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ORIGINAL RESEARCH

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Vagus nerve stimulation paired with tones for tinnitus suppression: Effects on voice and hearing

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Abstract

Objective: In individuals with chronic tinnitus, our interest was to determine whether daily low-level electrical stimulation of the vagus nerve paired with tones (paired-VNS*t*) for tinnitus suppression had any adverse effects on motor-speech production and physiological acoustics of sustained vowels. Similarly, we were also interested in evaluating for changes in pure-tone thresholds, word-recognition performance, and minimum-masking levels. Both voice and hearing functions were measured repeatedly over a period of 1 year.

Study design: Longitudinal with repeated-measures.

Methods: Digitized samples of sustained frontal, midline, and back vowels (/e/, /o/, /ah/) were analyzed with computer software to quantify the degree of *jitter*, *shimmer*, and *harmonic-to-noise ratio* contained in these waveforms. Pure-tone thresholds, monosyllabic word-recognition performance, and MMLs were also evaluated for VNS alterations. Linear-regression analysis was the benchmark statistic used to document change over time in voice and hearing status from a baseline condition.

Results: Most of the regression functions for the vocal samples and audiometric variables had slope values that were *not* significantly different from zero. Four of the nine vocal functions showed a significant improvement over time, whereas three of the pure tone regression functions at 2-4 kHz showed some degree of decline; all changes observed were for the left ear, all were at adjacent frequencies, and all were ipsilateral to the side of VNS. However, mean pure-tone threshold changes did not exceed 4.29 dB from baseline and therefore, would not be considered clinically significant. In some individuals, larger threshold shifts were observed. No significant regression/slope effects were observed for word-recognition or MMLs.

Meeting information: Portions of this study were presented at the Annual Meeting of the American Auditory Society, Scottsdale, AZ, March 3, 2017.

Conclusion: Quantitative voice analysis and assessment of audiometric variables showed minimal if any evidence of adverse effects using paired-VNS*t* over a treatment period of 1 year. Therefore, we conclude that paired-VNS*t* is a safe tool for tinnitus abatement in humans without significant side effects.

Level of evidence: Level IV.

KEYWORDS

epilepsy, hearing-threshold levels, linear-regression analysis, tinnitus, vagus-nerve stimulation, voice

1 | INTRODUCTION

There is growing interest in the use of *neuromodulation* to treat chronic tinnitus; defined as the perception of sound in the absence of overt acoustic stimulation. Neuromodulation paradigms used for tinnitus suppression include but are not limited to repetitive transcranial magnetic stimulation (*r*TMS), transcranial direct current stimulation (*t*DCS), transcutaneous electrical nerve stimulation (TENs), cortical neurofeedback, electrical stimulation of auditory cortex, magnetic or electrical stimulation of the dorsolateral prefrontal cortex, deep-brain stimulation (DBS), direct electrical stimulation of the vagus-nerve paired with tones (paired-VNS*t*)[1-13] and, other less invasive approaches like transcutaneous stimulation of the auricular branch of the vagus nerve (VN) located on the surface of the outer ear.[14-20] These novel experimental approaches can modify the physiology and neurochemistry of the underlying tinnitus substrate and have positive impact on the psychological, social, emotional, and/or psychiatric reactions to this abnormal phantom percept. Because a variety of factors can contribute to the overall problem, distinguishing the physiology and pathoanatomy from the psychological, social, and emotional-related "reactive components" of tinnitus has been advocated.[21] These reactive components which include: anxiety, fear, irritability, anger, depression, social/emotional instability, post-traumatic stress disorder (PTSD), hyperacusis, etc., can exaggerate the overall problem. Since chronic tinnitus can be debilitating, adversely affect activities of daily living, reduce occupational productiveness, and negatively impact quality-of-life, efforts to alleviate the burden of this condition represents an ongoing goal of human and animal research worldwide.[22-30]

Available evidence suggests that deafferentation-induced changes in the auditory periphery secondary to occupational, recreational, military noise, and/or blast exposure can be a primary trigger and predisposing factor for the induction and subsequent centralization of tinnitus-related neuronal activity. Trauma from concussive events (sports injuries to the head or neck, motor-vehicle accidents), side effects of medications, associations with oto-neurological disease, consequences of skull-base surgery, and/or a combination of these events can be contributing factors.[31-34] As a consequence, destabilization of auditory circuits following noise, blast, concussive trauma, and oto-neurologic surgery can account for spontaneous neuronal hyperactivity, increased levels of cross-fiber correlation, anomalous effects of cross-modal plasticity, and disruption of the normal balance between excitation and inhibition.[35-41] Many promising propositions put forth to account for these tinnitus-inducing effects fall under the rubric of several promising hypotheses. These include: the central-gain hypothesis, the neurochemical hypothesis, the deprivation based re-organization hypothesis of tonotopy in central lemnescal auditory pathways, the cross-modal plasticity hypothesis, and other postulates related to non-auditory cognitive, emotional, and/or behaviorally based reactive components thought to reside in connectomes or neural networks within the brain.[30,42-45]

Of particular interest in the paired-VNS*t* paradigm is the observation that noise and blast-induced hearing loss can alter downstream tonotopic properties of auditory cortex, well beyond the so-called "critical period;" a time frame in early development during which the central nervous system is most malleable to change.[5,46-49] As a phenomenological aspect of this effect, reactive neuroanatomical and neurophysiological changes to tonotopic areas of auditory cortex can take the form of expansion or contraction of specific anatomical spatial/frequency bandwidth relative to their "normal" unaffected neighboring regions. This manifestation corresponds to the way in which deafferentation of a digit alters receptive field maps in somatosensory cortex.[50] Notably, available research in this area invokes lateral inhibition as a key mechanism in this process.[51,52] In addition, it has been speculated that these reactive changes set the stage for large populations of neurons deprived of auditory input to synchronize their activity and respond to the same frequencies as their neighboring neurons that receive input from undamaged parts of the cochlea; thus, resulting in tinnitus.[53]

Indeed, the unique observation that paired-VNS*t* can "reverse" pathological plastic states in animals with behavioral evidence of tinnitus takes on additional significance when we consider that activation of solitary-tract pathways via electrical stimulation of the VN results in neurotransmitters, including but not limited to, norepinephrine and acetylcholine being released from the locus coeruleus and nucleus basalis[54-57] (Figure 1). Because tonal activation paired with VN electrical stimulation primes the targeting of neuronal activity in central auditory pathways, endogenous neurotransmitters noted above are thought to drive plasticity in auditory cortical areas that can lead to the success of this unique pairing methodology.[56,58]

While intriguing and theoretically justified, for the paired-VNS*t* paradigm to be applied on a much wider scale, additional evidence is necessary to demonstrate that this paradigm involves minimal risk, has limited

or no adverse side effects, and is efficacious. In this regard, based on well-known innervation properties of the VN to peripheral laryngeal structures[59] one logical and well-known concern relates to the potential influence VNS can have on vocal-fold physiology and its subsequent impact on motor-speech production and speech acoustics. Additionally, repeated VNS over time could potentially impact auditory functions by altering pure-tone thresholds, word-recognition performance, and MMLs. Because vocal-fold physiology and various auditory functions have *not* been studied together using the paired-VNS*t* paradigm on a long-term basis, evaluating these areas-of-interest forms the basis of this study.

2 | MATERIALS AND METHODS

2.1 | Participants

Seven adults (6 males, 1 female), 33–63 years-of-age (mean age: 51.6 years; SD [SD]: 11.6 years), participated in this experiment. These individuals were a subset of a larger multi-center cohort (n = 30) involving a prospective, randomized, double-blinded controlled clinical trial from data collection sites at Wayne State University (WSU), University at Buffalo, University of Iowa, and the University of Texas at Dallas, in which paired-VNS*t* was used as an investigational tool to treat chronic tinnitus.[11] Inclusion criteria required to participate in this study included individuals with sensorineural tinnitus primarily of a "tonal quality," had either unilateral or bilateral tinnitus, had experienced tinnitus for at least 1 year, and had engaged in at least one tinnitus therapy program found to be ineffective. Exclusion criteria included acute or intermittent tinnitus, Meniere's disease, retro-cochlear disease, or evidence of active middle-ear disease, any active implanted device such as a pacemaker or other neurostimulator or any other investigational device or drug, Beck Depression Inventory score of 30 or greater, any drug known to mimic, increase, or decrease release or removal of a diffuse neuromodulator, such as norepinephrine, dopamine, serotonin, benzodiazepines, acetylcholine, psychoactive medications or medication known to cause or increase tinnitus.

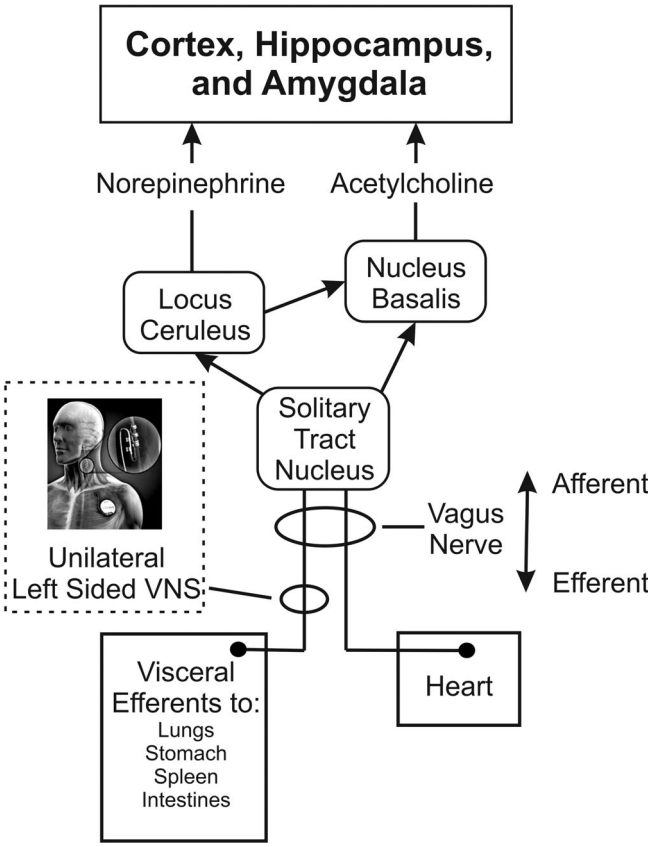

FIGURE 1 Simplified block diagram of afferent and efferent anatomical structures activated by electrical stimulation of the VN. The insert shows a drawing of the upper thorax/chest, including the neck and head region. The IPG is depicted in the upper chest region and the VN cuff electrode is shown in the blow up on the left side of the neck

All seven individuals were assessed, treated, and surgically implanted with VN hardware at the WSU Hearing Science Laboratory and at the Henry Ford Health Systems (HFHS) Otolaryngology clinics; either at their main hospital in Detroit or at its satellite facility in West Bloomfield, Michigan. The larger prospective study was performed under an approved Food and Drug Administration (FDA) Investigational Device Exemption (IDE, #G130140). This smaller sample was part of an amended WSU IRB protocol to include acquisition and analysis of acoustic-voice data.

All participants received the same experimental hardware devices; known as "The Serenity System;" which consists of an implanted pulse generator (IPG: Model 1000), a wire lead, and cuff electrode (Model: 3000). The surgical implantation has been described previously[60,61] and the procedure was followed closely herein. Briefly, after induction of general anesthesia, the neck is slightly extended and turned 30^0 to the right. A transverse cervical incision is made along a skin crease, centered midway down the anterior border of the sternocleidomastoid muscle. Then, the platysma is divided, and the dissection is continued deep to the anterior border of the sternocleidomastoid muscle. The carotid sheath is identified and opened, exposing the common carotid artery and the internal jugular vein. The vagus nerve is identified and dissected free from the surrounding tissue and elevated gently with vessel loops to avoid injury. Next, the incision for the IPG is made in the axilla below the left clavicle and a subcutaneous pocket is fashioned inferiorly by blunt and sharp dissection until its size is adequate for the diameter of the IPG. The lead connector is tunneled between the cervical and infraclavicular incisions. The cuff electrode, with three helices, is wrapped around the nerve. The lead is looped in a gentle curve and sutured through a silicone retainer adjacent to soft tissue to avoid tension on the lead. A second loop is made superficially and sutured to the fascia of the sternocleidomastoid muscle. The connector end of the lead is then inserted into the IPG and secured. The implanted system is tested to confirm electrical continuity and the IPG is placed in its chest pocket. All patients are sent home on the same day.

In addition, an external controller (Model 2000) is connected to a laptop computer (Dell, Inspiron) via a universal serial bus (USB) which communicates wirelessly with the IPG running the Tinnitus

Application Programming Software (TAPS: Model 4000; MicroTransponder, Inc., Austin, Texas). High-quality broad-bandwidth circumaural headphones (Sennheiser, HD280-PRO), attached to the laptop via a 1/8″ male plug with a stereo-headphone jack, served to present the auditory stimuli synchronized with the electrical pulse to the VN during the therapeutic sessions. In addition, the TAPS software enabled the audiologist to program and save stimulation parameters, including: amplitude (mA), frequency (Hz), pulse width (μs), duration (ms), and check for lead integrity, electrode impedance, battery status, and for the review of an individuals' programming history.

Participants started the therapy approximately 1 week following recovery from surgery. Stimulation was delivered to the left vagus nerve consistent with the most common practice used for epilepsy and depression and to avoid potential cardiac and other visceral effects from stimulating VN efferent fibers located mostly on the right side of the neck.[62] Each VNS consisted of fifteen 0.8 mA constant-current charge-balanced pulses (100 μs pulse width, at 30 Hz). The duration of the pulse train was 0.5 seconds and pulse trains were delivered every 30 seconds for 2.5 hours. It is emphasized that in no instance were stimulation settings outside those used for VNS in cases of epilepsy or depression. Specifically, output currents were ≤3.5 mA; frequencies were ≤30 Hz; pulse widths were≤1000 μs; and duty cycles (on/off times) were ≤50%.

In the paired VNS group, each electrical pulse from the IPG was presented simultaneously with a 0.5 second tone every 30 seconds for 2.5 hours. Therapeutic paired tones *excluded* one or more of the participant's tonal-tinnitus frequencies and were at least ½ octave away from the most prominent tinnitus frequency. Test frequencies ranged from 0.170 to 16 kHz and were selected from a basis-set consisting of 25 tones. Moreover, the stimulus output was based on the participants' comfort level and adjusted for any hearing loss that may exist. The sound-pressure level (SPL) of the stimulus was limited to 80 dB and during therapy, the pre-programmed frequency and SPLs of each tone were selected randomly each time an electrical pulse was delivered to the VN.

In the control group/condition, VNS was *not* paired with tonal stimuli (10 minutes of tones only, 5 minutes of silence and no VNS; 2 hours of VNS only; 5 minutes of silence, no VNS, and 10 minutes of tones only during the 2.5-hour period).

2.2 | Delivery of home-based therapy

Both groups received therapy for 6 weeks (termed the randomized portion of the study). The control group was then crossed over to the paired-VNS*t* group settings after the sixth week, while the VNS group continued with the original paired-VNS*t* therapy.

At the initial programming and training session in the Otolaryngology clinic, VNS was administered to determine whether the participant was able to tolerate the standard settings without any adverse effects and initiate therapy appropriately. If the participant was unable to tolerate the standard settings, output current was reduced from

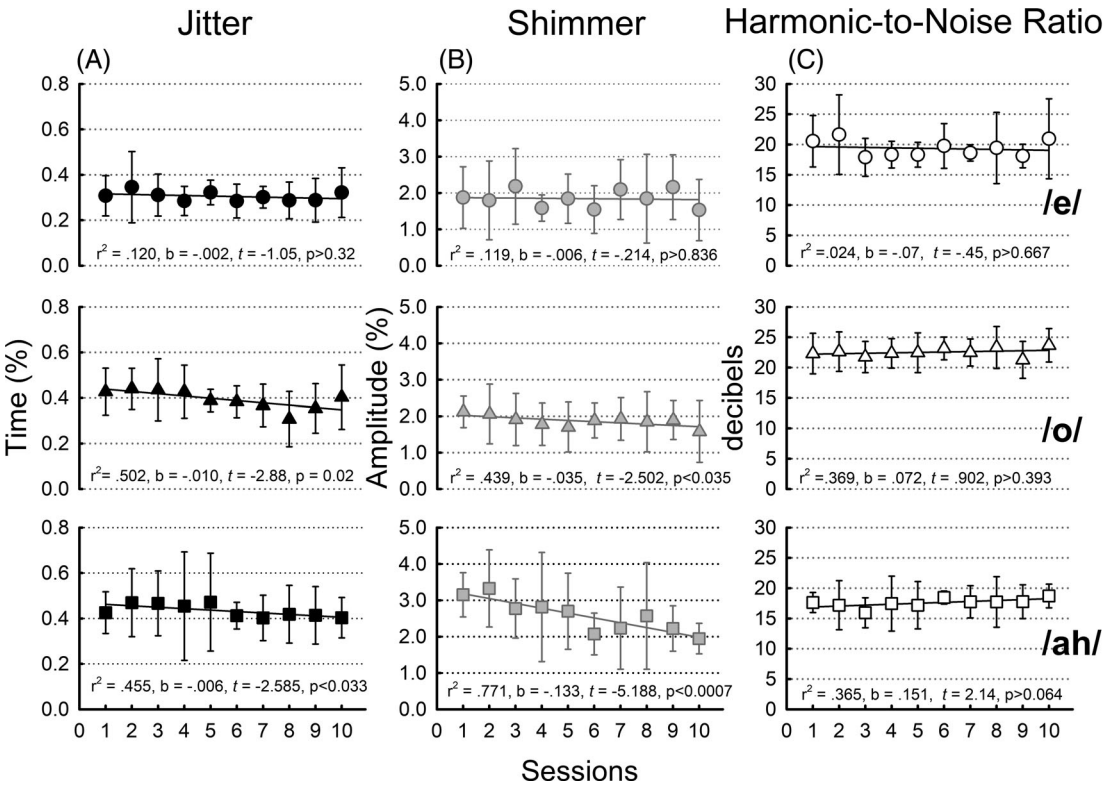

FIGURE 2 Mean data +1 SD are shown for jitter (Column A), shimmer (Column B), and harmonic-to-noise ratio (Column (C) for each of three sustained vowels (/e/, top row; /o/, middle row, and /ah/, bottom row). The coefficient-of-determination (r^2), slope (b), slope assessment (*t*) and probability value (*P*) for each linear regression function are shown at the bottom of each regression plot

0.8 mA, in 0.1 mA steps, until a tolerable level was reached. Once a tolerable level of output current was obtained, the audiologist/researcher verified that tones were audible and were perceived as coming from various spatial locations as intended.

In sum, all subjects in this sample received the same long-term therapy; they were included in all experimental analyses and collectively were treated as one group.

2.3 | Materials and procedures

Acoustic voice samples were obtained pre-operatively and after the Serenity System was activated post-operatively at the Henry Ford Otolaryngology Clinic. Additional samples were collected once a month for 6 months at the Hearing Science Laboratory at WSU; then at 6 months and 1 year when the study was terminated. The voice samples included a minimum of three trials for each sustained frontal, midline, and back vowels where participants were asked to maintain a steady phonation of ~2-3 seconds at a comfortable vocal-output level. The first trial was used as practice and was not included in the data analysis. Only the average of the last two trials was used. The sustained vowels were acquired on a digital recorder (Tascam: model DR-40; sampling rate: 44.1 kHz) within a sound-treated commercial test booth except for the initial post-surgical activation sample, which was obtained in a quiet exam room in the Otolaryngology clinic. The microphone of the digital recorder was held at a constant mouth-to-microphone distance of 12 in. maintained by a premeasured piece of string attached to the recorder. The distance was measured from the most anterior segment of the lips to the tip of the microphone inlet port of the recording device. The voice samples were stored in memory on the digital recorder, downloaded to the hard drive of a laptop computer, and subsequently backed up on an external hard drive. Then, individual voice samples were uploaded to the Praat analysis software for quantification[63] (also see Footnote*). In all instances, the most stable portion of the sustained glottal waveform was selected for analysis. A description of the three metrics of vocal function and the computations used for quantification are addressed below.

2.4 | Jitter

Jitter is the cycle-to-cycle variation of a sustained vocal fundamental frequency, that is, the average absolute difference between consecutive periods. Thus, the amount of jitter in an analysis interval is estimated by a measure of dispersion of the glottal-cycle lengths.[65] Although there are different formulae in the way in which jitter can be computed, we applied the five-point "*P*eriod *P*erturbation *Q*uotient (PPQ5)," which represents the average absolute difference between a single glottal period and the average of it and its four closest neighbors, divided by the average period, and multiplied by 100 to get a percent jitter value.

The mathematical equation governing these measures is shown below:

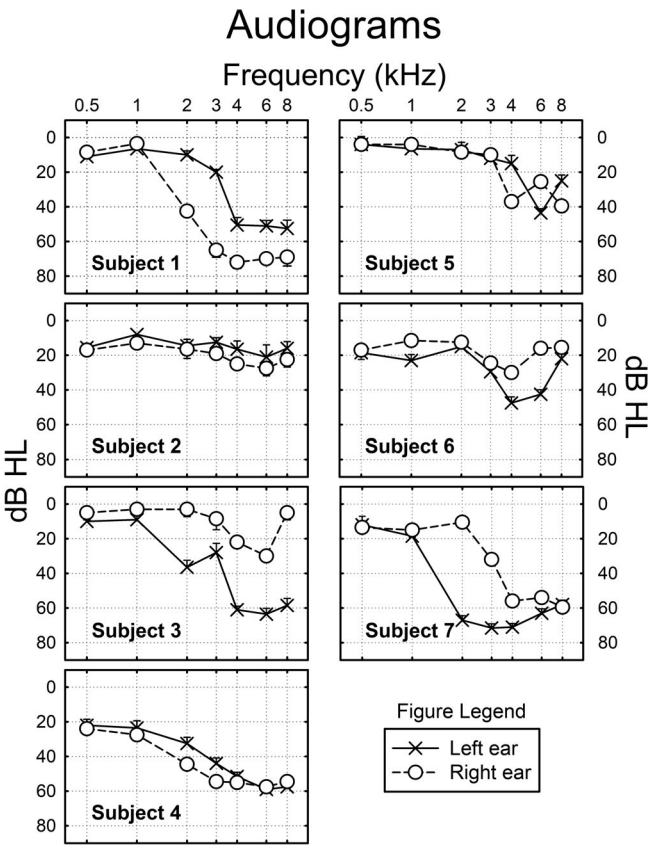

FIGURE 3 Pure-tone audiograms for left and right ears for each of the seven participants before the study began. The *x*-axis represents frequency in kHz and the y-axis represents dB hearing level (HL). Contralateral masking was used when necessary

$$\text{PPQ5} = \frac{\frac{1}{N-1}\sum_{i=2}^{N-2} \left| Ti - \left(\frac{1}{5}\sum_{n=i-2}^{i+2} Tn\right)\right|}{\frac{1}{N}\sum_{i-1}^{N} Ti} \times 100$$

where T_i is the duration of the *i*th interval; *N* is the number of intervals.

2.5 | Shimmer

Shimmer is the measurement of the cycle-to-cycle amplitude perturbations of a sustained phonation. For this measure, the five-point *A*mplitude *P*erturbation *Q*uotient (APQ5), which represents the average absolute difference between the amplitude of a period and the average of the amplitudes of it, and its four closest neighbors, divided by the average amplitude[64] and multiplied by 100 to get a percent shimmer value.

The mathematical equation governing this measure is provided below:

$$\text{APQ5} = \frac{\frac{1}{N-1}\sum_{i=2}^{N-2} \left| Ai - \left(\frac{1}{5}\sum_{n=i-2}^{i+2} An\right)\right|}{\frac{1}{N}\sum_{i-1}^{N} Ai} \times 100$$

where *N* is the number of intervals; *An* is the autocorrelation function.

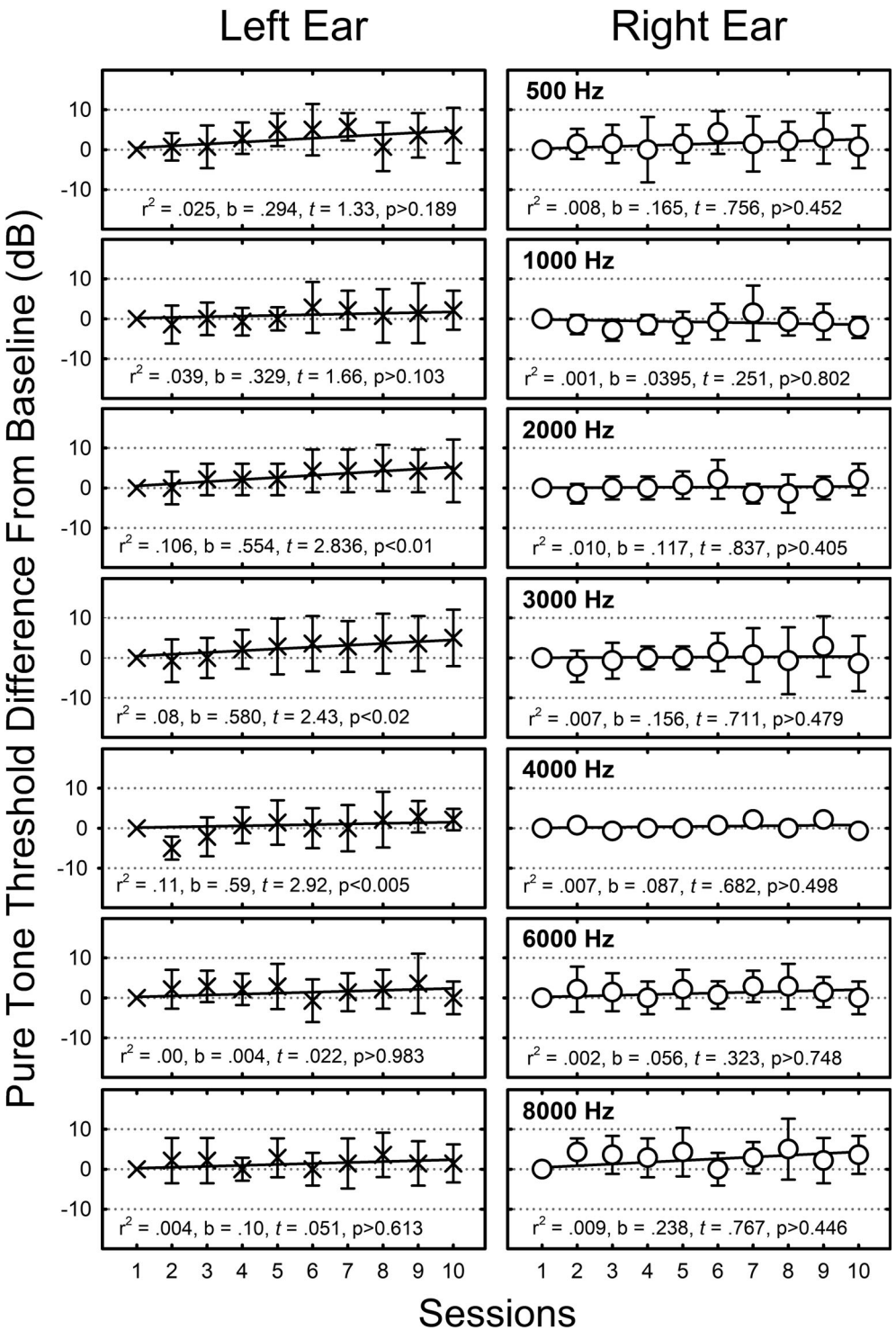

FIGURE 4 Mean data +1 SD are shown for each audiometric frequency for left and right ears. The *x*-axis represents sessions (repeat visits to the clinic) and the *y*-axis represents threshold difference in dB from the initial baseline test condition. The coefficient-of-determination (r^2), slope (b), slope assessment (*t*) and probability value (*P*) of the linear regression functions are shown at the bottom of each regression plot

2.6 | Harmonic-to-noise ratio

$$\mathrm{HNR}(dB) = 10 \times 10\log \frac{r'\mathrm{x}(\tau max)}{1 - r'\mathrm{x}(\tau max)}$$

Harmonic-to-noise ratio (HNR) or its inverse, the noise-to-harmonic ratio (NHR), assesses the presence of noise in a voice sample which is related to voice quality; specifically, a lower NHR or a higher HNR indicate superior voice quality.[66] The mathematical equation governing this metric is shown below:

where the autocorrelation of the normalized lag (numerator) is divided by 1 minus the normalized lag (denominator) then the logarithm to the base 10 of this ratio is taken. This resultant metric represents the HNR[67] (see p. 98 for additional details).

2.7 | Audiometric measures

Pure-tone thresholds, tinnitus-pitch matches, monosyllabic word recognition performance, and MMLs followed the methodology described by Tyler and colleagues.[11] Briefly, pure-tone air and bone-conduction thresholds were assessed at octave and mid-octave frequencies (0.5, 1, 2, 3, 4, 6, and 8 kHz) bilaterally and monosyllabic word recognition performance was obtained from pre-recorded word lists on compact disks (CDs; 50-word NU-6 word lists) presented separately to left and right ears at a sensation level (SL) of 40 dB. Tinnitus pitch matches were established using a modified method-of-limits and MMLs were made with a binaural white-noise stimulus where the level of the noise just masked the individual's tinnitus. All audiometric testing and voice acquisition recordings were performed in a well-lit, temperature-controlled, sound-attenuating test booth (Acoustic Systems, RS-144S, Austin, Texas).

2.8 | Statistical analysis

Linear regression analyses were based on 10 data points which included: pre-operative, post-operative and return visits to the Hearing Science Laboratory to evaluate for changes from baseline measures of the vocal functions (jitter, shimmer, harmonic-to-noise ratio) for each vowel (/e/, /o/, /ah/), for each of the 14 pure-tone thresholds (seven frequencies per ear), monosyllabic word recognition performances for each ear, and MMLs. The linear regression model took the form:

$$Y_i = \alpha + \beta x_i$$

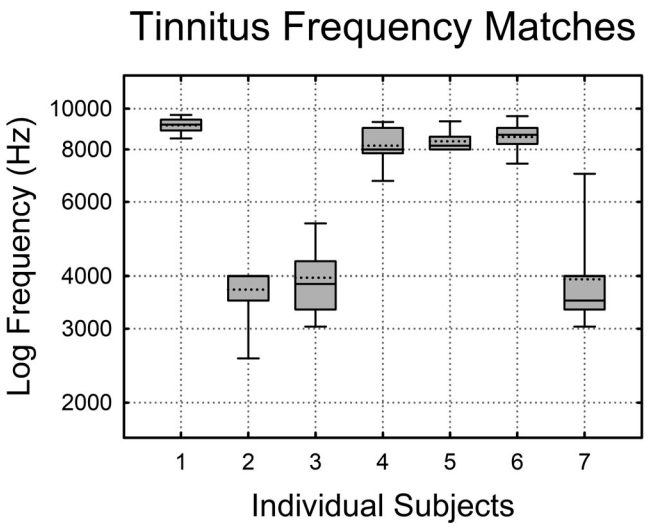

FIGURE 5 Vertical box plots showing: mean (solid line) within the box, median (dotted line) within the box, box boundaries indicate the interquartile range (IQR), and upper and lower error bars/whiskers represent (Q1–1.5*IQR) (Q3 + 1.5*IQR) of repeated tinnitus frequency matches to external tones. The *x*-axis represents individual subjects; the *y*-axis represents log frequency

where Y_i is the Y value for this observation; β is the slope, α is the intercept, x_i is the x value for observation i.

The null hypothesis (H_0) for vocal and audiometric variables states that the slope of individual regression function is *not* significantly different from zero based on an a priori probability level ($P \leq .05$). If this result occurs, then H_0 would be accepted. Furthermore, if a statistically significant "positive" or "negative" slope was obtained, that is, when H_0 is $\neq$ to zero, then H_0 would be rejected and an alternative hypothesis selected. A significant positive slope would indicate an "adverse" effect on voice or a threshold elevation for pure-tone thresholds; a significant negative slope would indicate an improvement in function over time. With these data, each subject acted as their own control where the regression functions assessed the difference from the baseline values.

We utilized Statistica (Version: 9.1) as the quantitative software tool for statistical analysis; SigmaPlot (Version: 11.2) for construction of all regression and scatter plots; and CorelDRAW (Graphics Suite, Version: 5) for implementing graphic illustrations.

3 | RESULTS

Linear regression functions of the scatter plots for the voice data are shown in Figure 2. Based on these analyses, only the jitter and shimmer variables for vowels /o/ and /ah/ had slopes that were negative and were significantly different from zero ($P < .05$). The remaining regression functions had slopes that were *not* significantly different from zero ($P > .05$). Statistical results for these regression data are shown at the bottom of each scatter plot.

Pre-study audiograms for the seven participants are shown in Figure 3. Except for Subject 2, who had normal hearing sensitivity bilaterally (pure-tone thresholds ≤20 dB HL, 0.5–8 kHz), all individuals had some degree of high frequency sensorineural hearing loss, which was slightly asymmetric between the ears.

Linear regression functions for each of the seven audiometric frequencies for each ear are shown in Figure 4. Most frequencies (11/14; 78.6%) had slope values that were *not* significantly different from zero. However, three regression functions at 2, 3, and 4 kHz; all for the left ear, had positive slopes indicating significant increases in thresholds from the initial baseline values ($P < .05$). Statistical results for these regression data are also shown at the bottom of each scatter plot.

None of the regression results for word-recognition or MMLs had slopes that were significantly different from zero ($P > .05$; data not shown). Estimates for psychoacoustic tinnitus frequency matching are shown in Figure 5. Two general clusters of frequency matches were observed; one near 4 kHz and the other near 8 kHz.

4 | DISCUSSION

In the 7 individuals where voice samples and audiometric data were collected at the WSU and HFHS clinics, there were minimal or no adverse side effects, and there were no morbidities associated with the surgical implantation of the IPG, the wire lead, or cuff electrode.

These results agree with the efficacy and safety record of VNS as an FDA approved treatment regime for drug-resistant epilepsy and/or depression.[68-73]

While the paired-VNS*t* paradigm is more focused towards modifying tinnitus-related neuronal activity than in altering vocal output, maintaining laryngeal-neutral effects remains as a high priority in moving forward. Deviant vocal output signatures like hoarseness, is a perceptual feature which is easily detectable in face-to-face communication situations and can affect quality-of-life, particularly in those individuals using their voices professionally. It is also well known that the objective voice measures used herein have high ecological validity in correlating with perceptual characteristics of abnormal vocal output.[74,75] Therefore, we echo the statement by Van Lierde and colleagues[76] that "…professional voice users and elite vocal performers must be informed before implantation." In fact, we emphasized the potential for adverse effects on vocal function during the recruitment phase and reiterated this material in our consent process; both in written form and in verbal recapitulation to ensure all participants clearly understood this information before signing the informed consent document and joining the study. Although these concerns cannot be overstated, a positive aspect of this study found that the vocal parameters we measured fell within the normative range of values reported by Goy and colleagues.[77] In some instances, the slopes of the regression functions were negative; indicating that these metrics also improved over time.

When quantitative voice analyses were applied to VNS following treatment for drug-resistant epilepsy, more variability was observed in these types of measurements. Although our study focused on acoustic-voice metrics *vs* other measures like laryngeal stroboscopy, endoscopy, electromyography, or questionnaire-based assessments, Lundy[78] reported increased jitter with increasing frequency of stimulation and Charous et al.[79] showed that jitter and shimmer measures increased at rest and during VNS. González et al.[80] cited four studies that included adverse effects of VNS on voice: hoarseness, cough, paresthesia, throat pain, dyspnea, headache, and infection when used for seizure control.[68,81-83] Moreover, when data from these studies were combined to represent a total sample size of 546 participants, by far, the most prominent adverse effect was hoarseness (31.8%, 173.5/546), followed by paresthesia (9.3%, 50.8/546), cough (9.2%, 50.3/546), throat pain (8.3%, 45.3/546), dyspnea (8.1%, 35/432), headache (7.4%, 40.4/546), and infection (2.9%, 14.8/511) (see footnote †). Therefore, these studies and other data[84-88] indicate that VNS effects on vocal function remains as a prominent area-of-concern. In addition, vagus nerve stimulation can also be a cause of stridor in a pediatric population with epilepsy.[89] Other issues like appropriate electrode size is an important consideration during surgical implantation, so that compression injury to the VN is avoided.[90] As noted by the surgeon-of-record (MDS), direct visualization of the VN was made meticulously in all instances during the surgery and this issue was *not* apparent in any of the individuals studied. Therefore, this factor and other specific parameters used during paired-*VNSt* had no adverse impact on voice. We suspect that the difference in the impact on vocal functions is likely due to the lower output current setting (0.8 mA *vs* 1.5-2.5 mA average) and shorter ON times (0.5 seconds *vs* 7-30 seconds) that we utilized.

With respect to pre-operative pure-tone audiograms, all individuals, except Subject 2, had some degree of sensorineural hearing loss before entering the study (Figure 3). Furthermore, with respect to pure tone threshold regression functions, three frequencies (2, 3, and 4 kHz), had positive slopes, indicating that these thresholds increased over time. These frequency-specific threshold shifts were all observed for the left ear, all occurred at adjacent frequencies, and all were ipsilateral to the ear of stimulation; but they were not large. Based on the regression functions, largest mean threshold shifts from baseline were found to be 4.29 dB at 2 kHz, 3.57 dB at 3 kHz, and 2.86 dB at 4 kHz (Figure 4). The largest absolute change from baseline in this sample was 15 dB at 2 kHz, 20 dB at 3 kHz, and 10 dB at 4 kHz. To our knowledge, there are no studies indicating what criteria should be used to identify clinically significant threshold shifts during electrical stimulation of the VN using a repeated-measures design; albeit experimental or clinical. However, studies that have addressed the issue of repeated audiometric testing have been made in a different context, specifically, with respect to ototoxicity and chemotherapy monitoring for severe infectious disease or cancer treatments.[91,92] The AAA document suggests that the most widely used criteria is based on the ASHA guidelines.[91] According to the ASHA document, "…significant ototoxic change must meet one of the following three criteria: (a) ≥20 dB decrease at any one test frequency, (b) ≥10 dB decrease at any two adjacent frequencies, or (c) loss of response at three consecutive frequencies where responses were previously obtained. Changes are always computed relative to baseline measures and must be confirmed by repeat testing, generally within 24 hours." The changes from baseline we observed, specifically with respect to the 10 successive hearing tests within a period of one-year, fulfill criteria *a* and *b* of the ASHA guidelines noted above. However, these changes noted above were not confirmed by repeat testing within a 24-hour period, which is also assumed in the ASHA document.

Monosyllabic word recognition and MMLs also had slope values that were *not* significantly different from zero but differed from the pure-tone threshold data because they were *suprathreshold* in nature.

Median psychoacoustic frequency matches to external stimuli occurred between 8 and 10 kHz in 4/7 (57%) of subjects and between 3 and 4 kHz in 3/7 (43%) of subjects. Previous research has suggested that pitch matches of the tinnitus frequency can occur at the "edge frequency" of the audiogram.[93] This observation held true for Subjects 2, 3, and 7, but *not* for the others. In those individuals with a notched audiogram, the tinnitus pitch was at or near 8 kHz; a result consistent with Pan et al.[94] Pitch matches could also be an octave above the notch frequency of the audiogram[95] or matched to frequencies where hearing thresholds were in the 40–60 dB HL range.[96]

4.1 | Safety and efficacy

To our knowledge, De Ridder et al.[8] was the only other study that investigated the safety of paired-VNS*t* in an open label pilot study.

Although their study did not include measures of vocal function, their audiometric data was *negative* for adverse effects. In the study using transcutaneous electrical stimulation of the VN, Kreuzer et al.[16] also reported no adverse side effects based on actual measures or via questionnaire assessment, but vocal functions were *not* studied. Moreover, tinnitus suppression was *not* successful.

5 | CONCLUSION

There is an urgent need to develop effective treatments for chronic tinnitus. The paired-VNS*t* paradigm holds promise as a useful adjunctive therapy based on its theoretical value as a targeted-neuroplasticity regimen,[38,40] compelling experimental data to move forward from animal studies to human testing, its veracity of purpose in gaining FDA approval, IDE authorization, and its legitimacy in initiating an NIH-sponsored multi-center clinical trial. Although recent clinical trials confirm the potential therapeutic benefit of paired-VNS*t*,[8,11] additional work is needed for implementing a larger "pivotal study" to further advance the field. Furthermore, we are also encouraged that electrical stimulation of the VN had no long-term adverse effects on vocal function and only minimal, if any, impact on auditory pure-tone thresholds. Indeed, other than some minor adjustments in stimulation parameters during the study, paired-VNS*t* was well tolerated and therefore, has promise in helping individuals with "tonal" tinnitus.[8,9,11,38,40]

Finally, to exploit the use of and developments made by neuromodulation therapeutics, evidence demonstrating safety, efficacy, and limited or no adverse side effects are crucial for the success of this paradigm. Although we realize that vocal measures like jitter, shimmer, HNR are only a subset of all dynamic quantitative and qualitative vocal metrics available for study, they are important. These measures provide unique clinical information which can document change-in-function over time and represent a comparatively easy way to establish safety and efficacy. They are non-invasive, reliable, correlate with perceptual deficits, and do not require expensive instrumentation to implement in a clinical setting.[64,97] In retrospect, just as VNS alone has offered a successful long-term intervention strategy for individuals with drug-resistant epilepsy, by reducing seizure frequency, lowering resource allocation, and reducing costs,[98] paired-VNS*t* could provide similar positive benefits when applied to the area of tinnitus abatement.

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CONFLICT OF INTEREST

Drs. Kochilas, Cacace, Arnold: none; Dr. Seidman: Body Language Vitamins, Founder of a small vitamin company; (7) patents Intellectual property; Acclarent Consultant; Auris Medical AM 101 & 111, Clinical trials for tinnitus—noncompensated (Research); Envoy Medical Assisting in post-market studies—non-compensated (Research); NIH Simulation Work, July 2012-June 2019 (Research); MicroTransponder, Inc., Vagal Nerve Stimulator Clinical Trial for tinnitus, non-compensated (Research). Mr. Tarver: MicroTransponder, Inc., employee; MicroTransponder stock options.

AUTHOR CONTRIBUTIONS

H. L. K. analyzed the voice data, contributed to data analysis, and contributed to writing of the manuscript. A. T. C. conceived the idea, had overall responsibility and oversight for the project, contributed to all data and statistical analysis, plotting and graphics, and contributed to writing of the manuscript. A. A. contributed to all data collection, data organization, data analysis, and writing of the manuscript. M. D. S. performed all surgeries and contributed to writing of the manuscript. W. B. T. aided in the conception and design of the experiment and contributed to writing of the manuscript.

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ENDNOTES

**Note*: the Praat voice analysis/synthesis software program is free-of-charge for anyone to download (www.fon.hum.uva.nl/praat). It produces results comparable to other systems that are commercially available.[63]

†*Note*: dyspnea was not reported by Ben-Menachem et al.[68] (total n = 432) and pain was not reported by Klinkinberg et al.[83] (total n = 511).

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