Otology & Neurotology
36:575–580 © 2015, Otology & Neurotology, Inc.

Placebo-Controlled Vagus Nerve Stimulation Paired With Tones in a Patient With Refractory Tinnitus: A Case Report

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Objective: Classical neuromodulation consists of applying electrical or magnetic stimuli to the nervous system to modulate ongoing activity and connectivity. However, recently, an exciting novel neuromodulation technique was developed in which stimulation of the vagal nerve was paired with simultaneous presentation of tones, demonstrating that it reverses a tinnitus percept in noise-exposed rats.
Study Design: To determine whether this therapy could also be effective in humans, we delivered a similar therapy in a patient with chronic tinnitus unresponsive to previous therapies. In this report, we describe the case of a 59-year-old man who suffered from bilateral tinnitus for 14 years that arose after a cervical fusion operation. Pharmacotherapy, transcranial magnetic stimulation, transcranial direct current stimulation, neurofeedback, and bilateral auditory cortex stimulation via implanted electrodes did not improve the tinnitus. After implanting the vagal nerve stimulator, the patient received daily vagus nerve stimulation tone pairings for 4 weeks in a non–placebo-controlled way.
Results: At the end of therapy, the patient experienced a significant reduction in tinnitus symptoms that lasted for 2 months after treatment. Tinnitus Handicap Inventory and Tinnitus Reaction Questionnaire were reduced by 48% and 68%, respectively. Symptoms of depression were also improved by 40%, as quantified by the Beck Depression Inventory. Three months after ending therapy, placebo stimulation was performed consisting of only tone presentation without the simultaneous electrical stimuli. This resulted in further continuation of the gradual relapse to the baseline state, without renewed improvement.
Conclusion: Our results suggest that vagus nerve stimulation paired with tones could become an effective therapy for the treatment of tinnitus. **Key Words:** Tinnitus—Vagus nerve stimulation.
Otol Neurotol **36:**575–580, 2015.

Classical neuromodulation consists of applying electrical or magnetic stimuli to the nervous system to modulate ongoing resting state or evoked activity as well as functional and effective connectivity (1). Its effects are determined by the brain state at the moment of the stimulation (2) and the stimulation parameters (1). It can suppress hyperactivity resulting from maladaptive plasticity but is poor in driving plasticity in a predetermined way.

One form of neuromodulation is vagus nerve stimulation (VNS), which is an approved treatment for refractory epilepsy and depression, and is being investigated for many other diseases (3). More than 60,000 patients have been implanted worldwide (4), and VNS is well tolerated with minimal side effects (3,4). Recently, it has been shown in animals that, by combining classical VNS with simultaneously presented tones that exclude tinnitus frequency, this difficulty can be overcome, resulting in the normalization of tinnitus (5).

Hyperactivity (6–9) and map plasticity of neurons in the central auditory system subsequent to noise trauma are generally accepted to be related to the tinnitus sensation. Although changes in the auditory cortex typically result from a loss of peripheral input such as cochlear damage caused by noise trauma, other factors (e.g., drugs, somatic input) may also be responsible (10). Recently, it has been demonstrated that reversing the tinnitus-related hyperactivity and map plasticity can eliminate the tinnitus percept in an animal model of noise-induced tinnitus (5). Repeatedly pairing tones with brief pulses of VNS completely

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Supplemental digital content is available in the text.

The authors disclose no conflicts of interest.

eliminated the physiologic and behavioral correlates of tinnitus in noise-exposed rats (5). These improvements persisted for weeks after the end of therapy (5).

Nucleus basalis stimulation or VNS paired with a tone 300 times a day for 4 weeks results in large-scale reorganization of the auditory cortex that was specific to the paired frequency (5,11). This concept was applied in tinnitus by pairing VNS with tones (excluding the tinnitus-matched frequency), reversing both the behavioral percept of tinnitus and the pathologic plasticity in noise-exposed rats (5).

The goal of this study was to provide preliminary evidence that translating this highly successful treatment in animals by VNS paired with tones is feasible, safe, and a potentially effective treatment for tinnitus in humans.

METHODS

Case

The subject was a 59-year-old man with chronic bilateral tinnitus with minimal hearing loss. This patient had previously tried numerous therapies before study enrollment but, because none of the previous therapies were providing benefit, the patient was not on any tinnitus therapy for more than 13 months before enrollment. He underwent preimplant baseline assessment 6 weeks before surgical implantation. Because this was a proof-of-concept case study to determine safety and efficacy of the therapy, we did not label assessments as primary or secondary endpoints. We wanted to determine which assessment measure would be most sensitive to the VNS tone-pairing therapy. The endpoints included a) audiometric measurements (standard audiogram with pure tones for both air and bone conduction, including speech audiogram; b) tinnitus questionnaires including Tinnitus Handicap Inventory (THI), Tinnitus Reaction Questionnaire (TRQ), Iowa Tinnitus Handicap Questionnaire (THQ), and Iowa Tinnitus Activities Questionnaire (TAQ); c) tinnitus pitch matching; d) loudness matching; and e) minimum masking level (MML). We collected this information at baseline immediately before the real or sham stimulation as well as immediately after 4 weeks (5 days a week) of real stimulation and immediately after 1 week of sham stimulation.

Surgery

The VNS cuff electrode was implanted using standard surgical procedures that are typically used for epilepsy (12–14). 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 waistline and 2 to 3 cm left of the midline. An extension lead was tunneled between the cervical and abdominal incisions. The extension lead was connected to the vagus nerve electrode. Patient was allowed to recover for 24 hours. After determining that the patient 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.

Treatment

The VNS system included a commercially available electrode (Cyberonics Model 302/303/304 Lead), a commercially

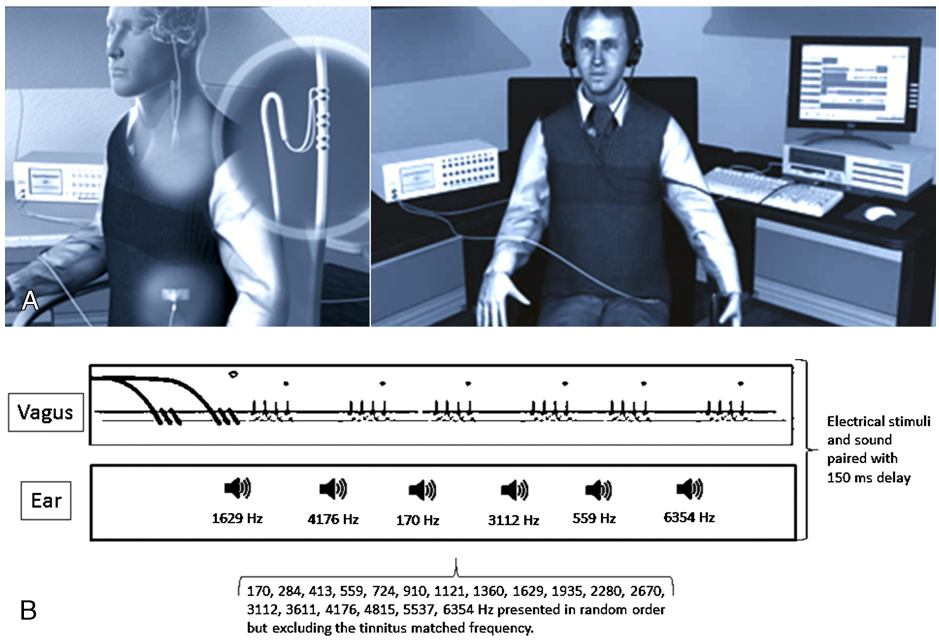

FIG. 1. *A*, Stimulation setup: the patient is connected to the DS8000 digital electrical stimulator *(white box on the left)*. A computer triggers the DS8000 to deliver electrical stimuli at the vagus nerve *(insert, left picture)* and after 150 milliseconds activates the tone presentation delivered by the earphones the patient is wearing. *B*, The pairing of sound stimuli and electrical delivered at the vagus nerve.

available external stimulator (World Precision Instruments-DS8000), and an external synchronization computer system (including MicroTransponder software) to deliver VNS pulses (via the external stimulator to the Cyberonics Lead). The VNS pulses were paired with tones that were delivered by the software. Therefore, this setup is a percutaneous modification of the VNS implant without the Implantable Pulse Generator typically used in standard VNS implants (Cyberonics Inc) (Fig. 1A). This modification was necessary because the shortest pulse train duration delivered by the Cyberonics Implantable Pulse Generator was 7 seconds, whereas our study used a short 0.5-second burst of VNS. The VNS cuff electrode was implanted using standard surgical procedures that are typically used for epilepsy (15) and connected to a custom-made extension lead, exiting the subcutaneous plane at the level of the lower abdominal wall. The patient was allowed to recover for 24 hours. After determining that the patient did not have any adverse events from the surgical procedure, the patient underwent a tone-only session the next morning, followed by the VNS tone-pairing therapy the next day (Fig. 1B). The patient underwent stimulation pairings for a total of 20 days, and tinnitus assessments were performed on Days 4, 10, 15, and 20 of stimulation. During delivery of the therapy, the external system (DS8000) was connected to the abdominal lead daily (Monday–Friday) to provide VNS and paired tones. During each trial, VNS started 150 milliseconds before a tone. Both the tone and VNS train duration (0.8 mA, 100 μs biphasic pulse at 30 Hz) were half a second long. The tone frequencies and intensities were selected based on the subject's audiogram and tinnitus frequency. The tinnitus frequencies were matched to 12.5 kHz in the right ear and 8 kHz in the left ear. Therefore, tones were delivered in a random order across most of the auditory frequency range: 170; 284; 413; 559; 724; 910; 1,121; 1,360; 1,629; 1,935; 2,280; 2,670; 3,112; 3,611; 4,176; 4,815; 5,537; 6,354 Hz but notched out the tinnitus frequencies. Tones half an octave on either side of the tinnitus frequency were excluded from the stimulus set. For each frequency, the tone intensity was based on the patient's audiogram. If the hearing 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 to 20 dB HL, the tone intensity was set to 60 dB HL. A typical stimulation session included a total of 300 stimulation-tone pairings for 2.5 hours per day (in the morning) 5 days a week for 4 weeks. This translates to 150 seconds of total daily stimulation compared with approximately 8,600 seconds of VNS that is typically delivered daily for epilepsy (~1% of that delivered for epilepsy). These stimulation parameters were chosen based on the efficacy of VNS tone pairing in a previously reported study (5). During the 2.5 hours of stimulation, the patient was sitting in a comfortable chair and could read a magazine but was not permitted to sleep. After 4 weeks of acute therapy, stimulation was discontinued for 2 months to assess continuation of response. The patient came in for follow-up assessments every 2 weeks during this period.

Sham Stimulation

At the end of the acute study (4 wk), the patient received no treatment for 2 months. After this washout period, subjective and objective assessments were again carried out. The patient was then treated with sham stimulation for 1 week. He would hear the tones, but after 5 minutes, the electrical stimuli on the vagus nerve were stopped. The patient reported that, in each session, he could feel the first three to four stimuli, as in the acute study, so the patient could not make a difference between sham and real stimulation. The sham period lasted for only 1 week, on request of the patient, because he did not feel any benefit but rather a worsening of the loudness perception of the tinnitus and wanted to stop the trial. He felt that the travel time plus the 2.5 hours of stimulation every day were not worthwhile if there was no improvement but rather worsening. For the same reasons, the effect of electrical stimulation without tones was not tested and the extension lead was removed.

RESULTS

No major adverse effects were observed or reported by the patient; the patient did feel stimulation and reported the typical VNS side effect of hoarseness during stimulation. The patient had a transient left vocal cord hypomobility and slight inflammation at the abdominal surgical site, but both resolved 2 weeks after implant surgery.

Subjective and objective assessments were carried out at baseline and 4 weeks after stimulation. At the end of 4 weeks, the THI score was reduced by 48% and the TRQ was reduced by 68%. A 14-point and 23-point reduction was observed on the THQ and TAQ (Fig. 2). In addition, a decrease was revealed on the THQ and TAQ of both 36%.

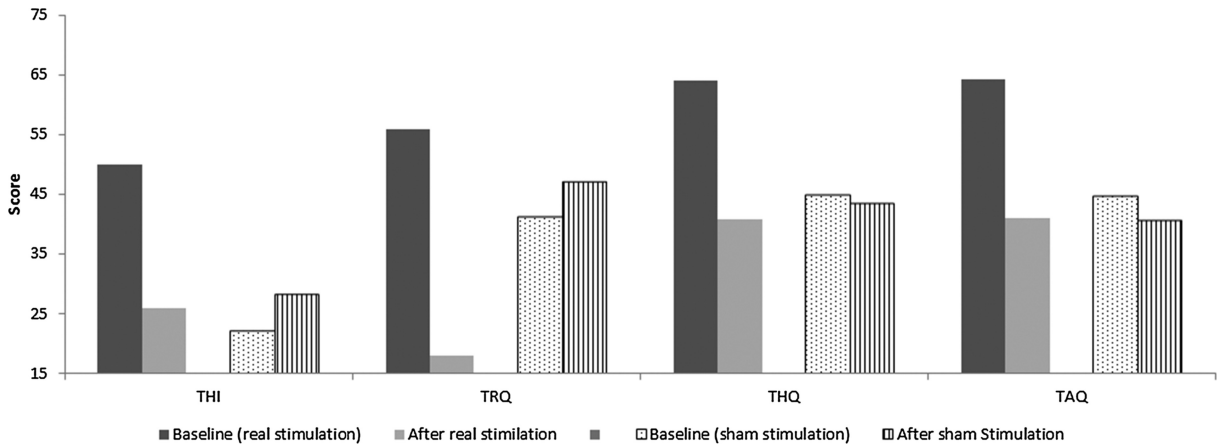

FIG. 2. Baseline (real stimulation), after real stimulation, baseline at 3 months after stimulation, and after sham stimulation: tinnitus questionnaire scores for THI, TRQ, THQ, and TAQ.

At the end of this sham stimulation, an increase on THI was observed of 27% and the TRQ of 15% (Fig. 3). Only small changes were observed for the THQ (3%) and TAQ (9%).

The MML was reduced by 19 dB SL in the right ear (58 to 34 dB SL) and 9 dB SL in the left ear (39 to 30 dB SL) (Fig. 3). Before the sham stimulation period, the MML could not be obtained at baseline (>70 dB SL). After the sham therapy, the MML for the left ear was 22 dB SL and for the right ear 19 dB SL.

In addition, audiogram, tinnitus pitch matching, and loudness matching are recorded for both baseline and after real and sham treatments (Fig. 3). For the audiogram and tinnitus pitch matching, no clinically relevant changes are noted. However, for the tinnitus loudness matching, a clear decrease can be reported for the left ear going from 25 to 5 dB SL whereas, during the sham therapy, it goes from 0 to 10 dB SL. No differences were shown for the right ear.

For the electroencephalography (EEG) resting-state neurophysiologic recordings (see supplementary materials, http://links.lww.com/MAO/A280), a similar comparison between baseline and 4 weeks after stimulation revealed a significant decrease of relative power in the delta, theta, alpha, beta, and gamma frequency band effects after VNS, suggestive of desynchronization (Fig. 4). A comparison between baseline and 4 weeks after stimulation on the sLORETA images revealed a significant ($p < 0.05$) decrease for beta in the dorsal anterior cingulate cortex (Fig. 4). A

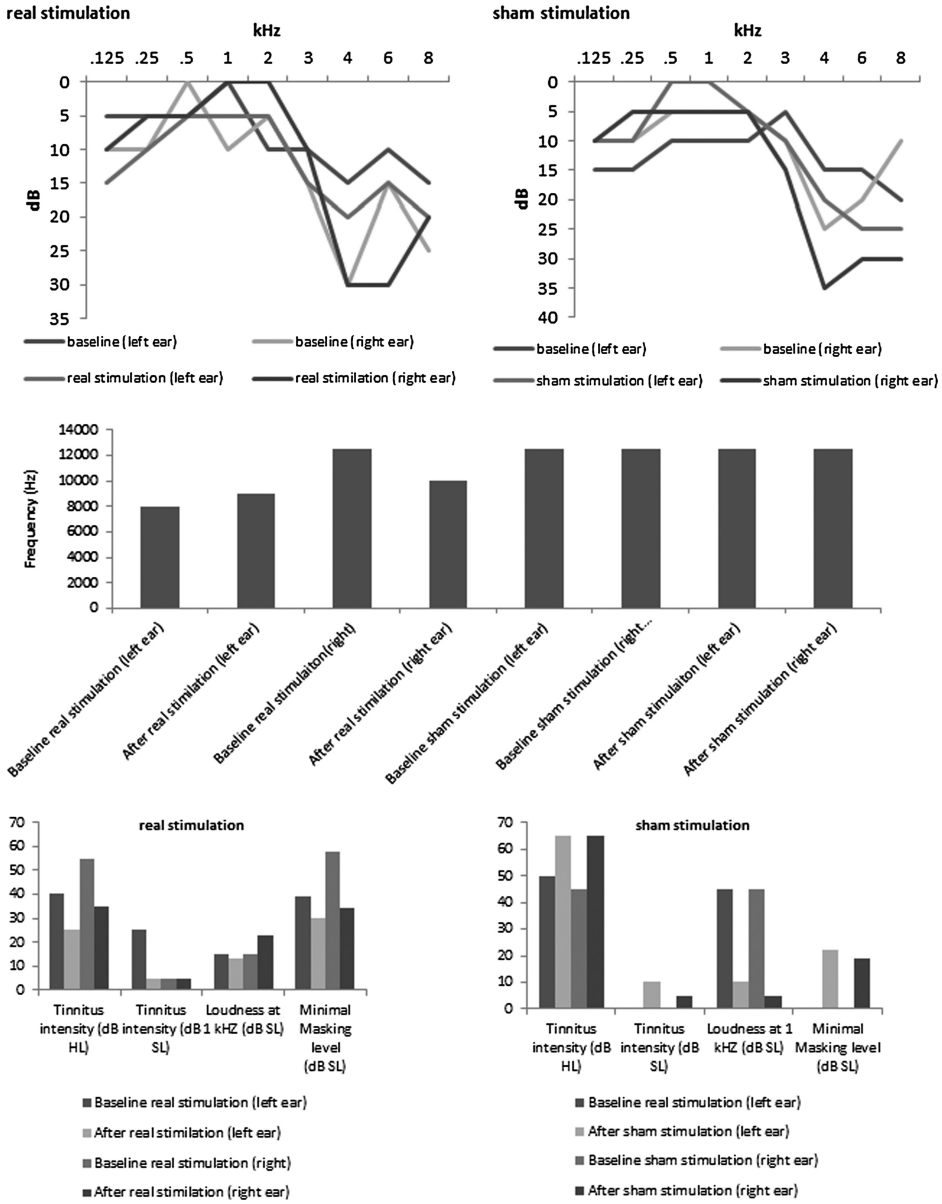

FIG. 3. Audiogram *(top)*, tinnitus frequency *(middle)*, and tinnitus analysis *(lower figure)* at baseline and after 4 weeks of stimulation *(postop)*, at 3 months after stimulation, and after sham stimulation.

similar comparison between the baseline before the sham stimulation and immediately after the sham stimulation period revealed no statistically significant changes.

DISCUSSION

This study demonstrates that brief periods of VNS pairing can decrease tinnitus symptoms, and these effects persist for at least 8 weeks after VNS pairing is discontinued. This study was similar in design to the rat studies in which VNS timed to coincide with tones modified the auditory cortex and eliminated chronic tinnitus by reversing the pathologic plasticity that results from exposure to intense noise (5). In both cases, identical VNS parameters for approximately 300 times a day for 20 days were used. Tone frequencies were obviously different because of differences in the range of frequencies in animal and man.

The effects of VNS pairing seem to last after therapy is discontinued. In this study, follow-up visits after VNS

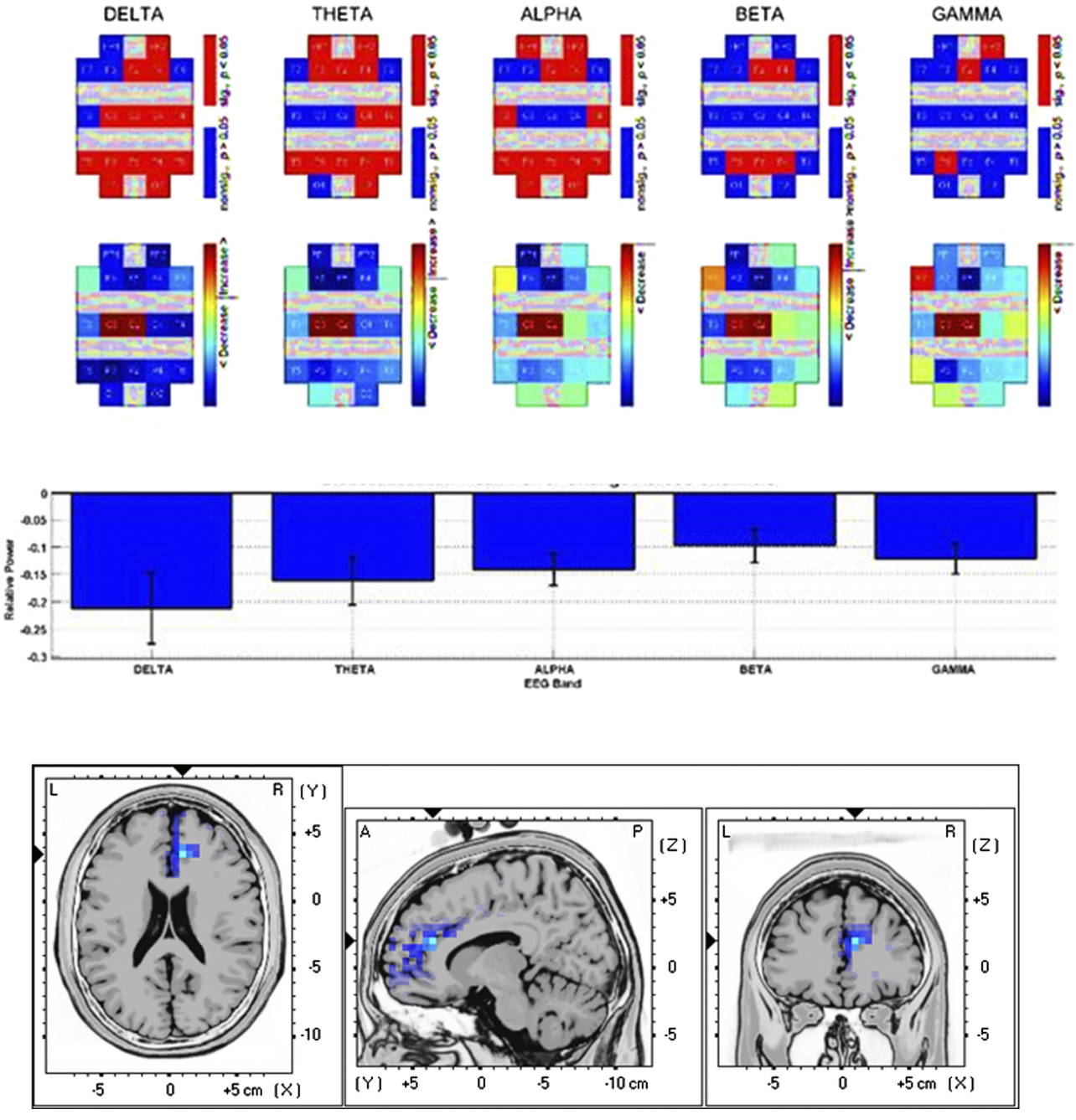

FIG. 4. *Top figure*: The patient shows significant power decreases across all bands during stimulation. *Lower figure*: A comparison of baseline versus 4 weeks after VNS paired with tone stimulation indicates a significant decrease for beta in the dorsal anterior cingulate cortex.

pairing showed that beneficial effects continued for at least 8 weeks but that the clinically beneficial effect decreased after 3 months. To rule out that the effect of the stimulation was caused by placebo, sham stimulation was performed presenting tones without the VNS. This resulted in continued worsening, suggesting that the combination of VNS paired with tones is efficacious.

Tinnitus can result from a number of causes, with the most common being cochlear damage as a result of noise trauma or drug-induced toxicity. This subject however had chronic bilateral tinnitus (14 yr) that developed on awakening from neck surgery. Because tinnitus is highly heterogeneous in its presentation, it is unclear whether this therapy will be effective in other types of tinnitus such as noise-induced or drug-induced tinnitus, nontonal tinnitus, unilateral tinnitus, or in patients with moderate to severe hearing loss. Both animal and human studies will be needed to optimize the current therapy and to determine whether paired VNS therapy is effective in other forms of tinnitus.

Previous research already indicated that tinnitus-related distress is associated with an increase in the dorsal anterior cingulate cortex of beta activity (16). After 4 weeks of stimulation, we found decreases of beta activity within the dorsal anterior cingulate cortex. This is in line with our findings that the tinnitus-related distress, as measured by different questionnaires, decreases. In addition, a decrease in desynchronization was demonstrated on resting-state EEG recordings during VNS stimulation in comparison with directly after stimulation. Previous reports in animals have already claimed that EEG desynchronization is required for plasticity (17). This suggests that the beneficial effect might indeed be related to plastic changes, as shown in the animal model (5).

A weakness of current study is that the control stimulation was only 1 week. A second weakness is that no control arm was provided during which only stimulation was provided without paired tones, which could be important to determine whether vagal stimulation per se is not already helpful. Furthermore, no control arm was provided in which the tones were unpaired in time from the vagal stimulation. This could provide information on how essential the strict pairing of the electrical stimuli 150 milliseconds after the tone presentation is, which is the main scientific underpinning of this treatment.

In conclusion, this is the first placebo-controlled VNS paired with tones approach to treat intractable tinnitus. Both the clinical and neurophysiologic results obtained propose that the effect is not caused by sham and warrant further placebo-controlled studies.

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