Interaural time difference sensitivity under binaural cochlear implant stimulation even at high pulse rates up to 900 pps

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Keywords

Deafness; prosthetics; cochlear implant; binaural hearing; interaural time difference; psychoacoustics; hearing experience

Abstract

Spatial hearing remains one of the major challenges for bilateral cochlear implant (biCI) users, and early deaf patients in particular are often completely insensitive to interaural time differences (ITDs) delivered through biCIs. One popular theory held is that this may be due to a lack of early binaural experience. However, previously we have shown that neonatally deafened rats fitted with biCIs in adulthood quickly learn to discriminate ITDs as well as their normal hearing litter mates (Rosskothen-Kuhl et al. 2021), and perform orders of magnitude better than human biCI users. Our unique behaving biCI rat model allows us to investigate other possible limiting factors of prosthetic binaural hearing, such as the effect of stimulus pulse rate and envelope shape. Previous work has indicated that ITD sensitivity may decline substantially at the high pulse rates often used in clinical practice. We therefore measured behavioral ITD thresholds in neonatally deafened, adult implanted biCI rats to pulse trains of 50, 300, 900 and 1800 pulses per second (pps), with either rectangular or Hanning window envelopes. Our rats exhibited very high sensitivity to ITDs at pulse rates up to 900 pps for both envelope shapes, a pulse rate commonly used in clinical practice. However, ITD sensitivity declined to near zero at 1800 pps, for both Hanning and rectangular windowed pulse trains. Current clinical cochlear implant (CI) processors are often set to pulse rates ≥900 pps, but ITD sensitivity in human CI listeners is often reported to decline sharply above ~300 pps. Our results suggest that the relatively poor ITD sensitivity seen at >300 pps in human CI users may not reflect the hard upper limit of biCI ITD performance in the mammalian auditory pathway. Perhaps with training or better CI strategies good binaural hearing may be achievable at pulse rates high enough to allow good sampling of speech envelopes while delivering usable ITDs.

Introduction

To date, cochlear implants (CIs) have been provided to over 500,000 severely hearing impaired patients across the globe (Ear Foundation, UK, 2016) and have greatly improved the quality of life of their recipients. However, substantial limitations remain in the CI hearing experience. For example, CI users suffering from prelingual deafness show invariably poor interaural time difference (ITD) performances, with even rare star performers only achieving thresholds of a few hundred µs (Poon et al. 2009; Conti-Ramsden et al. 2012; Litovsky et al. 2012; Goupell and Litovsky 2014; Laback et al. 2015; Litovsky and Gordon 2016; Ehlers et al. 2017; Thakkar et al. 2020). This poor ITD sensitivity is often hypothesized to be a result of the absence of auditory experience during

an early critical period (Kral 2013). However, in Rosskothen-Kuhl et al. (2021) we used a rat model to show that, even in the absence of early auditory input, near normal ITD sensitivities can be obtained, at least for low pulse rates, when stimuli were provided with precisely synchronized CI processors. This indicates that developmental critical periods may not be the main reason for the poor ITD sensitivity seen in bilateral CI (biCI) users, and that technological shortcomings may instead be the main limiting factors.

One critical factor is likely to be the pulse rate at which CIs operate. For example, a review by Laback et al. (2015) concludes that ITD performance of postlingually deaf biCI users tends to decline as pulse rates increase above ~300 pulses per second (pps). Several previous studies on human listeners (van Hoesel and Tyler 2003; van Hoesel 2004; Majdak et al. 2006; van Hoesel 2007; Laback et al. 2007; van Hoesel 2008) as well as physiological measures of sensitivity to ITDs obtained from experimental animals (Smith and Delgutte 2007; Chung et al. 2016; Chung et al. 2019) generally support this conclusion. However, accurately characterizing the dependence of ITD sensitivity on pulse rates in human listeners is marred with difficulties. The wide variety of patient histories and the very limited control that researchers have over variables such as the patients' CI hardware, implantation history, stimulation parameters, experience, daily routine or availability for psychoacoustic testing introduce numerous confounds, which make it very difficult to isolate the effect of pulse rate and to quantify it with high accuracy under otherwise favorable conditions. This context makes the recent development of a behavioral biCI rat model (Rosskothen-Kuhl et al. 2021) invaluable. Normal hearing rats exhibit behavioral high frequency ("envelope") ITD thresholds which are very similar to those seen in humans (Li et al. 2019), and even show very similar "precedence effects" as are seen in human ITD perception (Brown and Stecker 2010; Li et al. 2021). This makes rats a well validated model for human binaural hearing, well suited for characterizing the stimulus parameter ranges that allow high levels of ITD sensitivity with high accuracy and reproducibility.

Current CI processors generally run at fixed pulse rates between 900 and 3700 pps (Middlebrooks 2008). The rationale here is that faster temporal sampling of speech envelopes might improve speech recognition in CI users. However, Shannon et al. (2011) demonstrated that increasing pulse rates from 600 to 2400 pps resulted in little to no benefit for phoneme, word, and sentence recognition in quiet or in noise.

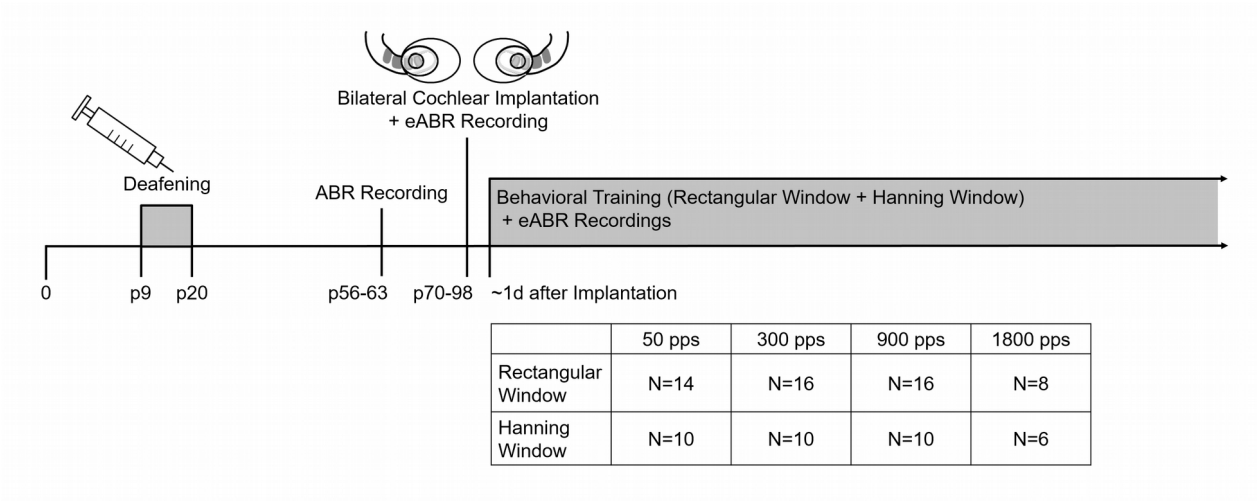
Generally speaking, modern CI processor designers face conflicting demands: they must use pulse rates that are fast enough to sample the envelopes of speech and other sound

inputs of interest with good detail, yet slow enough to allow ITD perception. However, neither the lower limits of pulse rates required for good speech encoding nor the upper limits of pulse rates for good ITD encoding have been determined definitively or with great accuracy, making it difficult to decide what pulse rates might be optimal for future biCI stimulation strategies. To start filling these important gaps in our knowledge, we conducted a series of positively reinforced two-alternative forced choice (2-AFC) ITD lateralization experiments on neonatally deafened (ND) rats which were fitted with biCIs in early adulthood, measuring their behavioral ITD thresholds with binaural pulse trains at a variety of pulse rates, and with either sharp (rectangular) or gentle (Hanning windowed) onsets and offsets. Based on previous studies in CI listeners (Litovsky et al. 2012; Ehlers et al. 2017; Thakkar et al. 2020) and electrophysiology studies in CI animals (Tillein et al. 2009; Hancock et al. 2012; Hancock et al. 2013; Chung et al. 2014; Chung et al. 2016; Tillein et al. 2016) we expected to see generally better ITD sensitivities for lower pulse rates and a rapid drop off above 300 pps. In addition, we expected to observe reduced ITD lateralization performances when presenting pulse trains with gently rising slopes (Hanning windowed) rather than sharp onset rectangle windowed pulse trains considering previous physiological and behavioral studies on ITDs demonstrating the precedence effect for these binaural spatial cues (Brown and Stecker 2010; Li et al. 2021). This study demonstrates these expectations were in part born out in the data, but not nearly as strongly as one might suspect. In particular, the behavioral ITD sensitivity of our biCI rats often remained remarkably good even for clinically relevant pulse rates as high as 900 pps, and using Hanning as opposed to rectangular envelopes led to only modest reductions in ITD sensitivity.

Results

Sixteen ND rats received chronic biCIs in early adulthood (postnatal weeks 10-14). All rats consistently showed well differentiated, electrically evoked auditory brainstem responses (eABRs) to intracochlear stimulation (Fig. S1). eABR recordings were repeated frequently throughout the training period. All ND rats were successfully trained to localize ITD cues within 3-5 days of behavioral training (8 sessions on average with 2 sessions per day), regardless of the starting pulse rate (50, 300 or 900 pps). Figure 1 shows the experimental timeline and the number of CI animals tested per condition. For details on the behavioral training and test setup see Rosskothen-Kuhl et al. (2021). Representative psychometric curves for ITD lateralization with rectangular windowed pulse trains from four of these ND

CI rats are shown in Figure 2. Supplementary Figure S2 shows the corresponding psychometric curves for all 16 animals tested for rectangle windowed stimuli. Uniformly good ITD sensitivity, as evidenced by steep slopes in the psychometric functions and very low error rates for absolute ITDs ≥ 80 µs, is seen at all pulse rates tested with the exception of 1800 pps. At 1800 pps the animals' performance dropped to near-chance with high variability in performance, as seen by the large error bars (Figs. 2, S3) even at large ITDs; whereas at lower pulse rates the same animals were performing well over 80% correct for ITDs ≥ 60 µs. In two of the CI animals shown in Figure 2, the decrease in ITD performance was accompanied by a bias for the rat's left spout (NDCI-14 and NDCI-15).



	50 pps	300 pps	900 pps	1800 pps
Rectangular Window	N=14	N=16	N=16	N=8
Hanning Window	N=10	N=10	N=10	N=6

Figure 1: Experimental pipeline with timeline and number of animals (N) tested per condition. Abbreviations: ABR = acoustically evoked auditory brainstem response, eABR = electrically evoked auditory brainstem response, p = postnatal day, pps = pulses per second, d= day.

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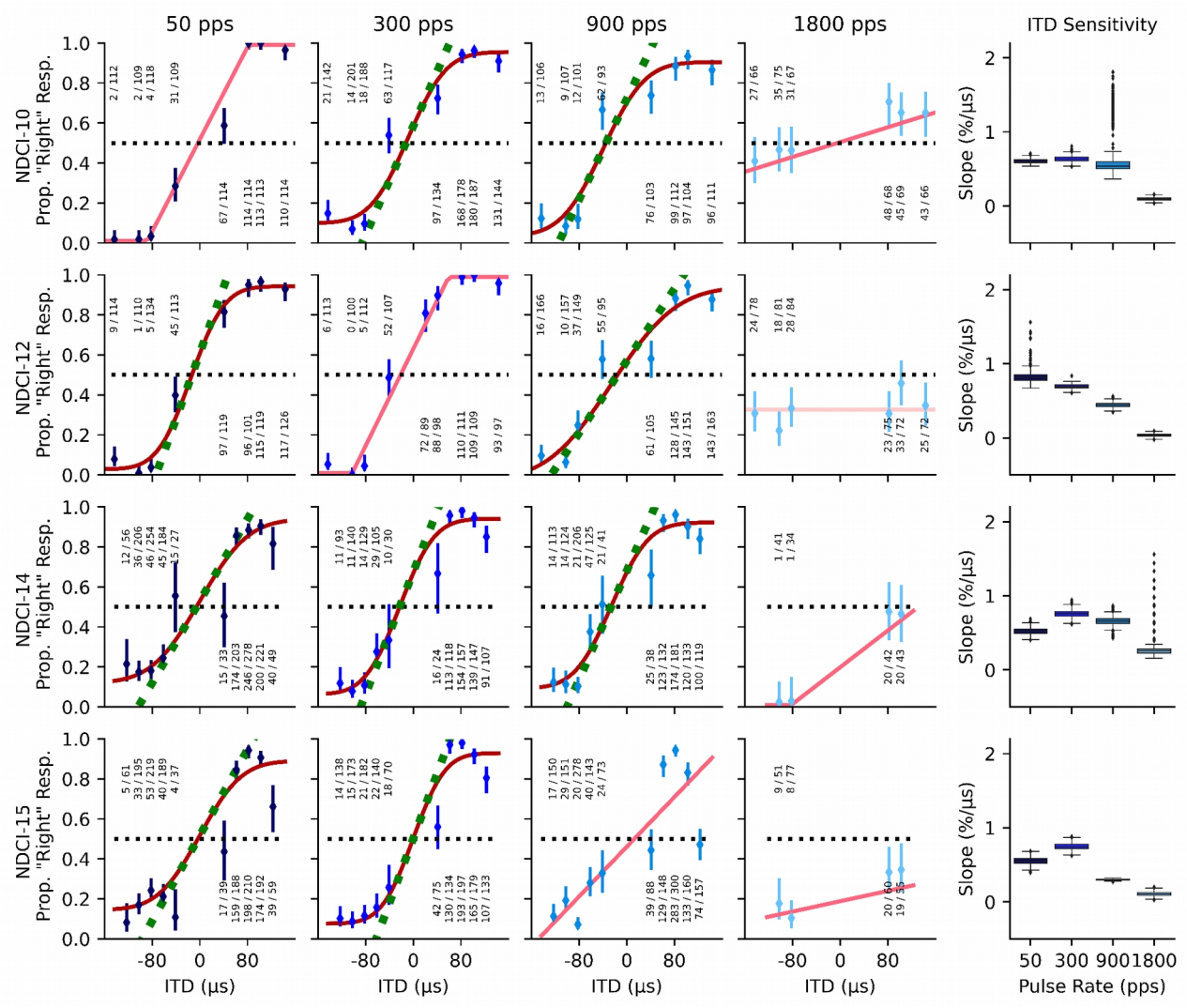

Figure 2: Psychometric curves for four example neonatally deafened, cochlear implanted (NDCI) rats localizing rectangular windowed pulse trains by interaural time difference (ITD). The first four columns represent a different pulse rate from left to right 50, 300, 900, and 1800 pulses per second (pps), each indicated with a different shade of blue. The y-coordinates reflect the proportion of trials during which the animal responded on the "right" hand spout (Prop. "Right" Resp.). The x-axis shows the tested ITD values from – 150 to + 150 µs. Negative ITD values indicate left leading ITDs. Annotations above or below each marker indicate the number of trials the animal chose the right hand side spout over the total number of presentations for the given ITD value on the abscissa. From dark to light the different shades of red indicate sigmoid, linear with bounds or null model psychometric curve fits. Green dashed lines show slopes of psychometric curves at ITD=0. Slopes serve to quantify the behavioral sensitivity of the animal to ITDs. The fifth column summarizes the ITD sensitivity across the different pps per animal as a function of slope. Each row shows the responses for a given animal. Psychometrics of all CI animals are shown in Figure S2.

In addition 10 out of 16 animals were tested for ITD sensitivity to pulse trains which were amplitude modulated with a slow rising and falling Hanning window at 50, 300 and 900 pps (N=10) as well as at 1800 pps (N=6) (see Figs. 1 and S3 for details). Again, all animals

showed good ITD sensitivity with steep slopes in the psychometric curves from the 2-AFC task at all pulse rates except for 1800 pps (Fig. S3). At this pulse rate the psychometric functions were completely flat for 5 out of 6 animals tested as shown in the fourth column of Figures 3 and S3. The slopes of the psychometric functions for Hanning windowed pulse trains were generally found to be more shallow compared to those from the sharp onset rectangular windowed stimuli shown in Figures 2 and S2. In addition, more variability in the animals' ITD performances appeared under Hanning windowed stimuli (see Figs. 3, S3) compared to that under rectangle windowed stimuli across pulse rates (Figs. 2, S2).

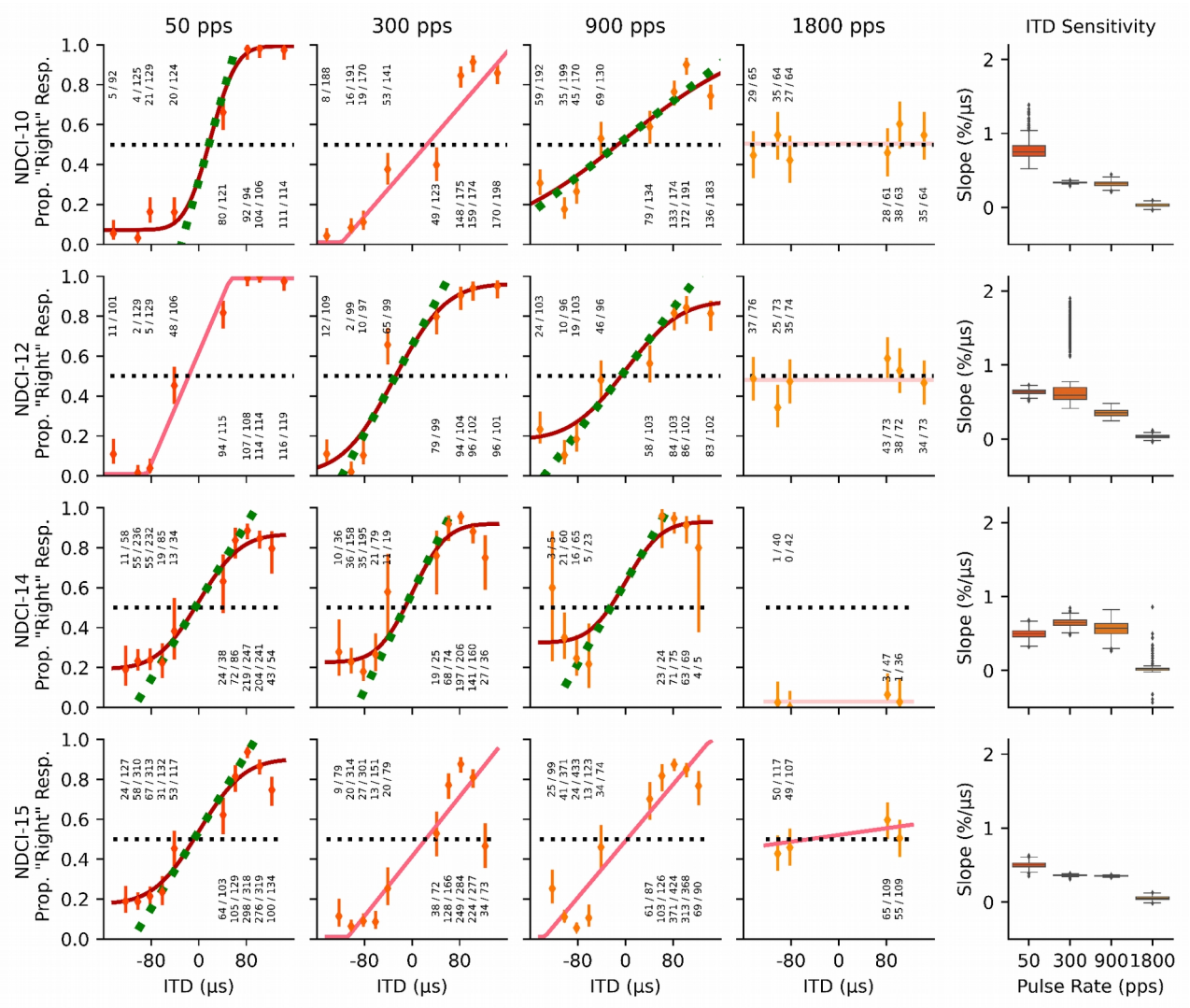

Figure 3: Psychometric curves for the same four example neonatally deafened, cochlear implanted (NDCI) rats as shown in Figure 2 localizing Hanning windowed pulse trains with varying interaural time differences (ITDs). Details are as for Figure 2. Psychometrics of all CI animals tested on Hanning windowed stimuli are shown in Figure S3.

To quantify the effect of pulse rate and pulse train envelope on ITD discrimination performance in biCI animals, we quantified behavioral sensitivity by the slope of the psychometric curve around the ITD=0 µs midline. We then used bootstrap tests (see

Methods for details) to estimate the distributions and confidence limits of these sensitivity values for all animals at each pulse rate and envelope type, and to estimate the probability that the observed differences in mean ITD sensitivity across our animals as a function of either pulse rate or envelope type were larger than expected by chance. Figure 4 shows the bootstrapped mean distributions of ITD sensitivities as a function of stimulus window type and pulse rate, averaged over all animals for which behavioral data at the relevant combination of stimulus parameters was available. The p-values for the null hypothesis that the sensitivity to ITD did not differ for a given pair of stimulus parameter combinations were Bonferroni corrected to account for multiple comparisons and are listed in Tables 1, 2 and 3. ITD sensitivities were usually higher with rectangular than Hanning windowed envelopes, and that effect was statistically significant at 300 and 900 pps. ITD sensitivity also tended to decline, often significantly, with increasing pulse rate, but good ITD sensitivity even with Hanning windowed stimuli was nevertheless common at pulse rates as high as 900 pps. In contrast, at 1800 pps, ITD sensitivity was generally poor independent of the presented window type.

Psychometric slopes are not necessarily a very intuitive metric for sensitivity. To help readers put the observed slope values into perspective and compare them against ITD discrimination thresholds reported in other previous studies, we also show what sort of 75% correct discrimination thresholds one might expect from the animals given their psychometric slopes. These estimated 75% ITD discrimination thresholds, in μs, are shown on the right y-axis of Figure 4. Some authors, including Ulrich and Vorberg (2009) and Lapid et al. (2008), refer to such 75% discrimination thresholds as the “just-noticable difference” (JND). Note, however, that our animals were only tested on a lateralization task, not a discrimination task. Task details can influence performance, so readers may wish to use some discretion when comparing our JND scores against those reported elsewhere. Table 4 gives the mean 75% discrimination thresholds, or JNDs, as estimated from the mean slopes of the psychometric curves (see Methods), for each of the eight different stimulation conditions. Overall, the smallest 75% discrimination thresholds were obtained for pulse rates of 50 and 300 pps with rectangular stimuli often resulting in better estimated discrimination. The only exception can be observed at 50 pps where Hanning windowed stimuli resulted in better discrimination thresholds than for rectangular windowed stimuli. For higher pulse rates, the estimated 75% discrimination threshold rose, but even at a clinical pulse rate of 900 pps, estimated JNDs were in the order of 50.5 - 62 μs which are well below ITD discrimination thresholds observed for most of the early deafened biCI patients which range from 200 μs to well above 1000 μs (van Hoesel and

Clark 1997; van Hoesel et al. 2002; van Hoesel et al. 2009; Litovsky et al. 2012; Litovsky et al. 2013; Laback et al. 2015; Ehlers et al. 2017; Thakkar et al. 2020) Note that the values shown in Table 4 for 1800 pps represent gross extrapolations of very small and quite variable psychometric slopes well beyond the range of ITDs tested. Thus, while the mean threshold values shown for 50, 300, and 900 pps can be considered reliable and accurate having been taken from the measured data, those at 1800 should be treated as very rough estimates.

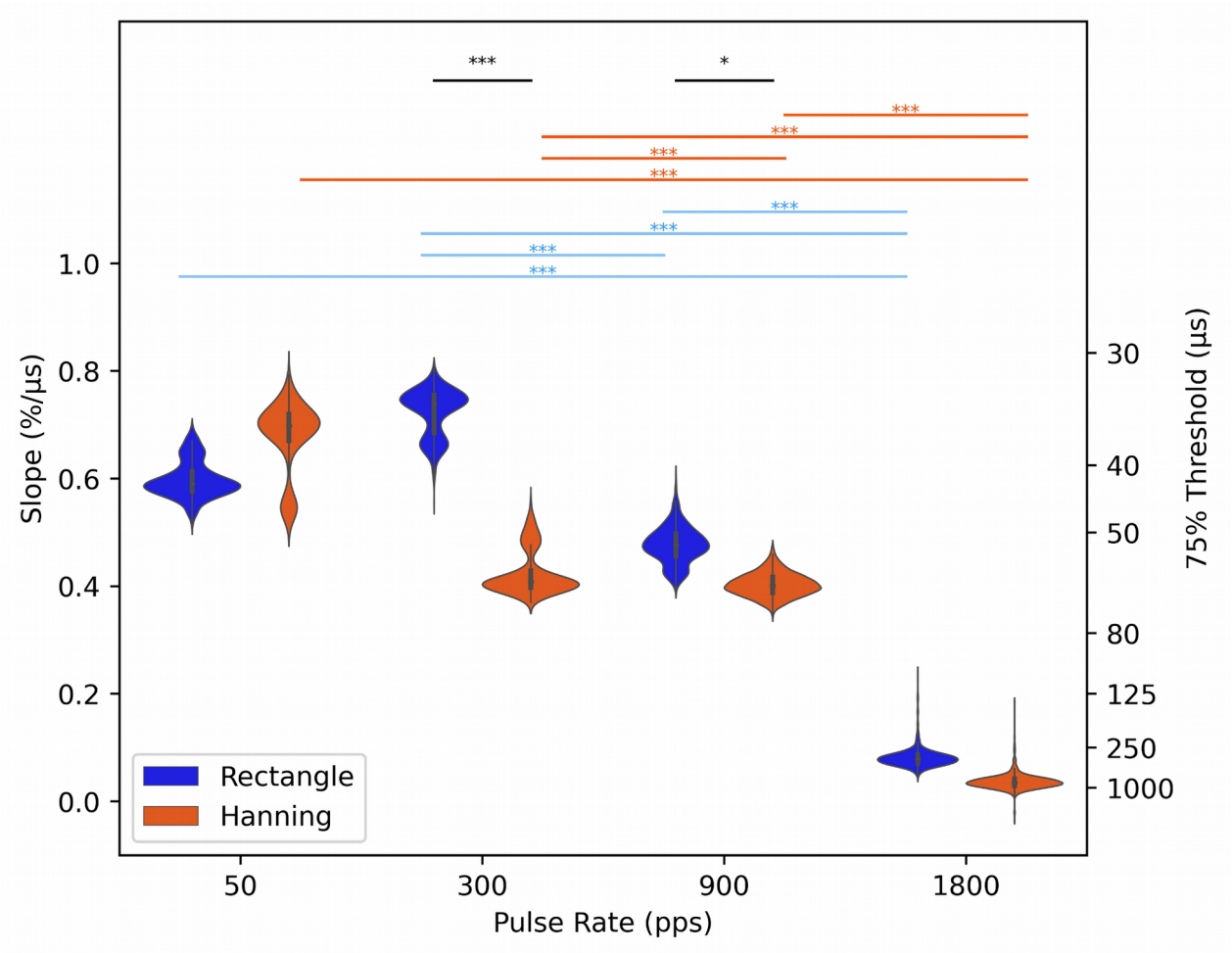

Figure 4: Violin plots showing the distribution of the mean group effects of ITD sensitivity for each pulse rate following permutation for rectangular (blue) and Hanning (orange) windowed stimuli. The left axis shows the ITD sensitivity as a function of the psychometric slopes, and the right y-axis the corresponding 75% ITD discrimination threshold estimate. Significant group statistics for the slopes comparing pulse rates are shown above violin plots for rectangular (blue) and Hanning (orange) windowed data. Significant differences between the two envelopes are shown in black. *** = ($p<0.001$), ** = ($0.001 \leq p<0.01$), * = ($0.01 \leq p<0.05$).

Rectangle	50 pps	300 pps	900 pps
300 pps	0.491		
900 pps	0.079	**<0.001**	
1800 pps	**<0.001**	**<0.001**	**<0.001**

Table 1: Bonferroni corrected p-values for the null hypothesis that mean ITD sensitivities do not vary as a function of pulse rate for rectangular windowed stimuli with pps values shown in the row and column headings. Significant p-values (<0.05) are shown in bold.

Hanning	50 pps	300 pps	900 pps
300 pps	**0.014**		
900 pps	**<0.001**	1	
1800 pps	**<0.001**	**<0.001**	**<0.001**

Table 2: p-values as in Table 1, but for Hanning windowed stimuli.

	at 50 pps	at 300 pps	at 900 pps	at 1800 pps
Hanning vs. Rectangle	>0.999	**<0.001**	**0.022**	0.061

Table 3: Bonferroni corrected p-values for the null hypothesis that mean ITD sensitivities do not vary as a function of envelope shape, rectangular or Hanning windowed stimuli, when tested at the pps values shown in the column headings. Significant p-values (<0.05) are shown in bold.

75% threshold	at 50 pps	at 300 pps	at 900 pps	at 1800 pps
Rectangle	**43.2 (N=14)**	**34.6 (N=16)**	**50.5 (N=16)**	401.5 (N=8)
Hanning	**40.5 (N=10)**	**61.8 (N=10)**	**62.0 (N=10)**	3575.8 (N=6)

Table 4: Mean estimated 75% ITD discrimination thresholds in µs, estimated from the slopes of the psychometric curves (see Methods) and averaged over all animals (N) tested at the corresponding stimulus condition.

Discussion

Early deafened biCI rats show good ITD lateralization for pulse rates up to 900 pps independent of envelope shape

In this study, we have demonstrated remarkably good ITD sensitivity despite early onset deafness under bilateral electric stimulation, including at electrical pulse rates in the range of those commonly used in current clinical practice. Even with Hanning windowed stimuli, all of our biCI rats routinely performed above 80% correct with ITDs greater than or equal

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to 80 μs at pulse rates of 900 pps. This gives rise to the hope that it may in principle be possible to devise binaural CI processing strategies capable of delivering very useful ITD cues to patients listening to speech enveloped stimuli. It should be emphasized that our animals received informative ITDs with microsecond precise relative timing of stimulus pulses delivered to each ear from the onset of their bilateral stimulation. Current clinical practice does not deliver binaural stimulation conditions, which are favorable for the development of good ITD sensitivity, to any human CI listeners. Consequently it is perhaps not surprising that the good ITD sensitivity we observe in our rats contrasts with the results obtained from human biCI users. Prelingually deaf CI users often fail to develop any usable sensitivity to ITDs (Litovsky 2010; Ehlers et al. 2017). CI users who do exhibit at least some ITD sensitivity tend to show a rapid drop-off in ITD lateralization performance with pulse rates above 300-500 pps (Laback et al. 2015). We also observed that ITD sensitivity was significantly lower with slowly rising Hanning envelopes than with very fast onset rectangular windowed pulses at rates of 300 and 900 pps. This is in qualitative agreement with studies in human CI listeners that have reported a reduced ability to use ITD cues in stimuli with speech waveforms (Laback et al. 2004; Grantham et al. 2008) which also consist of slow rising envelopes. While there is evidence that CI users may be able to use ITDs carried on slow rising envelopes, human studies demonstrated that this is only possible when the shape of the envelope is peaked (Laback et al. 2004; van Hoesel et al. 2009; Laback et al. 2011; Noel and Eddington 2013). This strongly suggests that a speech envelope, or any slow rising envelope for that matter (such as a Hanning windowed pulse train), delivered by current clinical speech processors does not contain the temporal features needed for effective encoding of ITD information. In addition, better ITD discrimination in stimuli with rapid onsets is perhaps unsurprising given that, for normal hearing subjects, onset ITDs are normally the most salient (Brown and Stecker 2010). Electrophysiological studies of ITD sensitivity have similarly demonstrated the importance of onset cues in ITD sensitivity at least at the level of the inferior colliculus (Buck et al. 2021; Haqqee et al. 2021; Li et al. 2021) with a fall in ITD sensitivity of between 24-48% when onset responses were excluded (Buck et al. 2021). Comparable results were also observed in a behavioral study in normal hearing rats across different pulse rates (Li et al. 2019).

In addition, ITD sensitivity under biCI stimulation has been shown to decrease with increasing pulse rates in studies when the onset cues were both included (Chung et al. 2016) or excluded (Smith and Delgutte 2007; Hancock et al. 2012; Hancock et al. 2013; Chung et al. 2019). For example, Chung et al. (2016) identified the best ITD sensitivity in

IC for pulse rates around 80-160 pps followed by a degraded sensitivity for higher pulse rates. However, in contrast to lower pulse rates, which are expected to improve ITD sensitivity (Joris and Yin 1998; van Hoesel 2007; Laback et al. 2007; Chung et al. 2016), there is evidence that temporal encoding is only improved at higher electrical pulse rates (Vollmer et al. 1999; Sunwoo et al. 2021)which again is interesting based on the evidence that ITD processing and temporal acuity may have similar mechanics (Snyder et al. 1995; Vollmer et al. 1999).

Our behavioural results in biCI animals presented here thus show similar trends to those seen in previous electrophysiological work, namely that ITD sensitivity may decline if stimulus envelopes are lacking pronounced onsets or if pulse rates are high (Hancock et al. 2012; Hancock et al. 2013; Chung et al. 2016; Buck et al. 2021). However, the most important observation to take away from our study is that, as already mentioned, our rats routinely achieved ITD thresholds well below 100 µs at 900 pps even with slowly rising Hanning envelopes. Thus, neither high carrier rates nor slow rising envelopes preclude the ability of biCI users to make use of ITD cues. If similar sensitivity to this binaural cue could be achieved with patients with improved CI techniques, this could potentially result in significant improvements in ITD performances and subsequent improvements in speech reception thresholds in noise.

The role of pulse rate and stimulation position in ITD perception of CI users

The ITD sensitivity of our CI animals even at pulse rates as high as 900 pps is surprisingly good when compared to the average ITD discrimination performance of postlingually deaf human biCI users, which show a drop in sensitivity for pulse rates above 300-500 pps (Majdak et al. 2006; van Hoesel 2007; Thakkar et al. 2018). There appears to be a general consensus that, for good ITD perception, pulse rates should ideally be quite low, but they do of course need to be fast enough to enable the high effective encoding of speech. However, that constraint need not be a major problem, since studies by Shannon et al. (2011) and Green et al. (2012) demonstrate that increasing the pulse rates above 600, at least up to 2400 pps, resulted in little to no benefit for phoneme, word and sentence recognition either in quiet or in noise.

To overcome the limited ITD sensitivity in biCI listeners, new strategies have been tried in studies on humans (Eklöf and Tideholm 2018; Srinivasan et al. 2018; Thakkar et al. 2018)

and animals (Buechel et al. 2018). For example, configurations with mixed stimulation rates, in which one low rate electrode was included among an array of higher rate electrodes, inducing ITD sensitivity similar to that seen with configurations comprising only low rates (Thakkar et al. 2018). In addition, stimulation strategies have been developed that allow the encoding of the fine structure of sound. In Eklöf and Tideholm (2018), 50% of the listeners using such a fine structure strategy showed an ITD sensitivity with a mean threshold at 330 µs, while listeners without fine structure strategy failed to detect ITDs > 1000 µs. Another proposed strategy involved combining both high and low pulse rates together. Srinivasan et al. (2018) report that the introduction of an additional slower pulse train overlying a faster pulse train, but with a small offset, improves ITD sensitivity beyond what might be expected from a simple, equivalent increase in stimulus amplitude. In biCI rabbits, Buechel et al. (2018) have shown that adding extra pulses to periodic pulse trains of high pulse rates introduces short inter-pulse intervals resulting in better ITD coding of auditory midbrain neurons.

These new stimulation strategies are ingenious, but it is noteworthy that, even with the improvements that they may have induced, the ITD discrimination of the human CI listeners tested still falls short of the performance that our early deafened rats were able to achieve at high pulse rates of up to 900 pps and without special strategies. This suggests that the factors limiting ITD perception in human biCI users may originate from other factors. For example, the CI stimulation our rats received always contained highly precise and informative ITD cues from the very beginning of implantation, where as the majority of binaural stimulation delivered to human CI listeners comes from current standard issue clinical processors which deliver uninformative ITDs. Our work thus raises the possibility that providing users with consistently precise and informative ITD cues might allow them to develop very good ITD sensitivity at clinically relevant pulse rates, at least up to 900 pps. Using lower pulse rates might improve ITD sensitivity further, as has been shown in previous studies on animal and human CI users (Smith and Delgutte 2007; van Hoesel et al. 2009; Hancock et al. 2012; Kan and Litovsky 2015; Laback et al. 2015; Chung et al. 2016), and has again been demonstrated here, but there should be plenty of scope to deliver very useful ITD cue information at pulse rates well within the range needed for effective speech coding.

In addition to stimulation strategies with modified or mixed pulse rates, the effects of changing intracochlear stimulation positions on ITD sensitivity in biCI users have also been considered in several studies. Shannon et al. (2011) and Thakkar et al. (2018) reported

that increasing the number of activated stimulation electrodes could improve both ITD localization and speech performance of CI users. Whether this was due to the increased amplitude and energy spread, thus increasing the chance of stimulating surviving spiral ganglion cells, or a result of wider frequency activation, is still an open question. It is possible that wider activation increases the energy reaching the apex of the cochlea, and thus the low frequency region, which, according to the duplex theory (Schnupp et al. 2011), is often thought of as particularly attuned to ITD processing. Moreover, directly stimulating the low frequency pathways in an animal model with monaural penetrating auditory nerve electrodes results in better temporal acuity than that observed when higher frequency fibres are stimulated with the same types of electrodes (Middlebrooks and Snyder 2007; Middlebrooks and Snyder 2010). Note that human intracochlear electrodes implanted with current tools and surgical techniques usually fail to reach the apical, most low-frequency end of the cochlea (Stakhovskaya et al. 2007). One might expect that this could reduce ITD sensitivity overall, but also that the best ITD sensitivity might be observed if the apical-most electrodes are stimulated. However, Kan et al. (2015) observed that ITD sensitivity could be optimized with a stimulation of sets of electrodes that spanned the full length of the CI electrode array. It has been shown a long time ago that normal hearing listeners can exhibit a high sensitivity to so-called “envelope ITDs” of high frequency carriers (Henning 1974). More recently, Kan et al. (2015) and Litovsky et al. (2012) have also demonstrated ITD sensitivity with electrical stimulation of the basal or middle part of the cochlea in human CI listeners. Furthermore, our studies (Buck et al. 2021; Rosskothen-Kuhl et al. 2021) show very high physiological and behavioral sensitivity to ITDs in the rat, even though we target mid frequency regions of the cochlea, regions equivalent to those on the human cochlea that are routinely covered by conventional CI electrode arrays. Together, these results strongly suggest that delivering ITDs at any part of the cochlea can be beneficial, and that the difficulty in reaching the most low-frequency parts of the tonotopic array with conventional CI electrodes is at best a very a minor limiting factor in the ITD sensitivity that is in principle achievable with bilateral CIs.

Possible causes of better ITD perception in ND biCI rats than in biCI human listeners

Why our rats exhibit much better ITD performance than that previously reported in biCI users is not known, but possible explanations, some of which we have touched on above, include species differences, differences in the nature of the stimulation and/or training effects. Species differences may of course play a role, but a multitude of studies indicate

365 that rats are a good animal model for human cochlear implantation (Rosskothen-Kuhl and Illing 2010; Rosskothen-Kuhl and Illing 2012; Rosskothen-Kuhl and Illing 2014; Rauch et al. 2016; Rosskothen-Kuhl et al. 2018; Jakob et al. 2019; Rosskothen-Kuhl et al. 2021; Weltin et al. 2022) and binaural hearing (Li et al. 2019; Li et al. 2021; Rosskothen-Kuhl et al. 2021). We thus think species differences are unlikely to be a major factor.

370 As already noted, our setup always provides informative ITDs with microsecond precision from the first stimulation, while clinical processors in current use do not. Devices in clinical use are typically based on two monaural processors with asynchronous clock times and at best modest time locking to the temporal fine structure of the input at each ear. Many human CI psychoacoustic studies are performed with research interfaces capable of more 375 precise binaural synchronization, but the vast majority of the auditory experience of the participants nevertheless comes from asynchronous clinical CI speech processors which deliver interaural pulse timing patterns that are uninformative and potentially misleading. The differences in ITD sensitivity could simply be driven by the fact that ITDs are a much more useful and reliable cue for our biCI rats than they are for the typical human biCI user. 380 This hypothesis is supported by a recent electrophysiological study by Thompson et al. (2021), which has demonstrated that animals that experienced reliable ITD information through “ITD-aware sound processors” have a higher neuronal ITD sensitivity than biCI animals supplied with standard clinical processors.

It has long been thought that the absence of binaural experience during early life may 385 preclude the development of normal ITD sensitivity in CI listeners (Litovsky 2010; Gordon et al. 2014). However, in Rosskothen-Kuhl et al. (2021) we demonstrate that a long period of hearing deprivation from ~p15 until early adulthood in our rats (~p70-98) does not impair the ability to use ITDs. In fact, the ITD sensitivity of neonatally deafened, adult implanted rats was found to be comparable to that of normally hearing, acoustically stimulated rats 390 (Li et al. 2019). ITD sensitivity thus does not appear to have a critical period. Providing auditory input with consistently informative ITDs from the onset of stimulation may play a much more important role in the development of ITD sensitivity than ensuring that this initial stimulation happens very early. Unlike typical early deaf human biCI users, our ND CI animals were able to lateralize ITDs with thresholds around 50 µs that appear no worse 395 than those seen in their normally hearing siblings (Li et al. 2019), but unlike human CI users our animals were also never exposed to prolonged periods of stimulation with arbitrary and uninformative interaural time delays as delivered by clinical speech processors.

Finally, one needs to consider the possibility that training effects may play a major role. For our biCI rats, lateralizing binaural pulse trains with precise ITDs but no other noteworthy features day after day constituted the entirety of their auditory experience, and they would spend approximately 10 hours a week for several months practicing lateralizing these sounds with instant positive reinforcement for correct performance. In contrast, human CI users spend most of their auditory experience trying to make sense of the cacophony of everyday life, and little if any of their time and attention is dedicated to honing their ITD detection skills. In this context it is of interest to note Goldsworthy and Shannon (2014) report that just 32 hours of training could lead to very substantial improvements in CI pulse rate discrimination. If monaural temporal processing in human CI users can improve with training, then the same may also be true for binaural temporal processing, as rate discrimination and ITD lateralization may share some common physiological mechanisms (Ihlefeld et al. 2015). Generally, psychoacoustic limits observed in largely untrained CI listeners may substantially underestimate the physiological limits that the CI stimulated auditory pathway is in principle capable of.

Furthermore, recent studies have demonstrated that lateralization training can lead to a reweighting of binaural cues in normal hearing listeners (Kumpik et al. 2019; Klingel et al. 2021) and biCI users (Klingel and Laback 2022), such that the listeners rely more or less heavily on ILDs or ITDs respectively depending on which cue is more reliable or informative. This could be relevant for CI listeners, as they could similarly down-weight ITD cues if the ongoing stimulation with clinical processors does not transmit reliable, informative ITDs which would thus encourage a reliance exclusively on ILDs to the detriment of ITDs. Conversely, it is conceivable that targeted ITD lateralization training under optimized bilateral stimulation might allow CI listeners to regain and rebalance their sensitivity to ITDs. However, even if training could improve ITD sensitivity in CI listeners for pulse rates up to 900 pps, our results in the CI animal model provide strong evidence that there is likely to be a physiological upper bound at pulse rates much above 900 pps, given that ITD sensitivity in our rats dropped precipitously at 1800 pps (see Figs. 2, 3, S2, and S3).

Conclusion

Under synchronized bilateral stimulation, we have shown that, at least in rats, clinical pulse rates of up to 900 pps should not prevent the development of good ITD sensitivity. This is not only important for better sound localization in human CI users but also for their speech understanding in noisy environments. Sharp onset stimulus envelopes and lower pulse

rates can further improve ITD sensitivity, but are not an absolute requirement, as good ITD sensitivity was still observed at 900 pps pulse trains with gentle onset Hanning envelopes. Delivering pulsatile binaural stimulation through neuroprosthetic devices at pulse rates that are fast enough to encode speech envelopes effectively and yet slow enough to allow the precise encoding of timing cues for ITDs may therefore not be as difficult as previously thought. This is an important finding for the development of future CI speech processor algorithms which may be able to provide biCI users of the future with a much better binaural listening experience.

Methods and Materials

All procedures involving experimental animals reported here were approved by the Department of Health of Hong Kong (#16-52 to 16-55; 18-81 to 18-83; 20-143 to 20-144 DH/HA&P/8/2/5) and/or the Regierungspräsidium Freiburg (#35-9185.81/G-17/124), as well as by the appropriate local ethical review committee. Sixteen female Wistar rats were neonatally deafened as described in (Rosskothen-Kuhl and Illing 2012). After verification of hearing loss using acoustic auditory brainstem recordings, young adult rats (postnatal weeks 10-14) were implanted simultanously with bilateral CIs from PEIRA (animal arrays ST08.45, ST05.45 or ST03.45, Cochlear Ltd, Peira, Beerse, Belgium) or with bilateral CIs kindly provided by MED-EL (3-patch animal arrays, Medical Electronics, Innsbruck, Austria). All rats underwent behavioral training as described in Rosskothen-Kuhl et al. (2021) (Fig. 1). As before, animals received binaurally synchronized input from the first stimulation. For details on the electric stimuli and stimulation setup see Rosskothen-Kuhl et al. (2021).

Psychoacoustic Training and Testing

The ability to discriminate ITDs of CI stimuli was tested in a 2-AFC ITD lateralization task in our custom made behavior setup as described in Rosskothen-Kuhl et al. (2021). Training and testing for the 16 animals was done in a pseudo random order following implantation (Fig. 1). Animals were tested on four pulse rates, 50, 300, 900, and 1800 pps, with rectangle (N=16) and Hanning (N=10) windowed pulse trains. For this experiment, both individual pulses and envelopes carried the same ITD information by keeping the fine structure and envelope ITDs equal for all trials. As in Rosskothen-Kuhl et al. (2021), the ITDs were presented between -150 and +150 µs, where negative represents a left leading and positive a right leading ITD. This range covers 125% of the animal's physiological range, which is between -120 and +120 µs (Koka et al. 2008). Each pulse train had a duration of 200 ms, and animals were stimulated at a maximum of 6 dB (0 dB relative to 100 µA peak pulse amplitude) above their eABR thresholds (see Rosskothen-Kuhl et al. (2021) for details). The eABRs of an example rat are shown in Figure S1 directly after implantation, 6 weeks, and 6 months post implantation. The starting frequency of the first training was assigned pseudo randomly to rule out any effects from the order in which they were trained and tested. Hanning windowed pulse trains consisted of a raised cosine waveform with a 100 ms rising and falling phase, respectively (Fig. 5).

If animals struggled with the higher frequencies (particularly 1800 pps) in training sessions, these rates were interleaved with trials at easier pulse rates in order to keep the animals motivated and to allow them to obtain sufficient water rewards for stimuli with both rectangular and Hanning windowed envelopes. All 16 CI animals were tested for ITD sensitivity under rectangular windowed stimuli at 300 and 900 pps. For rectangular windowed stimuli at pulse rates of 50 and 1800 pps, 14 and 8 CI animals were tested, respectively (Figs. 1, 2, S2). For ITD sensitivity under Hanning windowed envelope, ten CI animals were tested at 50, 300, and 900 pps, and six of them were additionally tested at 1800 pps (Figs. 1, 3, S3).

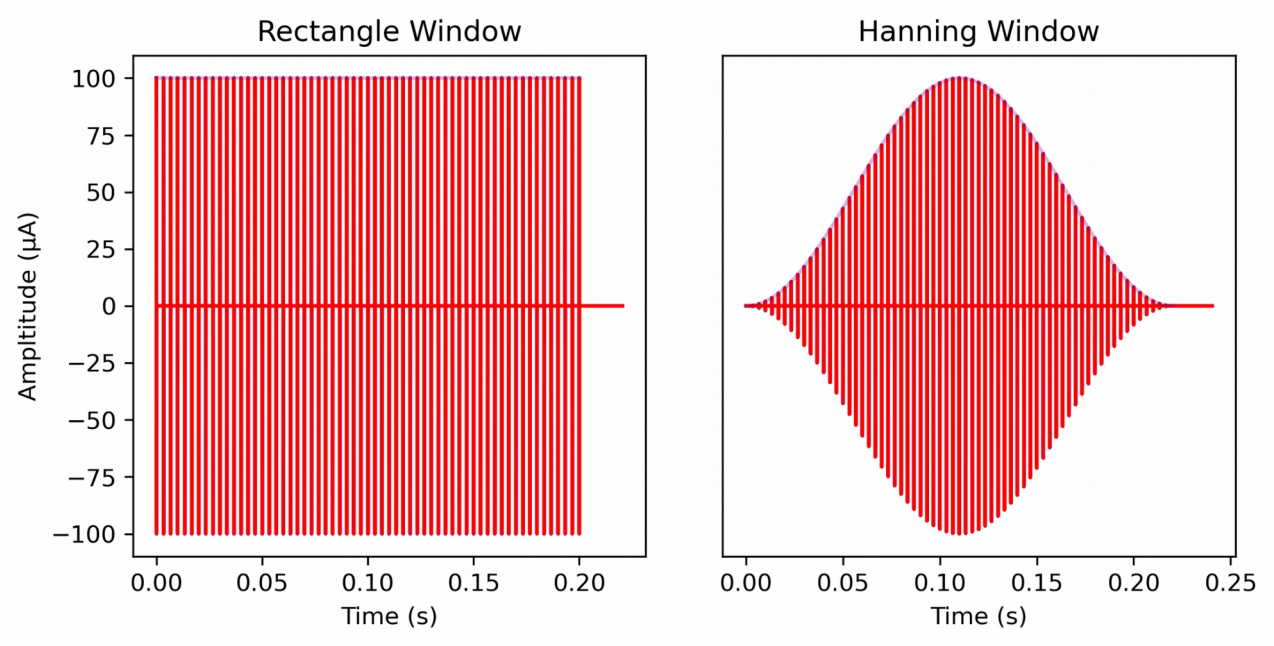

Figure 5: Waveforms of the electrical stimuli for rectangular (left) and Hanning (right) windowed stimulation. Waveforms shown are examples at 300 pps.

Data Analysis

Psychometric curve fits were estimated as described in Rosskothen-Kuhl et al. (2021). To determine behavioral ITD sensitivity, the proportions of “right” responses an animal made as a function of stimulus ITD were fitted using either linear or cumulative Gaussian sigmoid functions (Figs. 2, 3). Whether the sigmoid model gave a better fit than the linear model for a given animal and a given combination of stimulus envelope and pulse rate was determined using a deviance test. Once the best fit model was chosen, the slope of the fitted psychometric curve at ITD=0 was computed in units of % change in the animal’s preference for choosing the right water spout per microsecond increase in the value of

stimulus ITD. This slope served as a metric for the behavioral sensitivity of the animal to ITD at the given stimulus envelope and pulse rate.

In order to be able to estimate confidence limits and perform statistical inferences on these psychometric slope ITD sensitivity metrics, we then performed a bootstrap resampling analysis. The first step of this analysis consisted of an N-out-of-N resampling of the behavioral data to obtain bootstrap distributions of slope values. For each animal, we collected the N trials the animal performed for a given combination of ITD values, envelope and pulse rate, and drew, with replacement, a bootstrap sample of N trials from that set. Readers versed in probability theory may recognize that this step is equivalent to drawing a random number from a binomial distribution with a “hit” probability equal to the fraction of “right” choices made by the animal for this particular stimulus. After collecting these resampled trials for each ITD tested at the given envelope and pulse rate, the slope of the psychometric function for the resampled data was computed. Repeating this process 1000 times yielded a set of bootstrapped psychometric slopes. These were computed in turn for each animal, envelope type and stimulus pulse rate, and could serve to compute confidence intervals or as empirical distributions which could be further resampled for statistical inference on the effects of changes in stimulus pulse rate or envelope.

To examine the statistical significance of effects in envelope type or pulse rate changes, we decided to carry out 16 pairwise comparisons in total: 6 comparisons for each pair of pulse rates with rectangular envelopes (see Tab. 1), 6 with Hanning envelopes (see Tab. 2), and 4 comparing the two envelope types at each pulse rate tested (see Tab. 3). Because it was not possible to test all animals on every stimulus parameter combination, and because we wished to keep our statistical analysis “within subject”, in order to decide whether changing envelope type or pulse rates had a significant effect, we first identified the subset of animals which were tested at both of the stimulus parameter combinations to be compared. We then carried out resampling of the previously calculated bootstrapped psychometric slopes for each animal to generate mean bootstrap slopes for this cohort. For each animal, one bootstrap slope value was drawn for each of the two stimulus types to be compared, and the values were averaged across the cohort to produce a pair of mean slopes. This process was repeated 16,000 times to generate 16,000 pairs of cohort averaged bootstrap slopes $[s_1, s_2]_N$, $N \in \{1 \ldots 16{,}000\}$. An N of 16,000 repeats was chosen to resolve a smallest p-value of 0.001 after multiple comparison correction (see below). These pairs of resampled, cohort-averaged psychometric slopes were then used to calculate the p-value of the null hypothesis that there were no significant differences

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between the values s_1, s_2 in each pair on average. We first determined whether s_1 or s_2 had the smaller mean when averaged over the N cohort resampling trials. Let s_S and s_L denote the values in each pair that had the smaller (S) or larger (L) mean across N, respectively. Finally, we computed the proportion of the 16,000 pairs for which $s_S > s_L$. If there was no significant difference in the slopes for each condition, then we would expect $s_S \approx s_L$, and $s_S > s_L$ should then be true almost half the time, but if there was a significant difference, $s_S > s_L$ should be observed only rarely. The proportion of cases for which $s_S > s_L$ can therefore serve as an uncorrected p-value for the null hypothesis that the psychometric slopes for each of the two conditions under consideration did not differ significantly. This uncorrected p-value was then multiplied by 16, the total number of comparisons to be performed, and if necessary limited to a maximum of 1, to generate the p-values reported in Tables 1-3. After multiple comparison correction, the smallest p-value that this resampling method can resolve is 0.001, and p-values of 0 returned by this method are therefore reported as <0.001.

The estimated 75% ITD discrimination thresholds were determined from the slopes exhibited by the fitted psychometric curves at 0 μs ITD. As can be seen by inspection of Figures 2, 3, S2, and S3, the psychometrics were either fit directly with a straight-line equation (linear model) or were reasonably well approximated by a straight line tangent over the range of 25-75% right responses (green dashed lines on the sigmoid psychometric functions) with the slope just mentioned. In other words, the psychometric can be reasonably well approximated with a straight line of a constant slope over the range of 25-75% right responses. Consequently, one can estimate the 75% discrimination threshold easily as the change in ITD that would be required to “climb” along the (tangent to the) psychometric function by 25% points, from the 50% level of completely random guessing to the level of 75% correct “right” responses. Note that, due to symmetry, the same absolute change in ITD is required whether one climbs or descends by 25% points along the tangent line. Let s denote the slope of the (tangent to the) psychometric in %/μs, and θ_{75} denote the 75% discrimination threshold in μs, then, as just explained, $s \cdot \theta_{75} = 25$, or equivalently, $\theta_{75} = 25/s$. The mean of the 75% ITD discrimination thresholds, estimated using this simple formula and averaged across animals, are reported in Table 4 for each of the eight different stimulation conditions tested. These 75% thresholds may slightly underestimate thresholds that might be observed in ITD discrimination tasks. First, because they ignore the (usually small) effect of non-linearity for sigmoidal psychometrics, and second, because they estimate the threshold around the animal’s subjective 50% ITD value, rather than at ITD=0. This offsets the possible effects of a small ear-bias which

might elevate thresholds in other types of discrimination tasks, depending on the task details. Readers who are interested in precise comparisons of ITD thresholds across studies and species need to keep methodological differences in mind.

Supplementary Materials:

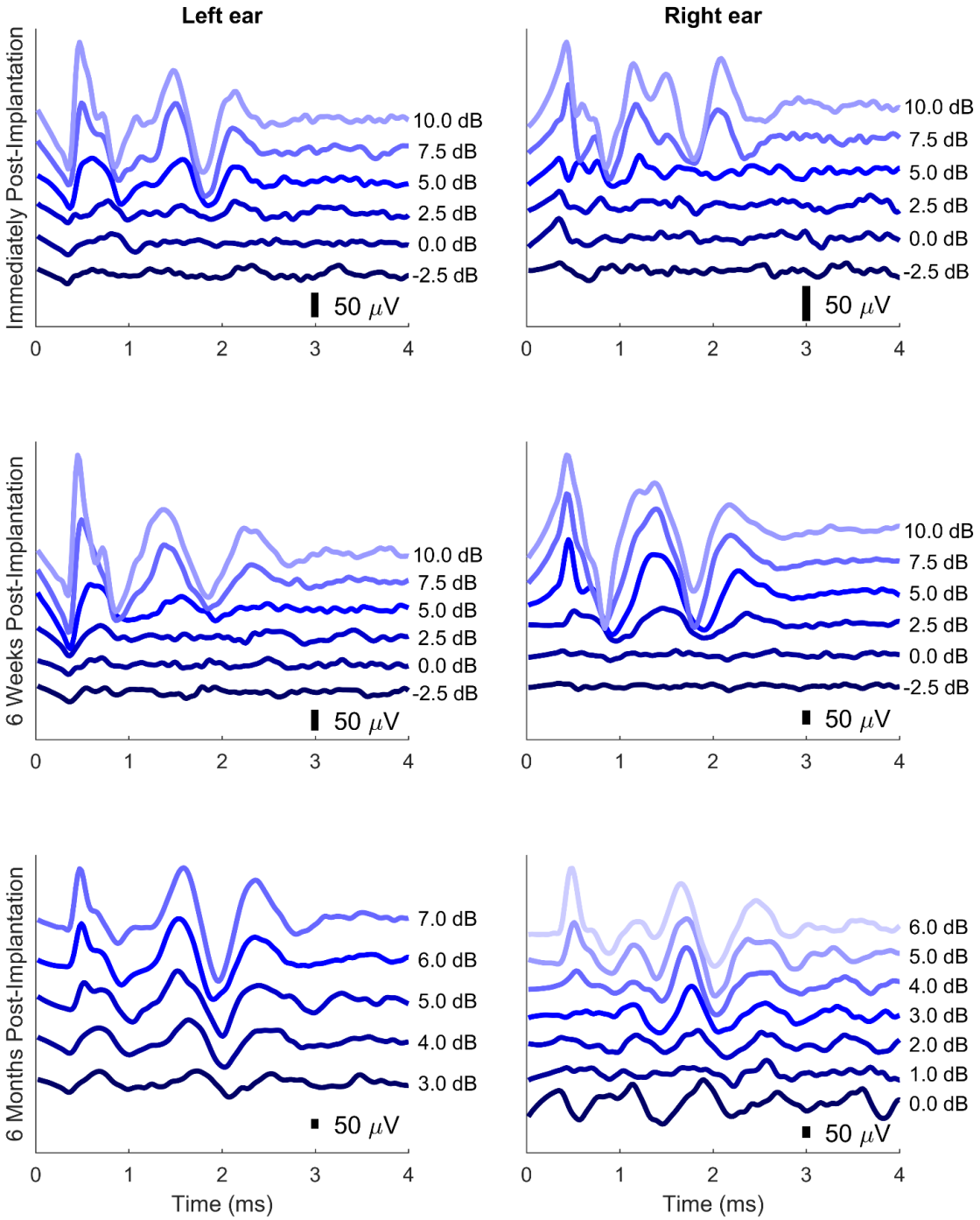

Figure S1: Example eABRs showing immediately after bilateral CI implantation, 6 weeks, and 6 months after implantation thresholds for the left and right ears of a neonatally deafened rat. Scale bars are shown in each plot with reference to 50 μV. Colour represents a different SPL with dark to light colors going from softest to loudest, and 0 dB SPL corresponding to 100 μA current level. Electric artefacts have been removed using interpolation over the duration of the stimulus. For details on the stimulus and presentation, see Rosskothen-Kuhl et al. (2021).

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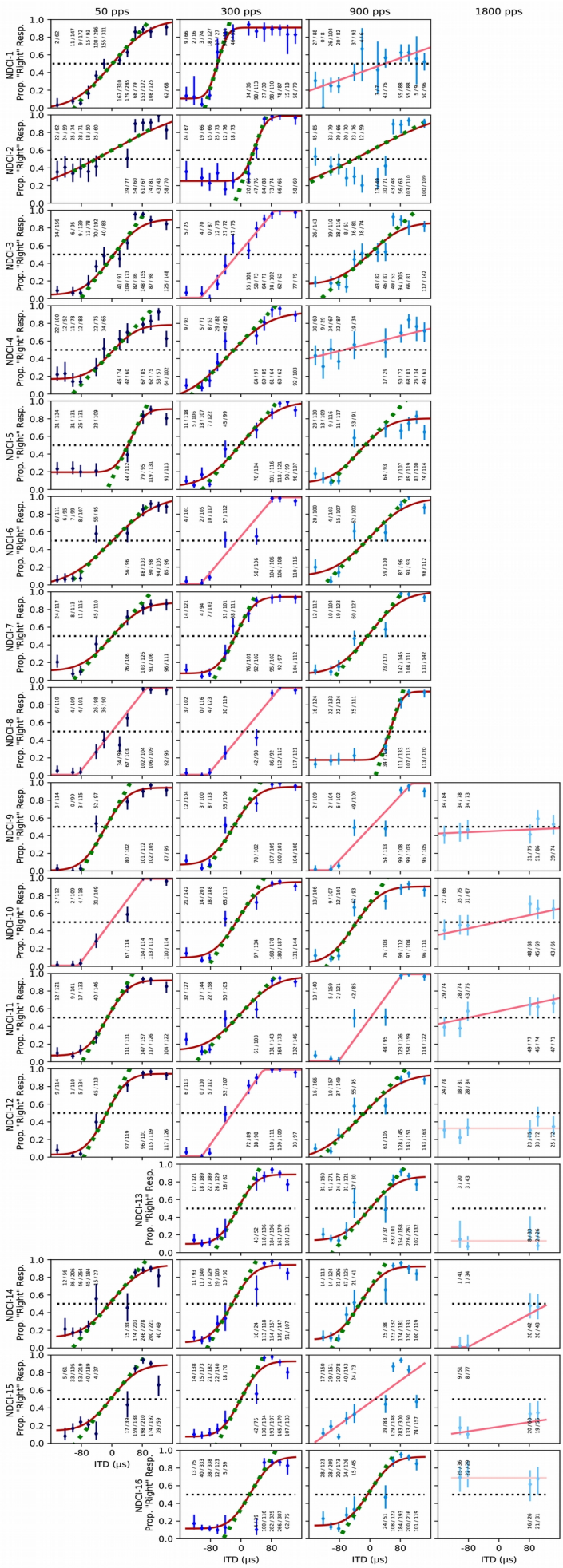
50 pps
300 pps
900 pps
1800 pps
NDCI-1
NDCI-2
NDCI-3
NDCI-4
NDCI-5
NDCI-6
NDCI-7
NDCI-8
NDCI-9
NDCI-10
NDCI-11
NDCI-12
NDCI-13
NDCI-14
NDCI-15
NDCI-16
Prop. "Right" Resp.
ITD (µs)

Figure S2: Psychometric functions of all 16 CI rats for rectangular windowed pulse trains at each pulse rate. Each column represents a different pulse rate from 50, 300, 900 and 1800 pulses per second (pps) (left to right). Each row shows the responses for a given animal. The y-axis reflects “right” responses where “right” refers to the right hand spout (Prop. “Right” Resp.). The x-axis shows the tested interaural time difference (ITD) values from – 150 to + 150 μs. Negative ITD values indicate left leading ITDs. Annotations above or below each marker indicate the number of trials the animal chose the right hand side spout over the total number of presentations for a given ITD value. From dark to light the different shades of red indicate sigmoid, linear with bounds or null model psychometric curve fits. Green dashed lines show slopes of psychometric curves at ITD=0. Slopes serve to quantify the behavioral sensitivity of the animal to ITD.

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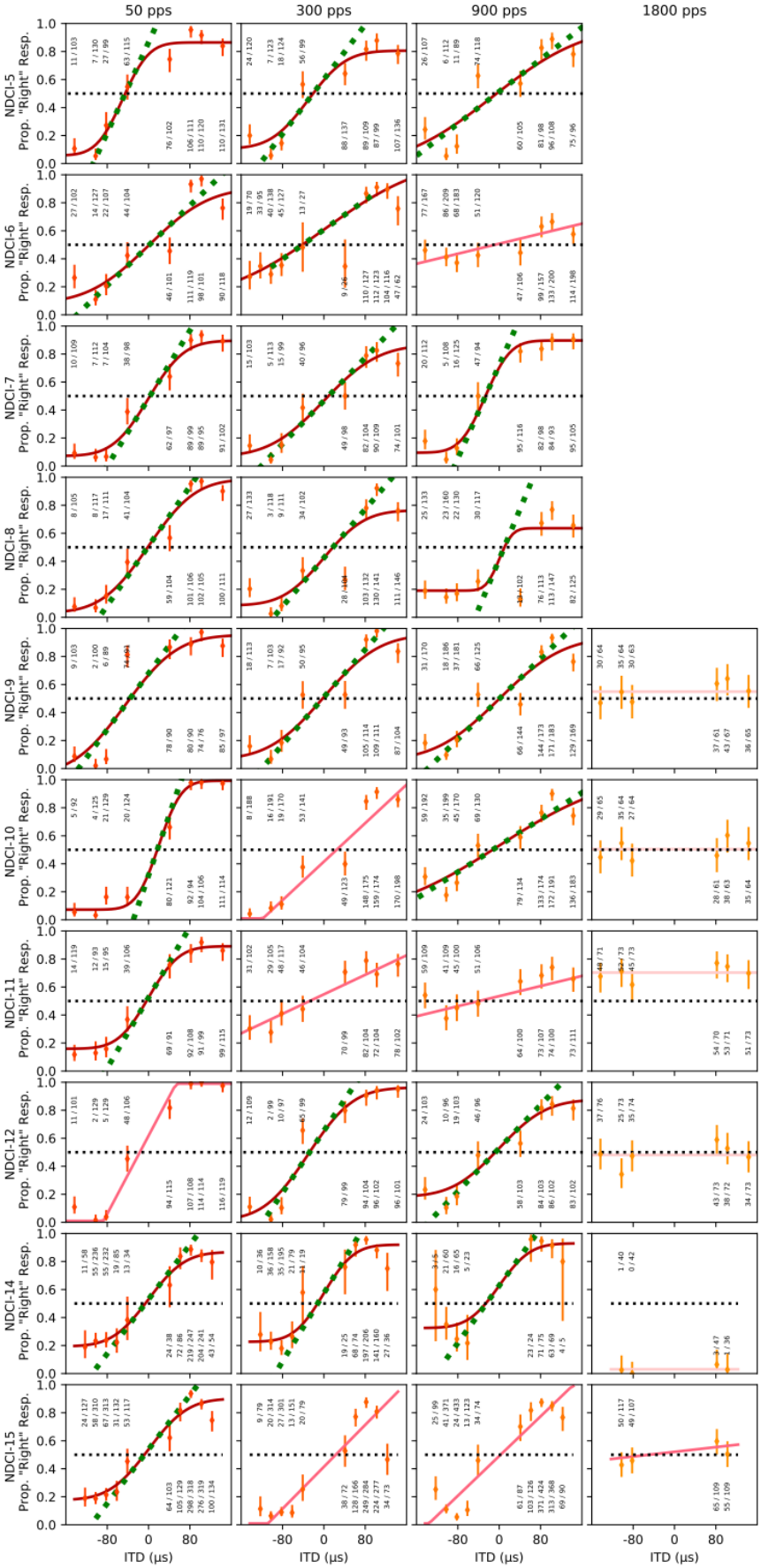

Figure S3: Psychometrics of 10 CI rats for Hanning windowed pulse trains with varying ITDs as in Figure S2**.** Details are as for S2.

Acknowledgements

We thank Felix Kleinschroth for his assistance in figure design as well as Felix Kleinschroth, Stella Mayer, and Lakshay Khurana for assisting behavioral training of CI rats. Work leading to this publication was supported by grants from the Hong Kong General Research Fund (11100219 and 11101020), the Shenzhen Science and Innovation Fund Grant (JCYJ20180307124024360), Health and Medical Research Fund (07181406), the German Academic Exchange Service (DAAD) with funds from the German Federal Ministry of Education and Research (BMBF) and the People Programme (Marie Curie Actions) of the European Union's Seventh Framework Programme (FP7/2007-2013) under REA grant agreement n° 605728 (PRIME – Postdoctoral Researchers International Mobility Experience), the Research Commission of the Medical Faculty of the Medical Center – University of Freiburg, and friends' association "Taube Kinder lernen hören e. V.". Eight cochlear implant animal arrays were kindly provided by MED-EL Medical Electronics, Innsbruck, Austria (Research Agreement PVFR2019/2).

Declaration of Interests

The authors declare no competing interests.

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