Title: Peripheral neural synchrony in post-lingually deafened adult cochlear implant users

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ABSTRACT

Objective: We recently developed a noninvasive method for quantifying neural synchrony in the cochlear nerve (i.e., peripheral neural synchrony) in cochlear implant (CI) users, which allows for evaluating this important physiological phenomenon in human CI users for the first time in the literature. This paper reports this new method in detail. In addition, this study assessed how peripheral neural synchrony was correlated with temporal resolution acuity and speech perception outcomes measured in quiet and in noise in post-lingually deafened adult CI users. It tested the hypotheses that 1) the degree of peripheral neural synchrony varied among CI users, and 2) peripheral neural synchrony was an important factor for temporal resolution acuity and speech perception outcomes in noise in post-lingually deafened adult CI users.

Design: Study participants included 18 post-lingually deafened adult CI users with a Cochlear™ Nucleus® device. Two study participants were implanted bilaterally, and each ear was tested separately. For each of the 20 ears tested in this study, peripheral neural synchrony, quantified using an index named the phase locking value (PLV), was measured at four electrode locations across the electrode array (default electrodes: 3, 9, 15 and 21) based on 400 sweeps of the electrically evoked compound action potential (eCAP). The PLV is a measure of trial-by-trial phase coherence among eCAP sweeps/trials and quantifies the degree of peripheral neural synchrony. Temporal resolution acuity was evaluated by measuring the within-channel gap detection threshold (GDT) using a three-alternative, forced-choice procedure, targeting 79.4% correct on the psychometric function in a subgroup of 9 participants (10 ears). For each ear tested in these participants, GDTs were measured at two electrode locations with a large difference

in PLVs. For 15 ears tested in 14 participants, speech perception performance was evaluated using Consonant-Nucleus-Consonant (CNC) word lists presented in quiet and in noise at signal-to-noise ratios (SNRs) of +10 and +5 dB. A Linear Mixed-effects Model (LMM) was used to evaluate the effect of electrode location on the PLV after controlling for the stimulation level effect. A partial correlation test was used to evaluate the association between the PLV and GDT while controlling for the effect of stimulation level on GDT. GDTs measured for electrode pairs with different PLVs were compared using a paired-samples t-test. The association between PLVs and CNC word scores measured in different conditions, as well as the association between the PLV and the degree of noise effect on CNC word scores were evaluated using Pearson product-moment correlation tests with Bonferroni correction for multiple comparisons.

Results: PLVs varied substantially across study participants and electrode locations. There was a significant correlation between the PLV and GDT, where higher PLVs were associated with lower GDTs. PLVs were not significantly correlated with CNC word scores measured in any listening condition or the effect of competing background noise presented at a SNR of +10 dB on CNC word scores. In contrast, there was a moderate, negative correlation between the PLV and the degree of noise effect on CNC word scores for a competing background noise presented at a SNR of +5 dB.

Conclusions: This newly developed method can be used to assess peripheral neural synchrony in living CI users, a physiological phenomenon that potentially plays a vital role in determining auditory perception outcomes in electrical hearing. Poorer peripheral neural synchrony is associated with lower temporal resolution acuity and larger detrimental effect of competing background noise on speech perception performance in

post-lingually deafened adult CI users.

Key Words: cochlear implants, cochlear nerve, neural synchrony, speech perception, temporal resolution acuity

INTRODUCTION

While many cochlear implant (CI) users can achieve excellent listening outcomes in quiet, speech recognition in background noise remains a significant challenge (Eisenberg et al., 2016; Torkildsen et al., 2019; Zaltz et al., 2020). The neural mechanisms underlying the observed speech perception deficits in noise in CI users remain unknown. In acoustic hearing, discharge synchronization of cochlear nerve (CN) fibers has been shown to play a critical role in neural representation of speech sounds presented in noise in animal models (e.g., Delgutte & Kiang, 1984; Heeringa & Koppl, 2022; Sachs et al., 1983). Simulation results from computational models demonstrated the importance of synchronized neural firing from CN fibers for robust encoding of consonants in spectro-temporally modulated background noises (Bruce et al., 2013; Viswanathan et al., 2022). These simulation results also showed that poor neural synchrony in the CN (i.e., peripheral neural synchrony) results in smeared neural representation of temporal envelope cues, which leads to deficits in processing these cues (Zeng et al., 2005; Zeng et al., 1999). Aligned with these results from animal models and computational simulations, listeners with poor peripheral neural synchrony (e.g., patients with auditory neuropathy spectrum disorder and elderly listeners) have temporal processing deficits and show excessive difficulties in understanding speech in noise (e.g., Harris et al., 2021; Kraus et al., 2000; Rance, 2005; Zeng et al., 2005). Overall, these results demonstrate the importance of peripheral neural synchrony for temporal processing and speech perception in noise in acoustic hearing.

Deteriorations in anatomical structures of the CN in CI patients have been well established based on the histological results of human temporal bone studies (e.g., Di

Stadio et al., 2020; Fayad et al., 1991; Fayad & Linthicum, 2006; Heshmat et al., 2020; Kumar et al., 2022; Kusunoki et al., 2004; Linthicum & Fayad, 2009; Makary et al., 2011; Merchant et al., 2005; Nadol, 1990, 1997; Nadol et al., 1989; Rask-Andersen et al., 2010; Suzuka & Schuknecht, 1988; Ungar et al., 2018; Wu et al., 2019; Xing et al., 2012). These deteriorations start with damages in the myelin sheath and peripheral axon degeneration (e.g., Heshmat et al., 2020; Kumar et al., 2022; Nadol, 1990; Wu et al., 2019; Xing et al., 2012). Damaged spiral ganglion neurons (SGNs) with only central axons (i.e., unipolar SGNs) can survive decades after peripheral axon loss (e.g., Kusunoki et al., 2004; Linthicum & Fayad, 2009; Nadol, 1990; Rask-Andersen et al., 2010) and still be activated by electrical stimulation (e.g., Javel & Shepherd, 2000; Shepherd & Hardie, 2001; Shepherd & Javel, 1997; Sly et al., 2007; van den Honert & Stypulkowski, 1984). Eventually, the SGN soma and the central axon degenerate, which leads to the disappearance of the entire SGN (e.g., Fayad et al., 1991; Fayad & Linthicum, 2006; Linthicum & Fayad, 2009; Suzuka & Schuknecht, 1988; Ungar et al., 2018). The number and the distribution of surviving SGNs, the number of bipolar vs unipolar SGNs, as well as the degree of axonal degeneration and demyelination of remaining SGNs, vary substantially along the cochlea within and across CI patients (Fayad et al., 1991; Fayad & Linthicum, 2006; Linthicum & Fayad, 2009; Merchant et al., 2005; Nadol, 1997).

Deteriorations in anatomical structures of the CN reduce its discharge synchronization (i.e., neural synchrony). Specifically, both axonal dystrophy and demyelination alter many neural properties, such as membrane capacitance and resistance, nodal leakage resistance, as well as nodal sodium and potassium channel permeability (e.g., Tasaki, 1955; Waxman & Ritchie, 1993). These changes cause a

reduction in the nodal current density, axonal spiking probability and propagation velocity, as well as an increase in temporal jitter, spike latency, and conduction vulnerability of individual CN fibers (e.g., Gonzalez-Gonzalez & Cazevieille, 2019; Heshmat et al., 2020; Kim et al., 2013; Tasaki, 1955). CN fibers with different degrees of axonal dystrophy and demyelination generate and conduct action potentials at different speeds, which reduces the synchronized discharge across the population of CN fibers (Kandel, 2002). Animals with more demyelination show greater reductions in neural synchrony in the CN (e.g., El-Badry et al., 2007). In electrical hearing, loss of the peripheral axon and altered membrane properties can also move the action potential initiation site distally to the SGN soma or central axon (e.g., Hartmann et al., 1984; Javel & Shepherd, 2000; van den Honert & Stypulkowski, 1984). Compared with responses initiated at peripheral axons, spikes initiated at central axons have less temporal dispersion or jitter (Javel & Shepherd, 2000). The difference in the action potential initiation site among CN fibers could further reduce discharge synchronization across CN fibers. Due to the lack of noninvasive tools to evaluate neural synchrony in the CN to electrical stimulation in living CI users in the past, our knowledge in this area is primarily based on the results showing the variance in the first spike latency after stimulus onset (i.e., temporal jitter) of individual CN fibers measured using single fiber recordings in animal models (e.g., Hartmann et al., 1984; Parkins, 1989; Shepherd & Hardie, 2001; Shepherd & Javel, 1997; Sly et al., 2007; van den Honert & Stypulkowski, 1984). How well this knowledge applies to human CI users remains unknown due to the differences in anatomical/morphometric and biophysical properties of CN fibers, as well as durations and etiologies of deafness between human listeners and experimental animals (Skidmore et al., 2022). In addition, these results do

not provide any information about discharge synchronization across electrically stimulated CN fibers or discharge synchronization of a group of CN fibers across repeated stimulations. To date, neural synchrony in the electrically stimulated CN in human listeners has not yet been evaluated and remains unknown. Its roles in processing temporal cues and understanding speech in noise in CI users also remain unknown despite the rich literature showing its importance for these processes in acoustic hearing.

To address these critical knowledge gaps, we recently developed a noninvasive, *in vivo* method for assessing neural synchrony of a population of electrically stimulated CN fibers by quantifying the trial-to-trial phase coherence in the summated activity to electrical stimulation using electrophysiological measures of the electrically evoked compound action potential (eCAP). The new method was developed based on a method for quantifying peripheral neural synchrony in listeners with acoustic hearing (Harris et al., 2021). Using this new method, we studied the effect of peripheral neural synchrony on temporal resolution acuity by assessing the association between the degree of peripheral neural synchrony and within-channel gap detection threshold (GDT) measured using psychophysical procedures. The association between the degree of peripheral neural synchrony and Consonant-Nucleus-Consonant (CNC) word scores measured in quiet and in noise was also evaluated. These experiments were designed to test the hypotheses that 1) the degree of peripheral neural synchrony varied among CI users, and 2) it was an important factor for temporal resolution acuity and speech perception outcomes in noise in post-lingually deafened adult CI users. This paper reports the details of the new method and the results of these two experiments.

MATERIALS AND METHODS

Study Participants

This study included 18 eighteen (9 Female, 9 Male) post-lingually deafened adult CI users ranging in age from 38.0 to 83.7 years (mean: 63.9 years, SD: 12.4 years). All study participants were native speakers of American English and used a Cochlear™ Nucleus® device (Cochlear Ltd, Macquarie, NSW, Australia) with a full electrode insertion in the test ear, as confirmed based on post-operative, high-resolution computerized tomography scans. Participants A3 and A11 were implanted bilaterally. For these two participants, each ear was tested separately. eCAPs were measured in each of 20 ears tested in these 18 participants. Due to time constraints and varied participant's availabilities, subgroups of nine and 14 participants completed psychophysical GDT measurements and speech perception evaluations, respectively. Detailed participant's demographic information and the tests that each participant completed are provided in Table 1. The deidentified information is listed by participant ID. The key linking the participant ID with individual study participants is only available to approved research staff. Written informed consent was obtained from all study participants at the time of data collection. The study was approved by the Biomedical Institutional Review Board (IRB) at The Ohio State University (IRB study #: 2017H0131).

Insert Table 1 about here

Stimuli

For eCAP recording, the stimulus was a charge-balanced, cathodic-leading, biphasic pulse with an interphase gap of 7 μs and a pulse phase duration of 25 μs. For measuring psychophysical GDT, the stimulus was a train of biphasic pulses with the same characteristics as those of the single-pulse stimulus that was presented for 500 ms at a

stimulation rate of 900 pulses per second (pps) per channel. For both measures, the stimulus was delivered to individual CI electrodes in a monopolar-coupled stimulation mode via an N6 sound processor interfaced with a programming pod.

Behavioral C Level Measures

The maximum comfortable level (i.e., the C level) for each type of the stimulus was determined using an ascending procedure. In this procedure, study participants were instructed to use a visual loudness rating scale [scale of 1-10, where 1 is “barely audible” and 10 is “Very uncomfortable”] to indicate when the sound reached the maximum comfort level (rating of 8). Stimulation was first presented at a relatively low level and gradually increased in steps of 5 clinical units (CUs) until a loudness rating of 7 was reached. Then, stimulation was increased in steps of 1-2 CUs until a rating of 8 (“maximal comfort”) was reached. The C level was measured for each type of stimulation delivered to each test CI electrode for each participant.

For the single-pulse stimulation used for eCAP recording, the stimulus was presented to individual CI electrodes using the “Stimulation Only” mode in the Advanced Neural Response Telemetry (NRT) function implemented in the Custom Sound EP (v. 5.1) commercial software (Cochlear Ltd, Macquarie, NSW, Australia) software. Due to the challenge of reliably rating loudness for an extremely brief single pulse with a duration of only 57 μs, the C level was determined for a group of five pulses presented at 15 Hz. This is a standard clinical practice for determining the C levels during the programming process. For the pulse-train stimulation, the stimulus was presented to individual CI electrode using a custom script prepared using Nucleus Interface Communicator Routine Library (NIC v. 4.3.1).

eCAP Measurements

The eCAP recordings were obtained using the NRT function implemented in the Custom Sound EP (v. 6.0) commercial software (Cochlear Ltd, Macquarie, NSW, Australia). The eCAP was measured at individual CI electrode locations using a two-pulse forward-masking-paradigm (Brown et al., 1990). In this paradigm, the masker and the probe pulse were presented to the test electrode at the participants' C level and 10 CUs below the C level, respectively. The stimulation was presented 400 times at a rate of 15 Hz to minimize the potential effect of long-term adaptation on the eCAP (Clay & Brown, 2007). The number of trials was chosen to be 400 because preliminary analyses indicated that this number of trials could ensure accurate estimation of neural synchrony in the CN while maintaining a feasible recording time (Skidmore, Bruce, et al., 2023). Results of one of our previous studies have demonstrated that using electrophysiological results measured at single CI electrode locations to correlate with auditory perception outcomes in CI users can lead to inaccurate, if not wrong, conclusions (He et al., 2023). In comparison, the averaged results across multiple testing electrode locations provide a better representation of overall neural function than the result measured at any individual CI electrode locations. Based on these results, four electrodes across the electrode array were tested for each participant to get an estimate of overall CN function while maintaining a feasible testing time. The default testing electrodes were 3, 9, 15, and 21. Alternate electrodes were tested in cases where there was an open- or short-circuit at the default electrode locations. The electrodes tested for each participant are listed in Table 1. Other parameters used to record the eCAP included a recording electrode located two electrodes away apically from the stimulating electrode except for electrode 21 which was

recorded at electrode 19, a 122-μs recording delay, an amplifier gain of 50 dB, and a sampling rate of 20,492 Hz.

Measure of Neural Synchrony

Peripheral neural synchrony at individual CI electrode locations was evaluated based on 400 individual sweeps (trials) of the eCAP. Neural synchrony was quantified using an index named the phase locking value (PLV) which is a measure of trial-to-trial phase coherence among the 400 eCAP sweeps. The PLV is a unitless quantity that ranges from 0 to 1. It represents both temporal jitter in spike firing of individual CN fibers and discharge synchronization across the population of activated CN fibers. A PLV of 0 means that the distribution of phase across trials is uniform (i.e., the responses across trials are uncorrelated). The PLV is 1 if phases across trials are perfectly correlated. As a result, larger PLVs indicate better/stronger neural synchrony in the CN. Mathematically, the PLV is the length of the vector formed by averaging the complex phase angles of each trial at individual frequencies obtained via time-frequency decomposition. Specifically, the PLV is calculated at a specific frequency and time window (i.e., frame) as

$$PLV(f,t) = \frac{1}{400}\sum_{k=1}^{400}\frac{F_k(f,t)}{|F_k(f,t)|}$$

where $F_k(f,t)$ is the spectral estimate of trial *k* at frequency *f* for the time window *t*. For this study, the time-frequency decomposition was performed at four linearly spaced frequencies (1280.8, 1921.1, 2561.5, and 3201.9 Hz) with Hanning fast Fourier transform tapers, a pad-ratio of 2 and a frame size of 16 samples (780.8 μs) using the newtimef function (v. 2022.1) included in the MATLAB plugin EEGlab (Delorme & Makeig, 2004).

The lower and upper frequencies (i.e., 1280.8 and 3201.9 Hz, respectively) were chosen based on the frame size used in the time-frequency decomposition and the shortest inter-peak latency (312.5 μs) of eCAPs measured at the C level from 409 CI electrodes tested in 63 adult CI users in our lab, respectively. A single PLV was obtained for each electrode tested by averaging 24 PLVs calculated at four frequencies for six frames within a time window where the eCAP is expected [179 - 1200 μs in Cochlear™ Nucleus® CI users (Botros et al., 2007)]. The use of six frames within the time window of interest allows for higher temporal resolution of the PLV, with PLV values in the early frames capturing the degree of synchrony in the low-latency spikes and values in the later frames being dependent on synchrony in the longer-latency spikes. Figure 1 uses example data recorded at one CI electrode location in two participants to illustrate this method.

Insert Figure 1 about here

Psychophysical Measures of Gap Detection Threshold

Within-channel GDTs were measured at two electrode locations with different PLVs in each of ten ears tested in nine participants (see Table 1 for the electrodes tested in each ear). Pulse trains with and without temporal gaps were presented in a three-alternative, forced-choice paradigm that incorporated a three-down, one-up adaptative strategy to estimate 79.4% correct on the psychometric function (Levitt, 1971). Individual trials consisted of three consecutive 500-ms listening intervals separated in time by 500 -ms silent intervals. The stimulus presented in two of the three listening intervals was a 500-ms pulse train without any interruption. The stimulus presented in the remaining listening interval, chosen at random, included a temporal gap centered at 250 ms of stimulation. The participant was asked to determine which of the three listening intervals

included two sounds. Feedback on correct/incorrect choices was not provided to participants. The gap duration began at 64 ms and was shortened/lengthened based on the correctness of the participants' choice. The initial step size of the change in gap duration was 32 ms. This step changed by a factor of two after three consecutive correct responses or one incorrect response. The minimum and maximum gap durations permitted were 1 ms and 256 ms, respectively. The GDT was calculated as the average across two trials in which the mean gap duration over the last four (of twelve) reversals was calculated.

Speech Measures

Speech perception performance for each ear was evaluated using Consonant-Nucleus-Consonant (CNC) word lists (Peterson & Lehiste, 1962) presented in quiet and in two noise conditions. All auditory stimuli were presented in a sound-proof booth via a speaker placed one meter in front of the subject at zero degrees azimuth. The target stimulus was always presented at 60 dB sound pressure level (SPL). For the noise conditions, speech-shaped noise was presented concurrently with the target stimulus at 50 dB SPL and 55 dB SPL to create signal-to-noise ratios of +10 dB and +5 dB, respectively. This test and these testing conditions are recommended for assessing clinical outcomes in adult CI users (Adunka et al., 2018; Audiology, 2019; Carlson et al., 2018).

Statistical Analyses

The results of Shapiro-Wilk tests indicated normal data distributions for the PLV ($w = 0.97$, $p = 0.787$), GDT ($w = -0.57$, $p = 0.11$), CNC word scores measured in all testing conditions (Quiet: $w = 0.96$, $p = 0.742$; +10 dB SNR: $w = 0.97$, $p = 0.818$; +5 dB SNR: w

= 0.97, p = 0.773), and the difference in CNC word scores measured in quiet and in noise (+10 dB SNR: w = 0.97, p = 0.785; +5 dB SNR: w = 0.94, p = 0.406). As part of the data exploration process with the goal of selecting an appropriate statistical analysis method for this study, the one-tailed Pearson product-moment correlation test was used to explore whether stimulation level was a confounding factor for the study results. Bonferroni correction for multiple testing was used when evaluating the association among the PLV, GDT and stimulation level for the results measured in 10 ears (α = 0.025). The strength of correlation was determined based on values of the Pearson product-moment correlation coefficient (r). Specifically, weak, moderate and strong correlation were defined as *r* values between 0 and 0.3 (0 and -0.3), between 0.3 and 0.7 (-0.3 and -0.7), and between 0.7 and 1.0 (-0.7 and -1.0), respectively. For PLVs measured in all 20 ears, the effect of electrode location on the PLV was assessed using a Linear Mixed-effects Model (LMM) with electrode location and stimulation level as fixed effects and subject as the random effect. For the data measured in 10 test ears with GDT results, stimulation level was significantly correlated with GDT (r = 0.63, p = 0.001) but not with the PLV (r = 0.36, p = 0.06). Therefore, the relation between the PLV and GDT was evaluated using a partial correlation test to control for the stimulation level effect on GDT. The difference in GDTs measured between two electrodes with different PLVs tested in each ear was evaluated using a paired-samples t-test. Finally, one-tailed Pearson product-moment correlation tests with Bonferroni correction for multiple comparisons were used to assess the association of the PLV with CNC word scores measured in different conditions (α = 0.017), as well as with the decrease in CNC word score with competing background noise (i.e., CNC word score measured in quiet - CNC word score

measured in noise, $\alpha = 0.025$). For these correlation analyses, PLVs measured at all electrode locations were averaged together for each participant/ear to obtain an estimation of the overall peripheral neural synchrony within the cochlea and to minimize electrode-location related bias in study results (He et al., 2023). All statistical analyses for this study were performed using MATLAB (v. 2021b) software (MathWorks Inc.). Following the recommended best practice in the field of biostatistics (Wasserstein & Lazar, 2016), p values were not solely used in this study to determine the significance of results in this study. This is due to the well-recognized fact that parameters that are statistically significant may not be clinically meaningful and vice versa.

RESULTS

Neural Synchrony Along the Cochlea

PLVs measured in this study ranged from 0.34 to 1.00 (mean: 0.76, SD: 0.17) across all electrodes tested. The means and standard deviations of PLVs measured at each of the four electrode locations are shown in Figure 2. The large standard deviations at all four electrode locations suggest substantial variations in the PLV in CI users. In addition, a trend for the mean PLV to be different across electrode locations is observed. PLVs measured at apical electrode locations (i.e., electrodes 15 and 21) appear to be larger than those measured at more basal electrode locations (i.e., electrodes 3 and 9). However, this data trend was not statistically significant, as evidenced by the results of the LMM showing a nonsignificant effect of electrode location on the PLV ($F_{3,59} = 0.79$, $p = 0.504$) after controlling for the significant effect of stimulation level on the PLV ($F_{1,59} = 8.05$, $p = 0.006$). There was no statistically significant interaction between electrode location and stimulation level ($F_{3,59} = 0.62$, $p = 0.603$).

Insert Figure 2 about here

Neural Synchrony and Temporal Acuity

Figure 3 shows psychophysical GDTs measured at two electrode locations per test ear in nine participants (10 ears) as a function of the PLV. Smaller GDTs are clearly associated with larger PLVs for each individual participant (data points connected by black lines). This observation is confirmed by the results of a paired-samples t-test (t_9 = 3.43, p = 0.004). The was also a moderate, negative partial correlation between the PLV and GDT across all data points while controlling for stimulation level, which was statistically significant (r = -0.57, p = 0.005).

Insert Figure 3 about here

Neural Synchrony and Speech Perception

Figure 4 shows CNC word scores measured in quiet and in two noise conditions as a function of the PLV for 14 participants (15 ears). There was substantial variability in CNC word scores measured in quiet (range: 54.0 – 96.0%, mean: 76.3%, SD: 12.5%) and in noise (+10 dB SNR, range: 38.0 - 84.0%, mean: 62.9%, SD: 13.2%; +5 dB SNR, range: 32.0 - 68.0%, mean: 49.7%, SD: 12.0%). There was no obvious relation between CNC word score and the PLV for each of the testing conditions. This observation was confirmed by the result of a Pearson product-moment correlation test with Bonferroni correction for multiple testing (Quiet: r = -0.19, p = 0.508; +10 dB SNR: r = -0.10, p = 0.734; +5 dB SNR: r = 0.20, p = 0.474).

Insert Figure 4 about here

The decrease in CNC word scores when competing background noise was added

is shown as a function of the PLV in Figure 5 for both noise conditions. There was no obvious relation between the noise effect on CNC word score and the PLV for the +10 dB SNR noise condition, which was confirmed by the result of Pearson correlation analysis ($r = -0.09$, $p = 0.376$). In comparison, there was a moderate, negative correlation between the PLV and the degree of detrimental effect of background noise on CNC word score for the results measured at a SNR of +5 dB ($r = -0.49$, $p = 0.033$), with larger PLVs associated with smaller negative effects of background noise.

Insert Figure 5 about here

DISCUSSION

This paper reports a newly developed method for quantifying neural synchrony in the electrically stimulated CN in human CI users. Using this newly developed method/tool, we evaluated the effects of peripheral neural synchrony on temporal resolution acuity and speech perception outcomes in human CI users. Results of this study showed substantial variations in the degree of peripheral neural synchrony among CI users and showed the important role that peripheral neural synchrony played in determining temporal resolution acuity in post-lingually deafened adult CI users. Our results also demonstrated a lack of association between the PLV and CNC word scores measured in quiet or in noise, as well as between the PLV and the amount of decrease in CND word scores when a competing background noise at a SNR of +10 dB was added. However, there was a moderate, negative correlation between the PLV and the degree of negative effect of background noise at a SNR of +5 dB. Overall, these results support our study hypothesis.

Peripheral Neural Synchrony in Electrical Hearing

PLVs measured in CI users in this study ranged from 0.34 to 1.00, which is much higher than those measured in listeners with acoustic hearing (Harris et al., 2021). These results are consistent with the literature in animal models showing lower temporal jitters (i.e., higher discharge synchronizations) of neural responses evoked by electrical stimulation than those evoked by acoustic stimulation (e.g., van den Honert & Stypulkowski, 1984). Results of previous histological and functional studies have shown unpredictable patterns of CN health in typical CI users with heterogeneous etiologies (e.g., DeVries et al., 2016; Nadol et al., 2012; Sagers et al., 2017; Schvartz-Leyzac & Pfingst, 2016). Therefore, substantial variations in peripheral neural synchrony would be expected across CI users and across electrode locations within individual patients, which is consistent with the wide ranges of PLVs being measured at various electrode locations across the cochlea in this study and might have contributed to the lack of electrode location effect on the PLV.

Peripheral Neural Synchrony and Auditory Perception Outcomes

GDTs measured in this study are consistent with those reported in other studies that used similar testing paradigms and conditions (e.g., Busby & Clark, 1999; Garadat & Pfingst, 2011; Shader et al., 2020). Despite substantial variations in GDTs and PLVs measured among participants, larger GDTs were always observed at the electrode locations with smaller PLVs within individual participants. These data clearly demonstrated that poor peripheral neural synchrony was significantly associated with declined temporal resolution acuity in CI users, presumably due to temporal smearing in the neural representation of the stimulus that results from dyssynchronous neural firing (Starr et al., 2003; Zeng et al., 2005). These results are consistent with those measured

in acoustic hearing (Michalewski et al., 2005; Zeng et al., 2005; Zeng et al., 1999).

Our results showed a lack of correlation between peripheral neural synchrony and CNC word scores. These results are not consistent with the significant correlation between peripheral neural synchrony and CNC word scores measured in quiet reported by Dong et al. (2023). However, it should be noted that peripheral neural synchrony was not directly assessed in the experimental design of Dong et al. (2023). Instead, it was estimated using computational modeling techniques by deconvolving intraoperative recordings of the eCAP with an estimated human unitary response to obtain the distribution of firing latencies summed across CN fibers. As acknowledged by the authors, the estimation of neural synchrony using this modeling approach is highly dependent on the shape of the assumed unitary response from CN fibers, which has not been assessed/validated directly in humans (Dong et al., 2020; Dong et al., 2023). It is possible that degeneration of CN fibers leads to changes in the effective unitary response functions for each fiber, such that their simulated results did not fully reflect the actual peripheral neural synchrony in CI users. This methodological difference could contribute to the discrepancy between the results of Dong et al. (2023) and the present study. Speech perception outcomes in noise were not evaluated by Dong et al. (2023).

One important finding of this study is the moderate, negative correlation between the PLV and the detrimental effect of background noise on speech perception outcomes measured for the +5 dB SNR noise condition. This finding suggested that the degree of neural synchrony, as quantified using the PLV, accounted for approximately 25% of the negative effect of competing background noise presented at a SNR of +5 dB on CNC word scores. Even though these results were not statistically significant at a significance

level of 0.025, they could be clinically meaningful given the fact that combining multiple factors could only explain less than 40% of variance in speech perception outcomes in CI users (Blamey et al., 1996; Blamey et al., 2013; Holden et al., 2013; James et al., 2019; Lazard et al., 2012). This association was not observed for speech perception outcomes measured at +10 dB SNR. Overall, these results indicated that peripheral neural synchrony was an important factor determining the degree of the noise effect on speech perception outcomes in CI users in the case of mixed speech and masker signals presented to the same ear. The importance of peripheral neural synchrony to speech perception seems to increase with elevated background noise, which is consistent with the literature reporting the stronger impact of CN function on speech perception outcomes in more challenging listening conditions (e.g., Canfarotta et al., 2021; Fitzpatrick et al., 2014; Skidmore, Oleson, et al., 2023).

Potential Study Limitations

This study has four potential limitations. First, the stimulation level could be a confounding factor for the results of this study because results of previous studies suggested a CN-health-dependent effect of stimulation level on peripheral neural synchrony. Specifically, Harris et al. (2021) reported larger PLVs measured at higher stimulation levels in listeners with acoustic hearing. However, this association was only observed in listeners with good CN health (i.e., young hearing listeners) and not in elderly listeners who have been shown to have poor peripheral neural synchrony and reduced CN densities. These results suggested that the stimulation level could be a confounding factor for the results of this study and thereby needs to be controlled for. Using stimulation levels that are balanced based on subjective perception of loudness has been widely

used to control/minimize the potential stimulation level effect in psychophysical studies. In this study, both single-pulse and pulse-train stimuli delivered to different CI electrodes tested in each participant were presented at the levels that were determined to be "maximal comfort" (rating 8 on the same visual loudness rating scale). Therefore, in a certain sense and to a certain degree, the stimulation levels used at different electrodes can be considered loudness balanced within each participant and even across participants. However, electrical biphasic pulses that evoke neural responses with comparable amplitudes or these matched in current level are not necessarily perceived as equally loud by CI users (Kirby et al., 2012). Similarly, neural responses evoked by pulses that are perceived equally loud by CI users can have a large difference in neural response amplitude (Kirby et al., 2012). In addition, comparing loudness for single pulse stimulation with a duration of only 57 μs could be impossible for many CI users, as demonstrated during our pilot study. Therefore, using loudness-balanced stimulation levels may not be a good solution to eliminate the potential level effect on study results. Instead, the stimulation level effect on results of this study was controlled using statistical analyses. Second, there were only 18 study participants tested in this study, which is a relatively small sample size. Given the substantial variations in reported anatomical structures of the CN and auditory perception outcomes among CI users, future studies with a larger sample size are warranted to confirm the results reported in this study. Third, as an initial step toward understanding the role of peripheral neural synchrony in determining CI clinical outcomes, this study only evaluated the association between neural synchrony in the CN and monoaural auditory perception outcomes in human CI users. The modeling study by Resnick and Rubinstein (2021) suggests that degraded

neural synchrony might have an even greater impact in binaural listening conditions where interaural timing difference cues are needed to help separate a speech stream from background noise. Further studies are warranted to determine the role of neural synchrony in the CN in binaural hearing. Finally, despite these exciting results, the exact biological underpinning (e.g., demyelination, peripheral axon degeneration, or total SGN loss) of the PLV remains unknown and requires further investigation. Due to the lack of noninvasive tools, it is not feasible to use experimental approaches to determine physiological conditions of the CN in living human listeners. Computational modeling techniques have been widely used to probe neuroanatomical conditions underlying neural response patterns in neuroscience, which holds the potential to be used to answer this important question.

CONCLUSIONS

Neural synchrony in the electrically stimulated CN could be estimated at individual electrode locations in CI users by calculating the phase coherence across repeated presentations of a single pulse stimulus using the method reported in this paper. Peripheral neural synchrony substantially varies across CI users and across electrode locations. Poorer peripheral neural synchrony is associated with lower temporal resolution acuity and larger detrimental effect of competing background noise on speech perception performance in post-lingually deafened adult CI users. Neural synchrony in the CN potentially plays a vital role in determining auditory perception outcomes in electrical hearing.

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TABLES

TABLE 1. Demographic information of all study participants.
CI24RE (CA), Freedom Contour Advance electrode array; SHL, sudden hearing loss

Participant ID	Sex	Ear tested	Age (years)	Internal device and electrode array	Etiology of hearing loss	Electrodes tested for PLV	Electrodes tested for GDT	Speech scores included
A1	M	L	60s	CI512	SHL	4, 6, 9, 12	4, 9	•
A2	M	L	60s	CI512	Meniere's	3, 9, 12, 15	3, 15	•
A3	F	L	60s	CI24RE (CA)	Hereditary	3, 9, 15, 21	3, 15	•
A3	F	R	60s	CI24RE (CA)	Hereditary	3, 9, 15, 21	3, 21	•
A4	F	L	30s	CI24RE (CA)	Trauma	3, 9, 15, 21	9, 21	•
A5	M	R	60s	CI522	Trauma	6, 9, 18, 21		•
A6	M	R	30s	CI24RE (CA)	Hereditary	3, 9, 15, 21	3, 15	•
A7	F	R	50s	CI24RE	Hereditary	3, 12, 15, 21	15, 21	•
A8	F	R	60s	CI532	Unknown	3, 9, 15, 20		•
A9	M	R	70s	CI532	Trauma	3, 9, 15, 21		•
A10	F	L	70s	CI422	Noise	4, 9, 15, 20		•
A11	M	L	60s	CI632	Unknown	3, 9, 15, 21		
A11	M	R	60s	CI532	Unknown	3, 9, 15, 20		
A12	F	L	70s	CI24RE (CA)	Autoimmune	3, 7, 12, 18	3, 12	•
A13	F	L	50s	CI532	Unknown	3, 9, 15, 21		
A14	F	L	70s	CI622	Unknown	6, 9, 15, 21		•
A15	M	R	80s	CI632	Unknown	3, 9, 15, 21		•
A16	M	R	50s	CI632	SHL	3, 9, 15, 21		•
A17	F	R	70s	CI622	Unknown	3, 9, 15, 21	3, 15	
A18	M	L	50s	CI532	Usher	3, 9, 15, 21	3, 9	

FIGURES

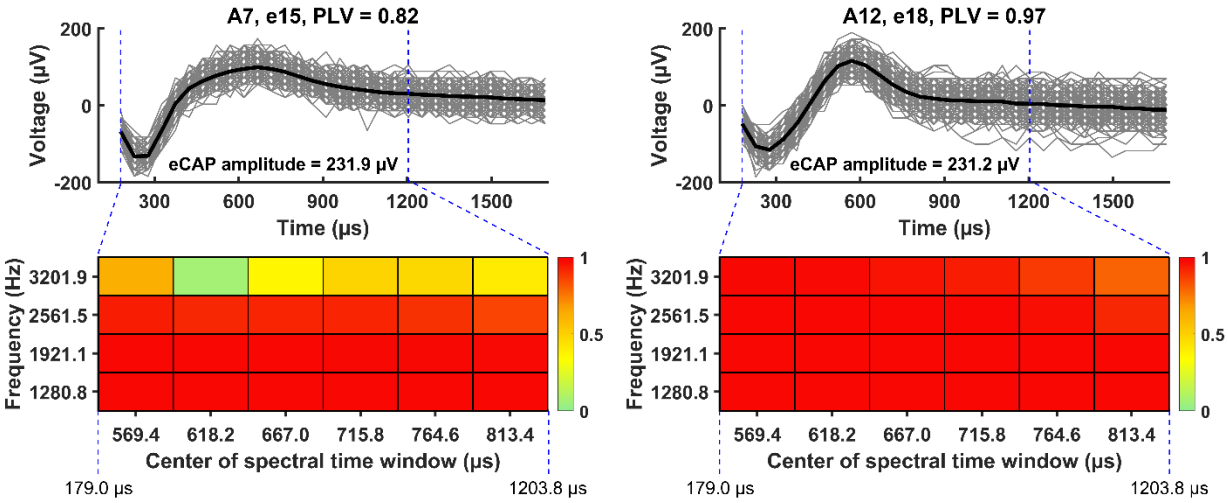

Figure 1. Representative data from two study participants (A7, left column; A12, right column) demonstrating the method for estimating neural synchrony at the level of the cochlear nerve at individual electrode locations in cochlear implant users. Top panels: Recordings of electrically evoked compound action potentials (eCAPs) for individual trials (gray lines) with the across-trial average (black line). The amplitude of the across-trial average is also provided. Bottom panels: Heat maps indicating the phase-locking value (PLV) as a function of time and frequency.

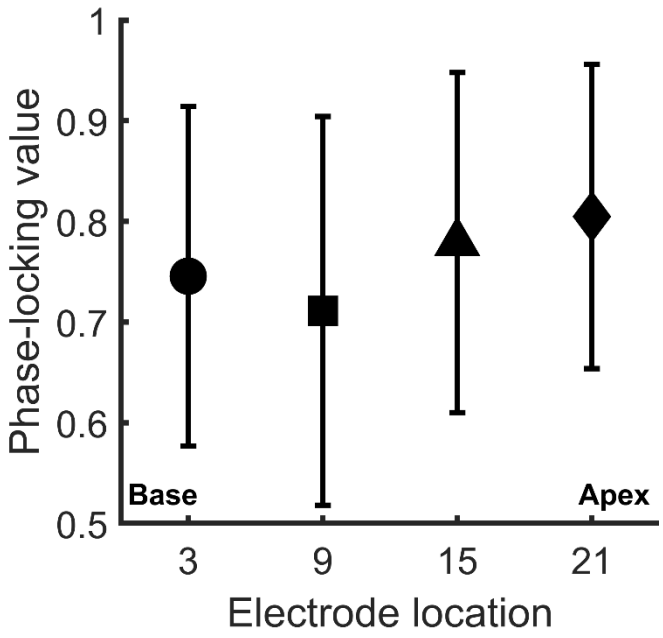

Figure 2. The means and standard deviations of phase-locking values measured at four electrode locations in 18 adult cochlear implant users (20 ears).

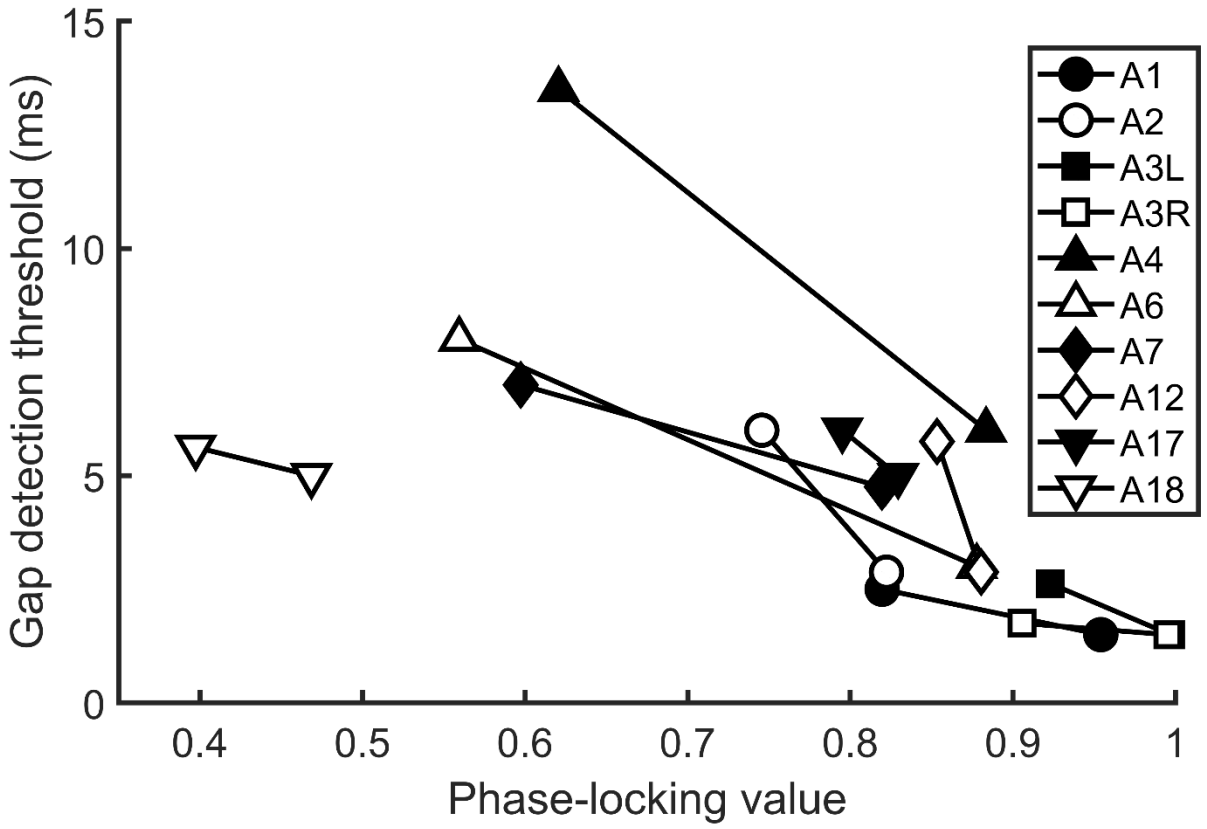

Figure 3. Phase-locking values and psychophysical gap detection thresholds measured at two electrode locations in ten ears of nine cochlear implant users. Black lines connect the data measured at the two electrode locations in the same study participant.

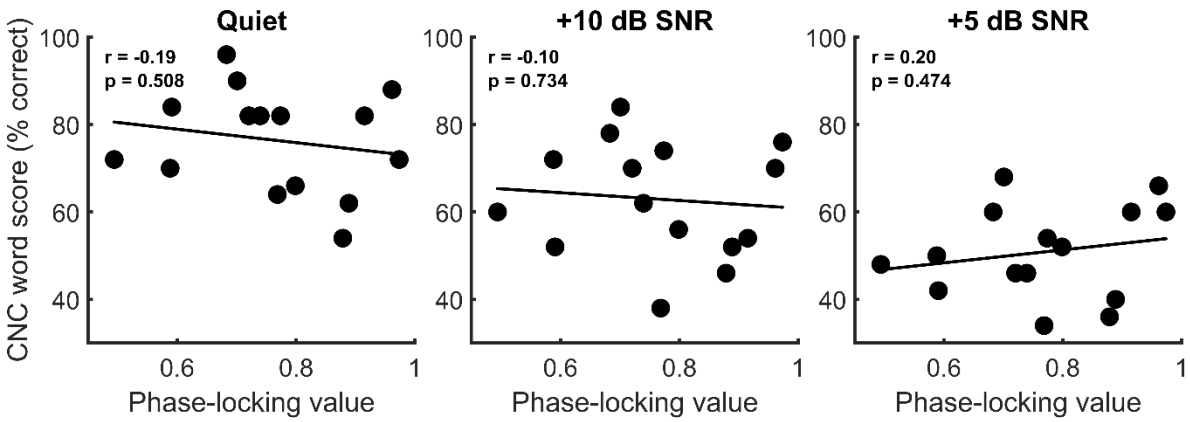

Figure 4. Consonant-Nucleus-Consonant (CNC) word scores measured in quiet and in two noise conditions as a function of the phase-locking value averaged across electrode locations for 14 adult cochlear implant users (15 ears). The best fit line across all 15 data points is illustrated with a solid line. The results from Pearson's correlation analysis are also provided in each panel.

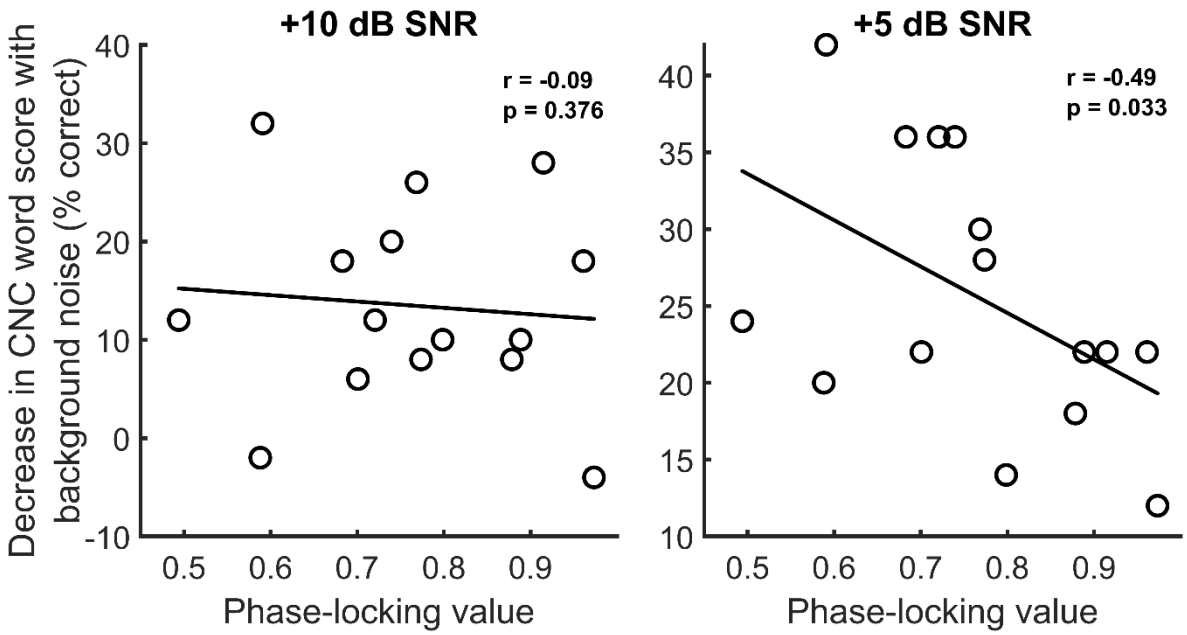

Figure 5. The decrease in Consonant-Nucleus-Consonant (CNC) word scores with the addition of background noise as a function of the phase-locking value averaged across electrode locations. The best fit line across all 15 data points is illustrated with a solid line. The results from Pearson's correlation analysis are also provided in each panel.