

1 **Title:** The relationships between cochlear nerve health and AzBio sentence
2 scores in quiet and noise in postlingually deafened adult cochlear implant
3 users

4 **Authors:** Zi Gao¹, PhD; Yi Yuan², PhD; Jacob J. Oleson³, PhD; Christopher R.
5 Mueller¹; Ian C. Bruce⁴, PhD; René H. Gifford⁵, PhD; Shuman He¹, MD,
6 PhD

7 **Affiliations:** ¹Department of Otolaryngology – Head and Neck Surgery, The Ohio State
8 University, Columbus, OH 43212
9 ²Department of Audiology, San José State University, San José, CA 95192
10 ³Department of Biostatistics, The University of Iowa, Iowa City, IA 52242
11 ⁴Department of Electrical and Computer Engineering, McMaster
12 University, Hamilton, ON, L8S 4K1, Canada
13 ⁵Department of Hearing and Speech Sciences, Vanderbilt School of
14 Medicine, Nashville, TN 37232

15 **Correspondence:** Shuman He, MD, PhD
16 Eye and Ear Institute
17 Department of Otolaryngology – Head and Neck Surgery
18 The Ohio State University
19 915 Olentangy River Road, Suite 4000
20 Columbus, OH 43212
21 Phone: 614-293-5963
22 Fax: 614-293-7292
23 Email: Shuman.He@osumc.edu

24 **Conflict of Interest:** None.

25 **Source of Funding:** This work was supported by grants from the National Institutes of Health

26 awarded to SH [grant numbers 1R01 DC016038 and R21 DC019458].

27 **Author Contributions:** ZG participated in data analysis, drafted and approved the final version

28 of this paper. YY participated in data collection, provided critical

29 comments, and approved the final version of this paper. JJO conducted

30 statistical analyses, provided critical comments, and approved the final

31 version of this paper. CRM participated in data collection and analysis,

32 provided critical comments, and approved the final version of this paper.

33 ICB and RHG provided critical comments and approved the final

34 version of this paper. SH designed this study, participated in data

35 analysis, provided critical comments, and approved the final version of

36 this paper.

The relationships between cochlear nerve health and AzBio sentence scores in quiet and noise in postlingually deafened adult cochlear implant users

ABSTRACT

Objectives: This study investigated the relationships between the cochlear nerve (CN) health and sentence-level speech perception outcomes measured in quiet and noise in postlingually deafened adult cochlear implant (CI) users.

Design: Study participants included 24 postlingually deafened adult CI users with a Cochlear® Nucleus™ device. For each participant, only one ear was tested. Neural health of the CN was assessed at three or four electrode locations across the electrode array using two parameters derived from results of the electrically evoked compound action potential (eCAP). One parameter was the phase locking value (PLV) which estimated neural synchrony in the CN. The other parameter was the sensitivity of the eCAP amplitude growth function (AGF) slope to changes in the interphase gap (IPG) of biphasic electrical pulses (i.e., the $IPGE_{slope}$). Speech perception was tested using AzBio sentences in both quiet and a ten-talker babble background noise with +5 dB and +10 dB signal-to-noise ratios (SNR). $IPGE_{slope}$ and PLV values were averaged across electrodes for each subject, both with and without weighting by the frequency importance function (FIF) of the AzBio sentences. Pearson and Spearman correlations were used to assess the pairwise relationships between the $IPGE_{slope}$, the PLV, and age. Multiple linear regression models with AzBio score as the outcome and the PLV and the $IPGE_{slope}$ as predictors were used to evaluate the associations between the three variables while controlling for age.

Results: The correlation between the $IPGE_{slope}$ and the PLV was negligible and not statistically significant. The PLV, but not the $IPGE_{slope}$, differed significantly across electrodes, where the apical electrodes had larger PLVs (better neural synchrony) than the basal electrodes. The $IPGE_{slope}$, but not the PLV, was significantly correlated with participant's age, where smaller $IPGE_{slope}$ values (poorer CN health) were associated with more advanced age. The PLV, but not the $IPGE_{slope}$, was significantly associated with AzBio scores in noise, where larger PLVs predicted better speech perception in noise. Neither the PLV nor the $IPGE_{slope}$ was significantly associated with AzBio score in quiet. The result patterns remained the same regardless of whether the mean values of the $IPGE_{slope}$ and the PLV were weighted by the AzBio FIF.

Conclusions: The $IPGE_{slope}$ and the PLV quantify different aspects of CN health. The positive association between the PLV and AzBio scores suggests that neural synchrony is important for speech perception in noise in adult CI users. The lack of association between age and the PLV indicates that reduced neural synchrony in the CN is unlikely the primary factor accounting for the greater deficits in understanding speech in noise observed in elderly, as compared to younger, CI users.

Key words: cochlear implants, cochlear nerve, neural synchrony, neural health, speech perception

INTRODUCTION

The cochlear implant (CI), a prosthesis that partially restores hearing through stimulating the cochlear nerve (CN) via electrodes surgically implanted into the inner ear, is a standard treatment option for listeners with sensorineural hearing loss (for a review, see Zeng 2004). Since electrical stimulation takes place at the auditory periphery, subsequent transmission of the signals by the CN is a prerequisite for the central auditory system's ability to access and process the sound information. Therefore, it is believed that the neural health of the CN is crucial for the success of CI treatment (e.g., He et al. 2017; Zamaninezhad et al. 2023). The association between the CN health and hearing performance in CI users has been supported by post-mortem observations, where within-subject between-ear comparisons showed that the ear with a larger amount of spiral ganglion neurons (SGNs) consistently yielded a better word recognition performance (Seyyedi et al. 2014). However, due to the invasiveness of the histological procedures, direct examination of the CN is not feasible in living human CI users. Rather, non-invasive electrophysiological measures, such as the electrically evoked compound action potential (eCAP), have been developed to assess the CN health status of human CI users in research and clinical settings.

The eCAP is a near-field recorded, synchronized response of a population of CN fibers elicited by electrically stimulating a CI electrode, which has been used to evaluate neural encoding of electrical stimulation at the CN, such as spectral resolution (Won et al. 2014), neural adaptation (Hughes et al. 2012; He et al. 2023), and amplitude modulation encoding (Tejani et al. 2017) in CI users. Morphologically, a typical eCAP waveform consists of a negative peak (N1) at around 0.2-0.4 ms after stimulus onset, followed by a positive peak (P2) at around 0.6-0.8 ms after stimulus onset (e.g., Brown et al. 1990). The amplitude of the eCAP waveform is defined as

the difference in voltages between P2 and N1, and it increases with the stimulation level. The relationship between stimulation level and eCAP amplitude can be depicted using an amplitude growth function (AGF), also known as the input/output (I/O) function.

The slope of eCAP AGF has been shown to be associated with the density of SGNs in animal studies, where steeper slopes indicate higher SGN density in pharmacologically deafened, implanted animals (Pfungst et al. 2015). Aligned with the animal results, shallower eCAP slopes were observed in pediatric CI users with CN deficiency (CND) compared to those with normal-sized CNs (He et al. 2018). However, since the raw eCAP responses are susceptible to inter-patient and inter-electrode differences in non-neural factors (Brochier et al. 2021), researchers have been seeking to overcome this drawback by using the differences between eCAP-derived measurements under various stimulation conditions to assess CN health. Animal studies have shown that the sensitivity of the eCAP amplitude to changes in the interphase gap (IPG) of biphasic, electrical pulses is correlated with SGN survival. Specifically, larger effects of IPG (IPG) on eCAP amplitude (Prado-Guitierrez et al. 2006) and the AGF slope (Ramekers et al. 2014; Schwartz-Leyzac et al. 2019) are associated with higher SGN density in guinea pigs. Consistent with these results measured in animal models, children with normal-sized CNs showed larger IPG effects on the AGF slope ($IPGE_{slope}$) than children with cochlear congenital CND (Yuan et al. 2022). In addition, the $IPGE_{slope}$ has been shown to be positively correlated with sentence and consonant recognition (Schwartz-Leyzac & Pfingst 2018) and speech reception threshold (SRT; Zamaninezhad et al. 2023) in postlingually deafened adult CI users. Brochier et al. (2021) reanalyzed data from previous animal (Prado-Guitierrez et al. 2006) and human (McKay & Smale 2017) studies and proposed based on computational modeling results that IPG effect on stimulation level offset ($IPGE_{offset}$) outperformed the $IPGE_{slope}$ in controlling for non-

neural factors, yet Zamaninezhad et al. (2023) failed to establish an association between the IPGE_{offset} and speech perception measurements in CI users. In a recent computational modeling study, Takanen et al. (2024) demonstrated that the IPGE_{slope} calculated as the absolute difference between the AGF slopes on a linear I/O scale is dependent on neural survival, and that non-neural factors had little interference on the IPGE_{slope}. Taken together, despite some discrepancies, evidence from animal, human and computational research are converging in suggesting that the IPGE_{slope} is an indicator of CN survival.

While having sufficient CN fibers responding to auditory input is a prerequisite for auditory perception, CN density alone does not guarantee good hearing functions in challenging listening environments. In theory, effective and accurate representation of sound signals that allows the listener to separate target signals from noise requires synchronous firing across neurons, which in turn depends on the health status of the CN, as demonstrated in animal and computational modeling studies (Kim et al. 2013; Heshmat et al. 2020). Neural desynchronization leads to a smeared representation of temporal cues, so that even though the ability to detect sound in quiet may be minimally affected, hearing performance in noise would degrade drastically. This scenario is exemplified by some listeners with auditory neuropathy spectrum disorder (ANSD), who have normal or relatively good behavioral audiometric thresholds and speech perception in quiet, but disproportionally impaired signal detection and speech perception in noise (Kraus et al. 2000; Zeng et al. 2005). The electrophysiological measures of patients with ANSD are characterized by a relatively normal cochlear microphonic and/or otoacoustic emission (OAE) response, and an abnormal or absent auditory brainstem response (ABR), which has been interpreted as a lack of synchrony across CN fibers despite a relatively normal hair cell function (e.g., Starr et al. 2008). The crucial role of neural synchrony

in acoustic hearing has been further supported by the compound action potential (CAP) recorded in normal hearing (NH) listeners, where the level of neural synchrony, quantified with the phase locking value (PLV) of trial-by-trial CAP measurements, was found to be a strong predictor of recognition scores for speech in noise and time-compressed speech in quiet (Harris et al. 2021).

Due to the difference between acoustic and electrical hearing, the observations in listeners with NH or ANSD may not be readily generalizable to CI users. For many CI users, speech perception in noise is a challenging task despite excellent hearing performance in quiet (Zaltz et al. 2020). Histological observations of SGN dystrophy and demyelination in listeners with various hearing profiles (Nadol 1997; Wu et al. 2019) suggest that reduced neural synchrony could be an underlying cause of poor speech perception in noise in CI users. However, this proposed relationship has rarely been evaluated, largely due to the lack of electrophysiological measures of neural synchrony of the CN. We recently developed a new method to quantify peripheral neural synchrony in CI users, where the PLV of trial-by-trial eCAP responses was used as an index to quantify the degree of neural synchrony in the responses generated by CN fibers across multiple electrical stimulations (He et al. 2024). We demonstrated that higher PLVs are associated with better temporal resolution and smaller effects of noise on word recognition in post-lingually deafened adult CI users, consistent with the hypothesized effect of neural synchrony on hearing performance in electrical hearing.

In summary, previous research has established both CN survival and neural synchrony as crucial factors contributing to hearing performance in CI users. However, considering that nerve damage can result in both lower neural density and poorer synchronization, as has been shown in computational models (Heshmat et al. 2020), little is known about whether the contributions of neural survival and synchrony to hearing performance are independent or overlapping.

Observations in NH listeners by Harris et al. (2021) suggest that neural engagement and synchrony are two separate dimensions that vary differently with changes in stimulus level. In human CI users, the number and synchrony of excited CN fibers have been modeled using retrospective deconvolution performed on intraoperative eCAP recordings, both significantly associated with postoperative speech recognition scores (Dong et al. 2023). However, the model was built upon assumptions about the shape of unitary response from CN fibers, which have not been directly validated in humans (Dong et al. 2020; Dong et al. 2023). While the $IPGE_{slope}$ and the PLV in CI users have been measured postoperatively in separate experimental studies to assess their association with speech perception (Schvartz-Leyzac & Pfingst 2018; Zamaninezhad et al. 2023; He et al. 2024), it is unclear whether the biological underpinnings of these two indices are orthogonal and impact speech perception differently depending on listening conditions.

To address this critical knowledge gap, we measured the $IPGE_{slope}$, the PLV and speech perception in the same group of postlingually deafened adult CI users and evaluated their relationships. Speech perception was measured using AzBio sentences (Spahr et al. 2012), a speech corpus consisting of multiple lists of everyday sentences with similar levels of difficulty. Based on previous studies on the effects of neural survival and neural synchrony on speech perception in listeners with various hearing profiles, we hypothesized that (1) the $IPGE_{slope}$ and the PLV are two independent measures of CN health (Harris et al. 2021; Kraus et al. 2000); (2) the $IPGE_{slope}$ is positively associated with speech perception in quiet (Zamaninezhad et al. 2023); (3) the PLV is positively associated with speech perception in noise (Zeng et al. 2005; Harris et al. 2021; He et al. 2024).

MATERIALS AND METHODS

Participants

Study participants included 24 postlingually deafened CI users (age range: 36.79-84.04 years, mean = 63.69 yrs, standard deviation $SD = 11.83$ yrs; 12 female, 12 male). Twenty of them also participated in our previous study on the development and validation of the eCAP PLV measurement (He et al. 2024), and their PLV data were reused in the current study. All participants were native speakers of American English and used a Cochlear® Nucleus™ device (Cochlear Ltd., New South Wales, Australia) in the test ear for at least two years prior to this study. All participants had a full 22-electrode insertion with their devices, as confirmed by postoperative computerized tomography scans. Only one ear was tested in each participant. None of the participants had any functional acoustic hearing in either ear. All participants achieved a score of 26 or above on the Montreal Cognitive Assessment (Nasreddine et al. 2005). Demographic information and hearing loss etiology of the participants are listed in Table 1. All participants provided written informed consent at their initial visit to the lab prior to data collection and were compensated for their time. The study was approved by the Biomedical Institutional Review Board at the Ohio State University (No. 2017H0131).

Table 1. Demographic information of all participants. The participant IDs are not known to anyone outside the research group, including the participants themselves.

Participant ID	Ear tested	Age range at testing (yrs)	Internal device and electrode array	Hearing loss etiology	Electrodes tested
S01	L	61-65	CI 512	Sudden SNHL	3, 9, 14, 20
S02	L	66-70	CI 512	Meniere's disease	3, 9, 15, 18
S03	R	66-70	CI 24RE(CA)	Unknown	3, 9, 15, 21
S04	L	56-60	CI 24RE(CA)	Head Trauma	3, 9, 15, 21

S05	R	61-65	CI 24RE(CA)	Unknown	8, 12, 15, 18
S06	L	51-55	CI 532	Unknown	4, 9, 15, 21
S07	R	61-65	CI 522	Head Trauma	6, 9, 18, 20
S08	R	36-40	CI 24RE(CA)	Unknown	3, 9, 15, 21
S09	R	56-60	CI 24RE(CA)	Unknown	3, 9, 15, 21
S10	R	61-65	CI 532	Unknown	3, 9, 15, 21
S11	R	66-70	CI 532	Unknown	3, 9, 15, 21
S12	L	76-80	CI 422	Unknown	4, 9, 15, 21
S13	L	61-65	CI 632	Unknown	3, 9, 15, 21
S14	R	66-70	CI 24RE(CA)	Unknown	3, 15, 21
S15	L	66-70	CI 532	Vestibular Schwannoma	3, 9, 15, 21
S16	R	81-85	CI 532	Unknown	3, 7, 10, 17
S17	L	71-75	CI 622	Unknown	6, 9, 15, 21
S18	R	81-85	CI 632	Unknown	3, 9, 15, 21
S19	R	51-55	CI 632	Unknown	3, 9, 15, 21
S20	L	56-60	CI 632	Unknown	3, 15, 18
S21	L	56-60	CI 532	Usher	3, 9, 15, 21
S22	L	76-80	CI 632	Unknown	3, 9, 15, 21
S23	L	41-45	CI 612	Vestibular Schwannoma	6, 15, 21
S24	L	51-55	CI 612	Unknown	5, 9, 15, 21

Stimuli and Apparatus

For eCAP recordings, the stimulus was a charge-balanced, cathodic leading biphasic pulse with a pulse-phase duration of 25 μ s. The IPG between the cathodic and anodic phases, as well as the presentation levels, varied across measurements, as detailed in the “Procedures” section. All eCAP recordings were performed using the neural response telemetry function implemented in the Custom Sound EP software v6.0 (Cochlear Ltd., New South Wales, Australia).

For speech perception tests, the stimuli were meaningful sentences (e.g., “The vacation was cancelled on account of weather.”) from the AzBio sentence corpus (Spahr et al. 2012), recorded by two female and two male native American English speakers. The sentences presented to each participant and for each condition were evenly distributed across the four

speakers. The background noise was a ten-talker babble presented at two signal-to-noise ratios (SNRs): +10 dB and +5 dB. All stimuli were delivered via a loudspeaker (RadioEar Corporation, PA) placed 1 m in front of the participant at 0° azimuth in a sound-attenuated booth.

Procedures

Testing electrodes

The default testing sites for eCAP measurements were electrodes 3, 9, 15, and 21 (i.e., e3, e9, e15 and e21). These electrodes were selected to cover a wide range along the array with relatively equal numerical separations in between, while keeping the testing time reasonable. In the case of an open- or short-circuit at a default electrode, a nearby alternative electrode was tested. Three participants (S14, S20, and S23) were tested at only three electrodes due to time constraints. The electrodes tested for each participant can be found in Table 1.

Behavioral C Level Measures

The maximum comfortable level (C level) for eCAP stimuli at each IPG level (7 μ s and 42 μ s) was determined via subjective rating using an ascending procedure. Prior to the measurement, participants were shown a visual scale of 1 (“barely audible”) to 10 (“very uncomfortable”) and were instructed to give a loudness rating using verbal responses or hand gestures following each stimulus presentation. Each presentation consisted of five pulses delivered at a probe rate of 15 Hz. The stimuli were first presented at a relatively low level and gradually increased in steps of 3-5 clinical levels (CLs) until a rating of “7” was reached, then in steps of 1-2 CLs until a rating of “8” was reached. The lowest level that corresponds to a rating of “8” (“maximal comfort”) was recorded as the behavioral C level.

248

249 *eCAP Measures*

250 The eCAP was measured using a two-pulse, forward-masking paradigm (Brown et al.,
251 1990), where the masker pulse was always presented at 10 CLs higher than the probe pulse. The
252 masker pulses were delivered at the testing electrode, and the eCAP responses were recorded two
253 electrodes away from the testing electrode in the apical direction. There was an exception for
254 electrode 21, which was recorded two electrodes away in the basal direction (i.e., electrode 19).
255 The probe pulses were presented at a probe rate of 15 Hz with a masker-probe interval of 400 μ s.
256 The total number of trials in each stimulation sequence differed across measurements, as detailed
257 below. Responses were recorded at a sampling rate of 20,492 Hz with a sampling delay of 122
258 μ s, an amplifier gain of 50 dB, and a monopolar-coupled stimulation mode.

259

260 *Measure of Neural Survival: the $IPGE_{slope}$*

261 In this study, the $IPGE_{slope}$ was operationally defined as the absolute difference (in
262 mV/dB) between the AGF slopes with IPGs of 42 μ s and 7 μ s, and therefore, its measurement
263 involved acquiring an AGF and calculating its slope at each IPG level for each participant. For
264 both IPG levels, the maximum presentation level of the stimuli was the behavioral C level
265 measured with an IPG of 42 μ s. To acquire AGFs, the eCAP measurement started at the
266 maximum presentation level and decreased in steps of 1 CL for five steps, then in steps of 5 CUs
267 until no peaks could be visually identified in the eCAP waveform, i.e., when the threshold is
268 reached. Additional presentation levels in steps of 1 CL for five steps near and above the eCAP
269 threshold were tested. At each presentation level, the eCAP waveform was acquired by
270 averaging the raw responses to 50 pulses. The visual identification of eCAP peaks, or lack

thereof, was performed by the experimenter at the time of testing and rechecked by an expert researcher (author S.H.) offline. The AGF slope at each IPG level was calculated using the window method developed by Skidmore et al. (2022), where linear regressions were performed on sliding windows along a resampled AGF, and the largest slope among all windows was regarded as the AGF slope. All calculations were performed using MATLAB 2021b (MathWorks, MA).

Measure of Neural Synchrony: the PLV

For each participant and electrode, the PLV was derived from 400 eCAP trials measured using biphasic pulses with an IPG of 7 μ s presented at the behavioral C level, using the method developed by He et al. (2024). The PLV is a unitless value between 0 and 1, where 0 means that the phases were randomly distributed across trials, and 1 means that the phases were perfectly correlated. To calculate the PLV, the eCAP responses were time-frequency decomposed at six linearly spaced frequencies (788.2, 1576.3, 2364.4, 3152.6, 3941.0, and 4729.2 Hz) and divided into six partially overlapped time frames with an onset-to-onset interval of 48.8 μ s and a length of 1561.6 μ s. At each frequency and within each time frame, the unit vectors representing the phases of the 400 individual trials were averaged, and the length of the averaged vector was taken as the time-frequency-specific PLV. The formula for calculating the PLV at the time t and the frequency f based on N individual trials is:

$$PLV(f, t) = \left| \frac{1}{N} \sum_{k=1}^N \frac{F_k(f, t)}{|F_k(f, t)|} \right|$$

The PLV of the electrode was then obtained by averaging all time-frequency-specific PLVs calculated from the eCAP responses at that electrode. The time-frequency decomposition and the

calculation of the PLV were performed using MATLAB R2021b and the newtimef.m function from EEGLAB v2022.1 (Delorme & Makeig 2004).

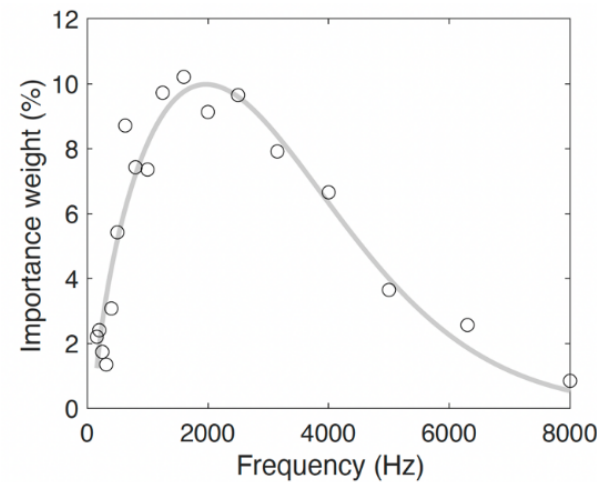
Measure of Speech Perception: AzBio Scores

Each participant was tested with AzBio sentences (Spahr et al. 2012) under three conditions: in quiet and in a ten-talker babble background noise with SNRs of +10 and +5 dB, respectively. The sentences were presented at 60 dB SPL in all conditions. For each participant and condition, a sentence list was randomly selected from Lists 1-8 of the AzBio corpus, each consisting of 20 sentences. For each participant, different word lists were used for different conditions. Participants were instructed to repeat back after each sentence and were encouraged to guess if they were unsure about what they heard. An experimenter recorded the number of words they correctly repeated in each sentence. The AzBio score was calculated as the number of words in the list correctly repeated by the participant, divided by the total number of words in the list. All words in the list, including prepositions, counted towards the score.

Averaging $IPGE_{slope}$ and PLV Values across Electrodes

For each participant, the values of the $IPGE_{slope}$ and the PLV were averaged across all tested electrodes as an overall representation of CN health across the cochlea. Both weighted and unweighted averages were calculated for both parameters. To calculate the weighted average, the results were weighted based on the frequency importance function (FIF) derived from AzBio scores under various spectral filtering conditions and SNRs in NH listeners (Lee & Mendel 2017). The FIF was fitted to a four-parameter Weibull function in SigmaPlot v15 (Grafiti LLC, CA). For each participant, the importance weight of each test electrode was calculated using the

316 fitted Weibull function based on the electrode's central frequency derived from the frequency-to-
 317 electrode table of the participant's everyday programming map. The individual values of the
 318 empirically measured AzBio FIF and the fitted curve are shown in Figure 1. The unweighted
 319 average was calculated as the arithmetic means of the $IPGE_{slope}$ and the PLV values across all
 320 tested electrodes for each participant.



321
 322 Figure 1. Individual AzBio FIF values (black circles) measured by Lee and Mendel (2017) and
 323 the fitted Weibull function (gray line)

325 Data Analysis

326 The $IPGE_{slope}$ and PLV values were compared across electrodes using linear mixed-effect
 327 models. Pairwise comparisons between the electrodes were performed using the Tukey method
 328 for p -value adjustment. The pairwise relationships between the $IPGE_{slope}$, the PLV, and age at
 329 testing were assessed using either Pearson or Spearman correlation tests for variable pairs
 330 depending on the results of the Shapiro-Wilk normality test. Multiple linear regressions with
 331 AzBio score as the outcome and the $IPGE_{slope}$ and the PLV as predictors were performed to
 332 evaluate the associations among the three variables under each testing condition (quiet, +10 dB,

and +5 dB SNR). Participant's age was added to the regression models as a covariate to control for the potential effects of advanced age on speech perception and/or eCAP measurements, as have been demonstrated in CI users (Roberts et al. 2013; Sladen & Zappler 2015; Xie et al. 2019; Jahn & Arenberg 2020). If the residuals were not approximately normally distributed, the outcome variables were transformed with appropriate methods to ensure that the normal residual assumption of linear regression is met. Correlation tests were performed in JASP v0.18.3 (JASP Team 2024), and the regressions were performed in R v4.4.1 (R Core Team 2024), with the lme4 (Bates et al. 2015), emmeans (Lenth 2024), and lmerTest (Kuznetsova et al. 2017) packages used for the linear mixed-effect models.

RESULTS

The individual IPGE_{slope} and PLV values measured at each electrode are shown in Figure 2, with the range, mean, and standard deviation (SD) listed in Table 2. To assess the potential differences in the two measurements across electrodes, two linear mixed-effect regressions were performed with the IPGE_{slope} and the PLV as the outcome variables, the electrode category as the fixed effect, and participant as the random effect. The electrode categories correspond to the four default testing locations: e3, e9, e15, and e21. If other electrodes were measured in lieu of the default electrodes, they were assigned to one of the categories based on their locations relative to the other electrodes tested in the same participant. For example, among the four electrodes tested in participant S05, e8 was the most basal electrode and therefore categorized as “e3” in the regression model. The category “e3” was used as the reference level in the regressions. The degrees of freedom were estimated using the Satterthwaite's method. The results reveal an overall effect for PLV across electrodes ($F_{(3, 66.2)} = 3.86, p = .013$). Focusing on

the pairwise comparisons, only two comparisons showed a statistically significant difference in PLVs which were e3 compared with the PLVs measured at e15 ($t_{(66.0)} = 2.99, p = .020$) and e21 ($t_{(66.0)} = 2.88, p = .027$). The other comparisons were not significantly different which were e3 with e9 ($t_{(66.4)} = 1.64, p = .364$), e9 with e15 ($t_{(66.4)} = 1.22, p = .615$), e9 with e21 ($t_{(66.4)} = 1.12, p = .682$), and e15 with e21 ($t_{(66.0)} = 0.11, p = .999$). The $IPGE_{slope}$ did not significantly differ across electrodes ($F_{(3, 66.6)} = 2.50, p = .067$). In the subsequent sections, the $IPGE_{slope}$ and the PLV refer to the weighted averages of the corresponding values across electrodes for individual participants unless otherwise stated.

Table 2. Descriptive statistics of the $IPGE_{slope}$ and the PLV values measured at different electrode locations. Values in each cell are listed in the format of “range, mean (SD)”.

Electrode category	e3	e9	e15	e21
PLV	0.117-0.590 0.309 (0.139)	0.092-0.734 0.342 (0.153)	0.109-0.741 0.384 (0.147)	0.160-0.755 0.381 (0.147)
$IPGE_{slope}$	-20.003-52.412 6.221 (16.515)	-4.982-79.901 12.152 (19.723)	-8.306-45.231 6.604 (13.486)	-10.068-28.455 3.203 (8.725)

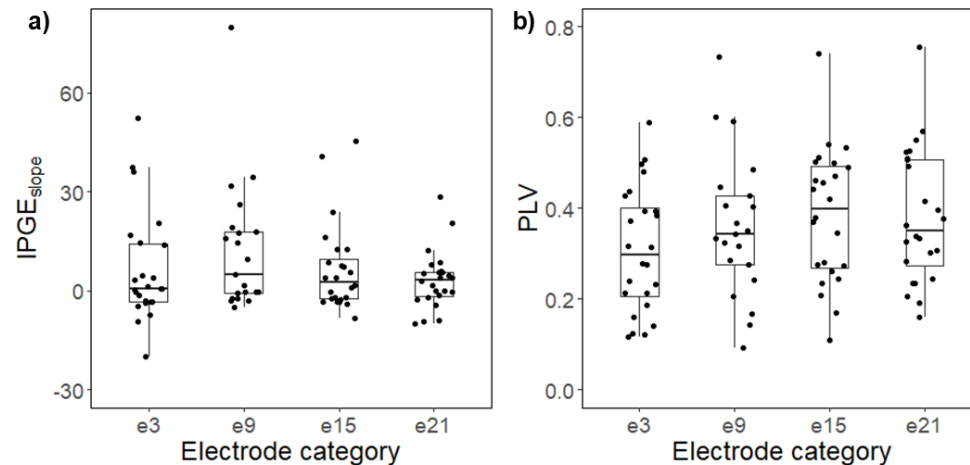


Figure 2. Individual values of (a) the $IPGE_{slope}$ and (b) the PLV by electrode category, which is named after the default electrodes. Values measured at non-default electrodes were categorized based on their locations relative to the other electrodes tested in the same participant. Boxes show the range between the first and the third quartile of the data values. The horizontal bars inside the boxes represent the median. The vertical whiskers show the range of values that are within 1.5 interquartile range (IQR) from the boxes.

Correlations between the $IPGE_{slope}$, the PLV, and age

The eCAP AGFs acquired at different IPG durations from one example participant (S06) are shown in Figure 3. Time-frequency specific PLV values of the same participant are illustrated in Figure 4. Figure 5 shows the $IPGE_{slope}$ and PLV values of individual participants (panel a), along with their age (panels b-c). The values of the PLV were relatively uniformly distributed, while one outlier (S08) for the $IPGE_{slope}$ was identified both through visual inspection and descriptive statistics (>2 SDs away from the mean). Spearman correlation tests showed that the $IPGE_{slope}$ and the PLV were not significantly correlated, either before ($\rho_{(22)} = 0.217, p = .308$) or after ($\rho_{(21)} = 0.206, p = .345$) removing the outlier.

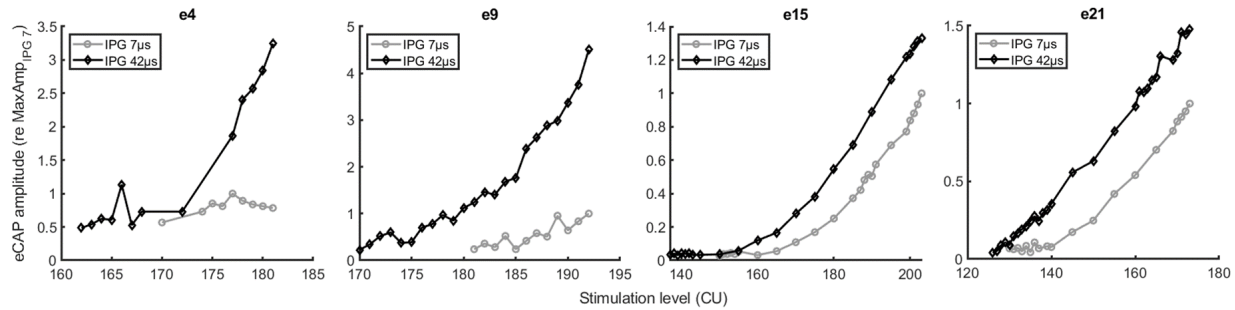


Figure 3. The AGFs measured with IPGs of 7 μ s and 42 μ s in one participant (S06), where the maximum stimulation level was set to the C level measured with a 42- μ s IPG at each electrode. The amplitudes were normalized by dividing the maximum amplitude among the trials with a 7- μ s IPG. Please note that the ranges of the axes are different across panels due to large variabilities in eCAP thresholds, C-levels, and amplitudes across electrodes.

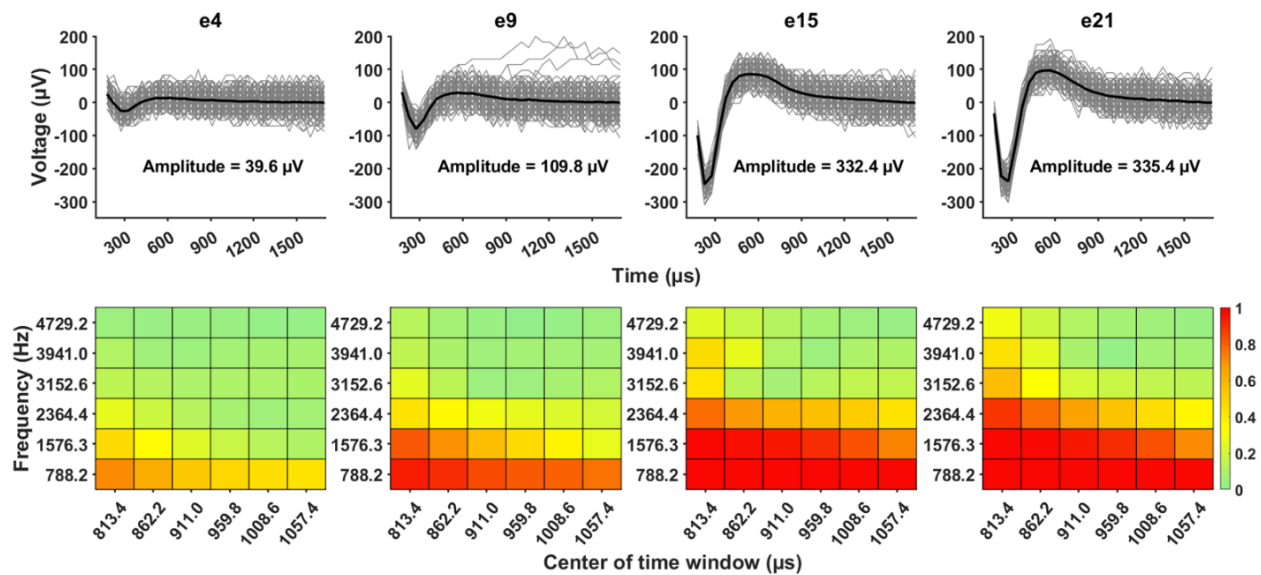


Figure 4. PLV values measured in one participant (S06). The time-frequency specific PLV values are shown in the heatmaps. Bolded black lines represent eCAP responses averaged across 400 trials. Responses in individual trials are plotted with gray lines.

Although not a focus of this study, we assessed the relationships between age and the two CN health measures. Spearman correlation test results revealed a significant negative correlation between the $IPGE_{slope}$ and age both before ($\rho_{(22)} = -0.526, p = .009$) and after removing the outlier ($\rho_{(21)} = -0.461, p = .028$). Pearson correlation test results showed that PLV was not significantly correlated with age, either before ($r_{(22)} = 0.155, p = .471$) or after ($r_{(21)} = 0.197, p = .369$) removing the outlier.

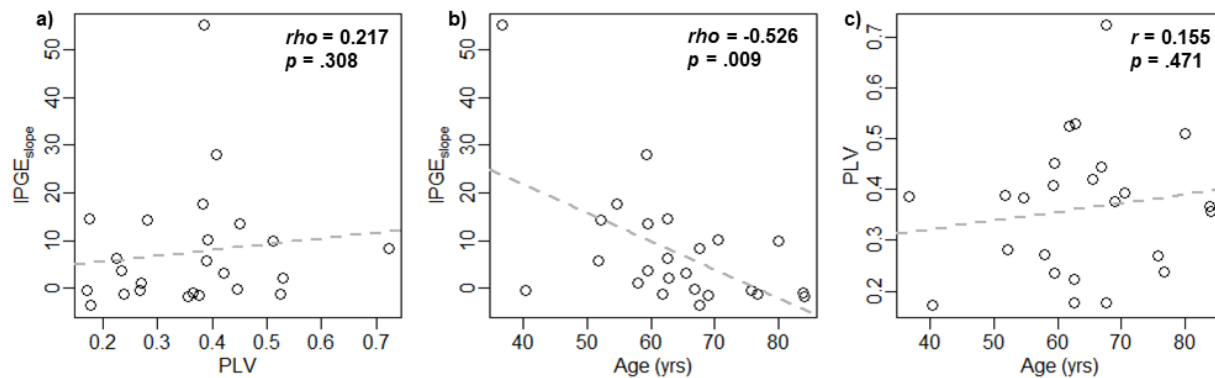


Figure 5. Correlations between (a) the $IPGE_{slope}$ and the PLV, (b) the $IPGE_{slope}$ and age, and (c) the PLV and age. Data from all 24 participants were included in the figures. Each symbol indicates the result measured in one participant. The results of correlation tests are shown in each panel.

The results reported in the subsequent sections were acquired from the full dataset without removing any outliers. It is worth noting that removing the $IPGE_{slope}$ outlier did not change the pattern or statistical significance of the linear regression results.

The associations among the IPGE_{slope}, the PLV and Speech Perception Scores

The AzBio scores in quiet and noise are plotted against either the IPGE_{slope} or the PLV in Figure 6. The AzBio scores in quiet were rank transformed (i.e., the lowest and highest scores were transformed into 1 and 24, respectively) due to non-normally distributed residuals when the raw scores were used in the linear regression model (not reported here). The results of linear regressions revealed significant associations between the PLV and AzBio scores in the two noise conditions (+10 dB SNR: $t_{(20)} = 2.19, p = .041$; +5 dB SNR: $t_{(20)} = 2.70, p = .014$) after adjusting for IPGE_{slope} and age, where larger PLVs (better neural synchrony) are associated with higher AzBio scores, but not in the quiet condition ($t_{(20)} = 1.36, p = .190$). No significant association between the IPGE_{slope} and AzBio scores was observed in any testing conditions ($p > .10$ in all cases) after adjusting for PLV and age. Detailed results of the linear regression models are available in Table 3. It is worth noting that rank-transformation of the AzBio scores in quiet did not change the pattern or statistical significance of the results.

Table 3. Results of linear models examining the relationships between the IPGE_{slope}, the PLV, and AzBio scores measured in quiet and in two noise conditions. The AzBio scores in the quiet condition were rank transformed to meet the normal residual assumption of linear regression.

Listening condition	Predictor	β (SE)	t	p	Multiple R^2
Quiet	IPGE _{slope}	0.1740 (0.1283)	1.355	.1905	0.3024
	PLV	14.0475 (10.3499)	1.357	.1899	
	age	-0.1348 (0.1394)	-0.967	.3451	
Noise, +10 dB SNR	IPGE _{slope}	0.0037 (0.0052)	0.708	.4870	0.2526
	PLV	0.9120 (0.4164)	2.190	.0405*	
	age	-0.0015 (0.0056)	-0.269	.7910	
Noise, +5 dB SNR	IPGE _{slope}	-0.0016 (0.0036)	-0.451	.6570	0.3050
	PLV	0.7951 (0.2943)	2.702	.0137*	
	age	-0.0061 (0.0040)	-1.550	.1367	

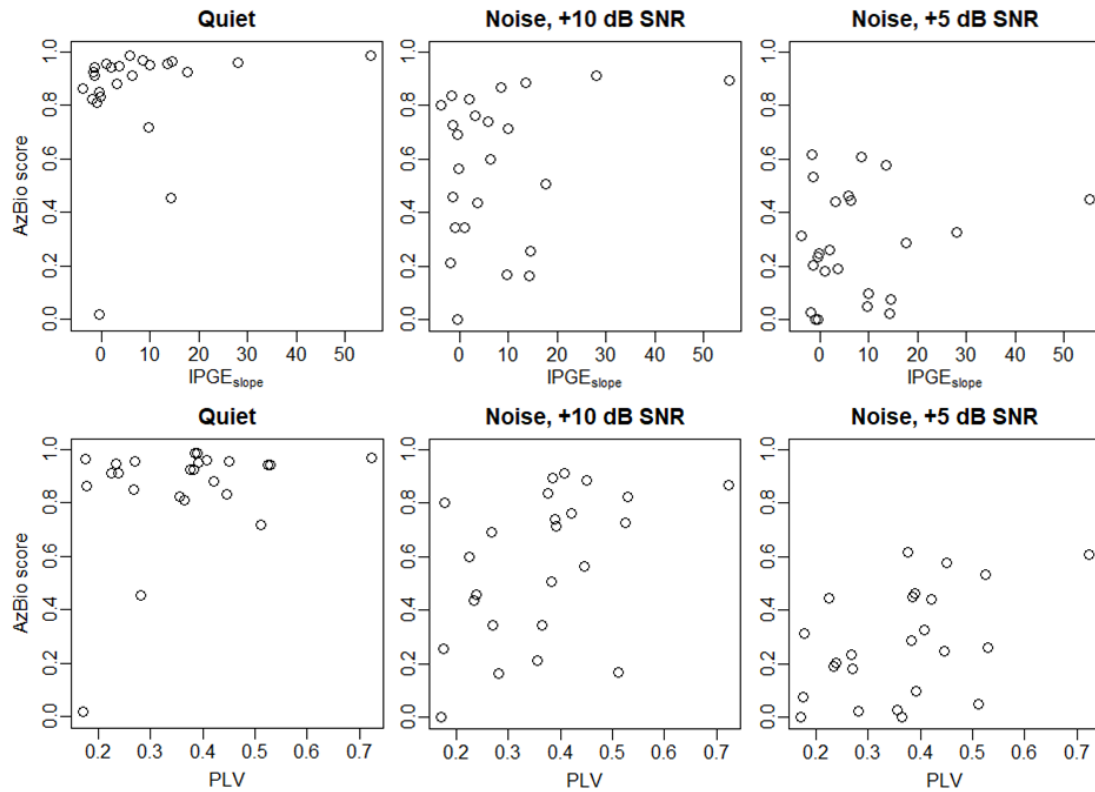


Figure 6. AzBio scores measured in quiet and in noise with +10 and +5 dB SNRs, plotted against the IPGE_{slope} (top panels) and the PLV (bottom panels). Each symbol represents the AzBio score measured in one participant.

Electrode Weighting by AzBio FIF

To qualitatively evaluate whether weighting the IPGE_{slope} and the PLV by the AzBio FIF modifies their relationships with AzBio scores, in a separate set of linear regressions, we used unweighted averages of the IPGE_{slope} and the PLV in lieu of their weighted counterparts. Overall, the result patterns and statistical significance remained the same in the unweighted version of the linear regressions, where the relationships between the PLV and AzBio scores were statistically significant in the two noise conditions (+10 dB SNR: $t_{(20)} = 2.29, p = .033$; +5 dB SNR: $t_{(20)} = 2.75, p = .012$) but not in the quiet condition ($t_{(20)} = 1.08, p = .292$), and no significant

relationship between the $IPGE_{slope}$ and AzBio scores was observed in any of the tested conditions ($p > .10$ in all cases).

DISCUSSION

This study assessed the relationships between two CN health measures, the $IPGE_{slope}$ and the PLV, and evaluated their contributions to speech perception in quiet and noise in postlingually deafened adult CI users. We hypothesized that the $IPGE_{slope}$ and the PLV are two independent measures predictive of speech recognition scores in quiet and in noise, respectively. The hypotheses were partially supported by the results showing that the correlation between the $IPGE_{slope}$ and the PLV was non-significant and negligible, and that the speech perception scores measured in noise were positively associated with the PLV. However, contrary to our hypothesis, we did not observe significant associations between the $IPGE_{slope}$ and speech perception measured either in quiet or in noise.

Peripheral Neural Survival and Synchrony

The lack of correlation between the $IPGE_{slope}$ and the PLV suggests that they are measuring different aspects of CN health. The result is consistent with the previously documented partial dissociation between neural survival and synchrony in patients with ANSD due to perinatal oxygen deprivation, where magnetic resonance imaging showed no white matter abnormalities in the auditory system compared to NH controls (Zanin & Rance 2024). These observations are aligned with the physiological process of neural deterioration: damages of the neuronal structure such as axonal dystrophy and demyelination progress at different rates across neurons (Leake & Hradek 1988), resulting in reduced level of firing synchrony across neurons

even without significant reduction in the number of surviving neurons (Resnick et al. 2018). The deterioration of the bipolar SGNs starts at the peripheral axon, which connects the SGN soma to the organ of Corti in the cochlea (Xing et al. 2012). Even after the complete loss of the peripheral axon, the soma and the central axon of the SGN (i.e., unipolar SGN) can survive for decades (Rask-Andersen et al. 2010), and the proportion of unipolar SGNs increases steadily with age (Wu et al. 2023). This process gives rise to a key difference between acoustic and electric hearing. While the loss of peripheral SGN axons likely contributes to impairment in acoustic hearing (Wu et al. 2019; Wu et al. 2020; Wu et al. 2021), electric hearing can be achieved even without the peripheral axons, as the stimulation can directly reach the somata and/or the central axons of SGNs (Javel & Shepherd 2000). Such differences in the initiation sites of CN action potentials in electric, as compared to acoustic, hearing could further increase the variabilities in neural synchrony among CI users, which may not be captured by measures of SGN survival such as the $IPGE_{slope}$.

The dissociation between the $IPGE_{slope}$ and the PLV was also corroborated by the observations on their different variabilities across electrodes and age. The PLV, but not the $IPGE_{slope}$, was significantly different across electrodes, showing better neural synchrony at the apical than the basal locations along the electrode array. This result is consistent with the typical pattern of hearing impairment, which starts with the basal locations (higher frequencies) and gradually extends in the apical direction (Huang & Tang 2010; Wu et al. 2020; Wu et al. 2023). In addition, the lack of difference across electrodes in the $IPGE_{slope}$ indicates that the gradient of hearing impairment across frequencies may be a result of varied degrees of damage in the peripheral axons, rather than in the count of SGN somata, at least in CI users. The negative association between the $IPGE_{slope}$ and listener's age suggests poorer neural survival in elders as

compared to younger listeners, which is consistent with the trend observed in a recent post-mortem temporal bone study in listeners with acoustic hearing (Wu et al. 2023). Interestingly, the PLV was not significantly correlated with age, indicating that reduced neural synchrony may not be the primary factor accounting for the age-related deterioration in speech-in-noise perception, at least in CI users. This observation challenges the hypothesized role of neural synchrony in age-related hearing loss (e.g., Rumschlag et al. 2022). Further research is warranted to compare the PLVs across listeners from a wider range of age groups and with various hearing-loss etiologies to fully investigate the role of neural synchrony, or lack thereof, in age-related hearing deterioration in CI users.

Peripheral Neural Synchrony Contributes to Speech Perception in Noise

We observed significant positive associations between the PLV and AzBio scores measured in noise, and a similar trend in the quiet condition that slightly missed significance, suggesting that neural synchrony is important for speech perception particularly in the presence of background noise. These results are consistent with the data from our previous study on CI users (He et al. 2024). This observation also agrees with and expands the findings by Harris et al. (2021), where the CAP-derived PLV was shown to be a strong predictor of the perception of time-compressed speech and speech in noise in NH listeners. These results highlight the importance of neural synchrony of the CN in speech perception in listeners with various hearing profiles. The difference between the PLV effects on speech perception in noise and in quiet is likely due to the heightened importance of temporal cues for speech perception in noise (Nie et al. 2006), and the lack of neural synchrony is associated with poor performance in psychophysical tasks requiring fine temporal perception (Zeng et al. 2005). The current results

can also provide validation for using the eCAP-derived PLV as a measure of neural synchrony in adult CI users (He et al. 2024). Future studies could measure neural synchrony of the CN in implanted deafened animals using both the eCAP-derived PLV and traditional single-neuron recording methods (e.g., Seki & Eggermont 2003) to further evaluate the validity of using the PLV as an index for neural synchrony of the CN.

Lack of significant associations between the $IPGE_{slope}$ and Speech Perception

The lack of significant associations between the $IPGE_{slope}$ and speech perception in quiet does not support our hypothesis on the contribution of neural survival to speech perception and is not consistent with the observations in a recent study by Zamaninezhad et al. (2023). This discrepancy could be due to some critical differences between the testing materials and methods used in the two studies. The German matrix sentences in Zamaninezhad et al. (2023) consisted of syntactically correct but semantically unpredictable sentences, while the AzBio corpus consisted of meaningful sentences on everyday topics; the Freiburg monosyllable test in Zamaninezhad et al. (2023) required the listeners to repeat a single word at a time, while the AzBio test required them to repeat a full sentence in each trial. These differences allow the AzBio sentence test to better simulate real-life listening situations, but also leave room for the effect of cognitive factors such as working memory (Ingvalson et al. 2015) to modulate the speech perception performance on top of CN health condition. Therefore, it is possible that the association between the $IPGE_{slope}$ and speech perception, if any, has been eclipsed by the individual differences in cognitive factors in the present study. Future research could test both cognitive abilities and the $IPGE_{slope}$ in the same group of CI users to evaluate their relative contributions to speech perception.

In addition, the $IPGE_{slope}$ values in Zamaninezhad et al. (2023) were calculated as the difference between the AGF slopes measured with IPGs of 30 μ s and 2.1 μ s, but the present study used the AGF slopes between 42 μ s and 7 μ s for the same calculation. It is possible that the sensitivity of the $IPGE_{slope}$ as an index of CN survival varies with the IPG levels used for eCAP recordings, and further investigation is warranted for optimizing the parameters in the $IPGE_{slope}$ measurement for the purpose of representing CN health condition.

Frequency Importance Function in Speech Perception Measures

While not a central focus of the present study, in the models evaluating the contributing factors to AzBio scores, we calculated the values of the $IPGE_{slope}$ and the PLV as both unweighted averages across the tested CI electrodes and weighted averages based on the AzBio FIF. The results were similar regardless of whether the AzBio FIF weights were applied, which seemingly contradicts the definition of the FIF (Lee & Mendel 2017). A possible explanation is that the FIF used in the current study was measured in NH listeners (Lee & Mendel 2017), and thus may not be fully generalizable to CI users due to the differences in the weighting of frequency bands in speech perception between CI users and NH listeners (Sladen & Ricketts 2015) and potentially larger individual differences in CI users than NH listeners (Mehr et al. 2001; Bosen & Chatterjee 2016). Furthermore, the weights of adjacent frequencies could differ considerably in some FIFs (Healy et al. 2013), so that estimating the weights of CI electrodes based on a smooth curve fitted to discrete values of the empirically measured AzBio FIF may have limited validity, even if the overall FIF shape of CI users is similar to that of NH listeners. Future research could develop and validate methods for measuring the FIF in CI users and test

whether weighting eCAP-derived indices by the CI-based FIF can improve their capability to predict speech perception.

Potential Study Limitations

One potential limitation of the present study is that only 24 post-lingually deafened adult participants with generally good speech perception outcomes were included in the study. Therefore, the variance in speech perception scores explained by the PLV or the IPGE_{slope} may not represent the variance explained in the entire CI patient population. Further studies in CI users with varied speech perception outcomes are warranted to assess the generalizability of the current observations. Another potential limitation of the study is that speech perception was measured only using AzBio sentences, which have high ecological validity but prone to the effects of central auditory processing and cognitive factors. In this study, only one ear was tested for each participant, including those who are bilateral CI users. Therefore, in the current dataset, it is not possible to control for potential individual differences in central auditory processing and cognitive abilities using within-participant between-ear comparisons. Future research can test both ears of bilateral CI users and/or add measurements for central auditory processing and cognitive abilities to pinpoint the crucial factors contributing to speech perception in adult CI users. Finally, the 10-talker babble was used as the competing background noise to assess speech perception performance. It does not fully capture the challenge of understanding speech in more complex environments.

CONCLUSIONS

The $IPGE_{slope}$ and the PLV are two eCAP-derived, independent indices for CN health. The significant positive associations between the PLV and AzBio scores measured in noise suggest that neural synchrony is important for speech perception in noise. The lack of association between age and the PLV indicates that reduced neural synchrony of the CN is not the primary factor accounting for the additional speech perception deficits in noise observed in elderly CI users as compared to their younger counterparts. Future studies can investigate the contribution of cognitive factors to speech perception and how they interact with the effects of CN health status, as well as use animal models or computational modeling techniques to better understand the biological underpinnings of the $IPGE_{slope}$ and the PLV.

REFERENCES

- Bates, D., Mächler, M., Bolker, B., et al. (2015). Fitting linear mixed-effects models using lme4. *J. Stat. Softw.*, 67. Available at: <http://www.jstatsoft.org/v67/i01/> [Accessed July 24, 2024].
- Bosen, A.K., Chatterjee, M. (2016). Band importance functions of listeners with cochlear implants using clinical maps. *J. Acoust. Soc. Am.*, 140, 3718–3727.
- Brochier, T., McKay, C.M., Carlyon, R.P. (2021). Interpreting the effect of stimulus parameters on the electrically evoked compound action potential and on neural health estimates. *J. Assoc. Res. Otolaryngol.*, 22, 81–94.
- Brown, C.J., Abbas, P.J., Gantz, B. (1990). Electrically evoked whole-nerve action potentials: Data from human cochlear implant users. *J. Acoust. Soc. Am.*, 88, 1385–1391.
- Delorme, A., Makeig, S. (2004). EEGLAB: an open source toolbox for analysis of single-trial EEG dynamics including independent component analysis. *J. Neurosci. Methods*, 134, 9–21.
- Dong, Y., Briaire, J.J., Biesheuvel, J.D., et al. (2020). Unravelling the temporal properties of human eCAPs through an iterative deconvolution model. *Hear. Res.*, 395, 108037.
- Dong, Y., Briaire, J.J., Stronks, H.C., et al. (2023). Speech perception performance in cochlear implant recipients correlates to the number and synchrony of excited auditory nerve fibers derived from electrically evoked compound action potentials. *Ear Hear.*, 44, 276–286.
- Harris, K.C., Ahlstrom, J.B., Dias, J.W., et al. (2021). Neural presbycusis in humans inferred from age-related differences in auditory nerve function and structure. *J. Neurosci.*, 41, 10293–10304.

611 He, S., Shahsavarani, B.S., McFayden, T.C., et al. (2018). Responsiveness of the electrically
612 stimulated cochlear nerve in children with cochlear nerve deficiency. *Ear Hear.*, 39, 238–
613 250.

614 He, S., Skidmore, J., Bruce, I.C., et al. (2024). Peripheral neural synchrony in postlingually
615 deafened adult cochlear implant users. *Ear Hear.* Available at:
616 <https://journals.lww.com/10.1097/AUD.0000000000001502> [Accessed May 14, 2024].

617 He, S., Teagle, H.F.B., Buchman, C.A. (2017). The electrically evoked compound action
618 potential: From laboratory to clinic. *Front. Neurosci.*, 11, 339.

619 He, S., Yuan, Y., Skidmore, J. (2023). Relationships between the auditory nerve’s ability to
620 recover from neural adaptation, cortical encoding of and perceptual sensitivity to within-
621 channel temporal gaps in postlingually deafened adult cochlear implant users. *Ear Hear.*,
622 44, 1202–1211.

623 Healy, E.W., Yoho, S.E., Apoux, F. (2013). Band importance for sentences and words
624 reexamined. *J. Acoust. Soc. Am.*, 133, 463–473.

625 Heshmat, A., Sajedi, S., Johnson Chacko, L., et al. (2020). Dendritic degeneration of human
626 auditory nerve fibers and its impact on the spiking pattern under regular conditions and
627 during cochlear implant stimulation. *Front. Neurosci.*, 14, 599868.

628 Huang, Q., Tang, J. (2010). Age-related hearing loss or presbycusis. *Eur. Arch.*
629 *Otorhinolaryngol.*, 267, 1179–1191.

630 Hughes, M.L., Castioni, E.E., Goehring, J.L., et al. (2012). Temporal response properties of the
631 auditory nerve: Data from human cochlear-implant recipients. *Hear. Res.*, 285, 46–57.

632 Ingvalson, E.M., Dhar, S., Wong, P.C.M., et al. (2015). Working memory training to improve
633 speech perception in noise across languages. *J. Acoust. Soc. Am.*, 137, 3477–3486.

634 Jahn, K.N., Arenberg, J.G. (2020). Electrophysiological estimates of the electrode–neuron
635 interface differ between younger and older listeners with cochlear implants. *Ear Hear.*,
636 41, 948–960.

637 JASP Team (2024). JASP. Available at: <https://jasp-stats.org>.

638 Javel, E., Shepherd, R.K. (2000). Electrical stimulation of the auditory nerve: III. Response
639 initiation sites and temporal fine structure. *Hear. Res.*, 140, 45–76.

640 Kim, J.H., Renden, R., Von Gersdorff, H. (2013). Dysmyelination of auditory afferent axons
641 increases the jitter of action potential timing during high-frequency firing. *J. Neurosci.*,
642 33, 9402–9407.

643 Kraus, N., Bradlow, A.R., Cheatham, M.A., et al. (2000). Consequences of neural asynchrony: A
644 case of auditory neuropathy. *J. Assoc. Res. Otolaryngol.*, 1, 33–45.

645 Kuznetsova, A., Brockhoff, P.B., Christensen, R.H.B. (2017). lmerTest package: Tests in linear
646 mixed effects models. *J. Stat. Softw.*, 82. Available at: <http://www.jstatsoft.org/v82/i13/>
647 [Accessed July 24, 2024].

648 Leake, P.A., Hradek, G.T. (1988). Cochlear pathology of long term neomycin induced deafness
649 in cats. *Hear. Res.*, 33, 11–33.

650 Lee, S., Mendel, L.L. (2017). Derivation of frequency importance functions for the AzBio
651 sentences. *J. Acoust. Soc. Am.*, 142, 3416–3427.

652 Lenth, R.V. (2024). emmeans: Estimated marginal means, aka least-squares means. Available at:
653 <https://cran.r-project.org/web/packages/emmeans/index.html>.

654 McKay, C.M., Smale, N. (2017). The relation between ECAP measurements and the effect of
655 rate on behavioral thresholds in cochlear implant users. *Hear. Res.*, 346, 62–70.

656 Mehr, M.A., Turner, C.W., Parkinson, A. (2001). Channel weights for speech recognition in
657 cochlear implant users. *J. Acoust. Soc. Am.*, 109, 359–366.

658 Nadol, J. (1997). Patterns of neural degeneration in the human cochlea and auditory nerve:
659 Implications for cochlear implantation. *Otolaryngol. Head Neck Surg.*, 117, 220–228.

660 Nasreddine, Z.S., Phillips, N.A., Bédirian, V., et al. (2005). The Montreal Cognitive Assessment,
661 MoCA: A brief screening tool for mild cognitive impairment. *J. Am. Geriatr. Soc.*, 53,
662 695–699.

663 Nie, K., Barco, A., Zeng, F.-G. (2006). Spectral and temporal cues in cochlear implant speech
664 perception. *Ear Hear.*, 27, 208–217.

665 Pflugst, B.E., Hughes, A.P., Colesa, D.J., et al. (2015). Insertion trauma and recovery of function
666 after cochlear implantation: Evidence from objective functional measures. *Hear. Res.*,
667 330, 98–105.

668 Prado-Guitierrez, P., Fewster, L.M., Heasman, J.M., et al. (2006). Effect of interphase gap and
669 pulse duration on electrically evoked potentials is correlated with auditory nerve survival.
670 *Hear. Res.*, 215, 47–55.

671 R Core Team (2024). R: A language and environment for statistical computing. Available at:
672 <https://www.R-project.org/>.

673 Ramekers, D., Versnel, H., Strahl, S.B., et al. (2014). Auditory-nerve responses to varied inter-
674 phase gap and phase duration of the electric pulse stimulus as predictors for neuronal
675 degeneration. *J. Assoc. Res. Otolaryngol.*, 15, 187–202.

676 Rask-Andersen, H., Liu, W., Linthicum, F. (2010). Ganglion cell and ‘dendrite’ populations in
677 electric acoustic stimulation ears. In P. Van De Heyning & A. Kleine Punte, eds.

678 *Advances in Oto-Rhino-Laryngology*. (pp. 14–27). S. Karger AG. Available at:
679 <https://pubmed.ncbi.nlm.nih.gov/19955718/> [Accessed October 23, 2024].

680 Resnick, J.M., O’Brien, G.E., Rubinstein, J.T. (2018). Simulated auditory nerve axon
681 demyelination alters sensitivity and response timing to extracellular stimulation. *Hear.*
682 *Res.*, 361, 121–137.

683 Roberts, D.S., Lin, H.W., Herrmann, B.S., et al. (2013). Differential cochlear implant outcomes
684 in older adults. *The Laryngoscope*, 123, 1952–1956.

685 Rumschlag, J.A., McClaskey, C.M., Dias, J.W., et al. (2022). Age-related central gain with
686 degraded neural synchrony in the auditory brainstem of mice and humans. *Neurobiol.*
687 *Aging*, 115, 50–59.

688 Schwartz-Leyzac, K.C., Colesa, D.J., Buswinka, C.J., et al. (2019). Changes over time in the
689 electrically evoked compound action potential (ECAP) interphase gap (IPG) effect
690 following cochlear implantation in Guinea pigs. *Hear. Res.*, 383, 107809.

691 Schwartz-Leyzac, K.C., Pfungst, B.E. (2018). Assessing the relationship between the electrically
692 evoked compound action potential and speech recognition abilities in bilateral cochlear
693 implant recipients. *Ear Hear.*, 39, 344–358.

694 Seki, S., Eggermont, J.J. (2003). Changes in spontaneous firing rate and neural synchrony in cat
695 primary auditory cortex after localized tone-induced hearing loss. *Hear. Res.*, 180, 28–38.

696 Seyyedi, M., Viana, L.M., Nadol, J.B. (2014). Within-subject comparison of word recognition
697 and spiral ganglion cell count in bilateral cochlear implant recipients. *Otol. Neurotol.*, 35,
698 1446–1450.

699 Skidmore, J., Ramekers, D., Colesa, D.J., et al. (2022). A broadly applicable method for
700 characterizing the slope of the electrically evoked compound action potential amplitude
701 growth function. *Ear Hear.*, 43, 150–164.

702 Sladen, D.P., Ricketts, Todd.A. (2015). Frequency importance functions in quiet and noise for
703 adults with cochlear implants. *Am. J. Audiol.*, 24, 477–486.

704 Sladen, D.P., Zappler, A. (2015). Older and younger adult cochlear implant users: speech
705 recognition in quiet and noise, quality of life, and music perception. *Am. J. Audiol.*, 24,
706 31–39.

707 Spahr, A.J., Dorman, M.F., Litvak, L.M., et al. (2012). Development and validation of the AzBio
708 sentence lists. *Ear Hear.*, 33, 112–117.

709 Starr, A., Zeng, F.G., Michalewski, H.J., et al. (2008). Perspectives on auditory neuropathy:
710 disorders of inner hair cell, auditory nerve, and their synapse. In *The Senses: A*
711 *Comprehensive Reference*. (pp. 397–412). Elsevier. Available at:
712 <https://linkinghub.elsevier.com/retrieve/pii/B9780123708809000335> [Accessed
713 September 12, 2024].

714 Takanen, M., Strahl, S., Schwarz, K. (2024). Insights into electrophysiological metrics of
715 cochlear health in cochlear implant users using a computational model. *J. Assoc. Res.*
716 *Otolaryngol.* Available at: <https://link.springer.com/10.1007/s10162-023-00924-z>
717 [Accessed September 12, 2024].

718 Tejani, V.D., Abbas, P.J., Brown, C.J. (2017). Relationship between peripheral and
719 psychophysical measures of amplitude modulation detection in cochlear implant users.
720 *Ear Hear.*, 38, e268–e284.

721 Won, J.H., Humphrey, E.L., Yeager, K.R., et al. (2014). Relationship among the physiologic
722 channel interactions, spectral-ripple discrimination, and vowel identification in cochlear
723 implant users. *J. Acoust. Soc. Am.*, 136, 2714–2725.

724 Wu, P., O’Malley, J.T., De Gruttola, V., et al. (2020). Age-related hearing loss is dominated by
725 damage to inner ear sensory cells, not the cellular battery that powers them. *J. Neurosci.*,
726 40, 6357–6366.

727 Wu, P., O’Malley, J.T., Liberman, M.C. (2023). Neural degeneration in normal-aging human
728 cochleas: Machine-learning counts and 3D mapping in archival sections. *J. Assoc. Res.*
729 *Otolaryngol.*, 24, 499–511.

730 Wu, P.Z., Liberman, L.D., Bennett, K., et al. (2019). Primary neural degeneration in the human
731 cochlea: Evidence for hidden hearing loss in the aging ear. *Neuroscience*, 407, 8–20.

732 Wu, P.-Z., O’Malley, J.T., De Gruttola, V., et al. (2021). Primary neural degeneration in noise-
733 exposed human cochleas: Correlations with outer hair cell loss and word-discrimination
734 scores. *J. Neurosci.*, 41, 4439–4447.

735 Xie, Z., Gaskins, C.R., Shader, M.J., et al. (2019). Age-related temporal processing deficits in
736 word segments in adult cochlear-implant users. *Trends Hear.*, 23, 2331216519886688.

737 Xing, Y., Samuvel, D.J., Stevens, S.M., et al. (2012). Age-related changes of myelin basic
738 protein in mouse and human auditory nerve O. Bermingham-McDonogh, ed. *PLoS ONE*,
739 7, e34500.

740 Yuan, Y., Skidmore, J., He, S. (2022). Interpreting the interphase gap effect on the electrically
741 evoked compound action potential. *JASA Express Lett.*, 2, 027201.

742 Zaltz, Y., Bugannim, Y., Zechoval, D., et al. (2020). Listening in noise remains a significant
743 challenge for cochlear implant users: evidence from early deafened and those with
744 progressive hearing loss compared to peers with normal hearing. *J. Clin. Med.*, 9, 1381.

745 Zamaninezhad, L., Mert, B., Benav, H., et al. (2023). Factors influencing the relationship
746 between cochlear health measures and speech recognition in cochlear implant users.
747 *Front. Integr. Neurosci.*, 17, 1125712.

748 Zanin, J., Rance, G. (2024). Objective determination of site-of-lesion in auditory neuropathy.
749 *Ear Hear.* Available at: <https://journals.lww.com/10.1097/AUD.0000000000001589>
750 [Accessed September 30, 2024].

751 Zeng, F.-G. (2004). Trends in cochlear implants. *Trends Amplif.*, 8, 1–34.

752 Zeng, F.-G., Kong, Y.-Y., Michalewski, H.J., et al. (2005). Perceptual consequences of disrupted
753 auditory nerve activity. *J. Neurophysiol.*, 93, 3050–3063.

754