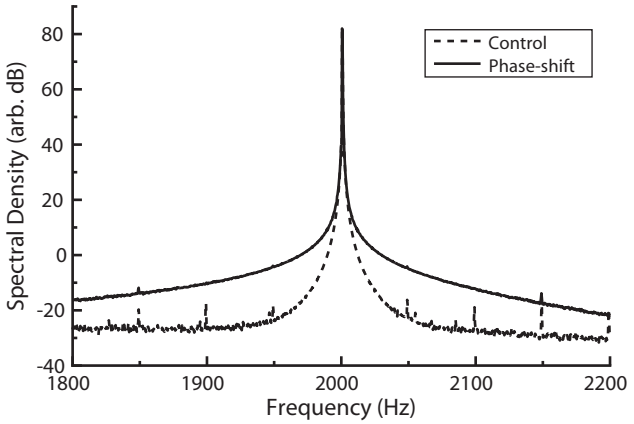

Figure 4. Spectrum of the phase-shift stimulus and the pure-tone control treatment stimulus. Here, the stimulation frequency was set at 2000 Hz.

was matched in loudness to the tinnitus. No significant improvement was demonstrated. Other measures, such as the tinnitus loudness and annoyance rating, filled in by the subjects in a diary, showed no beneficial improvement after the phase-shift treatment in comparison with the effect of control treatment for individual subjects.

The TRQ, THI, HADS total, and MQ questionnaire scores showed no significant treatment effect for either treatment as well (**Figure 6**). Furthermore, the scores after each treatment were not significantly different (**Table 1**).

Finally, the individual effects of the phase-shift treatment and control treatment (ie, the score after a treatment minus the score before the treatment) were visually analyzed in a scatter plot to see if there were individuals in whom one of the treatments performed better (**Figure 7**). This graph shows that individual subjects who benefited from 1 treatment also experienced relief from the other treatment (ρ = 0.89, $P < .001$). This was also found for the THI and the other questionnaires.

Discussion

The main result of our study is that the phase-shift treatment did not have a significant beneficial group effect on tinnitus, as far as this could be evaluated with questionnaires, audiological matching procedures, and loudness and annoyance ratings of tinnitus (**Figures 4-6**). Both the phase-shift and the control treatments had effects in some patients. However, when the phase-shift treatment was compared with the control treatment, there were no significant differences in outcome (**Tables 1** and **2**). In addition, the outer ranges of the confidence intervals indicate that even in higher numbered future studies, a clinical meaningful effect is not to be expected.

Our control treatment consisted of a pure-tone stimulus. This does not imply that we think that the pure tone has no effect on tinnitus; we therefore did not use the term *placebo*. Rather, our study was designed to investigate whether the small phase shifts in the treatment tone have a *specific* effect on tinnitus. None of the outcome measures suggests any additional positive effect of the phase-shifting technique.

Nevertheless, both treatments changed the audiological and questionnaire outcomes in individual patients. For example, in 1 patient, the THI and TRQ score improved by more than 30 points. Thus, the phase-shift and control treatments may possibly have a positive effect in a selected patient population. Criteria on how to select such patients are, however, presently unknown, and additional research would be necessary to investigate this.

The stimulus exposure time, which was chosen to be in line with the expected residual inhibitory effect, is a limitation of this study. We cannot rule out that longer exposures could lead to an effect, possibly explained by a neuronal

Table 1. Pretreatment Patient Characteristics and Effects of the Phase-Shift and Control Treatments

	Pretreatment Results	Effect Phase Shift		Effect Control	
	Median and 95% Confidence Intervals	Median and 95% Confidence Intervals across Subjects	*P* Value	Median and 95% Confidence Intervals Across Subjects	*P* Value
Tinnitus loudness, dB HL[a]	55.5 (48.9, +68.1)	–0.5 (–4.0, +0.0)	.06	–2.5 (–4.1, +0.0)	.002[b]
THI (0-100)[a]	33.0 (20.0, +43.8)	–3.0 (–6,0, +1.8)	.32	–4.0 (–6.0, +3.8)	.06
TRQ (0-104)[a]	34.5 (16.8, +44.3)	–1.5 (–6.1, +1.0)	.16	–1.0 (–4.1, +1.0)	.24
MQ (0-42)[a]	25.0 (21.9, +35.1)	0.0 (–2.0, +3.0)	.61	0.0 (–2.0, +2.0)	.97
HADS total (0-28)[a]	12.0 (4.9, +14.0)	–2.0 (–3.5, +0.5)	.12	0.0 (–5.0, +1.0)	.18
Loudness rating (0.0-10.0)	5.0 (3.0, +5.0)	0.0 (0.0, +1.0)	.33	0.0 (0.0, +1.0)	.09
Annoyance rating (0.0-10.0)	6.0 (5.0, +6.0)	0.0 (0.0, +0.0)	.55	0.0 (0.0, +0.8)	.59

The second column shows the patient characteristics at the start of the study. The last columns show the effects of the 2 treatments, reported as median difference with the 95% confidence intervals across subjects. The effects were calculated as the score after treatment minus the score before treatment (thus a negative effect denotes a lower score after the treatment). Analyses were performed using the paired Wilcoxon signed rank test. Abbreviations: HADS, Hospital Anxiety and Depression Scale; HL, hearing level; MQ, Maastricht Questionnaire; THI, Tinnitus Handicap Index; TRQ, Tinnitus Reaction Questionnaire.

[a]Measurement/questionnaires with a positive value indicate increased severity.

[b]Significant at the 5% (P = .05) level.

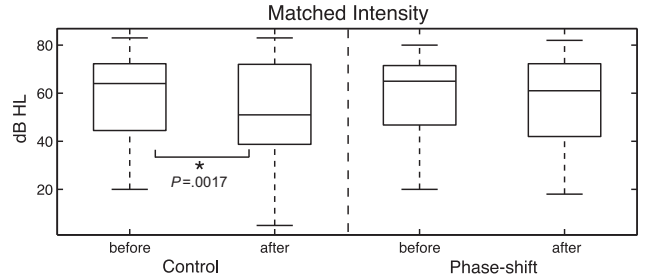

Figure 5. Box and whisker plots showing the matched tinnitus intensity before and after each treatment (third session). Only the matched intensity for the control treatment was significant (*). The boxes have lines at the lower quartile, median, and upper quartile values; whiskers are at the extreme data values. HL, hearing level.

Table 2. Difference between the Phase-Shift Treatment and the Control Treatment

	Median Treatment Differences and 95% Confidence Interval	*P* Value
Tinnitus loudness, dB HL[a]	0.5 (–1.0, +4.1)	.19
THI[a]	3.0 (–2.0, +6.0)	.19
TRQ[a]	0.0 (–1.3, +3.0)	.82
MQ[a]	0.0 (–1.0, +2.1)	.51
HADS total[a]	0.0 (–1.5, +1.5)	1.00
Loudness rating	0.0 (–0.3, +0.0)	.65
Annoyance rating	0.0 (–1.0, +0.6)	.41

For each subject, the paired difference was calculated by subtracting the effect of the control treatment from the effect of the phase-shift treatment. The second column shows the median of the differences across subjects. For the first 5 quantities in the first column ([a]), larger values correspond to a poorer condition, whereas for the last 2 quantities, larger values correspond to a better condition. Thus, a positive difference for the questionnaires or the tinnitus loudness match in the second column and a negative difference for both ratings indicate a disadvantage of the phase-shift treatment over the control treatment. Analyses were performed using the paired Wilcoxon signed rank test. Abbreviations: HADS, Hospital Anxiety and Depression Scale; HL, hearing level; MQ, Maastricht Questionnaire; THI, Tinnitus Handicap Index; TRQ, Tinnitus Reaction Questionnaire.

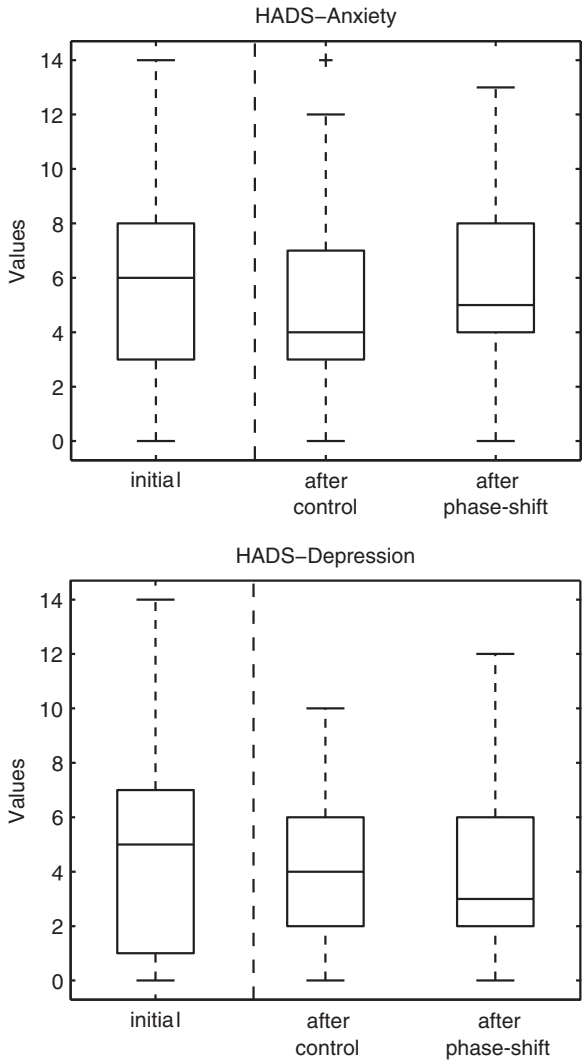

Figure 6. Box and whisker plots of the Hospital Anxiety and the Depression Scale (HADS), filled out at the start of the study and after each treatment. No significant differences were found. The boxes have lines at the lower quartile, median, and upper quartile values; whiskers are at the extreme data values (within 1.5 times the interquartile range); outliers are denoted by a "+".

plasticity mechanism leading to the inhibition of tinnitus. On the other hand, this study does demonstrate that phase shifting has no auxiliary residual inhibitory effect compared with a non-phase-shifting pure-tone stimulus. We suggest that the effects reported by other authors of nonrandomized crossover designs may be biased by a placebo effect.

Choy et al[21] hypothesized that the phase-shift treatment would cancel out neuronal activity in the auditory cortex by a mechanism similar to the acoustic cancellation by antiphasic sound. However, such cancellation is improbable for neuronal signals. Note that our tinnitus subjects on average had a tinnitus pitch that matched a tone of 6.6 kHz. Because auditory neurons have negligible phase locking to tones above 4 kHz (see, eg, Johnson[22]), the phase of the stimulus tone will not be coded in the neural response, ruling out the option of neuronal antiphasic cancellation. Thus, the neural activity in response to the phase-shift tone presumably has characteristics nearly identical to that of a pure tone, and as a consequence, subjects do not hear the difference between a pure tone and the phase-shift tone. This gave us the possibility to set up a double-blind study. However, it also shows that the physiological basis for an effect of the phase-shift treatment remains unclear.

Other authors[13,15,21] have reported more positive outcomes of the phase-shift treatment. Like the present study, Lipman and Lipman[13] used a pure-tone stimulus as a control. This control condition was administered in the 2 weeks prior to the phase-shift treatment, where its presentation was nonrandomized and not blinded to the investigator. Furthermore, they described an effect lasting up to 1 week. Consequently, it cannot be dismissed that possible long-term effects of the control condition could influence the test

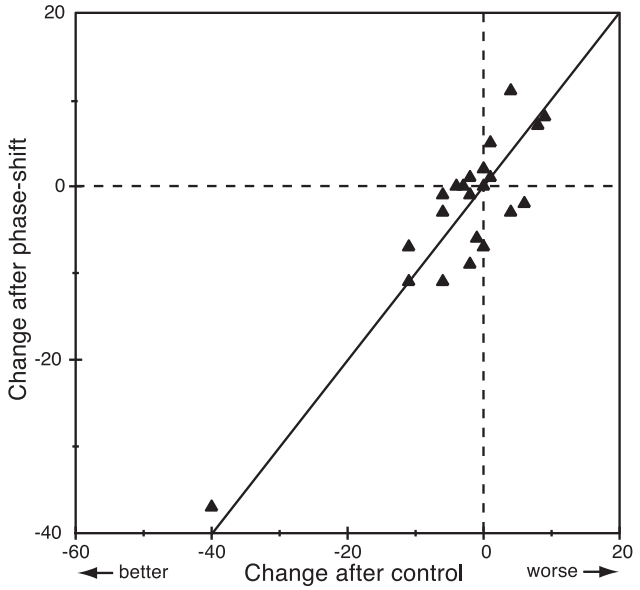

Figure 7. Scatter plot of the changes in Tinnitus Reaction Questionnaire (TRQ) outcomes after the control treatment vs changes after the phase-shift treatment. Each data point represents 1 individual. The solid line (x = y) shows where both treatments had the same effect.

condition in this study. Vermeire et al[15] lacked a control treatment and included only those subjects who responded positively to a test with the phase-shifting device similar to our testing situation. One could argue that the measured effects in their selection procedure could for the most part be caused by a placebo effect, which is strong in tinnitus therapies.[9] Selectively proceeding with these positive subjects may further enlarge the amount of placebo contributing to the measured effect. Their treatment protocol differed also from ours and Lipman and Lipman's in that subjects could take the phase-out device home for a longer period of time. Possibly, the long take-home treatment period has a positive effect, explained by neuroplasticity, and this could be a focus for further research.

Choy et al[21] described a control setting in a part of their combined study (n = 35). This crossover design was not blinded or randomized. The time between the different treatments was not mentioned, and only the phase-shift treatment was applied at the tinnitus loudness, whereas the 2 control treatments had a fixed loudness and were presented at 77-dB loudness. This design may have resulted in a significant placebo effect on the tinnitus.

To our knowledge, our study is the first double-blind crossover efficacy study of the phase-shift treatment. The main conclusion is that, on average, the phase shifting had no significant effect on tinnitus. In individual patients, we did observe changes during the phase-shift treatment period, but these changes were similar to those of a pure-tone control treatment.

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Author Contributions

Karin M. Heijneman, contributions to concept and design, acquisition of data, analysis and interpretation of data, drafting the article, and final approval of the version to be published; **Emile de Kleine**, contributions to concept and design, analysis and interpretation of data, revising the article, and final approval of the version to be published; **Pim van Dijk**, contributions to concept and design, analysis and interpretation of data, revising the article, and final approval of the version to be published.

Disclosures

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