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Safety and Efficacy of Vagus Nerve Stimulation Paired With Tones for the Treatment of Tinnitus: A Case Series

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Objective: Classical neuromodulation applies current to the nervous system in an attempt to alter ongoing activity. However, classical neuromodulation interferes with activity but does not drive it in a controlled way. Recently, an animal study demonstrated it is possible to drive plasticity in a controlled way by using stimulation of the vagus nerve paired with tones. This reversed the tinnitus percept and pathological neural plasticity in noise-exposed rats with behavioral characteristics of tinnitus. The aim of the current study was to translate this innovative neuromodulation method to humans suffering from tinnitus.

Materials and Methods: Ten patients with severe chronic tinnitus were implanted with electrodes on their left vagus nerve. Two and a half hours each day for 20 days, the patients heard tones, excluding the tinnitus-matched frequency, paired with brief electrical stimulation of the vagus nerve.

Results: The therapy was well tolerated, and no patient withdrew from the study due to complications or side-effects. Four of the ten patients exhibited clinically meaningful improvements in their tinnitus, both for the affective component, as quantified by the Tinnitus Handicap Inventory, and for the sound percept, as quantified by the minimum masking level. These improvements were stable for more than two months after the end of therapy. Of the ten patients, five were on medications that included muscarinic antagonists, norepinephrine agonists, and γ-amino butyric acid agonists, thereby possibly interfering with acetylcholine and norepinephrine release induced by vagus nerve stimulation (VNS) and essential for inducing plasticity. These patients had no improvement in contrast to medication-free patients.

Conclusion: VNS paired with tones excluding the tinnitus-matched frequency is safe and feasible. It seems to exert a beneficial effect in nonmedication-taking patients, both with regard to the perceived sound and the distress. Further studies are therefore mandated.

Keywords: Tinnitus, vagal nerve stimulation

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INTRODUCTION

Tinnitus often results from exposure to occupational- or leisure-related loud sounds (1,2) that could transiently or permanently damage the inner hair cells of the cochlea (3–5). This loss of auditory input may set up a cascade of neurophysiologic changes in the central auditory system culminating in the perception of a phantom sound. Neurophysiologic changes likely result from the imbalance between excitation and inhibition that can lead to map reorganization and increased synchronous firing of auditory neurons (6). Auditory neurons that are deprived of input begin to respond to the same frequencies as neighboring neurons that receive input from undamaged parts of the cochlear (7–9). This change in neuronal behavior results in reorganization of the auditory cortex map, and an increase in the number of neurons generating synchronous activity might be responsible for the tinnitus sensation (6,10,11).

Therapies including passive (i.e., hearing aids) (12) and active sound therapy, consisting of either masking (13) or customized sound therapy (14), pharmacotherapy (15,16), and frequency discrimination training (17), have shown some benefit. Unfortunately, these interventions are nonspecific and insufficient to reverse the pathological changes that cause tinnitus. Recently, neuromodulation techniques have been developed to treat tinnitus (18). Transcranial magnetic stimulation targeting the auditory (19,20) or cingulate cortex (21,22), transcranial direct current

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stimulation (23–25), and implantation of electrodes overlaying the auditory (26–33) or frontal cortex (34) or into the amygdalohippocampal area (35) all have been used in attempt to silence the phantom sound percept. Improvement in tinnitus also has been observed by modulation of the caudate nucleus via electrodes inserted for other indications (36,37). Other neuromodulation techniques try to modulate the auditory system via somatosensory interactions (38,39). Transcutaneous electrical nerve stimulation (40,41) and subcutaneously implanted electrodes (35) targeting the C2 nerve have been used for controlling tinnitus as well. Yet these techniques most likely only disrupt ongoing activity without driving plasticity in a controlled and therapeutic direction.

Recently, a new method was introduced that can drive auditory cortex plasticity in a controlled and therapeutic direction by pairing repeated short-term simulation of the vagus nerve with simultaneously presented tones (42–45). That is, repeatedly pairing a brief burst of vagus nerve stimulation (VNS) with a 9 kHz tone in normal rats causes a dramatic expansion of the region of primary auditory cortex that responds to 9 kHz (42). Tinnitus is associated with a similar overrepresentation of the tinnitus-matched frequency (42). To treat tinnitus in noise-exposed rats, VNS was paired with a variety of tones that exclude the tinnitus frequency, thereby eliminating the behavioral and physiologic manifestations of tinnitus in a rat model (42). Based on this animal study (42) noninvasive transcutaneous VNS with (46) or without (47) sound therapy has been performed in tinnitus patients, demonstrating that the transcutaneous VNS is safe (47) and that transcutaneous VNS plus sound therapy can improve the tinnitus-related distress and severity (46).

The aim of the current study was to verify whether these results can be translated to a human population of tinnitus patients in a safe and efficient way using invasive VNS. We therefore repeatedly gave short-term simulation of the vagus nerve paired with tones, excluding the tinnitus frequency, in ten subjects with chronic tinnitus. All stimulation and auditory presentation parameters are kept as similar as possible to the previous animal study. The goals of this proof-of-concept feasibility study were to provide preliminary evidence that VNS paired with tones 1) is potentially safe; 2) is safe in a diverse tinnitus population; 3) is safe as an effective treatment for tinnitus; and 4) determines the effect size to power a randomized placebo-controlled study.

METHODS

Participants

The study took place at the Tinnitus Research Initiative multidisciplinary Tinnitus Clinic at the University Hospital of Antwerp, Belgium between December 2010 and February 2012. The trial was registered on clinicaltrials.gov under reference number NCT01253616.

Inclusion criteria to be enrolled in the study were 1) age between 18 and 65 and 2) diagnosed as suffering from subjective tinnitus due to hearing loss with sensorineural aspects and at least some tonal quality of the tinnitus. Patients had to be 3) diagnosed with tinnitus for at least one year and 4) have a Tinnitus Reaction Questionnaire (TRQ) score of 18 or greater. Furthermore, 5) the patients should have had no new tinnitus treatment for at least four weeks prior to study entry and 6) have the ability to give informed consent and understand study requirements with the 7) ability to quantify tinnitus severity using a 0–100 numeric rating scale; 8) be medically and neurologically stable as determined by medical history and documented neurologic examination; 9) willing and able to understand and comply with all study-related procedures during the course of the study; 10) be motivated to maintain an accurate diary for the study duration.

The exclusion criteria were 1) acute or intermittent tinnitus; 2) severe hearing loss that, in the opinion of the investigator, will interfere with the study; 3) history of significant ear disease, such as Meniere's disease, ear tumors, or evidence of active middle ear disease (such as fluids, infection, tumor, mass, etc.); 4) active infection; 5) any other implanted device such as a pacemaker or other neurostimulator and any other investigational device or drug; 6) untreated drug habituation or dependence; 7) psychologically or medically unstable; 8) pregnant, plans to become pregnant, or is breastfeeding; 9) currently require, or likely to require, diathermy during the study duration; 10) history of adverse reactions to anesthetics (e.g., lidocaine); 11) have major active psychiatric illness that may, in the opinion of the principal investigator, interfere with required study procedures or treatments; 12) ingesting a drug(s) known to cause tinnitus.

Several patients were screened, and in total, 15 patients were potential candidates for this treatment as all other possible noninvasive treatments did not help. In total, 12 patients agreed with the VNS treatment and signed the informed consent. However, two patients dropped out of the study before implantations as they preferred to try another treatment. Ten adult subjects (eight men; two women) 23–59 years (M = 45.6 years, SD $\pm$ 9 years) were implanted in the study. Subjects had unilateral or bilateral tinnitus for more than a year (M = 5.4 years; SD $\pm$ 4.1). In nine out of ten patients, the tinnitus was described as ringing (tonal), whereas in one patient, the tinnitus was described as roaring. There was no history of neurologic disorders: three patients had Beck Depression Inventories between 30 and 35. All patients were intractable to audiological, drug, and neuromodulation treatments. They all completed baseline evaluations and were good candidates to be implanted with an electrode surrounding the left vagus nerve using the same technique described for the treatment of epilepsy and depression (48–52). For the ten patients implanted, all had VNS tone therapy and completed the four-week study. Medications in patients were kept stable during the trial.

Adverse events were defined as any undesirable medical occurrence in a study participant, whether or not considered related to the study devices or procedure, which is identified or worsens during the clinical study. Adverse events were assessed and documented by the investigator at all study visits. Patients were actively asked about the possible adverse events. Hearing function was tested before, weekly during the trial, and six months after the treatment. Both the Antwerp University Hospital Ethics Committee and Belgian Competent Authority reviewed and approved the study and all applicable documents prior to study initiation. All patients signed an approved informed consent in order to enroll into the study.

Audiological Assessment

Audiological assessment included the audiometry (high-frequency audiogram with pure tones for both air and bone conduction including speech audiogram) and the tinnitus matching (pitch and loudness). All patients were screened for the extent of hearing loss using a pure tone audiometry using the British Society of Audiology procedures at 0.125, 0.25, 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 14, and 16 kHz (53). Tinnitus patients were tested for the tinnitus frequency by doing a tinnitus analysis. In unilateral tinnitus patients, the tinnitus analysis was performed contralateral to the tinnitus ear. In bilateral tinnitus patients, tinnitus analysis was performed contralateral to the worst tinnitus ear.

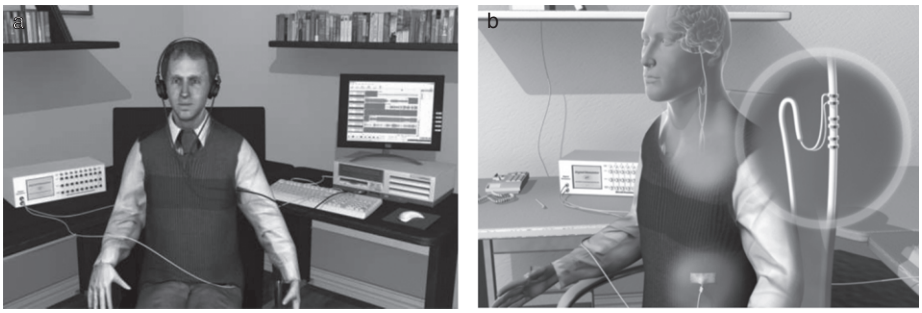

Figure 1. Stimulation setup: (A) The patient is connected to the DS8000 digital electrical stimulator (white box on the left). A computer triggers the DS8000 to deliver electrical stimuli at the vagus nerve (B) and after 150 msec activates the tone presentation delivered by the ear phones the patient is wearing.

The tinnitus matching analysis consisted of the assessment of the tinnitus pitch and loudness. First, a 1-kHz pure tone was presented contralateral to the (worst) tinnitus ear at 10 dB above the patient's hearing threshold in that ear. The pitch was adjusted until the patient judged the sound to most resemble his/her tinnitus. The loudness of this tone was then adjusted in a similar way until it corresponded to the patient's perceived tinnitus loudness as well. The tinnitus loudness (dB SL) was computed by subtracting the absolute tinnitus loudness (dB HL) with the auditory threshold at that frequency (54,55).

Surgical Implantation and Postimplantation Procedures

The VNS cuff electrode was implanted using standard surgical procedures that are typically used for epilepsy (48–50). Briefly, the patient was anesthetized and positioned in a reclining position with the head rotated to the right. An incision along the anterior border of the left sternocleidomastoid muscle was made. After a superficial neck dissection, the carotid sheath was defined, and the vagus nerve was dissected free from the surrounding tissue. The electrodes were attached to the nerve, and the nerve was then placed back in its normal anatomic position. The lead was looped in a gentle curve and sutured through a silicone retainer adjacent to soft tissue to avoid tension on the lead. A second loop was made superficially and sutured to the fascia of the sternocleidomastoid muscle. Next, an abdominal incision was made above the waist line and 2–3 cm left of midline. An extension lead was tunneled between the cervical and abdominal incisions. The extension lead was connected to the vagus nerve electrode. Patients were allowed to recover for 24 hours. After determining that the patients did not have any adverse events from the surgical procedure, they underwent a tone-only session the next morning. The extension lead was removed at the end of the trial, whereas the vagus nerve electrode remained in place.

VNS Tone Pairing Therapy

The VNS system included a commercially available electrode (Cyberonics model 302/303/304 lead, Cyberonics, Inc., Houston, TX, USA), a commercially available external stimulator (DS8000, World Precision Instruments, Sarasota, FL, USA), and an external synchronization computer system (including MicroTransponder software [MicroTransponder, Dallas, TX, USA]) to deliver VNS pulses (via the external stimulator to the lead). Therefore, this setup was a percutaneous modification of the VNS implant without the implantable pulse generator (IPG; Cyberonics Inc.) typically used in standard VNS implants. This modification was necessary because the shortest pulse train duration delivered by the IPG was seven seconds, whereas our study utilized a short 0.5-sec burst of VNS.

The external stimulation system (http://www.wpi-europe.com/en/products/stimulators/DS8000.shtml) was connected to the abdominal lead to provide VNS (see Fig. 1).

Stimulation was delivered at an intensity of 0.8 mA, 100 μsec pulse width at 30 Hz, every 30 sec. If necessary, the output current (0.8 mA) could be reduced to 0.05 mA steps for comfort if the patient so desired. These stimulation parameters were chosen based on the efficacy of VNS tone pairing in a previously reported study (42). The stimulation intensity was lower and pulse width shorter than what is typically delivered for epilepsy (48–50). This translates to 150 sec of total daily stimulation compared with approximately 8600 sec of VNS that is typically delivered daily for epilepsy (i.e., around 1% of that delivered for epilepsy). Moreover, patients did not receive VNS during most of the study period (i.e., >21.5 hours per day).

A pure tone was paired with each VNS pulse. Each tone frequency was delivered to both ears via headphones. VNS was delivered 150 ms prior to each tone, and both the tone and VNS train duration were 0.5 sec long. Patients underwent ~2.5 hours of daily VNS tone pairing for 20 days for five days a week (i.e., Monday through Friday) for four weeks.

Tone frequencies ranged from 170 to 16,000 Hz. Tones were selected from a stimulus set consisting of 25 tones (170, 284, 413, 559, 724, 910, 1121, 1360, 1629, 1935, 2280, 2670, 3112, 3611, 4176, 4815, 5537, 6354, 7278, 8324, 9506, 10,843, 12,355, 14,066, and 16,000 Hz). Tones half an octave on either side of the tinnitus frequency were excluded from the stimulus set. When the tinnitus frequency was different on each side, both frequencies were excluded, and the surrounding tones were played. The total number of tones presented would depend on one or more tinnitus frequencies and varied from patient to patient depending on the patients' tinnitus frequencies. The order of the tones was randomized. This selection was based on the rationale that pairing VNS with multiple tones surrounding the tinnitus frequency would decrease the number of neurons representing the tinnitus frequency and decrease synchrony and spontaneous activity (42). In order to prevent the overrepresentation of a few frequencies, a wide variety of tones covering the entire auditory spectrum, but excluding the tinnitus-matched frequency, was presented.

For each frequency, the tone intensity was based on the patient's audiogram. If the threshold exceeded 40 dB HL, the intensity of the tone delivered was 80 dB HL. For thresholds between 20 and 40 dB HL, the tone intensity was 70 dB HL, and finally, for thresholds 0–20 dB HL, the tone intensity was set to 60 dB HL.

After four weeks of acute therapy, stimulation was discontinued for two months to assess continuation of response.

Tinnitus Assessment

For tinnitus assessment, we obtained both subjective and objective measures from each of the patients. Patients were assessed on each measure at baseline and then every week for four weeks (until end of therapy). Patients were then followed up with assessments up to six months after therapy.

The primary outcome measures were both the Tinnitus Handicap Inventory (THI) (56) and the minimum masking level (MML) so that we include both a subjective and a more objective measure for the tinnitus. The secondary outcome measures were administered to each of the patients and included the TRQ (57), Iowa Tinnitus Handicap Questionnaire (THQ) (58), and the Iowa Tinnitus Activities Questionnaire (TAQ) (58) as well as electroencephalogram (EEG) recordings. All questionnaire measures have been used in previous research on tinnitus and have shown to be good psychometric measures with a good reliability and validity (41,43).

Tinnitus assessments were performed before the stimulation, immediately after the stimulation (at four weeks), and at follow-up (between three and six months) after the end of therapy.

PRIMARY OUTCOME MEASURES

THI

The THI was selected for adoption because it is a brief and easy-to-administer questionnaire that is suitable for use in busy clinical settings (56). The THI is a 25-item self-administered questionnaire that aims to quantify the impact of tinnitus on daily life. Respondents are asked to answer the questions with "yes" (4 points), "sometimes" (2 points), or "no" (0 points). A higher THI score (maximum 100) is indicative of a greater tinnitus handicap.

Minimal Masking Level

The MML test attempted to determine the lowest level at which a standard band of noise "covered" the tinnitus (i.e., rendered it inaudible). The test ear was typically on the side with the louder or predominant tinnitus; if there was no difference between the sides, each ear was tested separately. The test stimulus consisted of a standardized band of noise generated (2–12 kHz, rolling off at approximately 12 dB per octave). The patient's threshold for the noise band was measured, and the level of the noise band was then raised in 1 dB increments until the patient reported that the tinnitus was no longer audible (up to the limits of the equipment or the patient's tolerance level, whichever was reached first). The level at which the tinnitus was just rendered inaudible was recorded in dB SL and was referred to as the MML.

SECONDARY OUTCOMES MEASURES

TRQ, THQ, and TAQ

TRQ

The TRQ is a scale designed to assess the psychological distress associated with tinnitus and is a useful index of distress related to tinnitus for subject selection and clinical assessment and has potential as a measure of change in coping ability (57). This scale consists of 26 items. Respondents are asked to answer the questions with "almost all the time" (5 points), "most of the time" (4 points), "now and then" (3 points), "very occasionally" (2 points), and "not at all" (1 point).

THQ

The THQ (58,59) is a scale comprised of 27 items and is a well-established measure for the assessment of a broad spectrum of tinnitus-related psychological complaints. Patients were asked to indicate on a scale from 0 (they strongly disagree) up to 100 (they strongly agree) if they agree.

TAQ

The Iowa TAQ quantifies the emotional aspect of tinnitus as well as problems that are associated with concentration, hearing, and sleep due to tinnitus. Patients were asked to score questions on a scale from 0 (they strongly disagree) up to 100 (they strongly agree).

EEG recordings

EEG data were recorded from seven subjects during therapy sessions using standard methods. We recorded one time between 15 and 45 min during a stimulation session during the last week of the treatment (expect on the last). Data were recorded from 19 silver chloride electrodes mounted in an elastic cap over the following International 10–20 System sites: Fp1, Fp2, F7, F3, Fz, F4, F8, T3, C3, Cz, C4, T4, T5, P3, Pz, P4, T6, O1, and O2. EEG was low-pass filtered at a cutoff frequency of 150 Hz and notch-filtered at 50 Hz and then digitized with a sampling rate of 500 Hz. VNS trials and non-VNS trials were identified in the EEG data by the presence or absence, respectively, of VNS artifact. Trials in which movement noise exceeded half the average amplitude of the VNS artifact were discarded.

The power spectrum of the EEG was calculated over a five-second pre (before stimulation) ending 100 ms prior to VNS and beginning one-second post-VNS Windows, respectively. Change in band power between pre- and postanalysis windows was calculated for standard delta (1–4 Hz), theta (4–8 Hz), alpha (8–13 Hz), beta (13–30 Hz), and gamma (30–100 Hz) bands, and the effect of VNS (during stimulation) was quantified by subtracting the band power change for no stimulation trials from the band power change for VNS trials. The effect of VNS on band power was averaged across all channels within each subject and then compared with changes in THI and MML taken prior to and following the full course of therapy. Correlation was measured with Pearson's *r*.

RESULTS

Compliance and Safety

Patient 001 had redness at the abdominal site and vocal cord hypomobility after the surgery; both resolved within two weeks of the surgery. Patient 003 had an infection of the extension lead during the long-term follow-up period and had their Cyberonics' lead and electrode explanted. Patient 004 had an increase in tinnitus symptoms for the first week after the implant. The patient also had an already ongoing depression which resolved within two weeks after deanxit (melitracen + flupentixol), lormetazepam, and quetiapine (see Table 1 for overview). This patient also had hoarseness during stimulation and had difficulty tolerating standard settings (output current was reduced from 0.8 to 0.6 mA for the duration of the acute study). Upon return to the site for a long-term therapy visit, the patient was staying by themselves in a hotel and experienced a depressive episode and a subsequent failed suicide attempt. The patient had not received VNS therapy for four days prior to the attempt, so the therapy is not thought to have impacted the attempt. The patient recovered and returned home.

For the ten patients implanted, all had paired VNS therapy and completed the four-week study. All patients except one returned for at least one follow-up visit. Patients returned for varying amounts of follow-up, for as little as a month and as much as a year.

Table 1. Patient Demographics, Tinnitus Characteristics, and Scores on the THI and MML for the Baseline, Immediately After One Month of Treatment, and Follow-up.

Patient	Sex	Age	Tinnitus (years and cause)	Tinnitus location	Type	Tinnitus frequency (kHz)	NE/GABA antagonist
001	M	59.5	14 (neck surgery)	Bilateral	Ringing	R: 10–12.5; L: 6–8	N
002	M	46.7	2.5 (blast)	Left	Ringing	10	N
003	M	42.9	7 (noise)	Left	Roaring	4–6	N
004	M	51.1	5 (unknown)	Bilateral	Ringing	8	Y
005	M	45.2	7 (unknown)	Bilateral	Ringing	R:12.5; L:10	Y
007	M	46.9	10 (unknown)	Right	Ringing	R: 8	N
008	M	45	3 (noise)	Right	Ringing	14	Y
010	F	51.3	2 (unknown)	Bilateral	Ringing	6–8	Y
011	F	23.8	1.5 (noise)	Bilateral	Ringing	1	Y
012	M	44.2	2 (noise)	Right	Ringing	R: 14–16	N

M, male; F, Female; R, right; L, Left; THI, Tinnitus Handicap Inventory; MML, minimum masking level; NE, norepinephrine; GABA, γ-amino butyric acid.

Table 2. Patients' Treatment for Tinnitus Before NVS and Medication During NVS.

Patient	Previous known treatments for tinnitus	Medication during NVS
001	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone), TMS, tDCS, neurofeedback, cortical implant	Acetylcysteïne, Algocod (acetaminophen + codeine phosphate), Cinnarizine, Perindopril, Duloxetine, Allopurinol, Fentanyl, Epsipam -Tetrazepam, Fenofibrate, Trazodone, Paracetamol, Amitryptiline
002	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone), TMS, tDCS, hearing device	—
003	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone), TMS, tDCS, neurofeedback, hearing device, tinnitus masker, cortical implant	
004	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone), TMS, tDCS, hearing device, neurofeedback, cortical implant	Deanxit (melitracen + flupentixol), Quetiapine, Lorazepam, Lormetazepam
005	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone), tDCS, TMS	Clonazepam, deanxit (melitracen + flupentixol), Mirtazapine
007	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone), TMS, tDCS, hearing device, tinnitus masker, neurofeedback	—
008	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone), tDCS, TENS, TMS	Deanxit (melitracen + flupentixol), Naporex, Deinsercroin
010	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone, zonegram), TMS, TDCS, TENS	Deanxit (melitracen + flupentixol), Clonazepam
011	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone, silnoct), TMS, TENS, tDCS	Clonazepam
012	Medication (clonazepam, deanxit [melitracen + flupentixol], cyclobenzaprine, naltrexone, zonegram), TMS, tDCS, TENS, tACS, rTRNS, hearing device	—

NVS, nervus vagus stimulation; TMS, transcranial magnetic stimulation; tDCS, transcranial direct current stimulation; TENS, transcutaneous electrical nerve stimulation; tACS, transcranial alternating current stimulation; rTRNS, transcranial random noise stimulation.

Tinnitus Population

The tinnitus population that was included in this study was relatively diverse in terms of tinnitus causes and tinnitus characteristics. Four patients had tinnitus due to noise trauma, one due to a blast, and one due to surgery. Four patients did not know what caused their tinnitus. Five patients located their tinnitus bilaterally, whereas two patients on the left side and three on the right side. Nine perceived their tinnitus as a ringing sound and one patient as a roaring sound. See Table 2 for an overview.

Audiological Measurements

All ten subjects underwent audiological evaluation to assess the degree of hearing loss. Most subjects had mild to moderate hearing loss (25–60 dB HL) for frequencies >3 kHz (Fig. 2). Five subjects had severe hearing loss (60–80 dB HL) for frequencies ≥12.5 kHz. None of the patients had profound hearing loss (80 dB HL). Tinnitus frequency matching was performed to determine the best match to the perceived tinnitus frequency. The tinnitus frequencies ranged from 1 to 16 kHz but were typically greater than 5 kHz ($M = 8.8$ kHz; $SD = 4.1$).

Primary Outcome Measures

THI

The scores for each patient over the different time points can be found in Figure 3 (Table 3 gives an overview of the baseline scores). Overall, the average decrease in THI score from the baseline was

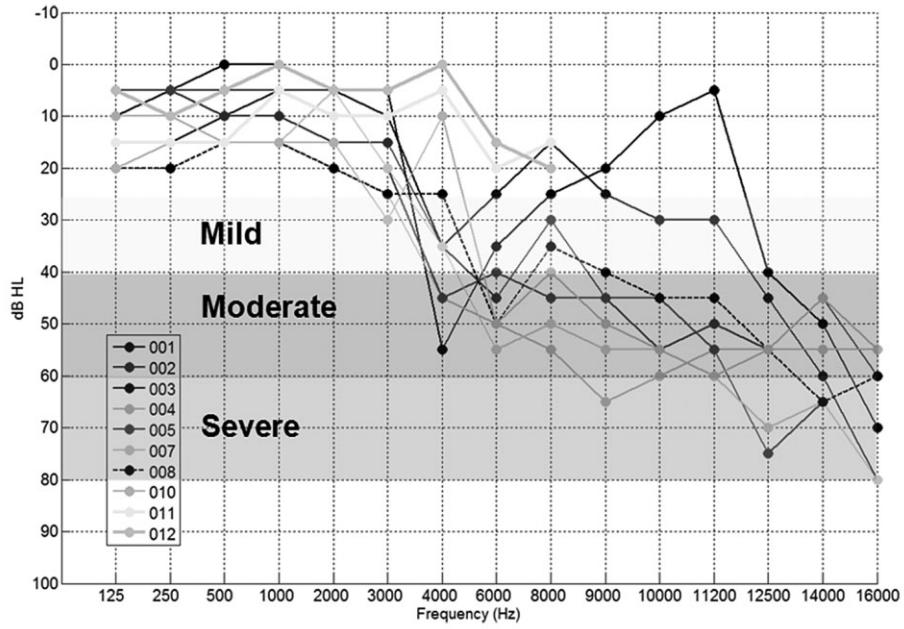

Figure 2. Audiograms of each patient before the treatment.

10.92% immediately after the treatment and 11.78% for the follow-up in comparison with the baseline. To determine whether certain drugs might have interfered with the VNS therapy, patients were classified into a drug group ($n = 5$ patients) and no-drug group ($n = 5$ patients). An overview is given of the obtained results for each patient separately in Table 1. Patients in the drug group were taking medications for other problems (e.g., depression) that included muscarinic antagonists, noradrenergic reuptake inhibitors, and γ-amino butyric acid agonists. Patients in the no-drug group showed a mean decrease of 28.17%, whereas patients in the drug group showed an increase of only 0.97% on the THI immediately after the treatment. Three out of five patients (60% of patients) in the no-drug group had a clinically meaningful decrease in the THI (44.3% decrease). For the follow-up, we saw an overall decrease of 26.06% for the no-drug group, whereas a decrease was demonstrated of only 1.94% was demonstrated for the drug group in comparison with the baseline.

MML

The average drop in MML for all patients was 12.33 dB immediately after the treatment and 14.17 dB for the follow-up (see Fig. 3). Patients in the no-drug group showed a mean decrease of 18.8 dB, whereas patients in the drug group showed a decrease of 4.25 dB immediately after the treatment. Four out of five patients (80% of patients) in the no-drug group had a clinically meaningful decrease in the MML (26.7 dB decrease). These patients continued to maintain the benefit of the therapy in the long term (29 dB decrease) suggesting that the beneficial effects of VNS are long lasting. For the follow-up, patients in the no-drug group had a decrease of 12.75 dB, whereas patients in the drug group had an increase of 2.25 dB. For patient 004, no MML was obtained.

Secondary Outcome Measures

TRQ, THQ, and TAQ

Overall, the improvement on the TRQ, THQ, and the TAQ was respectively 12.98%, 4.81%, and 2.17% immediately after the treatment period (Table 3 gives an overview of the baseline scores). For the follow-up, an overall improvement was obtained of 15.98% for the TRQ, 6.48% for the THQ, and 10.11% for the TAQ. When focusing only on the no-drug group, a reduction of 28.20%, 7.58%, and 8.41% immediately after the treatment period was recorded and a reduction of 32.06%, 15.69%, and 18.43% at follow-up. For the drug-group patients immediately after treatment, changes were recorded of 6.27%, 2.56%, and –1.08%, and for the follow-up, –0.10%, 2.73%, and 1.79% on respectively the TRQ, THQ, and TAQ.

EEG Results

EEG data were recorded from subjects 001, 003, 004, 005, 007, 008, and 011 during therapy (see Fig. 4). EEG recording durations varied between subjects so that there were EEG data for between 87 and 226 trials, with a median of 143 trials per subject. Due to technical problems, EEGs of three patients were not recorded.

Generally, VNS pulse trains decreased band power in the delta (1–4 Hz) and theta (4–8 Hz) bands in subjects who responded to therapy, and increased band power in those bands in subjects who did not respond. The average difference in band power change between VNS and sham trials was strongly correlated with the THI for both the delta ($r = 0.83$, $p = 0.022$) and theta ($r = 0.74$, $p = 0.055$) bands. As the results were similar between the delta and theta bands, they were combined into a single band of 1–8 Hz, and the average difference in 1–8 Hz band power change between VNS stimulation and no stimulation is plotted against changes in THI ($r = 0.90$, $p = 0.006$) scores in Figure 4. This latter effect remained after correction for multiple comparisons. The effects of VNS on band power change in the alpha (8–13), beta (13–30), and gamma (30–100 Hz) bands were not significantly correlated with changes in THI. For the MML, no significant effects were obtained.

DISCUSSION

The aim was to translate a recent animal study in which VNS was paired with a variety of tones that exclude the tinnitus frequency as

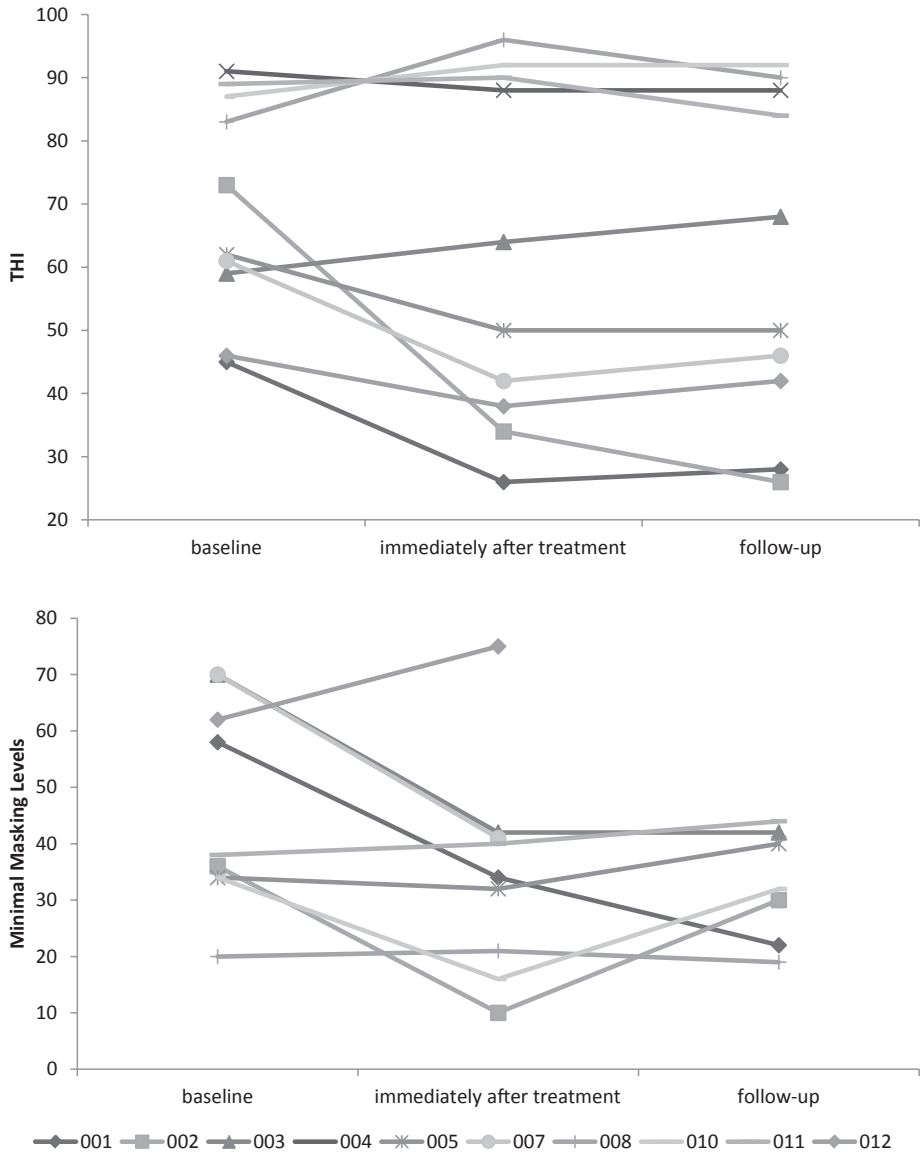

Figure 3. The time course (baseline, immediately after the treatment, and follow-up) for the Tinnitus Handicap Inventory and the minimal masking levels for every patient separately (patients with a square did not take any medications that modifiy neuromodulator action, whereas patients with a star took medication which impairs neuromodulator action).

Table 3. Patient Baseline Scores for the THI, TRQ, THQ, and TAQ.

Patient	THI	TRQ	THQ	TAQ
001	45	46	60	56
002	73	58	72	65
003	59	61	67	88
004	91	103	87	78
005	62	52	60	71
007	61	59	75	80
008	83	76	91	86
010	87	95	92	85
011	89	73	74	71
012	46	43	42	52

THI, Tinnitus Handicap Inventory; TRQ, Tinnitus Reaction Questionnaire; THQ, Tinnitus Handicap Questionnaire; TAQ, Tinnitus Activities Questionnaire.

a way to drive plasticity and thereby treat tinnitus. This study was similar in design to animal studies in which VNS tone pairing reversed the tinnitus percept and pathological plasticity in noise-exposed rats (42). In both the animal and human studies, identical VNS parameters were used, approximately 300 times a day for four weeks. In both cases, tones that were paired with VNS covered the range of hearing but excluded tones within half an octave of the tinnitus frequency.

This is a first open-label pilot study attempting to bring this research to a human clinical setting. This includes all the weaknesses and strengths of these kinds of studies. All new invasive neuromodulation studies are initially performed on small groups and usually in an open-label setting, as this is easier, cheaper, and quicker. If there is no sign of a benefit in the preliminary data, it doesn't make sense clinically, ethically, or financially to proceed with larger studies.

Unlike the animal study, all patients did not get the benefit of the VNS paired therapy. Several reasons could account for this. One of

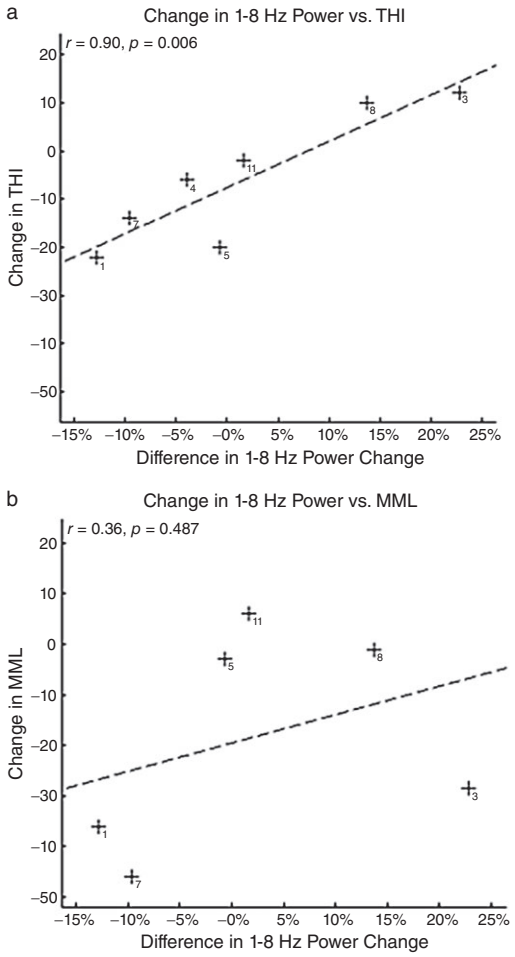

Figure 4. Correlation between the transient reduction in low frequency electroencephalogram (EEG) power triggered by vagus nerve stimulation (VNS) and improvement in tinnitus as measured by the Tinnitus Handicap Inventory (THI) (A) and MML (B). Cases 4, 5, 8, and 10 were patients that took norepinephrine (NE)/γ-amino butyric acid (GABA) antagonist.

the reasons could be the variability of our study population: The tinnitus group selected was relatively diverse for the cause of tinnitus, the tinnitus laterality, the tinnitus frequency, and tinnitus pitch. However, these preliminary results do not indicate that specific patients have a better response due to these specific tinnitus characteristics. Yet further research is needed to verify whether these can influence our potential outcome in a larger group, as previous research on transcranial magnetic sitmulation (20,60) and transcranial direct current stimulation (24) indicated that the outcome can depend on specific tinnitus characteristics.

However, it is also possible that the clinical efficacy is not strong in comparison with the animal studies because the treatment started late after the tinnitus onset in tinnitus patients. The inclusion criteria stipend that patients were required to suffer from tinnitus for at least one year, whereas in animals, the treatment was started a month after inducing tinnitus. Previous research on neuromodulation (i.e., transcranial magnetic stimulation [TMS]) for the treatment of tinnitus already demonstrated that the effects are influenced by the duration of the tinnitus (61–63). Furthermore, hearing thresholds were different in the patient population, which has important effects on the presence of map plasticity (64) critical in the treatment.

It is also not known whether the stimulation parameters used to activate the human vagus nerve are optimal. It is possible that different stimulation frequencies and different pulse widths or amplitudes might yield better results, as these factors influence stimulation effectiveness (65).

Another factor possibly explaining why our preliminary clinical findings were inferior to the preclinical study in rats might be related to the study subjects. When performing an animal study, most rats are genetically closely related. In humans who present at a tinnitus clinic, there might be a bigger genetic variability. In view of the fact that the response to neuromodulation seems to be genetically influenced, at least for transcranial direct current stimulation (tDCS) and TMS, by for example BDNF polymorphism, it is possible that factors such as the genetic makeup of the patient partially determine whether or not he/she might respond to VNS and auditory stimulation.

The post hoc analysis identified another possible factor influencing the results, which could also explain part of the difference with the animal data, namely the intake of medication, a finding which could possibly in the future become the most important finding of the study. As the group that took medication had no benefit from the VNS tones pairing in contrast to the medication-free group, it is possible that the medications prevented the beneficial effect of the therapy. It is well-known that drugs can interfere with the acetylcholine and norepinephrine metabolism and release, and thereby they could have blocked the effects of VNS (66,67). When VNS is used for the treatment of epilepsy (68) or depression (69), the drugs taken by the patients don't seem to interfere with the outcome of VNS. This could be explained by the fact that most antiepileptic medication does not act on norepinephrine or acetylcholine, and most of the modern antidepressant medication preferentially targets serotonin. Another explanation could be that the drugs do not interfere with the direct electrical VNS component in itself, which could be of clinical importance but only on the induction of acetylcholine- or norepinephrine-mediated plasticity when pairing sounds with VNS. Even though it is likely, based on theoretical neurobiological reasons that the medication interfered with the VNS and auditory stimulus-related neuroplasticity, it cannot be excluded that the medicated group did not respond to the treatment because of other reasons, such as the disease itself for which the medication was given.

When evaluating the clinical benefit of a treatment, it should be evaluated in the light of alternative treatments. The patients selected for this treatment were highly bothered by their tinnitus and have already undergone all possible treatments available at a specialized multidisciplinary tinnitus clinic, the Tinnitus Research Initiative Clinic in Antwerp, Belgium. Thus, a future study incorporating an internal pulse generator is essential, the more so because no control group was used in this study.

It could be argued that the tinnitus improvement obtained could be solely explained by an antidepressant effect of the VNS, as VNS is used to treat depression. Even though this cannot be excluded, it is however unlikely in view of the fact that the applied method delivers less than 1% of the typical VNS protocol for epilepsy and depression. However, further studies should unpair the VNS from the auditory stimuli (as in the preclinical study (42)) to clearly demonstrate that this is not the case.

An important aim of this pilot study was to provide preliminary evidence that VNS paired with tones is a potentially safe and feasible in humans. Our initial report suggests that the side-effects were comparable with VNS in the clinic and did not interfere with compliance or efficacy. All patients completed the four-week study, and side-effects due to stimulation were rare (hoarseness).

The results suggest that VNS paired with auditory stimuli is as safe as isolated VNS as the findings are similar to VNS used in more than 60,000 people worldwide for the treatment of severe depression and epilepsy. Complications can result from the surgery itself or during use of the device. Potential risks related to the implantation procedure include bleeding and bruising around the incision site, pain in the incision site, infection, and adverse reaction to anesthesia. Other side-effects of VNS include dyspepsia, diarrhea, dyspnea, hiccups, laryngismus, muscle twitch, nausea, vomiting, paresthesia or skin tingling at site, and pharyngitis. A small number of patients (0.1% of patients or fewer) have reported cardiac effects during implantation, but these are typically transient and caused no long-term complications. The currently applied VNS pairing therapy uses 100 times less VNS than the US Food and Drug Administration has approved to treat epilepsy and depression. As a result, we did not expect severe side-effects in this study. Our data demonstrated that VNS paired with tones excluding the tinnitus-matched frequency seems safe and feasible as no complications were mentioned that were specifically related to the pairing of the vagus and sound stimulation. Larger studies should be performed as (1) the sample was very small; (2) the tinnitus did not improve in some patients; (3) the follow-up period was short.

Furthermore, stimulation of the vagus nerve in the neck is a less invasive method compared with cortical implantation (26–29,32,33,70) or deep brain stimulation (36,71).

Another aim of this study was to determine the effect size to power a randomized placebo-controlled study. It has been previously claimed that potential clinical effects of promising new tinnitus treatments should be tested first in an open-trial design, which can give important information about the effect size of the treatment and may help to identify subgroups of patients being more likely to respond to the tested intervention (72). This information is necessary to design prospective placebo-controlled clinical trials, which are more costly and time consuming (72). The results of this study demonstrate that VNS with tone pairing is promising for patients who are drug-free. It should be noted that these patients had previously attempted several noninvasive and invasive therapies including drugs, TMS targeting auditory and frontal cortex, tDCS, neurofeedback, and one patient even bilateral auditory cortical implants, none of which had any benefit. This suggests that if confirmed by larger studies, the combined electrical and auditory stimulation can result in improvements not obtained by other treatment approaches. Therefore, future research is needed in a well-designed controlled study with adequate sample size to document the effectiveness of this technique on tinnitus.

In conclusion, even though this was a small open-label pilot study, it has some important findings. Technically, it seems safe and feasible to translate this technique from animals to humans as no complications arose specifically from pairing sound to VNS. Secondly, the results in humans are clearly not as good as in animals for which multiple possible reasons can be given: patient characteristics, medication use, tinnitus characteristics, stimulation parameter choice, etc. In view of the fact that the selected patients were intractable to all other treatments, giving benefit to 60–80% of drug-free patients with chronic severe tinnitus seems sufficient to warrant further studies, tailored to drug-free patients.

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Authorship Statement

Dr. De Ridder designed the study, recruited the patients, performed the implant surgery, and wrote the manuscript. Dr. Vanneste designed the study, recruited the patients, performed the data analysis, and wrote the manuscript. Dr. Engineer developed the technology, designed the study, and wrote the manuscript. Dr. Kilgard developed the technology, designed the study, and wrote the manuscript.

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COMMENT

A very interesting approach utilizing neuromodulation to harness the processes of neuroplasticity. Tinnitus is the "neuropathic pain" of the auditory circuitry, representing a multimodal dimension of sensation, attention and emotional responses as is the case with neuropathic pain. While many neuromodulation approaches have focused on interrupting the activity underlying the tinnitus percept, this novel approach seeks to re-train the brain. While this was a pilot effort, future studies must include a controlled design. I look forward to these studies.

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Comments not included in the Early View version of this paper.

