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Transcutaneous Cervical Vagus Nerve Stimulation Improves Speech Comprehension in Noise: A Crossover, Placebo-Controlled Study

Michael Jigo, PhD[1]; Jason B. Carmel, MD, PhD[1,2,3]; Qi Wang, PhD[1,4]; Charles Rodenkirch, PhD[1,5]

ABSTRACT

Background: Speech comprehension in noisy environments remains a significant challenge, even among individuals with clinically normal hearing and users of hearing aids and cochlear implants. Although conventional assistive hearing devices address limitations in the auditory periphery, they do not directly enhance the brain's capacity to segregate speech from background noise. Because tonic vagus nerve stimulation (VNS) has shown potential for rapidly improving central sensory processing, this study investigated whether tonic transcutaneous cervical VNS (tcVNS) can enhance speech-in-noise intelligibility.

Materials and Methods: Two cohorts of older human adults (aged 60–84 years) participated in a placebo-controlled, crossover study. Participants completed speech-in-noise assessments using either QuickSIN or AzBio sentences while receiving tonic tcVNS to the neck, or placebo stimulation to the neck-shoulder junction. Speech-in-noise performance was assessed by measuring participants' accuracy in repeating sentences presented at varying signal-to-noise ratios (SNR) within background babble.

Results: Tonic tcVNS improved speech-in-noise intelligibility compared with placebo. At the group level, the SNR threshold for 50% speech intelligibility (SNR-50) improved by 0.76 dB in QuickSIN ($p = 0.016$) and by 0.38 dB in AzBio ($p = 0.045$). For individual participants, 50% showed improvements that met a minimum clinically important difference (MCID) of 1 dB. Tonic tcVNS evoked progressively greater improvements as SNR increased in QuickSIN ($p = 0.021$) and AzBio ($p = 0.00023$), with the largest gains at SNRs >0 dB. In 55% of participants, tcVNS improved intelligibility beyond an MCID benchmark of 4.9% at 5 dB SNR. Although the magnitude of tcVNS-evoked improvements was inversely related to baseline speech-in-noise impairment ($p = 0.028$), with the individuals having the most impaired speech-in-noise intelligibility showing the largest gains, it did not correlate with hearing loss severity ($p = 0.97$) or age ($p = 0.88$).

Conclusions: Our findings indicate that tonic tcVNS can evoke immediate and clinically meaningful enhancements in speech-in-noise comprehension. This suggests tcVNS may complement conventional assistive hearing technologies and inform novel therapies for sensory processing disorders.

Keywords: Aging, locus coeruleus, norepinephrine, speech in noise, vagus nerve stimulation

INTRODUCTION

Speech comprehension in noisy environments poses a significant challenge, especially for older adults and the 1.5 billion individuals worldwide with hearing loss.[1,2] Notably, 10% to 12% of people with clinically normal hearing still report difficulty hearing in noise.[3,4] Age-related decreases in peripheral and central auditory systems exacerbate speech-in-noise (SIN) challenges in older adults.[5,6] Although hearing aids, cochlear implants, and over-the-counter sound amplifiers can compensate for peripheral deficits,

Address correspondence to: Charles Rodenkirch, PhD, The Jacobs Technion-Cornell Institute at Cornell Tech, 11 E Loop Rd, New York, NY 10044, USA. Email: charles@sharpersense.com

[1] Sharper Sense, Inc, New York, NY, USA;
[2] Division of Child Neurology, Department of Neurology, Weinberg Family Cerebral Palsy Center, New York, NY, USA;
[3] Department of Orthopedics, Weinberg Family Cerebral Palsy Center, New York, NY, USA;
[4] Department of Biomedical Engineering, Columbia University, New York, NY, USA; and
[5] The Jacobs Technion-Cornell Institute at Cornell Tech, New York, NY, USA

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they do not resolve central limitations that continue to distort SIN perception.[7–9] Therefore, interventions targeting brain-based auditory processing could complement existing assistive hearing strategies to augment speech intelligibility in noise.

Vagus nerve stimulation (VNS) offers a promising method to address auditory processing limitations, with well-documented effects on the central nervous system. Invasive VNS, delivered through implanted electrode cuffs on the cervical branch of the vagus nerve in the neck, is a Food and Drug Administration (FDA)-approved therapy for intractable epilepsy, pharmacologic-resistant depression, and poststroke motor rehabilitation.[10,11] More recently, transcutaneous VNS (tVNS), which stimulates the vagus nerve noninvasively through its cervical (tcVNS) or auricular (taVNS) branches, has emerged as a potential method for vagal activation.[12–14] The established safety and tolerance of tVNS in humans[15] have spurred numerous studies in various applications including language learning,[16–18] cognitive performance,[19,20] and sensory processing.[21–23]

Recent preclinical[21] and pilot clinical studies[23] suggest that delivering VNS in a continuous, tonic fashion induces rapid and sustained central sensory improvements. Tonic VNS builds on conventional paradigms, including duty-cycled protocols that deliver VNS for brief durations (eg, 30 seconds "on" followed by ≥60 seconds "off"[24–26]) and phasic protocols that pair VNS bursts with motor or sensory events to accelerate rehabilitation.[11,27–29] Although duty-cycled and phasic VNS effectively induce delayed, long-term neuroplasticity through short on periods,[11,24–29] tonic VNS provides the distinct benefit of rapid, short-term sensory enhancements that are sustained through continuous vagal activation.[21,22]

VNS-driven changes to sensory processing result from the activation of the locus coeruleus (LC)-norepinephrine (NE) system, which has long been hypothesized to contribute to the clinical benefits by VNS.[30] VNS engages the LC-NE system in both animals and humans[31–33] through afferent vagal projections to the nucleus tractus solitarius,[34] which in turn sends excitatory signals to the LC through the nucleus paragigantocellularis.[35] In rodents, tonic electrical or optogenetic LC stimulation was shown to enhance sensory processing through its projections to the thalamus, a critical stage for sensory perception.[36,37] Tonic LC activation optimized thalamocortical neurons for sensory processing, increasing their efficiency and rate of sensory information transmission, and ultimately improving perceptual sensitivity during a go/no-go vibrotactile discrimination task.[38] Pharmacologic manipulation revealed that improvements stemmed from a steady increase in NE concentration, which suppressed T-type calcium channel activity in the thalamus. This suppression reduced neural bursts that otherwise degrade sensory signal transmission.[38] Given the afferent vagal projection to the LC, tonic invasive VNS similarly induced thalamocortical optimization that enhanced central sensory processing.[21]

Given the effects of tonic VNS on central sensory processing in rodents, a pilot translational study in humans explored the ability of tonic tcVNS and taVNS to improve sensory performance.[23] Although tcVNS enhanced performance on visual and auditory psychophysics tasks, taVNS showed no such benefit. Crucially, tonic tcVNS improved performance in an auditory gap discrimination task[23] that relies on the same precise temporal processing essential for speech perception.[39,40] Building on these findings, we hypothesized that tonic tcVNS could enhance SIN perception. To test this, we recruited older adults to receive tonic tcVNS or placebo stimulation while completing standard SIN assessments (QuickSIN[41] and AzBio[42]) commonly used to guide hearing aid and cochlear implant recommendations.[43,44]

MATERIALS AND METHODS

Ethics

Participants provided written informed consent and were compensated $30/h. Protocols complied with the Declaration of Helsinki and were approved by Cornell University's Institutional Review Board (IRB) for Human Participant Research. Informed consent was provided for the images in Figure 1 to be published.

Protocol

We followed international standards for reporting the stimulation protocol and study design,[45] and summarize stimulation parameters in Table 1.

Stimulation Sites and Equipment

Hydrogel electrodes (diameter: 1"; PALS, Axelgaard Manufacturing, Fallbrook, CA) were placed on the skin, with center-to-center spacing adjusted for individual neck/shoulder anatomy. For tcVNS, electrodes were placed within the left carotid triangle—lateral to the larynx, medial to and oriented parallel to the sternocleidomastoid muscle. For off-target (placebo) stimulation, electrodes were placed over the trapezius muscle at the neck-shoulder junction where the vagus nerve is absent. The skin was prepared with hypoallergenic sanitary wipes.

Study Design

A placebo-controlled, single-blind, within-subject crossover design was used. Participants received tcVNS and off-target stimulation in a counterbalanced order, separated by a 29-minute washout period (95% CI: [25, 32]). Stimulation duration was determined by the duration of each test, which lasted approximately 8 minutes for QuickSIN and 21 minutes for AzBio cohorts, with sessions conducted in a single morning (9 AM–12 PM) or afternoon (1 PM–6 PM).

Stimulation Parameters

An FDA-cleared neuromuscular stimulator operating in constant current mode (Mettler Sys*Stim 240, Mettler Electronics Corporation, Anaheim, CA) delivered tonic, nonburst stimulation for both tcVNS and off-target conditions. Stimulation comprised biphasic square pulses (100 μs/phase, 200 μs total) delivered at 30 Hz, in a continuous, tonic manner (100% duty cycle). Current amplitudes were individually calibrated using a standardized ramping procedure: Current was initiated at 5 mA and increased gradually until muscle contractions or pain was reported, then decreased to the maximum level that was perceptible, tolerable, and did not induce muscle activation.

Intensity Rating

Immediately before stimulation ended, participants were prompted: "At this moment, how intense does the stimulation sensation feel?" and responded as follows: 1 = not intense, 2 = slightly, 3 = moderately, 4 = very, or 5 = extremely intense.

Blinding

The experimenter read a standardized cover story to participants: "The purpose of this study is to understand how electrical stimulation affects the clarity of your hearing. I will place a pair of electrodes at two different locations—on your neck or your

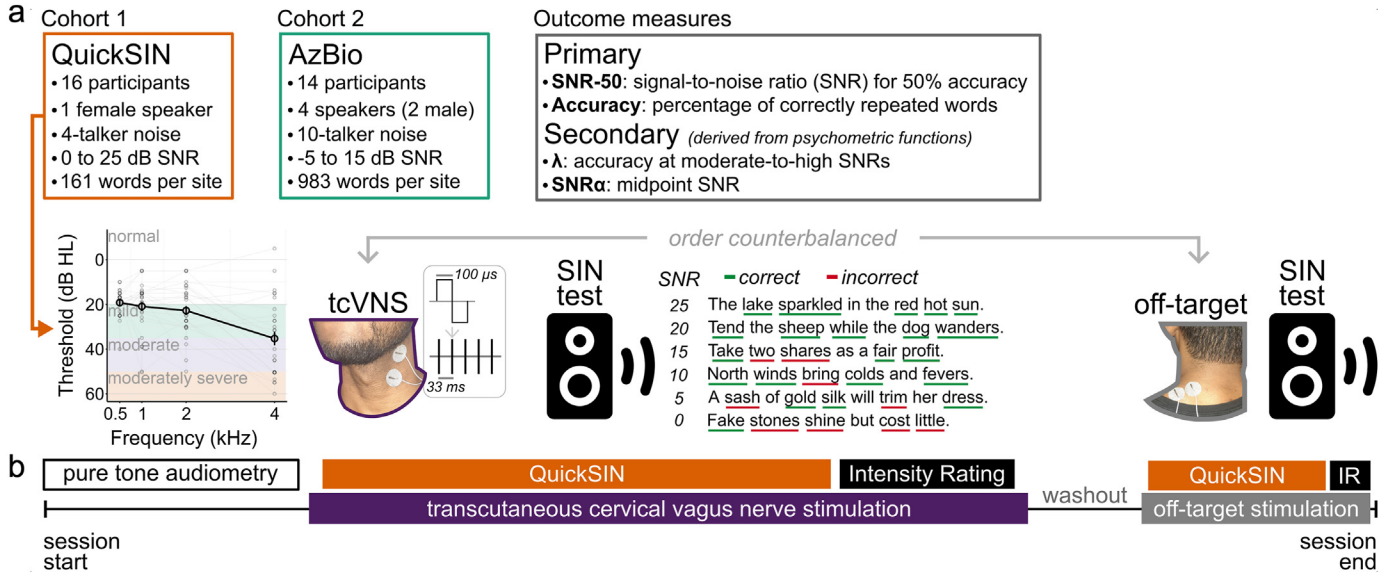

Figure 1. SIN assessments and stimulation protocol. a. Characteristics of each cohort, along with the study's primary and secondary outcome measures. b. Timeline of a testing session for the QuickSIN cohort; the AzBio cohort followed an identical timeline. Pure tone audiometry (PTA) was completed without electrical stimulation; data for all participants are shown, with large points and error bars showing the group-average and ±1 SEM connected by a dark black line. Hearing loss cutoffs are shown as different colors in the audiogram. After PTA, tonic tcVNS or off-target stimulation was delivered in a counterbalanced order; the stimulation waveform and frequency are shown beside "tcVNS." Participants provided an intensity rating of the stimulation after each SIN assessment. [Color figure can be viewed at www.neuromodulationjournal.org]

upper back—that will activate the same nerve under your skin. While that's happening, you will hear and repeat sentences played from a loudspeaker in the testing room." Participants were not informed of the cervical branch location of the vagus nerve. After this cover story, the experimenter described the QuickSIN or AzBio assessments. Electrical stimulation was delivered continuously during both tcVNS and placebo conditions to elicit similar physical sensations across conditions.

Adverse Events

All adverse events were required to be reported to the IRB and to the medical oversight physician within 24 hours of occurrence. No adverse events occurred.

Sample

Demographics

Participants were passively recruited from the Roosevelt Island community and Carter Burden Network. The inclusion criteria were age 60 to 85 years, no history of neurologic or psychiatric disorders, no history of substance abuse, not taking β adrenergic blockers, no medical implants, no history of cardiac surgery, no severe cardiac disorders, no history of heart conduction abnormalities, not currently pregnant, no prior abnormalities or surgeries involving the neck or vagus nerve, and a passing score (≥12/15) on the 5-minute Montreal Cognitive Assessment (MoCA).[46] Of the 43 individuals who inquired about the study, 19 declined to participate, and 2 were excluded owing to a history of heart conduction abnormalities. The remaining 22 participants met the eligibility criteria and provided informed consent. Testing occurred in two

Table 1. Stimulation Parameters and Ratings of Perceived Intensity.

		tcVNS	Off-target	*p* Value
QuickSIN	Current [mA]	7.71 (6.80, 8.62)	8.15 (7.40, 8.90)	0.13
	Intensity [1 = low, 5 = high]	1.69 (1.44, 2.00)	1.63 (1.19, 2.19)	0.94
	Distance [cm]	3.84 (3.55, 4.12)	3.04 (2.97, 3.11)	0.00016
	Duration [min]	8.00 (7.29, 8.72)	7.89 (7.23, 8.55)	0.65
AzBio	Current [mA]	8.59 (7.97, 9.21)	8.86 (8.18, 9.55)	0.25
	Intensity [1 = low, 5 = high]	1.43 (1.07, 1.86)	1.71 (1.29, 2.21)	0.38
	Distance [cm]	4.00 (3.76, 4.24)	3.04 (3.00, 3.09)	0.0000024
	Duration [min]	20.95 (19.73, 22.17)	20.93 (19.95, 21.91)	0.95

Average values, 95% confidence intervals (within parentheses), and *p* values for the difference between tcVNS and off-target parameters. Intensity ratings were measured with a five-point Likert scale (1 = not intense, 5 = extremely intense).

cohorts, 16 months apart, with eight individuals participating in both. The first cohort (n = 16, 11 women; age = 69.50 years; SD = 7.87) was tested with QuickSIN.[41] Following advice from audiologists and an otolaryngologist, we conducted a conceptual replication of the QuickSIN findings in a second cohort with AzBio[42] (n = 14, nine women; age = 71.19 years; SD = 6.70). Two participants in QuickSIN wore hearing aids, and one participant in AzBio was left-handed; all were included in the sample. Participants were asked to refrain from stimulants (eg, caffeine, nicotine) for three hours before the study.

Power Analysis

Although a sample size of 12 was sufficient to indicate statistically significant tcVNS-evoked sensory enhancements in younger adults,[23] we used a simulation-based approach[47] to determine sample sizes in advance with ≥95% power for SIN perception. The smallest assumed change (SAC) we would observe was informed by studies deploying SIN assessments before and during sound amplification. For QuickSIN's signal-to-noise ratio required for 50% speech intelligibility (SNR-50), the SAC was 1.14 dB, the median improvement after two weeks of hearing aid use.[48] For AzBio, the SAC for accuracy was 2.5%, based on improvements by a personal sound amplifier product.[49] To estimate the variance, six younger adults (five women; age, 27.5 years; SD, 6.12) completed QuickSIN in a pilot that mimicked the present study in design and analyses. After 10,000 Monte Carlo simulations and assuming a 5% false positive rate, a sample of 16 had 95% power to detect the SAC for SNR-50 in QuickSIN, and 14 had 97% power to detect the SAC for SIN accuracy in AzBio.

SIN Measures

QuickSIN and AzBio both involve repeating sentences read by a speaker, but AzBio is notably more complex, with varied voices, denser background babble, and more scored words (Table 2).

QuickSIN

Participants completed one practice list of sentences without electrical stimulation. Next, a median of six unique lists (30 keywords each) were played per stimulation site in randomized order. For each site, three participants completed four lists (eight total lists); four participants completed five lists (ten total), and nine participants completed six lists (12 total). In each list, a female speaker read six sentences with increasing four-talker babble that decreased signal-to-noise ratio (SNR) from +25 to 0 dB in 5 dB decrements. Target speech was presented at 70 A-weighted decibel sound pressure level (dBA SPL), adhering to test guidelines.[50]

Table 2. SIN Measures.

	QuickSIN	AzBio
Scoring	Keywords	All words within a sentence
Target(s)	1 female	2 male and 2 female
Babble	4-talker	10-talker
Levels	+25–0 dB SNR (in 5-dB steps)	−5 to +15 dB SNR (in 5-dB steps)
Order	Descending (6 SNRs per list)	Fixed (1 SNR per list)
Quantity	30 keywords per list	133–154 words per list
Metric	SNR loss	Percentage correct

AzBio

We used AzBio Ver. 2.0,[51] featuring 15 equivalent lists (20 sentences each) spoken by two male and two female talkers against a ten-talker babble background (−5 to 15 dB SNR, 5-dB steps). Speech was presented at 60 dBA SPL, consistent with test guidelines,[52] except for one participant with 50 decibel hearing level (dB HL) sensitivity, who required 70 dBA SPL owing to reported inaudibility. List 15 was used for practice, and the remaining lists were ordered using a balanced Latin square design to control for first-order carry-over effects. SNRs were fixed within and randomized between lists. Recommended SNRs (5, 10 dB)[44] were tested twice, totaling seven lists per stimulation site.

Accuracy, SNR-50, and SNR Loss

SIN intelligibility was measured as the percentage of words accurately repeated. Adhering to standard audiologic testing procedures,[53] we estimated SNR-50 using Spearman-Kärber equations. QuickSIN is designed to use a simplified equation[50] whereas for AzBio, we used a generalized form.[54] In QuickSIN, SNR-50 is typically converted to SNR Loss (SNR Loss = SNR-50 − 2); however, because the AzBio test does not have a similar conversion, we only report SNR-50.

Psychometric Function

Three-parameter logistic functions were fit to accuracy as a function of SNR using quickpsy:[55] $p(SNR)=(1–\lambda) / (1+exp(-\beta[SNR–SNR\alpha]))$. SNRα defined its midpoint at low SNRs, λ defined its upper asymptote at high SNRs, and β defined its steepness. Pearson's χ^2 determined goodness-of-fit.

Apparatus

Sound Field

Participants were tested in a sound-treated room. Stimuli were delivered through a single loudspeaker (JBL 308P MkII; JBL, Northridge, CA) using Psychtoolbox-3 in MATLAB (MathWorks, Inc., Natick, MA) on Windows 10 (Microsoft Corp., Redmond, WA), with audio processed through a digital-to-analog converter and amplifier (Atom DAC+ and Amp+, JDS Labs; JDS Labs, Collinsville, IL). The system was calibrated for a flat frequency response (0.25–8 kHz) using a miniDSP UMIK-2 microphone (miniDSP Ltd., Kowloon Bay, Hong Kong) and Room EQ Wizard (AV Nirvana LLC, Tucson, AZ). The loudspeaker was positioned 1 meter in front of participants (0° azimuth). Participant responses were streamed to an experimenter outside the room through a FIFINE K669B microphone (FIFINE Technology, Shenzhen, China) and VB-Audio VoiceMeeter (VB-Audio Software, Sigoules, France).

Audiometry

Monaural thresholds at 0.5, 1, 2, and 4 kHz were measured using a MAICO MA 40 audiometer (MAICO Diagnostics, Eden Prairie, MN) and the modified Hughson-Westlake procedure, with the average in the better ear (PTA4) defining hearing loss. For participants in QuickSIN, binaural thresholds (PTA-Binaural) were initially measured in the sound field using a single-interval, yes-no detection task and the QUEST[56] method, converging on 50% hit rates. To estimate PTA4 from PTA-Binaural, seven participants in QuickSIN completed a separate pure tone audiometry session with the audiometer. Their PTA4 and PTA-Binaural thresholds were highly

correlated ($r = 0.91$, $p = 0.0049$), and we used linear regression ($R^2 = 0.82$) to estimate PTA4 for all participants in QuickSIN with the equation: *PTA4 = 13.67 + 1.05(PTA-Binaural)*.

Statistics

All analyses were performed in R 4.4.0.[57]

Hierarchical Modeling

Linear mixed-effects models (LMEs) were implemented in lmerTest[58] and modeled differences between stimulation sites and SNRs as fixed effects. The variance among participants, lists, and/or SIN tests were random effects. Generalized LMEs with a binomial link function modeled changes in the percentage of correct responses. Bootstrapping estimated confidence intervals. *p*-Values for fixed effects were determined with Satterthwaite approximations, following best-practice guidelines,[59] then adjusted for multiple comparisons to control the false discovery rate.[60] Post hoc comparisons on marginal means were Bonferroni-corrected, as implemented in emmeans.[61]

Model Selection

Final LME models were selected from among candidates using the Bayesian Information Criterion to balance model fit and complexity, favoring parsimonious models best supported by the data.[62,63] Models that produced a singular fit or could not converge were excluded. Details on model formulas are presented in the Supplementary Methods and Tables.

Controlling for Collinearity and Regression to the Mean

Multivariable LME models assessed the relationship between tcVNS effects and individual differences in baseline SIN performance (SNR-50 during placebo), hearing loss (PTA4), or age. All predictors were standardized to z-scores. tcVNS effects were defined as the difference in the upper asymptote of intelligibility between tcVNS and off-target conditions. Additional models included baseline SIN accuracy and MoCA scores as predictors. Variance Inflation Factors were used to assess multicollinearity. Permutation analyses, with maxT correction for multiple comparisons,[64] corrected for regression to the mean in the final model.[65]

Sex

Owing to the small sample of each sex, and because sex-based differences were not the primary focus of this study, sex-related effects were assessed in exploratory and post hoc analyses. SNR-50 was pooled across cohorts to create a larger sample of males; next, LMEs evaluated whether tcVNS efficacy interacted with sex.

MoCA, PTA, and Stimulation Parameters

Exploratory, post hoc analyses tested differences between cohorts' MoCA scores and PTA thresholds (Kruskal-Wallis test), differences in stimulation parameters (paired *t*-test), and differences in perceived stimulation intensity (paired Wilcoxon signed rank test).

RESULTS

Tonic tcVNS Was Well-Tolerated

Before SIN testing, participants in two cohorts underwent cognitive screening (MoCA) and pure tone audiometry (PTA) without electrical stimulation (Fig. 1). All participants passed the cognitive screen (≥12/15 points), but MoCA scores differed between cohorts (H value = 4.38, $p = 0.030$), with the QuickSIN cohort showing higher scores (mean = 13.5, SD = 1.15) than the AzBio cohort (mean = 12.6, SD = 0.84). PTA thresholds (PTA4) did not differ significantly between cohorts (H = 1.17, $p = 0.28$), with both exhibiting mild hearing loss on average (QuickSIN: mean = 26 dB HL, SD = 8.22, range = [15, 40]; AzBio: mean = 23 dB HL, SD = 11.69, range = [5, 50]).

During SIN testing, each participant received both tonic tcVNS and off-target (placebo) stimulation in a counterbalanced order, which minimized order effects (Supplementary Analyses). Continuous tonic stimulation (biphasic square pulses delivered at 30 Hz) was well-tolerated, with its perceived intensity rated between "not intense" and "slightly intense" on average (Table 1).

Speech Intelligibility Thresholds Improved During tcVNS

SNR-50 was estimated using the Spearman-Kärber method,[54] with lower values indicating better SIN performance. LMEs (Supplementary Data Table S1) found a significant reduction in SNR-50 during tcVNS compared with off-target stimulation: 0.76 dB in QuickSIN (Fig. 2a; SE = 0.30, $t(155.03) = -2.53$, $p = 0.016$) and by 0.38 dB in AzBio (Fig. 2b; SE = 0.17, $t(13) = -2.22$, $p = 0.045$; Supplementary Data Table S2), corresponding to improvements of 12% and 13%, respectively. Exploratory analyses found no evidence of sex-related differences in both cohorts (Supplementary Data Tables S3 and S4; interaction: $t(174.98) = 0.094$, $p = 0.93$).

Improvements by tcVNS met the 1 dB minimum clinically important difference (MCID) established for an FDA-approved cochlear implant (Nucleus 24[67]) in nine of 16 participants in QuickSIN (56%; Table 3) and in two of 14 participants in AzBio (14%). Overall, 11 of the 22 individuals in the study (50%) showed MCID-level improvements, suggesting a clinically meaningful benefit. This overall count reflects all individuals in the study, with those participating in both cohorts counted only once if they met the MCID in either test. Therefore, this total is not the sum of the two cohort results.

tcVNS Improved Speech Intelligibility in Low-to-Moderate Noise

The relationship between SIN intelligibility and SNR was well-fit by logistic functions (Fig. 3; $\chi^2 > 12$, $p > 0.067$). This function is defined by two key parameters:[68] SNRα, the SNR at its midpoint, and λ, the upper asymptote of accuracy at high SNRs. LME models (Supplementary Data Tables S5 and S6) indicated that tcVNS increased the upper asymptote by 3.74% in QuickSIN (Fig. 3a; SE = 1.43, $t(15) = 2.62$, $p = 0.031$) and by 2.43% in AzBio (Fig. 3b; SE = 0.99, $t(13) = 2.45$, $p = 0.039$). However, tcVNS did not significantly change the function's midpoint (QuickSIN: $t(15) = -0.066$, $p = 0.95$; AzBio: $t(13) = 0.15$, $p = 0.95$), suggesting its benefits are primarily on SIN intelligibility in low-to-moderate noise.

Generalized LME models (Supplementary Data Tables S7 and S8) indicated that tcVNS-evoked improvements increased with SNR (Fig. 3c), with a 0.028 log odds increase per SNR in QuickSIN (SE = 0.011, z = 2.42, $p = 0.021$) and by 0.025 log odds in AzBio (SE = 0.0067, z = 3.81, $p = 0.00023$). Post hoc comparisons of marginal means found significant performance gains at SNRs >0 dB. These comparisons were conducted on the odds ratio scale, which is well-suited for evaluating the binary outcome of correct versus incorrect SIN perception. In QuickSIN, tcVNS improved the odds of accurate SIN comprehension by 43% on average (Fig. 3d), with significant effects at 10 (z = 3.15, $p = 0.0098$), 15 (z = 3.52, $p = 0.0026$), 20 (z =

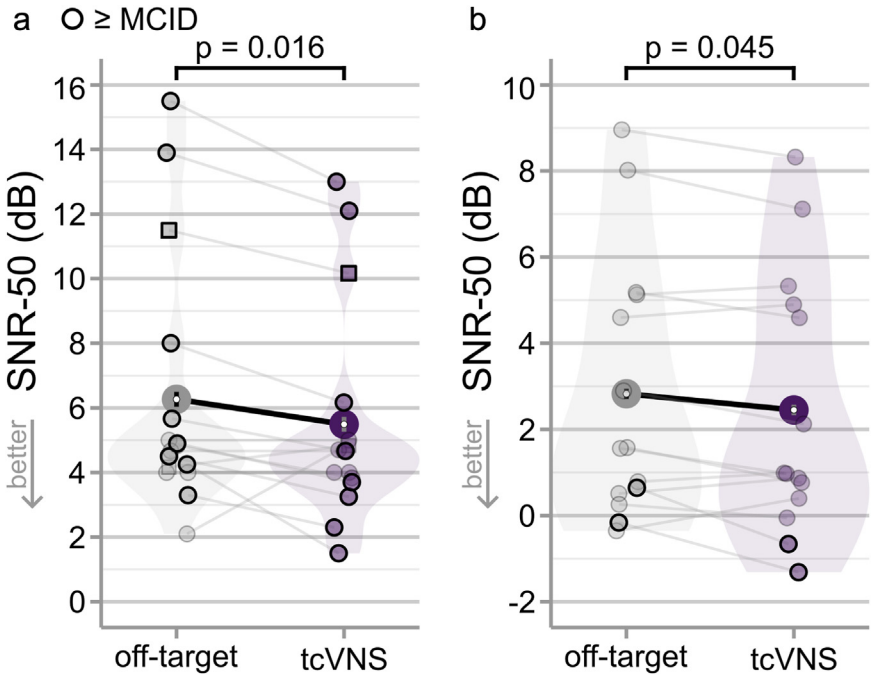

Figure 2. Speech intelligibility thresholds improved during tcVNS. SNR-50 estimated with QuickSIN (panel a) and AzBio (panel b). Lower values indicate better SIN performance. Two individuals in the QuickSIN cohort wore hearing aids during the test and are depicted as square markers. Participants in whom tcVNS improvements met or exceeded the MCID are highlighted with darkened outlines. Large data points connected by black lines show group means, with errors ±1 within-subject SEM.[66] *p* Values are corrected for multiple comparisons using the Benjamini-Hochberg procedure. [Color figure can be viewed at www.neuromodulationjournal.org]

3.37, $p = 0.0046$), and 25-dB SNR ($z = 3.20$, $p = 0.0083$). In AzBio, the odds of accurate performance increased by 20%, on average, with significant improvements at 5 ($z = 4.79$, $p = 8.49 \times 10^{-6}$), 10 ($z = 5.67$, $p = 7.10 \times 10^{-8}$), and 15 ($z = 5.27$, $p = 7.00 \times 10^{-7}$) dB SNR.

Individual participants showed clinically significant gains (Table 3). A 4.9% improvement to SIN intelligibility at 5-dB SNR defined the MCID.[69] Although average tcVNS-evoked improvements at 5 dB were 3.02% in QuickSIN (SE = 3.22) and 2.33% in AzBio (SE = 2.23), 56% of participants in QuickSIN (nine/16) and 29% of participants in AzBio (four/14) met the MCID. Overall, 55% (12/22) showed MCID-level improvements, supporting the potential for meaningful clinical benefits with tcVNS.

Improvements Increased With the Severity of SIN Deficits but Not With Hearing Loss or Age

To explore the variability in individual responses to tcVNS, we analyzed whether differences in age (mean = 70.4 years, SD = 7.19), hearing loss, or baseline SIN performance influenced efficacy. SNR-50 scores during off-target stimulation indexed baseline SIN ability (QuickSIN: mean = 6.27 dB, SD = 3.92; AzBio: mean = 2.83 dB, SD = 3.06), and pure tone thresholds (PTA4) indexed hearing loss.

Participants exhibited varying degrees of SIN deficits and hearing loss. Using normative SNR-50 data for QuickSIN,[50] 69% of participants had normal/near-normal SIN performance (<5 dB SNR-50); 12% had mildly impaired performance (5–9 dB), and 19% had moderately impaired performance (9–17 dB). Although equivalent categories are less established for AzBio, a higher SNR-50 indicated greater SIN deficits. Hearing loss also varied: 27% had normal hearing (<20 dB HL); 60% had mild (20–<35 dB HL); 10% had moderate (35–<50 dB HL), and 3% had moderately severe hearing loss (50–<65 dB HL). As expected, SIN deficits correlated with hearing loss and age (Supplementary Data Fig. S1 and Supplementary Data Tables S9 and S10).

Exploratory LME modeling evaluated whether these individual differences influenced tcVNS efficacy. Baseline measures of SNR-50,

Table 3. Improvements to SIN Performance Met Established MCID Benchmarks.

	SNR-50	SIN accuracy						
		−5 dB	0 dB	5 dB	10 dB	15 dB	20 dB	25 dB
QuickSIN [*n* = 16]	9 (56%)	—	6 (38%)	9 (56%)	6 (38%)	8 (50%)	5 (31%)	7 (44%)
AzBio [*n* = 14]	2 (14%)	1 (7%)	5 (36%)	4 (29%)	3 (21%)	2 (14%)	—	—
Overall [*n* = 22]	11 (50%)	1 (5%)	10 (46%)	12 (55%)	8 (36%)	10 (46%)	5 (%)	7 (32%)

Displayed are the number and percentage of participants in whom improvements by tcVNS met or exceeded the MCID for SNR-50 (≥1 dB) or word recognition accuracy (≥4.9%). The "Overall" row represents the total number of individuals who indicated MCID-level improvements across both cohorts. Individuals who participated in both cohorts are counted once if their performance met the MCID in either test. As a result, the Overall row may not equal the sum of each individual cohort.

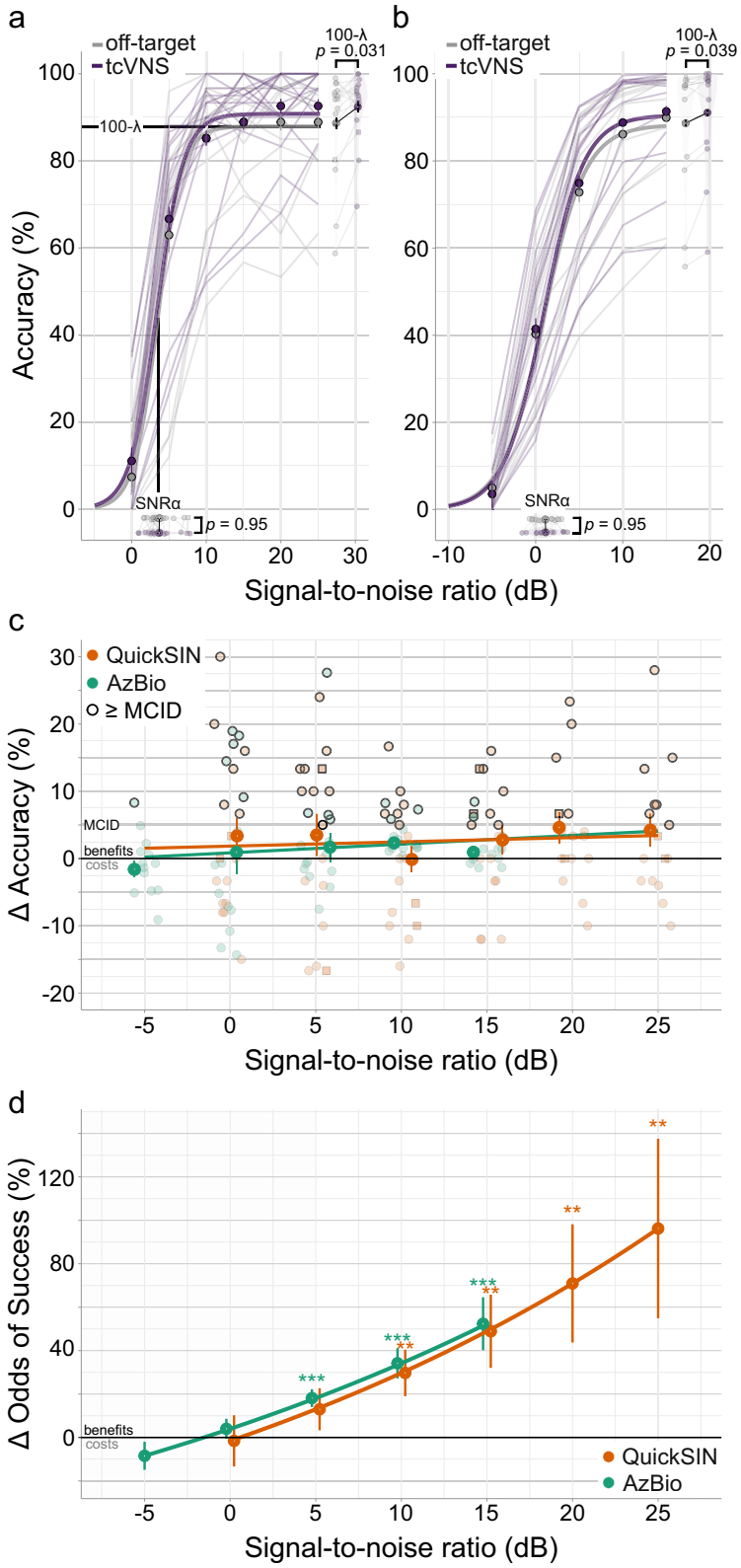

Figure 3. tcVNS improved speech intelligibility in low-to-moderate noise. Psychometric functions for QuickSIN (panel a) and AzBio (panel b). Smooth lines depict the fitted logistic functions whereas the transparent, jagged lines show the raw accuracy for individual participants. Parameter estimates for SNRα and λ are displayed beside the respective x- and y-axes, with large points connected by black lines indicating the group average and error bars of ±1 within-subject SEM.[66] *p* Values correspond to the result of linear mixed-effects modeling and are corrected for multiple comparisons using the Benjamini-Hochberg procedure. c. Change in SIN intelligibility as a function of SNR. Positive values indicate better accuracy during tcVNS. Large points and errors bars show the group-average difference and ±1 within-subject SEM[66]; smaller points show individual participants, with those meeting the MCID highlighted with darkened outlines. The best fitting regression lines for each cohort are displayed. d. Percentage change in the odds of accurate SIN comprehension. Positive values indicate higher odds during tcVNS. Points and vertical lines depict the marginal means and their standard error. Star signifiers denote Bonferroni-corrected *p*-values for post hoc comparisons: ** $p < 0.01$, *** $p < 0.001$. [Color figure can be viewed at www.neuromodulationjournal.org]

PTA4, and Age were included as predictors, whereas other baseline measures (MoCA scores and SIN accuracy) were excluded owing to high collinearity (Variance Inflation Factors >6.7; Supplementary Data Tables S11 and S12). Given that tcVNS had the largest effects at moderate-to-high SNRs, changes in the upper asymptote (λ) quantified its efficacy. Results showed that tcVNS-evoked improvements increased by 3.59% (SE = 1.01, $t(21.66) = 3.55$, $p = 0.028$) for each standardized unit of change in baseline SNR-50 (Fig. 4a). However, neither hearing loss ($t(21.03) = -0.63$, $p = 0.97$; Fig. 4b), age ($t(21.16) = 0.89$, $p = 0.88$; Fig. 4c) nor any two-way or three-way interactions significantly predicted tcVNS-evoked improvements ($p > 0.93$; Supplementary Data Table S13). These findings suggest that tcVNS efficacy was primarily determined by the severity of preexisting SIN deficits rather than hearing loss or age.

DISCUSSION

Age-related changes in auditory processing impair speech comprehension in noisy environments. Across two cohorts of older adults performing standard SIN assessments, tonic tcVNS improved clinically relevant metrics used to guide hearing aid and cochlear implant recommendations.[43,44] SNR-50 thresholds improved by an average of 0.76 dB in QuickSIN and 0.38 dB in AzBio. SIN intelligibility improved by 3% when speech was louder than noise (SNRs >0 dB), with larger gains for individuals with preexisting SIN deficits. Overall, tcVNS met the MCID for SNR-50 in 50% of participants and for SIN intelligibility in 55%, suggesting that tcVNS may meaningfully alleviate difficulties understanding SIN.

Given these significant improvements in SIN performance, we explored how tonic tcVNS measures against established solutions: hearing aids, personal sound amplification products (PSAP), and cochlear implants. For instance, two weeks of use with self-fitted or audiologist-fitted hearing aids (Lexie Lumen) yielded SNR-50 improvements in QuickSIN of 0.47 dB and 1.14 dB, respectively.[48] Here, 8 minutes of tonic tcVNS produced a comparable 0.76 dB improvement, placing its gains in-between these hearing aid results. In an assessment of five PSAPs, intelligibility with AzBio sentences improved by an average of 5.8%, although with considerable variation ranging from −11% to +11%. The 3% improvement observed during tonic tcVNS fell well within this range, near the average PSAP benefit. However, the 12% improvement reported for a hearing aid (Oticon Nera) exceeded tcVNS.[49] It is important to note, however, that the PSAPs and hearing aid were tested with a 180° spatial separation between speech and noise, providing an additional cue to aid in speech perception.[70,71] Our study had speech and noise colocated at 0°, eliminating spatial cues. Moreover, although our cohorts included individuals with clinically normal hearing, they are typically not the target population for studies on assistive hearing devices.[44,48,49] Therefore, even when tested under more challenging conditions and with a wider range of hearing sensitivities, tonic tcVNS paralleled conventional assistive hearing solutions, with MCID-level gains in QuickSIN and AzBio.

Our findings also suggest that tonic tcVNS may improve SIN intelligibility in realistic communication scenarios. In normal conversation, speakers adjust their speech levels to overcome background noise.[72–75] As a result, speech is usually louder than background noise by 5 to 10 dB in everyday settings including

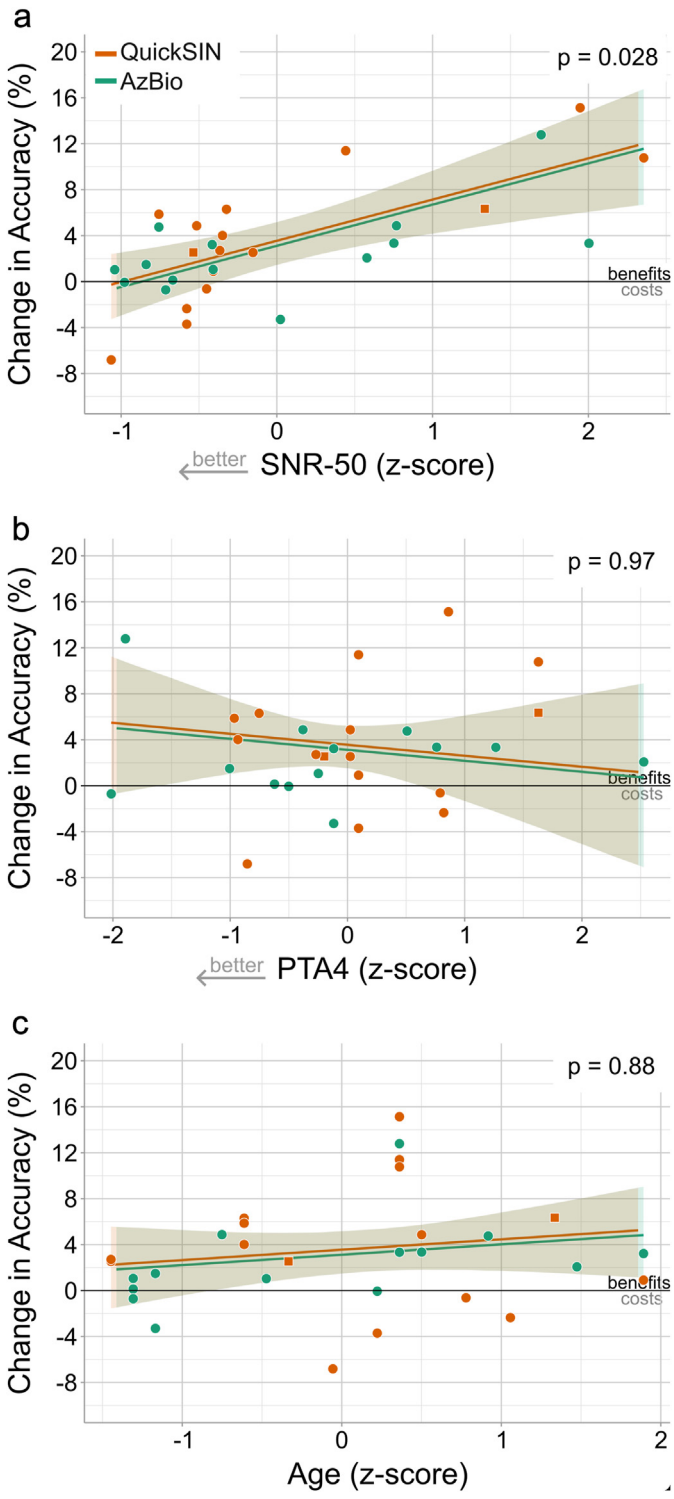

Figure 4. Improvements increased with the severity of SIN deficits, but neither hearing loss nor age. tcVNS-evoked changes in the upper asymptote of SIN accuracy (λ) are displayed as function of baseline SNR-50 measured during off-target stimulation (panel a), hearing loss (PTA4) (panel b), and age (panel c). In all panels, each dot depicts individual participants in a cohort; lines depict the marginal regression for each independent variable determined using LME modeling, with shaded areas indicating 95% confidence intervals. All p values were corrected for regression to the mean and for multiple comparisons using the maxT method.[64] [Color figure can be viewed at www.neuromodulationjournal.org]

stores, restaurants, and in moving traffic.[73–75] Here, we found that improvements by tonic tcVNS increased with SNR, delivering significant gains at SNRs ≥5 dB, which implies its effects are well-adapted to the demands of real-world listening situations.

Growing evidence supports the effectiveness of tonic tcVNS for enhancing central auditory processing.[21–23,38] Sensory processing depends on neuromodulatory systems that regulate attention and arousal, such as the LC-NE.[22,76] In line with this, tonic LC-NE activation, either directly[38] or indirectly through VNS,[21] has been shown to rapidly improve and sustain accurate central sensory processing. In rodents, tonic LC stimulation caused a steady increase in NE concentration, which suppressed burst spiking responses that would otherwise reduce the rate and efficiency of sensory transmission.[21,38] Although direct evidence of this suppressive mechanism in humans is lacking, our prior work in younger adults suggests that tonic tcVNS improves sensory performance in a manner consistent with this mechanism of action.[23] Specifically, tonic tcVNS improved the detection of brief gaps in sound, a task that depends on precise temporal processing by the central auditory system,[39,40,77] which decreases with age and limits speech intelligibility.[40,77] Therefore, our present results provide support for tcVNS-induced gains to central auditory processing that facilitate accurate speech perception in older adults.

The improvements observed during tonic tcVNS also may derive from gains in selective attention and working memory—key cognitive functions for successful SIN perception.[78–81] The LC-NE system has been shown to modulate goal-directed attentional selection[76,82] and maintain stable working memory capacity,[83,84] shaping cognitive function in aging.[85] In older adults, deficits in these functions are exacerbated by age-related hearing loss, which accelerates cognitive decline.[86,87] Impaired attention limits the ability to focus on relevant speech and suppress background noise, whereas working memory deficits reduce the retention of recently heard words, increasing susceptibility to distraction in multispeaker environments[88,89] and weakening the utility of contextual cues.[6,90] Deficits in these functions have been linked to a disrupted excitation-inhibition balance within thalamocortical circuits that support rapid temporal processing and auditory perceptual organization.[91] Increased LC activation, and a concomitant elevation in NE concentration, has been shown to increase the efficacy of excitatory (glutamic) and inhibitory (γ-amino butyric acid-ergic) responses within the thalamus,[38,92] providing a potential mechanism by which tcVNS-mediated activation of the LC-NE could alleviate excitation-inhibition imbalances to improve cognitive function for SIN perception.

Other neuromodulation approaches have shown limited success in improving SIN intelligibility. Transcranial direct current stimulation (tDCS) over the left superior temporal gyrus improved SIN performance in the City University of New York Sentences Test[93] but used a sham condition without adequate control for the tDCS sensation.[94] In contrast, tonic tcVNS and placebo stimulation were perceived as equivalently intense in our study. Intermittent theta-burst transcranial magnetic stimulation was initially found to improve SIN intelligibility when delivered to the left ventral premotor cortex.[95] However, a follow-up study did not replicate these effects.[96] Instead, benefits occurred only in individuals with poor baseline performance, mirroring the compensatory benefits of tonic tcVNS we found in younger adults[23] and now in older adults. Lastly, pairing brief VNS bursts with auditory tones or sensory training can accelerate and strengthen recovery from sensory disruption.[11,27–29] However, in a rat model of hearing loss, pairing VNS with training did not improve speech perception beyond training alone.[97] This contrast between the SIN enhancements we observed in humans with and without hearing loss, and the lack thereof after phasic VNS in an animal model of hearing loss, suggests that stimulation parameters play a critical role for effective neuromodulation.

Our stimulation protocol was designed using prior research. First, the off-target stimulation site has been shown to have no effect on sensory performance, matching the impact of forearm stimulation or a no-stimulation baseline in previous work.[23] Second, the spatial configuration of the electrode montage has shown auditory enhancements in humans[23] and is supported by computational modeling indicating that our parameters can drive action potentials in afferent and efferent fibers of the cervical branch of the vagus nerve.[12] Moreover, on the basis of prior finite-element simulations,[98,99] we used a farther interelectrode spacing during tcVNS than during off-target stimulation to enhance electrical field penetration and improve the likelihood of vagal activation. Third, our tcVNS protocol has been shown to modulate heart rate variability,[23] a marker of efferent vagal activation.[100] Lastly, given that VNS-evoked thalamocortical optimization dissipates within seconds after stimulation ends,[21] our approximately 30-minute washout period ensured a return to baseline between tcVNS and placebo conditions—a shorter duration (20 minutes) yielded robust tcVNS effects in prior work.[23]

Our findings corroborate evidence that tcVNS can improve sensory and cognitive performance in humans,[18–20,23,101–103] with its effects exceeding those of taVNS when compared head-to-head.[18,23] Although we ascribe our findings to a tcVNS-mediated activation of the LC-NE system, evidence supporting that link is mixed. Although functional magnetic resonance imaging studies have shown evidence of tcVNS-evoked activity in afferent vagal projections to the LC,[32,33] data from noninvasive NE biomarkers, including pupil diameter, P300, and salivary alpha amylase, are inconclusive.[104] This variability has been attributed to studies being statistically underpowered, a lack of an appropriate active placebo control, and differences in stimulation parameters.[104] Although our study had design elements that addressed some limitations—power analyses, conceptual replication in two SIN tests, an active placebo control, and stimulation parameters informed by prior studies—future work is required to replicate our findings and confirm the role of the LC-NE system.

Lastly, our study had several limitations. First, two participants in the QuickSIN cohort wore hearing aids during SIN testing, introducing a potential confound. However, repeating all statistical analyses without these participants did not alter the pattern of results, so both were included in the final data set (marked with square symbols in all plots). For one participant with hearing aids, tcVNS evoked MCID-level gains in SNR-50 (Fig. 2a) and recognition accuracy (Fig. 3c), suggesting that tcVNS complemented their hearing aids to enhance SIN perception. Future studies are needed to explore this interaction. Second, we did not formally evaluate blinding integrity; therefore, it remains uncertain whether participants could guess the active condition. However, several factors likely minimized this possibility: The perceived intensity between tcVNS and placebo was matched; participants were read a standardized cover story with no mention of vagal anatomy; and participants were laypersons without expertise regarding the cervical branch of the vagus nerve. Third, because VNS-mediated LC-NE activation can increase arousal to regulate performance,[19,76] it is plausible that group-level improvements may have been driven primarily by individuals participating during their off-peak hours when arousal is low, typically in the afternoon/evening for older adults.[105] Our sample size was not powered to assess this;

future work is needed to distinguish general arousal effects from sensory enhancements by tcVNS.

In conclusion, tonic tcVNS evoked immediate and clinically meaningful improvements to speech comprehension in noise, particularly for individuals with preexisting SIN deficits. This study adds converging evidence for an LC–NE-mediated enhancement to auditory processing in the brain, triggered on demand by tonic tcVNS. Our findings highlight the potential for tcVNS to complement conventional assistive hearing technologies and offer promising implications for novel treatments of sensory disorders.

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Authorship Statements

Michael Jigo, Jason B. Carmel, Qi Wang, and Charles Rodenkirch conceived the study. Michael Jigo led the design of the study, with input from Jason B. Carmel, Qi Wang, and Charles Rodenkirch. Michael Jigo led participant recruitment, data collection, and data analysis. Michael Jigo drafted the article and figures, with input from Jason B. Carmel, Qi Wang, and Charles Rodenkirch. All authors approved the final manuscript.

Conflict of Interest

All authors are stockholders in Sharper Sense, Inc, a company developing methods for enhancing sensory processing with vagus nerve stimulation. Jason B. Carmel is a founder and stockholder in BackStop Neural and has received honoraria from Pacira, Motric Bio, and Restorative Therapeutics.

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SUPPLEMENTARY DATA

To access the supplementary material accompanying this article, visit the online version of *Neuromodulation: Technology at the Neural Interface* at www.neuromodulationjournal.com and at https://doi.org/10.1016/j.neurom.2025.04.007.

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COMMENT

This study uses VNS, a growing therapeutic approach to many neurologic and cognitive disorders, to examine its potential benefits on speech-in-noise comprehension. Invasive cervical VNS has shown success in improving sensory perception, but the invasive and surgical approach to do so limits clinical applicability to the large population of adults who struggle with speech-in-noise perception with advancing age. In this study, the authors used a tcVNS, that requires placement of small electrodes on the neck, with the goal of improving performance on clinical tests of speech perception. Their results are promising—tcVNS led to speech-in-noise improvements. However, additional research is necessary to understand the mechanism of action, particularly whether tcVNS is effective at activating the locus coeruleus-norepinephrine system. These findings will have impacts in the field as researchers continue to search for viable rehabilitative approaches to speech-in-noise comprehension challenges in adults, particularly for those who may not be ideal candidates for traditional assistive devices such as hearing aids.

Jacie R. McHaney, PhD.
Chicago, IL, USA.