Research Article

Improved Neural Coding of ITD with Bilateral Cochlear Implants by Introducing Short Inter-pulse Intervals

BRIAN D. BUECHEL,^{1,2} KENNETH E. HANCOCK,^{1,3} YOOJIN CHUNG,^{1,3} AND BERTRAND DELGUTTE^{1,3}

¹*Eaton-Peabody Laboratories, Massachusetts Eye & Ear, 243 Charles St, Boston, MA 02114, USA*

²*Program in Speech and Hearing Bioscience and Technology, Harvard Medical School, Boston, MA 02115, USA*

³*Department of Otolaryngology, Harvard Medical School, Boston, MA 02115, USA*

Received: 8 June 2016; Accepted: 17 July 2018; Online publication: 6 September 2018

ABSTRACT

Bilateral cochlear implant (CI) users have poor perceptual sensitivity to interaural time differences (ITDs), which limits their ability to localize sounds and understand speech in noisy environments. This is especially true for high-rate (> 300 pps) periodic pulse trains, which are used as carriers in CI processors. Here, we investigate a novel stimulation strategy in which extra pulses are added to high-rate periodic pulse trains to introduce short inter-pulse intervals (SIPIs). We hypothesized that SIPIs can improve neural ITD sensitivity similarly to the effect observed by randomly jittering IPIs (Hancock et al., *J. Neurophysiol.* 108:714–28, 2012). To test this hypothesis, we measured ITD sensitivity of single units in the inferior colliculus (IC) of unanesthetized rabbits with bilateral CIs. Introducing SIPIs into high-rate pulse trains significantly increased firing rates for ~60 % of IC neurons, and the extra spikes tended to be synchronized to the SIPIs. The additional firings produced by SIPIs uncovered latent ITD sensitivity that was comparable to that observed with low-rate pulse trains. In some neurons, high spontaneous firing rates masked the ITD sensitivity introduced by SIPIs. ITD sensitivity in these neurons could be revealed by emphasizing stimulus-synchronized spikes with a coincidence detection analysis. Overall, these results with SIPIs are consistent with the effects observed previously with jittered pulse trains, with the added benefit of retaining control over the timing

and number of SIPIs. A novel CI processing strategy could incorporate SIPIs by inserting them at selected times to high-rate pulse train carriers. Such a strategy could potentially improve ITD perception without degrading speech intelligibility and thereby improve outcomes for bilateral CI users.

Keywords: cochlear implant, interaural time difference, inferior colliculus, single-unit electrophysiology, binaural hearing, temporal coding

INTRODUCTION

Bilateral cochlear implants (CI) are increasingly the standard of care for the treatment of severe to profound hearing loss, with the goal of providing access to the binaural cues important for sound localization and speech reception in noise. Bilateral CI users do show binaural benefits, but the localization benefits stem largely from the use of interaural level differences (Seeber and Fastl 2008; van Hoesel 2008; Aronoff et al. 2010), while the benefits for speech reception in noise are mostly attributed to the monaural head shadow effect (see van Hoesel 2012; Litovsky et al. 2012 for reviews). In contrast, the perception of interaural time differences (ITD) is significantly poorer than normal, producing substantial deficits in sound localization and spatial release from masking, for which ITD is a major cue in normal hearing (Laback et al. 2015). There are several reasons for these deficits, such as processor limitations, possible interaural mismatches in electrode array insertion depth into the cochlea, and alterations

Correspondence to: Bertrand Delgutte · Eaton-Peabody Laboratories · Massachusetts Eye & Ear · 243 Charles St, Boston, MA 02114, USA. Telephone: 617-573-3876; email: Bertrand_Delgutte@meei.harvard.edu

in binaural circuits as a result of deafness (Long et al. 2003; Poon et al. 2009; Tillein et al. 2010; Hancock et al. 2010, 2013; Tirko and Ryugo 2012; Kan et al. 2013, 2015). However, even with carefully pitch-matched electrodes and using direct stimulation bypassing the processor, CI users still have poor perceptual ITD sensitivity to high-rate (>300 pps) electric pulse trains (Laback et al. 2007; van Hoesel 2007; Laback and Majdak 2008; van Hoesel et al. 2009). High-rate stimuli (~ 1000 pps) are used as carriers in current CI processing strategies to faithfully represent speech envelopes (Loizou et al. 2000). Thus, there is a need for new stimulation strategies that would improve ITD perception without degrading speech intelligibility.

One possible approach is suggested by the finding that introducing binaurally coherent jitter into the timing of pulses significantly improves ITD discrimination at high rates (Laback & Majdak 2008). Laback and Majdak reasoned that the jittered pulses cause a release from “binaural adaptation,” a phenomenon first observed for trains of high-frequency acoustic clicks in normal hearing listeners (Haftner and Buell 1990). However, the neural mechanisms underlying binaural adaptation and its possible release through jitter are unclear. Specifically, the effect of jitter could result from either long inter-pulse intervals (IPIs) allowing a recovery from adaptation or short IPIs (SIPIs) producing a strong enough increment in short-term stimulus energy to overcome the adaptation.

Direct evidence for the importance of SIPIs comes from an investigation of neural correlates of the jitter effect in animal models of bilateral CIs (Hancock et al. 2012). Most neurons in the inferior colliculus (IC) of deaf animals exhibit weak or unsynchronized responses to high-rate (>100 – 200 pps) electric pulses with little or no ITD tuning, even if they show robust synchronized responses and good ITD sensitivity at low pulse rates (Smith and Delgutte 2007; Hancock et al. 2012; Chung et al. 2016). Hancock et al. (2012) found that introducing binaurally coherent jitter increased firing rates and improved ITD sensitivity in about half the tested neurons. The increased spiking consistently occurred with short latencies after short IPIs in the jittered pulse trains, but not after long IPIs. This finding implies the temporal irregularity in jittered stimuli is not important per se, but jitter introduces occasional occurrences of SIPIs that can elicit new spikes in an adapted IC neuron.

In the present work and a parallel psychophysical study of human CI listeners (Srinivasan et al. 2018), extra pulses were inserted into high-rate, isochronous pulse trains to directly test the effect of SIPIs on neural responses and perceptual ITD sensitivity. This

approach allows for greater flexibility compared to jitter, since the number and timing of SIPIs can be controlled. This control may be necessary in a sound processing strategy to maintain the integrity of speech envelope representation. We used an unanesthetized rabbit model of bilateral CIs (Chung et al. 2016) to measure the effect of introducing SIPIs on firing rates and ITD sensitivity of single units in the IC. We find that, similar to jitter, the introduction of SIPIs increases firing rates in about half of IC neurons, and this increased activity reveals latent ITD sensitivity comparable to that seen in response to low-rate pulse trains.

METHODS

We measured responses of single units in the IC of two unanesthetized, female Dutch-belted rabbits to electric stimulation presented bilaterally through cochlear implants. All procedures were approved by the animal care committee of Massachusetts Eye and Ear.

Surgical Procedures

The surgical procedures used for chronic cochlear implantation in adult rabbits and recording from single units in the IC of unanesthetized rabbits were as described by Chung et al. (2014, 2016). Each rabbit underwent three surgical procedures separated by recovery and training periods: a first surgery to affix a headpost and stainless steel cylinder to the skull, a second surgery to implant intracochlear electrode arrays, and third, a craniotomy for accessing the IC. The rabbits were implanted with eight-contact animal electrode arrays (Cochlear Ltd.: Z60274 in one rabbit, HL-8 in the other) inserted into the cochlea through the round window, which was slightly enlarged to facilitate insertion. Before inserting the electrode array, 5–10 μ L of distilled water was injected into the cochlea through the round window to deafen the ear by causing hypotonic stress to the organ of Corti (Chung et al. 2014, 2016). Percutaneous connectors to the implants were fixed to the sides of the stainless steel cylinder. Success of cochlear implantation was verified shortly after surgery by measuring the electrically evoked auditory brainstem response (EABR) to biphasic pulses. Efficacy of the deafening procedure was confirmed by measuring the acoustic ABR to 100- μ s clicks, with no discernible response up to at least 100 dB SPL. Single-unit recording sessions started after 2–3 days of recovery from the craniotomy surgery. During the 2.5-h sessions, the rabbit's head was fixed through the headpost. Rabbits were moni-

tored on a closed-circuit video system throughout the recording sessions. They only received stimulation through the implants during the recording sessions.

Table 1 provides information about the rabbits' ages and the timing and number of recording sessions. Recording sessions for both rabbits began ~1 month after the cochlear implantation surgeries, but some sessions were used to collect data for other experiments. Table 1 only includes the recording sessions in which data were collected for the present study.

Electrophysiological Recording Methods

Stimuli. The stimuli were 300-ms trains of biphasic pulses (cathodic/anodic, 50 μ s/phase, no inter-phase gap) separated by 300 ms of silence. Pulse trains were generated using 16-bit D/A converters (PXI-6221; National Instruments) at a 100-kHz sampling rate and delivered to each cochlear implant through a pair of custom-built, high-bandwidth, isolated current sources. Stimulation was between the most apical and most basal intracochlear electrodes, and the same configuration was used for every session. This wide bipolar electrode configuration stimulates auditory nerve fibers over the entire length of the tonotopic axis while reducing stimulus artifact compared to monopolar stimulation (Litvak et al. 2001).

Three types of pulse train stimuli were used to collect neural responses (Fig. 1a). The SIPI stimulus consisted of a high-rate, isochronous pulse train with extra pulses inserted at periodic intervals. The two comparison stimuli were a high-rate isochronous pulse train (without the extra pulses), referred to as the "base pulse train," and a low-rate, isochronous pulse train (only the extra pulses). Two parameters of the SIPI stimuli are the rate of extra pulse insertions, referred to as the SIPI rate, and the temporal separation between the two pulses forming a SIPI, called SIPI fraction because it is expressed as a percentage of the period of the base pulse train (Fig. 1b). For example, a SIPI fraction of 20 % at 640 pps corresponds to a 312.5 μ s interval between the two pulses forming a SIPI.

For all tested neurons, we first studied the effect of introducing SIPIs on responses to high-rate isochro-

Fig. 1. Description of SIPI stimuli. **a.** Schematics of biphasic pulse trains show how SIPI stimuli (blue) are constructed by adding extra pulses to a high-rate, isochronous pulse train (black). These extra pulses can be thought of as a low-rate, isochronous pulse train (red), which is used as a control when measuring ITD sensitivity. **b.** Stimulus parameters varied for SIPI stimuli. Extra pulses are highlighted in red

nous pulse trains with base rates from varying 320 to 1280 pps using "standard" SIPI parameters (SIPI rate 25 pps, SIPI fraction 20 %). Neural ITD sensitivity was then characterized for the three sets of stimuli in Fig. 1a by varying the ITD from -2000 to $+2000$ μ s in 200 or 400 μ s steps, also using the standard SIPI parameters. In some neurons, the parameters of the SIPI stimuli were systematically varied: the SIPI rate was varied from 12.5 to 200 pps in octave steps, and the SIPI fraction was varied from 10 to 50 %. An additional stimulus condition was tested in some neurons (Fig. 10a); the amplitude of the occasional pulse in a high-rate pulse train was incremented as opposed to adding an extra pulse. The pulse amplitude was incremented in 2 dB steps from 0 dB (i.e., a constant-amplitude, isochronous pulse train) to 6 dB (double the amplitude).

When varying a stimulus parameter (base rate, ITD, SIPI rate, SIPI fraction, or level increment), all other parameters were held constant, and these constant values are noted in the figure captions and text (see Table 2). All stimuli were presented diotically (same current amplitude and timing at both ears) except when explicitly varying the ITD.

Single Unit Recordings. Single units were isolated using microelectrodes advanced with a remote-controlled microdrive. The electrode was advanced in a dorso-ventral direction through the cerebral cortex down to the IC, which was identified by background entrainment to the search stimulus. The search stimulus was

TABLE 1

History of implantation and neural recording for each rabbit

Rabbit ID	Age at implantation (months)	Age at first recording session (months)	Age at last recording session (months)	Number of recording sessions
B05	8	9.5	24	21
B07	10	14.5	33	74

TABLE 2

SIPI parameters that were varied and held constant in each figure

<i>Varied parameter</i>	<i>Figure(s)</i>	<i>Base rate (pps)</i>	<i>SIPI rate (pps)</i>	<i>SIPI fraction (%)</i>	<i>ITD (μs)</i>
Base rate	2, 3, 4	320–1280	25	20	0
SIPI rate	5, 9D–F	640	12.5–200	20	0
ITD	6, 7, 8	640 or 896	25–50	10–20	± 2000
SIPI fraction	9A–C	640	25	10–50	0
Level increment	10	640	25	N/A	0

a sequence of three biphasic pulses (“triplet”), consisting of a bilateral diotic pulse, followed by monaural pulses to the left and right implants. The interval between consecutive pulses was 100 ms, and the last pulse in a triplet was separated from the first pulse of the next triplet by a 200 ms silent interval. The recording electrodes were 4-contact polyimide-insulated platinum/iridium wire arrays with 150 μ m spacing between contacts (linear microelectrode array, MicroProbes). To reduce stimulus artifact, recordings were made differentially between the contact of interest (containing an isolated unit) and a reference obtained by averaging the signals from the three other contacts. This signal was acquired by a unity gain headstage (Plexon HST/16050), filtered (100–8000 Hz), amplified (Plexon PBX2), and sampled at 100 kHz (PXI-6123; National Instruments).

During recording sessions, spikes were detected by software triggering on level crossings. The stimulus artifact was removed by gating out a short interval (0.3–0.5 ms) after each stimulus pulse. This technique was helpful for getting a rough sense of spiking activity in order to select stimulus parameters, but more accurate artifact removal and spike detection was performed offline (see below). Only well-isolated single units were studied, as assessed by the stability of spike waveforms and amplitudes, which were always well above the noise floor and clearly distinct from the local field potential. Stimuli were presented in random order (interleaving stimulus conditions) for 10–30 repetitions. Pulse trains were presented at a level 2–4 dB above the single-pulse threshold, which was determined by measuring responses to the search stimulus as a function of level.

Stimulus Artifact Removal and Spike Sorting. The gating technique for removing stimulus artifact previously used in our laboratory (Hancock et al. 2012; Chung et al. 2014, 2016) is quite effective at low pulse rates, but has the disadvantage of removing short segments of the waveform after each pulse, during which spikes could occur at high pulse rates. This method was found to have significant impact on firing rate and ITD sensitivity for high stimulation rates (e.g., 896 or 1280 pps). To avoid these problems, an offline artifact rejection method based on template subtraction was used for the final spike detection. The artifact

template was constructed for each stimulus by averaging the voltage waveform from the microelectrode over repeated sections within a stimulus. For example, if extra pulses were inserted at a rate of 100 pps, all 10-ms windows during the stimulus were averaged together to create a 10 ms template, and this short template was concatenated 30 times to create the full 300 ms template used to subtract the stimulus artifact. This template subtraction method was effective in reducing the stimulus artifact below the spike detection threshold and recovering spikes missed by gating.

A final spike sorting process was used to remove any remaining false triggering on stimulus artifact, local field potentials, or other units. A short segment (0.8 ms) was extracted around the peak of each candidate spike to construct a set of feature vectors for clustering. Principal component analysis was used to reduce dimensionality and a Gaussian mixture model was fit to the first 5 principal component weights. Any putative spikes not belonging to the largest spike cluster were removed. The validity of this procedure was confirmed by visual analysis of the selected spike waveforms. In two cases from different recording sessions, two well-isolated units present on the same electrode were easily separated with this technique; both units were included in the data set. In all other cases, only a single cluster was used.

Histological Processing. In the last recording session, electrolytic lesions were made to mark the borders of the region showing activity evoked by CI stimulation while the animal was under deep anesthesia (xylazine 6 mg/kg, s.c., and ketamine 44 mg/kg, i.m.). The rabbit was then perfused intracardially using a solution of 1.5 % paraformaldehyde and 2.5 % glutaraldehyde in phosphate buffer. The brain was immersed in fixative for 24 h and then transferred to 25 % sucrose solution for several days. In one rabbit, coronal sections (80 μ m) were cut with a freezing microtome and mounted on subbed slides. Sagittal sections were made in the other rabbit, which made it easier to visualize the lesions aligned along the electrode tracks. Cell bodies were stained with azure-thionin. Borders of IC regions were visually identified using an atlas of the rabbit brain (Shek et al. 1986). In both rabbits, all identified lesions were located within the central nucleus of the IC or at its border.

Data Analysis

Firing Rate. Firing rates in response to pulse trains were averaged over the 300 ms stimulus duration, excluding the onset response (first 25 ms). The effect of introducing SIPIs was quantified by the difference in mean firing rates between the SIPI stimulus and the corresponding isochronous pulse train with the same base rate (i.e., the stimuli represented by the blue and black traces in Fig. 1a). To test the statistical significance of this change in firing rate for individual neurons, confidence intervals were constructed with 10,000 bootstrapped samples of the difference in the mean firing rates by resampling independently across stimulus trials. An effect was considered significant if the 99 % confidence interval of the bootstrapped mean rate differences did not include the origin.

Synchrony. To quantify the temporal spiking patterns with SIPI stimuli, synchronization was calculated not to the base rate, but to the rate of extra pulses (the SIPI rate). Period histograms *modulo* the extra pulse period were calculated using all spikes elicited during stimulus presentation, excluding the smallest integer number of periods ≥ 25 ms following onset. The strength of phase locking to a periodic stimulus is usually quantified by the vector strength, a.k.a. synchronization index (Goldberg and Brown 1969). The Rayleigh test used for assessing the statistical significance of vector strength assumes a von Mises distribution of spike times within each stimulus period, i.e., a circular normal distribution. However, because our stimulus consisted of sparse extra pulses separated by long intervals, von Mises distributions were rarely appropriate to model our period histograms, which could even be bimodal (e.g., Fig. 4b).

To overcome this limitation, we used the Kuiper test (Kuiper 1960) to test for deviations of our empirical spike distributions from a uniform distribution and thereby quantify spike synchrony to extra pulses. The Kuiper test is the homolog of the Kolmogorov-Smirnov test for cyclic distributions. Unlike the Rayleigh test, the nonparametric Kuiper test can detect all deviations from uniformity including multimodal distributions. As an alternative to vector strength as measure of phase locking, we used the test statistic from the Kuiper test, which is the sum of the maximum positive and negative differences between the empirical and theoretic (here, uniform) cumulative distributions (see inset in Fig. 4b for example). This metric, which we refer to as the Kuiper statistic (KS), is similar to vector strength in that it is bounded between 0 and 1 with higher values indicating stronger synchrony.

Comparison Between Responses to Low-Rate and SIPI Stimuli. In some neurons, responses to SIPI stimuli were measured as a function of the rate of extra pulses (the SIPI rate) and compared to the responses to low-rate, isochro-

nous stimuli as a function of pulse rate (Fig. 5). We used orthogonal regression (Deming 1943) to quantify the relationship between the firing rates to these two stimuli. Because the exact pulse rates tested were slightly different for the two sets of stimuli (20 to 225 pps in half-octave steps for low-rate isochronous stimuli, vs. 25 to 200 pps in octave steps for SIPI stimuli), the firing rates to isochronous stimuli were linearly interpolated at the tested SIPI rates in order to get matching pairs of data points. The goodness of fit is reported as the fraction of variance accounted for by the orthogonal regression, which we call the “orthogonal R^2 ” to avoid confusion with ordinary linear regression. This metric represents the fraction of variance that can be explained by the first component in a principal component analysis of a 2D dataset (Jackson 1991).

ITD Sensitivity. To assess ITD sensitivity in individual neurons, we used a one-way ANOVA to determine whether ITD had a significant effect on the average firing rate across stimulus trials ($p < 0.025$). The strength of ITD tuning was quantified by the fraction of variance in firing rate attributable to ITD, which we call the “signal-to-total-variance ratio” (STVR) (Hancock et al., 2012; Hancock et al., 2010). Similar to mutual information, the STVR makes no assumptions about the shapes of ITD tuning curves, but requires fewer stimulus repetitions for reliable estimation as it only depends on the mean and variance of the spike count at each ITD.

Coincidence Detection. A previous study (Chung et al. 2016) showed that ITD sensitivity of IC neurons to low-rate, isochronous pulse trains can be enhanced by selecting spikes synchronous to the stimulus rather than including all spikes. Chung et al. used the cross-correlation between the stimulus pulse train and the neural spike train to extract the synchronous spikes. This method has the disadvantage of requiring that the timing of stimulus pulses be known. With the goal of developing a more biologically plausible method to select synchronous spikes, we implemented a coincidence detection analysis similar to those used in previous studies of auditory processing (e.g., Colburn et al. 1990; Wang and Delgutte 2012; Franken et al. 2014). The goal was to derive ITD tuning curves that emphasize the spikes synchronized to extra pulses (Fig. 7). Conceptually, the coincidence detector is a neuron central to the IC that receives inputs from two IC neurons. The coincidence detector neuron fires whenever spikes from both inputs occur within a 1-ms running coincidence window. Since simultaneous recordings from pairs of IC neurons were not available, we used two complementary approaches to select inputs to the coincidence detectors. First, we took random pairs of spikes trains recorded from the *same* neuron in response to repeated stimulus presentations at the same ITD. This implementation effectively assumes that the two inputs to the coincidence

detector have statistically identical response properties (including ITD tuning curves and spike latencies), and thus represents a best case scenario.

The second implementation of coincidence detection used as inputs a pair of spike trains recorded from two *distinct* neurons in response to the same stimulus and same ITD. This approach was applied for all possible pairs of neurons in our sample. In this implementation, we allowed a fixed delay between the spike trains from the two input neurons to optimize the chance of coincident spikes. To determine this fixed delay, we computed the cross-correlation of the post-stimulus time histograms from the two input neurons for each ITD, averaged the cross-correlations across all ITDs, and selected the lag that maximized the average cross-correlation. Importantly, the same delay was used for all stimulus conditions (both SIPI and isochronous stimuli, and all ITDs).

For both implementations, the width of the coincidence window was set to 1 ms based on a pilot analysis showing that ITD sensitivity (as assessed by STVR) at the output of the coincidence detector improved with increasing width of the coincidence window up to about 1 ms, after which it saturated or declined. We also included a refractory period of 1 ms after each output spike to produce realistic firing patterns. To ensure the variances in estimated firing rates would be comparable between the inputs and output of the coincidence detector, we used the same number of pairs of stimulus trials as in the original recordings to compute the mean rate of coincident spikes. For example, for the single-neuron implementation of the coincidence detector with 10 stimulus trials at a given ITD, there are 45 unique pairs of trials, only 10 of which were selected at random to compute the mean rate of coincident spikes at that ITD. For the two-neuron implementation of coincidence detection with 10 trials from each neuron at each ITD, there are 100 possible pairs of spike trains, 10 of which were selected at random. For both implementations, ITD tuning curves for coincident spikes were computed 50 times using a different random set of pairs of trials for each curve, and the final STVR reported is the mean of the STVRs for these 50 tuning curves. To test for ITD sensitivity of the coincidence detector output, we applied the same criterion as for overall firing rate ($p < 0.025$) using the geometric mean of the 50 individual p values derived from a one-way ANOVA.

RESULTS

Effect of SIPIs on IC Firing Rates

We recorded from 98 candidate single units in the IC of two unanesthetized rabbits with bilateral cochlear implants. After eliminating units that poorly

responded to the search stimulus, units whose firing rates greatly fluctuated over time and poorly isolated units as determined by the post hoc spike sorting procedure, we were left with 70 well-isolated, reliably firing units in the data set.

We first tested the effect of adding SIPIs to high-rate, isochronous pulse trains with base rates of 320–1280 pps, using “standard” SIPI parameters: 25 pps SIPI rate and 20 % SIPI fraction. We observed substantial variability among neurons in the responses to these stimuli, as illustrated by the three examples in Fig. 2. The neuron in Fig. 2a shows only an onset response to high-rate, isochronous pulse trains (i.e., without SIPIs). Introducing SIPIs elicits additional spikes that are synchronized to the extra pulses. The neuron in Fig. 2b shows a robust response to isochronous pulse trains at 320 and 448 pps, but only sporadic firing that does not rise above background activity at higher rates. Introducing SIPIs produces a clear increase in the responses to higher base rates, and the spikes are synchronized to the SIPIs. The neuron in Fig. 2c shows a very different pattern in which the high spontaneous rate of firing is partially suppressed by high-rate pulse train stimulation. Introducing SIPIs results in additional suppression occurring after each extra pulse. The right column in Fig. 2 displays the mean firing rates as a function of the base rate of both isochronous and SIPI stimuli for these three neurons. Introducing SIPIs greatly increased firing rate across the entire range of base rates for the neuron of Fig. 2a, while the neurons in Fig. 2b, c only showed large changes (increase in b and decrease in c) for base rates ≥ 640 pps.

We measured the firing rates to SIPI stimuli over a range of base rates (320–1280 pps) in 62 neurons using the standard parameters (SIPI rate = 25 pps, SIPI fraction = 20 %). Figure 3a shows a scatter plot of the firing rate to SIPI stimuli against the rate for isochronous stimuli for the 896-pps base rate. A majority of points lie above the diagonal, indicating that adding SIPIs increased the firing rates for most neurons. Importantly, increases occur for neurons with both high and low average firing rates to the isochronous stimuli. This pattern also held for the other base rates (not shown). To further quantify the effect of SIPIs on firing rate, we calculated the difference in the mean firing rates between SIPI stimuli and the corresponding isochronous stimuli for each base rate. Figure 3b shows the change in firing rate as a function of base rate for all tested neurons ($n = 62$). Positive values indicate increases in firing rate with SIPIs, while negative values indicate suppression. Despite considerable variability, a majority of neurons show increases in firing. A repeated measures, two-way ANOVA of the firing rates revealed significant main effects of both base rate

FIG. 2. Introducing SIPIs to high-rate, isochronous pulse trains change stimulus-driven firing rates of IC neurons. **a–c** Responses from three IC neurons. Temporal responses in the form of raster plots are in the left and center columns for high-rate, isochronous and SIPI stimuli, respectively. These plots show the times of each spike as single dots; the alternating color shades distinguish blocks of

stimulus trials presented at different pulse rates. The times of the extra pulses in the SIPI stimuli are marked with blue lines in the stimulus schematic above the center column. The right column shows the mean firing rates over the stimulus duration as a function of base rate. The SIPI fraction and SIPI rate were held constant at 20 % and 25 pps, respectively.

[$F(4,244)=9.35$, $p<0.001$] and stimulus condition, i.e., with/without SIPIs [$F(1,61)=40.08$, $p<0.001$]. There was also a significant interaction term between base rate and stimulus condition [$F(4,244)=16.81$, $p<0.001$]. The interaction occurs because SIPIs increased firing rates to a larger degree at higher base rates (640–1280 pps) than at lower base rates (320–448 pps). To determine the statistical significance of the change in firing rate for individual neurons, we used bootstrap resampling to construct 99 % confidence intervals for the difference in mean firing rate at each base rate, and calculated the fraction of neurons for which this difference was significantly above or below 0 spike/s. The fraction of neurons showing a significant increase in firing rate with SIPIs increased with the base rate (Fig 3c). At the two highest base rates (896 and 1280 pps), approximately 60 % of the neurons

showed a significant increase. A much smaller fraction showed a significant decrease in firing rate as did the example neuron in Fig. 2c.

The above analyses included data from all recording sessions in both rabbits (Table 1). For a base rate of 640 pps (or 896 pps if 640 was not tested), there was no significant difference between the two rabbits in the mean change in firing rate from introducing SIPIs across the samples of neurons [$t(68)=-1.72$, $p=0.090$]. Thus, SIPIs tended to increase firing rates similarly in both rabbits. We also tested whether the effect of SIPIs varied across recording sessions in each rabbit. There was no significant correlation between the change in firing rate from introducing SIPIs and the time since deafening (and cochlear implantation) for either rabbit B07 [$F(1,58)=2.58$, $p=0.11$] or B05 [$F(1,8)=0.961$, $p=0.36$]. Thus, the effects of SIPIs appear to be stable over time in each rabbit.

FIG. 3. Most IC neurons show increased firing with SIPIs. **a** Scatter plot of the firing rates of 62 neurons to a high-rate, isochronous pulse train (abscissa) vs. the rates for SIPI stimulus (ordinate). The base rate in both cases was 896 pps. The SIPI fraction and SIPI rate were 20 % and 25 pps, respectively. Points in blue represent neurons for which SIPIs caused a significant increase in firing rate ($p < 0.01$, bootstrap test, see “METHODS” section); points in red show neurons for which SIPIs caused a significant decrease in rate. **b**. Change in firing rate resulting from the introduction of SIPIs as a function of base rate for

the same 62 neurons (blue lines). Positive values indicate that SIPIs produced an increase in firing rate over the isochronous condition. The mean value at each pulse rate is marked with red squares. **c**. Fraction of units for which introducing SIPIs produced statistically significant changes in firing rate ($p < 0.01$, bootstrap test, see “METHODS” section) as a function of pulse rate. **d**. Fraction of units with significant synchrony to SIPIs based on the Kuiper statistic KS ($p < 0.001$, Kuiper test)

Temporal Firing Patterns to SIPI Stimuli

A clear trend in the raster plots of Fig. 2 is the temporal patterning of spikes in response to SIPI stimuli. To quantify the degree to which these responses are synchronous with the SIPIs, we constructed period histograms based on the period of SIPIs (e.g., 40 ms for a SIPI rate of 25 pps). Examples are shown in Fig. 4 for the same three neurons as in Fig. 2. The left and center columns show period histograms for the isochronous and short-IPI stimuli, respectively. The right column shows the Kuiper statistic (KS) as a function of base rate for both stimulus conditions. Larger KS indicate greater deviations from a circular uniform distribution, i.e., greater synchrony to the SIPIs. For isochronous stimuli (left column), there is no fundamental periodicity at the SIPI rate, so the period histograms should have a flat envelope. As expected, there was no major envelope modulation for any of the example neurons, resulting in low KS that were not significantly greater than zero. For the 320-pps isochro-

nous stimulus in the left panel of Fig. 4b, the period histogram shows multiple peaks indicating phase locking to the base rate, but the envelope of the period histogram is still mostly flat. The KS statistic computed with the 3.125 ms base rate period was significant in this case (not shown), but the important point for comparison to the SIPI condition is that the KS computed over the 40 ms SIPI period was not significant.

In contrast to the isochronous stimuli, there are prominent peaks in most period histograms for the SIPI stimuli, indicating that spikes tend to occur at specific latencies after the extra pulses. In Fig. 4b, most of the period histograms are bimodal because this neuron often produced spike doublets after a SIPI. These bimodal histograms also yielded highly significant KS . For a base rate of 320 pps in Fig. 4b, the SIPI transiently suppressed the phase locked response to the base rate. This transient suppression also resulted in a significant KS for the short-IPI stimulus. Stronger and prolonged suppression is observed in the histograms of Fig. 4c. This suppres-

FIG. 4. Spikes tend to be temporally synchronized to SIPIs. **a–c** Synchrony analysis for the same neurons as in Fig. 2a–c, respectively. As in Fig. 2, the base rate was varied while the SIPI fraction and SIPI rate were held constant at 20 % and 25 pps, respectively. Period histograms in the left and center columns correspond to isochronous and SIPI stimuli, respectively, while the right column shows the Kuiper test statistic (KS). Period histograms are constructed modulo the period of extra pulse insertion (40 ms for the SIPI rate of 25 pps).

Asterisks in the right column indicate statistically significant KS ($p < 0.001$). Inset: Demonstration of KS calculation for the 640 pps SIPI stimulus with neuron B. The blue trace is the empirical cumulative distribution of spike times modulo each period, and the black diagonal line represents the cumulative uniform distribution. The maximum positive and negative deviations from the uniform distribution are marked with red lines and labeled K^+ and K^- , respectively. KS is the sum of these two values

sion constitutes a significant departure from uniformity as measured by KS . In fact, the KS for SIPI stimuli were significant at every tested base rate in all three neurons ($p < 0.001$, see *'s in the right column of Fig. 4), confirming that extra spiking (or suppression) was temporally synchronous with SIPIs. (The high KS values for isochronous stimuli at 896 and 1280-pps base rates in Fig. 4a are not statistically significant because the firing rates are too low.)

The fraction of neurons with significant KS for SIPI stimuli is plotted as a function of base rate in Fig. 3d. The proportion increases with base rate, and roughly parallels the fraction of neurons that showed an increase in firing rate in Fig. 3b. This similarity suggests that the increased firing rates produced by SIPIs primarily results from extra spiking that is synchronized to the SIPIs. The fraction of synchro-

nized neurons is nevertheless higher than the fraction showing an increase in firing rates, indicating that the temporal firing patterns of neurons may be more sensitive to SIPIs than the overall firing rates. For example, the change in firing rate for the neuron in Fig. 2c was not significant for base rates of 320 and 448 pps, but the synchronization was significant (Fig. 4c).

Comparison with Responses to Low-Rate, Isochronous Pulse Trains

We compared the responses to SIPI stimuli with responses to low-rate, isochronous pulse trains. Since both stimuli often produced synchronized firings, the responses to SIPI stimuli may resemble the responses to low-rate pulse trains when the low

base rate matches the SIPI rate. To test this idea, we varied the SIPI rate from 25 to 200 pps for SIPI stimuli with a 640 pps base rate. These responses were compared with the interpolated responses to isochronous pulse trains at matching base rates (see “METHODS” section). Figure 5a shows the mean firing rates of four example neurons as a function of both the SIPI rate for SIPI stimuli and the base rate for low-rate, isochronous stimuli. The same three neurons from Figs. 2 and 4 are shown, along with a fourth neuron. Neurons A–C showed very similar patterns of firing rates between the two stimulus conditions even though the firing rates tended to increase with pulse rate for Neuron B, decrease for Neuron C, and peak near 100 pps for Neuron A. Neuron D was an exception in that it poorly responded to SIPI stimuli compared to isochronous stimuli for SIPI rates near 100 pps. To quantify the similarity between response patterns to the two stimuli, Fig. 5b shows scatter plots of the firing rates for SIPI stimuli against the

interpolated firing rates to matching low-rate, isochronous pulse trains for the four neurons of Fig. 5a. The orthogonal regression lines (Deming 1943) fit the data closely for neurons A–C (orthogonal $R^2 > 0.98$); for neuron D; however, the fit is not as good (orthogonal $R^2 = 0.80$).

Figure 5c shows the distribution of orthogonal R^2 values, fitted slopes, and intercepts for the 37 neurons for which we collected responses to both SIPI and low-rate, isochronous stimuli. Most neurons showed a strong positive correlation (81 % have orthogonal $R^2 > 0.95$), suggesting the responses to low-rate and SIPI stimuli have similar patterns of dependence on pulse rate. The slope and intercept distributions had a fairly wide spread, but were centered near 1 and 0, respectively, as indicated by the 95 % confidence intervals for the mean. This implies that, in many neurons, the firing rate in response to SIPI stimuli is nearly equal to the firing rate to isochronous stimuli with base rates matching the SIPI rate.

FIG. 5. Responses to SIPI stimuli resemble responses to isochronous low-rate pulse trains. **a** Mean firing rates of four IC neurons as a function of either the base rate (for low-rate, isochronous stimuli, dashed lines) or SIPI rate (for SIPI stimuli, solid lines). Neurons A–C are the same as in Fig. 2a–c, respectively. The SIPI stimuli had a constant base rate of 640 pps and SIPI fraction of 20 %. **b** Scatter plots of firing rates to SIPI stimuli against firing rates to low-rate isochronous stimuli for the same four neurons. The lines are the

orthogonal regression fits to the data; the orthogonal R^2 values are given in the legend. **c** Results of orthogonal regression fits for all tested neurons ($n = 37$). The histograms show the distributions of orthogonal R^2 (left), regression slopes (center), and y -intercepts (right). Markers over the slope and intercept histograms show 95 % bootstrapped confidence intervals for the mean. These intervals contain the values 1 and 0 for the slope and intercept, respectively

Effects of SIPIs on ITD Sensitivity

We next investigated whether the increase in firing rates from introducing SIPIs also leads to improved ITD sensitivity. For comparison, we also characterized ITD sensitivity for low-rate, isochronous pulse trains. Specifically, we used the three stimuli in Fig. 1a (high-rate isochronous pulse trains, SIPI stimuli, and low-rate, isochronous pulse trains) to characterize ITD sensitivity in 56 IC neurons by measuring firing rates as a function of ITD from -2000 to $+2000$ μ s. Most neurons (39/56, 70 %) were tested with a standard SIPI stimulus (base rate = 640 pps, SIPI rate = 25 pps, SIPI fraction = 20 %). The remaining neurons were tested with various combinations (one per neuron) of 640–1280 pps base rates, 25 or 50 pps SIPI rates, and 10 or 20 % SIPI fractions.

Temporal response patterns of an example IC neuron are shown as a function of ITD in Fig. 6a. With the high-rate, isochronous pulse train (640 pps),

the neuron produced a strong onset response followed by weak sustained activity that did not depend on ITD. In contrast, there was strong synchronized spiking to both the low-rate and SIPI stimuli. This synchronized activity was weaker for very negative (ipsilaterally leading) ITDs than for positive and near-zero ITDs. The resulting ITD tuning curves for both SIPI and low-rate, isochronous stimuli (Fig. 6b) were sigmoidal with a preference for contralaterally leading stimuli. ANOVAs verified that the effect of ITD on firing rate was significant for both low-rate [$F(10,88) = 8.94$, $p < 0.001$] and SIPI stimuli [$F(10,88) = 6.35$, $p < 0.001$], but not for high-rate, isochronous stimuli [$F(10,88) = 0.497$, $p = 0.89$]. This was reflected in the higher STVR for low-rate and SIPI stimuli, indicating an increased sensitivity to ITD compared to high-rate isochronous stimuli.

The distributions of STVRs across the neuronal sample (Fig. 6c) show that many neurons have low values (i.e., weak ITD sensitivity) for all three stimuli.

FIG. 6. SIPIs improve neural ITD sensitivity in IC neurons. **a** Raster plots of an IC neuron in response to high-rate, isochronous pulse trains (left), SIPI stimuli (center), and low-rate, isochronous stimuli (right) presented at various ITDs. Extra pulses in SIPI stimuli were placed at the same times as single pulses in the low-rate stimuli (cf. schematics above the raster plots). The SIPI parameters were held constant: base rate = 640 pps, SIPI rate = 25 pps, SIPI fraction = 20 %. **b** Mean firing rates as a function of ITD for the neuron in **a**. **c** ITD STVR values (see “METHODS” section) for all tested neurons

($n = 56$), using the same color codes as in **a** and **b** to denote the different stimulus conditions. The median STVRs are marked with horizontal lines. **d** Percentage of ITD-sensitive units ($n = 56$) for the three stimulus conditions. Sensitivity was determined for each neuron as a significant effect of ITD on mean firing rates with a one-way ANOVA ($p < 0.025$). Color as in **a–c**. **e** Scatter plot of the change in STVR resulting from the introduction of SIPIs against the change in firing rate at 0 μ s ITD across the neuronal sample ($n = 56$). The rank correlation coefficient is Kendall's τ

However, there were more neurons with higher STVRs for low-rate and SIPI stimuli than for high-rate isochronous stimuli. Stimulus condition had a significant effect on the median STVR [Friedman test, $\chi^2(2) = 25.75$, $p < 0.001$]. Post hoc, pairwise comparisons with Bonferroni corrections indicate that the median STVR was significantly larger for both low-rate [Wilcoxon signed-rank test, $W = 229$, $n = 56$, $p < 0.001$] and SIPI stimuli [$W = 212$, $n = 56$, $p < 0.001$] compared to high-rate isochronous stimuli, but the difference in median STVRs between low-rate and SIPI stimuli was not significant [$W = 739$, $n = 56$, $p = 0.63$]. The percentage of neurons with significant ITD sensitivity (Fig. 6d) increased from approximately 7 % with high-rate isochronous stimuli to 34 % and 38 % for SIPI and low-rate stimuli, respectively. Taken together, these results show that the increased spiking caused by the introduction of SIPIs can improve ITD sensitivity and bring it in line with sensitivity to low-rate pulse trains.

A regression analysis was used to test whether the change in firing rate resulting from introducing SIPIs was predictive of the improvement in ITD sensitivity. Figure 6e shows a scatter plot of the difference in ITD STVR between SIPI stimuli and high-rate, isochronous stimuli against the difference in firing rates at 0 μ s ITD between these two stimuli across the neuronal sample. The rank correlation between these values was significant [Kendall's $\tau = 0.26$, $n = 56$, $p = 0.006$], suggesting the increased spiking caused by SIPIs was associated with an increase in ITD sensitivity. However, around 20 % of the neurons showed large increases in firing rate but little increase in STVR. These neurons responded to the SIPIs but were not ITD sensitive, at least when ITD sensitivity was characterized by the overall firing rate. This group of neurons is discussed in more detail in the next section.

The above analyses combined data from all recording sessions in both rabbits. We found no correlation between ITD STVR and the time since deafening/implantation for SIPI stimuli in either animal [B07: $F(1,45) = 1.16$, $p = 0.29$, B05: $F(1,7) = 0.0035$, $p = 0.95$]. The same held true for low-rate, isochronous pulse trains [B07: $F(1,45) = 0.730$, $p = 0.40$, B05: $F(1,7) = 0.0082$, $p = 0.93$]. This lack of dependence of ITD STVR on time post deafening for low-rate, isochronous pulse trains is consistent with earlier results for a larger sample of neurons in rabbit IC (Chung et al. 2016). While there was no effect of time after deafening on STVR in either animal, the median STVR for SIPI stimuli was significantly larger in rabbit B05 (median = 0.197) than in B07 (0.124) [Wilcoxon rank-sum test, $U = 1233$, $n = (47.9)$ $p = 0.018$]. This difference may arise from the sampling of different regions of the IC in the two animals, combined with the small number of neurons tested in B05, although of course we cannot rule out genuine inter-animal differences. Despite these differences, introducing SIPIs caused a significant increase in

the median ITD STVR relative to the high-rate, isochronous condition in each of the two rabbits [B07: $W = 934$, $n = 47$, $p < 0.001$, B05: $W = 45$, $n = 9$, $p = 0.004$]. Moreover, when data from our two animals are combined, the median STVR for low-rate isochronous pulse trains is statistically undistinguishable from the median STVR for comparable stimuli in the rabbit IC study of Chung et al. (2016) [Wilcoxon rank-sum test, $U = 2680$, $n = (56.45)$ $p = 0.23$]. Thus, the pooled data from the present study seem to provide a representative sample of IC neurons with respect to ITD sensitivity.

Effect of Spike Synchrony on ITD Sensitivity

Chung et al. (2016) found that unsynchronized background activity could mask ITD sensitivity to low-rate, isochronous pulse trains (20–40 pps) in IC neurons of unanesthetized rabbits. A similar masking effect could occur with SIPI stimuli since the most frequently tested SIPI rates were 25 and 50 pps. The fact that some of our neurons had synchronized responses to SIPI stimuli, but were not ITD sensitive—where sensitivity was assessed using overall firing rate—is consistent with this hypothesis. The neuron in Fig. 7a is one such example. This neuron shows clear synchronized firing to the SIPIs superimposed on unsynchronized activity. The overall firing rate of this neuron was not ITD sensitive by an ANOVA test [$F(10,99) = 0.708$, $p = 0.72$]. We hypothesized that ITD sensitivity present in the synchronized activity of such neurons to SIPIs may be masked by the high background firing rates.

Chung et al. (2016) used cross-correlation between the stimulus pulse train and the neural spike train to select synchronized spikes, and found that synchronized activity can be ITD sensitive even when the overall firing rate is not. This cross-correlation method has the disadvantage of requiring knowledge of the timing of stimulus pulses. As a more biologically plausible alternative, we used coincidence detection between pairs of spike trains to emphasize synchronized activity and test whether it contains ITD information not present in the overall firing rate for SIPI stimuli. Specifically, our analysis assumes that a central coincidence detector (CD) model neuron receives inputs from two IC neurons and fires only when spikes occur at both inputs within 1 ms of each other (Fig. 7b). Since simultaneous recordings from pairs of IC neurons were unavailable, the coincidence analysis was implemented in two ways: first using pairs of spike trains obtained from the same neuron in response to different presentations of the same stimulus, and second, using spike trains from pairs of non-simultaneously recorded neurons. Figure 7c illustrates how CD analysis for pairs of trials from the same neuron preferentially selects the spikes synchronized

FIG. 7. Single-neuron coincidence detection analysis. **a** Raster plot for an IC neuron that displays pulse-locked spiking to a low-rate isochronous pulse train (25 pps), but no visible effect of ITD on firing rates. **b** Random pairs of spike trains from repeated presentations at the same ITD were selected (blue traces), and then coincident spikes were detected using a running 1-ms window (black boxes). The selected spikes form a new spike train (red trace), which is used for

the same analyses as the original spike train. **c** Temporal firing pattern at the output of the coincidence detector for the neuron in **a**. **d** Mean firing rates based on all spikes (blue) and coincident spikes (red) as a function of ITD for the neuron in **a**. The red trace is the average ITD tuning curve from 50 random repetitions of the coincidence detection process

to SIPIs, thereby revealing a preference for ipsilaterally leading ITDs in this example neuron. The ITD tuning curve at the output of the CD (Fig. 7d) demonstrates that the coincident spiking activity was significantly sensitive to ITD by an ANOVA test [$F(10,99) = 8.84$, $p < 0.001$].

Figure 8 shows the results of the single-neuron coincidence analysis for the 56 neurons in which ITD sensitivity was characterized. For high-rate, isochronous stimuli (Fig. 8a), the median STVR based on coincident spikes was greater than the median STVR based on all spikes [Wilcoxon signed-rank, $W = 424$, $n = 56$, $p = 0.004$], but the fraction of ITD-sensitive units did not increase (Fig. 8b). This lack of effect is consistent with the fact that high-rate, isochronous stimuli rarely produced synchronized firings (Fig. 4). In contrast, coincidence detection significantly increased the fraction of ITD-sensitive neurons from

33 to 55 % and 38 to 64 % for SIPI and low-rate stimuli, respectively. The median STVR was also increased for both SIPI stimuli [$W = 351$, $n = 56$, $p < 0.001$] and low-rate, isochronous stimuli [$W = 166$, $n = 56$, $p < 0.001$]. These increases in STVR are similar to those reported by Chung et al. (2016) for low-rate isochronous pulse trains using cross-correlation between spike trains and stimulus pulses. Overall, these results demonstrate that the synchronized firings to SIPI and low-rate stimuli contain ITD information that is masked in the average firing rate but can be uncovered using a coincidence detection process.

Implementing coincidence detection using pairs of spike trains recorded from the same neuron effectively assumes that the two inputs to the CD have statistically identical response properties, i.e., the same average firing rates, the same temporal firing patterns, and the same ITD tuning. The existence of such idealized pairs is questionable given the large variability in response properties among IC neurons. We therefore tested whether coincidence detection can still enhance ITD sensitivity in the face of cross-neuron variability by implementing a CD that takes as inputs spike trains recorded (non-simultaneously) from two distinct neurons in response to the same stimulus.

Figure 9 shows example results for two pairs of neurons. Panels a and c show the ITD tuning curves of the two input neurons and the CD output for low-rate, isochronous pulse trains. Panels b and d show corresponding data for SIPI stimuli. Responses to high-rate, isochronous pulse trains are not shown because coincidence analysis is less effective for these stimuli. For the neuron pair shown in Fig. 9a, b, the CD output showed improved ITD sensitivity (higher STVR) over the sensitivities of both input neurons. In this example, the average firing rates of the two input neurons were comparable. While both inputs were

Fig. 8. Spike timing contains additional ITD information not present in firing rates for low-rate isochronous pulse trains and SIPI stimuli. **a** Distribution of ITD STVRs across the neuronal sample ($n = 56$) based upon the original spike train (blue) and the product of single-neuron coincidence analysis (red). The median values are marked by horizontal lines. **b** Fraction of ITD-sensitive units (one-way ANOVA, $p < 0.025$) based on original spike train and post-coincidence analysis

FIG. 9. Result of the two-neuron coincidence detection analysis for two pairs of neurons. Each panel shows the ITD tuning curves of each input to the CD (dotted and dashed lines) and the CD output (solid line) for a given stimulus and neuron pair. **a, b** ITD tuning curves to low-rate, isochronous stimuli and SIPI stimuli, respectively

for one neuron pair in which coincidence detection improved the ITD STVR over the STVRs for both inputs. The “better” input is the neuron which had the larger STVR to SIPI stimuli. **c, d** ITD tuning curves for a neuron pair in which the STVR at the CD output was intermediate between the STVRs for the two input neurons

ITD sensitive for low-rate, isochronous stimuli (Fig. 9a), one input showed better ITD tuning than the other for SIPI stimuli (Fig. 9b). The tuning of the better input is both reflected and enhanced in the CD output, which had a higher STVR than the better input for both stimuli. The increase in STVR results from an overall reduction in firing rate that brought the response for negative ITDs close to zero. This pair demonstrates that coincidence analysis can improve ITD sensitivity, even when operating on inputs with different statistical properties.

Figures 9c, d show results for a more typical pair of neurons in which ITD sensitivity at the CD output was intermediate between those of the two inputs. The “worse” input neuron had a much higher firing rate than the “better” input and showed no ITD sensitivity. The ITD tuning curve of the CD output paralleled that of the better input neuron, but with a lower firing rate, resulting in less spiking reliability and lower STVRs compared to the better input. The STVRs at the CD output were significant for both stimuli ($p = 0.041$ for low rate, $p < 0.001$ for SIPI).

The coincidence analysis was applied to 844 pairs of neurons for which responses were measured at matching sets of ITDs. For low-rate, isochronous stimuli, the ITD STVR at the CD output was larger than the STVRs at both inputs in 212 pairs (25.1 %);

for SIPI stimuli, this proportion was 20.7 %. In 53.3 % of pairs, the output STVR for low-rate, isochronous stimuli was between the STVR for the worse input and the STVR for the better input; this proportion was 48.9 % for SIPI stimuli. Thus, coincidence analysis improved ITD sensitivity in a minority of neurons pairs, but typically the sensitivity at the CD output was intermediate between those of the two input neurons. In addition, coincidence analysis was somewhat more effective at improving ITD sensitivity for low-rate pulse trains than for SIPI stimuli.

Coincidence analysis of a neuron pair may fail to improve ITD sensitivity for at least three reasons: (1) The input firing rates may be too low to yield a sufficient number of coincidences so that responses of the CD are weak and unreliable. (2) Spikes from the two input neurons may be poorly synchronized with the stimulus and with each other, again resulting in a low likelihood of coincidences. (3) The ITD tuning curves from the two neurons may be too disparate to yield clear ITD tuning in the CD output. To shed light on the relative importance of these factors, we correlated the ITD STVR at the CD output with metrics quantifying each of the three above factors. Without presenting results in detail for the sake of brevity, we conclude from these analyses that all three factors can affect the effectiveness of coincidence

detection in improving ITD sensitivity, but the synchrony in the spike timing between the two input neurons appears to be the most important one.

Effects of SIPI Rate and SIPI Fraction on Firing Rates

So far, we have shown that introducing SIPIs can increase firing rates and improve ITD sensitivity with a standard set of SIPI parameters (SIPI rate = 25 pps, SIPI fraction = 20 %). To explore the parameter space of the SIPI effect, we measured responses of a subset of neurons when independently varying the SIPI rate and the SIPI fraction. Figure 10a shows the firing rates from the two neurons in Fig. 2a, c as a function of the SIPI fraction (the interval between the two pulses forming a SIPI expressed as a percentage of the base period). The other parameters were held constant (base rate = 640 pps, SIPI rate = 25 pps, ITD = 0). For neuron A, the firing rate decreased with increasing SIPI fraction and approached the rate evoked by a

640-pps, isochronous stimulus (dashed line) for a 50 % SIPI fraction. Neuron C was one of the relatively rare neurons in which introducing SIPIs suppressed firing rates (Fig. 2c). In this neuron, the firing rate increased with increasing SIPI fraction and approached the firing rate evoked by a 640-pps isochronous pulse train for 40–50 % SIPI fractions. In both neurons, the largest changes in firing rate relative to the isochronous condition occurred for the shortest SIPI fractions, although the changes were in opposite directions in the two neurons.

Figure 10b shows the change in firing rate caused by the introduction of SIPIs as a function of SIPI fraction for the 36 neurons in which this parameter was varied. For most neurons, the firing rate increased maximally at the lowest SIPI fraction (10 %) and the effect decreased with increasing IPI. The SIPI fraction had a significant effect on the mean change in firing rate across the neuronal sample in a one-way repeated measures ANOVA [$F(4,140) = 20.02$, $p < 0.001$]. Also, the fraction of neurons that individually showed a

FIG. 10. Extra pulses are most effective at increasing firing rates at low SIPI fractions and intermediate SIPI rates. **a** Mean firing rates to SIPI stimuli as a function of SIPI fraction for the same neurons as in Fig. 2a, c. The base rate and SIPI rate were held constant at 640 and 25 pps, respectively. The dashed lines show the mean firing rates to an isochronous 640 pps pulse train. **b** Change in firing rate resulting

from the introduction of SIPIs for each neuron as a function of SIPI fraction ($n = 36$). The mean change across neurons is marked with red squares. Base rate = 640 pps, SIPI rate = 25 pps. **c** Fraction of units with significant changes in firing rate against SIPI fraction. **d–f** Same as in **a–c**, respectively, but now varying the SIPI rate while holding the SIPI fraction constant at 20 % ($n = 43$)

significant increase in firing rate due to SIPIs decreased with increasing SIPI fraction (Fig. 10c). Among the small set of neurons whose firing rates were suppressed by introducing SIPIs, the suppression was slightly stronger at the 10 % SIPI fraction than at 50 %.

Figure 10d–f illustrate the effect of varying SIPI rate on firing rates while the base rate and SIPI fraction were held at 640 pps and 20 %, respectively. The responses from the same two neurons as in Fig. 10a are plotted in Fig. 10d. In neuron A, the firing rate had a non-monotonic dependence on SIPI rate, reaching a maximum at 100 pps and then falling steeply to approach the rate produced by the isochronous pulse train at 200 pps. For suppressive neuron C, the firing rate was similar to the rate for isochronous pulse trains at the lowest SIPI rate and then decreased monotonically with increasing SIPI rate. The variability in the effects of SIPI rate is apparent in Fig. 10e, which shows the change in firing rate relative to the isochronous condition for 43 neurons. Some neurons showed monotonic increases in firing rate with increasing SIPI rate; others showed monotonic decreases and yet others showed a maximum for a particular rate. For many neurons (e.g., neuron A), the firing rate decreased markedly for SIPI rates between 100 and 200 pps. In particular, some neurons were suppressed by a SIPI rate of 200 pps even though they were not very sensitive to SIPIs at lower rates. Despite the large inter-neuron variability, there was still a significant effect of SIPI rate on the change in firing rate with a one-way repeated measures ANOVA [$F(4,168) = 4.72$, $p = 0.0012$].

The large inter-neuron variability also led to complicated trends in the fraction of neurons showing significant changes in firing rate (Fig. 10f). The fraction of neurons showing a significant increase was maximum for SIPI rates of 50 pps and then decreased, i.e., the pattern was non-monotonic (Fig. 10f). In contrast, the fraction of neurons showing significant suppression increased monotonically with increasing SIPI rate to reach 40 % at 200 pps. Two distinct groups of neurons contributed to this trend: (1) SIPI-sensitive neurons for which 200 pps was above the limit of synchronized firing to SIPIs and (2) neurons that were not sensitive to SIPIs at low SIPI rates but were nevertheless suppressed at higher rates. The marked suppression of responses at the higher SIPI rates resembles the decrease in firing rate frequently observed above 200–300 pps for isochronous pulse trains (Smith and Delgutte 2007; Chung et al. 2014, 2016).

Effect of Incrementing Pulse Amplitude

Lastly, we investigated the limiting case when the SIPI fraction goes to zero, so that the two pulses forming a

SIPI completely overlap, resulting in a doubling of pulse amplitude. More generally, we investigated the effect of incrementing the amplitude of occasional pulses in a high-rate, isochronous, constant-amplitude pulse train by 0 to 6 dB, referred to as the “level increment” (Fig. 11a). The base rate was held at 640 pps, and the rate of incremented pulses was set to 25 pps to match the standard SIPI rate. Figure 11b shows firing rate as a function of the level increment for the same two neurons as in Fig. 2a, b. Both neurons showed large increases in firing rate between 0 and 2 dB, with little or no additional increase from 2 to 6 dB. The firing rates evoked by increments of 2–6 dB were similar to the rates produced by an analogous SIPI stimulus (base rate 640 pps, SIPI rate 25 pps, SIPI fraction 10 %) as marked by the dashed lines.

Figure 11c shows firing rate as a function of level increment for the 27 neurons in which this parameter was varied. Despite substantial inter-neuron variability, the firing rates of many neurons increased from 0 to 2 dB but not from 2 to 6 dB. However, some neurons showed a monotonic increase (or decrease) throughout the 6 dB range of level increments. The level increment had a significant effect on the mean firing rate across the neuronal sample in a one-way repeated measures ANOVA [$F(3,78) = 19.2$, $p < 0.001$]. The relatively small change in mean firing rate between 2 and 6 dB fell within the 95 % confidence interval (gray rectangle) for the mean firing rate produced by the analogous SIPI stimulus (SIPI fraction = 10 %), suggesting a similar mean response for SIPI stimuli and stimuli with 2–6 dB level increments. Similar results were obtained when using the 0 dB condition as a reference to calculate the fraction of neurons with significant changes in firing rate (Fig. 11d): ~60 % of neurons had significant increases in firing rate for 2 dB, with only a minor increase in this fraction at 4 and 6 dB. These percentages are very similar to the percentage for comparable SIPI stimuli, as shown alongside for the same 27 neurons in Fig. 11d.

To further quantify the degree to which the effects of level increments are similar to those of SIPIs, Fig. 11e shows a scatter plot of the changes in firing rate produced by level increments against changes in firing rate for SIPI stimuli for the same 27 neurons, along with best fitting lines obtained by orthogonal regression for each increment. The slopes were significantly larger than zero for each level increment [2 dB: $t(25) = 3.76$, $p < 0.001$, 4 dB: $t(25) = 2.78$, $p = 0.010$, 6 dB: $t(25) = 2.68$, $p = 0.013$]. The strongest correlation was obtained for the 2 dB increment (orthogonal $R^2 = 0.86$), with only slightly lower values for the 4 dB and 6 dB increments, respectively (orthogonal $R^2 = 0.81$ and 0.80). This suggests a 2 dB

FIG. 11. The effect of introducing SIPIs resembles the effect of incrementing the amplitudes of selected pulses. **a** Schematic of "level-increment" stimuli, where instead of adding extra pulses, the amplitude of occasional pulses is increased. **b** Mean firing rate as a function of level increment for the same neurons as in Fig. 2a, b. The base rate was held constant at 640 pps and the increment rate at 25 pps (40 ms between level increments). The dashed lines are the firing rates for an analogous SIPI stimulus (base rate = 640 pps, SIPI rate = 25 pps, SIPI fraction = 10%). **c** Mean firing rate for each neuron as function of the level increment ($n = 27$). The mean is marked with red squares. Base rate = 640 pps, increment rate = 25

pps. The gray bar represents the bootstrapped 95% confidence interval for the mean firing rate with the analogous SIPI stimulus (base rate = 640 pps, SIPI rate = 25 pps, SIPI fraction = 10%). **d** Fraction of neurons with significant change in firing rate as a function of level increment ($n = 27$), using a reference of 0 dB. For comparison, the fraction of significant changes is shown for the analogous SIPI stimulus for the same 27 neurons. **e** Scatter plot of the change in firing rates for level increment stimuli against change in firing rate for SIPI stimuli across the neuronal sample. Best fit lines by orthogonal regression are shown for each level increment

increase in pulse amplitude produced the most similar rate responses to the analogous SIPI stimulus.

DISCUSSION

We measured responses of IC neurons to high-rate pulse trains with SIPIs in unanesthetized rabbits with bilateral cochlear implants. Consistent with earlier studies of IC neurons, high-rate isochronous pulse trains (≥ 320 pps) rarely produced sustained, synchronized responses (Smith and Delgutte 2007; Hancock et al. 2012; Chung et al. 2014). Introducing SIPIs significantly increased firing rates for ~60% of neurons, and the additional spikes were synchronized to the SIPIs. This increase in firing rate uncovered latent ITD sensitivity in these neurons, which in some cases only became evident after selecting the synchronized spikes with a coincidence analysis. These results are consistent with the effects of jittered pulse trains on IC neurons in anesthetized cats, where increases in firing rates and improvements in ITD sensitivity were observed in about half the neurons

(Hancock et al. 2012). While direct comparisons are difficult due to species differences and the confound of anesthesia (Chung et al. 2014, 2016), it is likely that these results reflect a similar underlying mechanism. Hancock et al. (2012) were able to predict the occurrence of spikes based on the timing of occasional SIPIs in the jittered pulse trains, and we have confirmed that spikes occur with well-defined latencies after SIPIs (Figs. 3d and 4). Overall, these findings support the idea that high-rate stimulation places most IC neurons in an adapted state, but the adapted threshold can nevertheless be exceeded by a transient increase in stimulation strength through either SIPIs or level increments.

Mechanism of the SIPI Effect

The precise mechanism of the SIPI effect is unknown. Hancock et al. (2012) suggested a role for low-voltage-activated K^+ (I_{KLVA}) currents, which are present in auditory brainstem neurons of the ITD processing circuit, including the auditory nerve (Mo et al. 2002), bushy cells in the ventral cochlear nucleus (Manis and

Marx 1991; Rothman and Manis 2003; Cao et al. 2007), the medial nucleus of the trapezoid body (Brew and Forsythe 1995), the medial superior olive, or MSO (Smith 1995; Svirskis et al. 2002; Scott et al. 2005), the lateral superior olive (Barnes-Davies et al. 2004), and possibly the IC itself (Sivaramakrishnan and Oliver 2001). When isolated in vitro, this current produces a shunting effect by increasing membrane conductance near rest, making these neurons capable of depolarizing and repolarizing rapidly in response to excitatory post-synaptic currents (EPSC). In MSO cells, I_{KLVA} is thought to shape the dendritic inputs to facilitate the binaural coincidence detection that is responsible for ITD sensitivity (Svirskis et al. 2004; Mathews et al. 2010). While the role of I_{KLVA} with cochlear implant stimulation has not been studied experimentally, kinetics of I_{KLVA} currents can qualitatively explain the firing rate adaptation observed with high-rate isochronous stimulation in models of electrically stimulated MSO cells (Colburn et al. 2009; Chung et al. 2015).

We suggest that the EPSCs produced by two pulses forming a SIPI summate quickly enough to overcome the counteracting sustained I_{KLVA} current produced by high-rate stimulation and thereby depolarize neurons sufficiently to elicit spikes. The observed increase in firing rates with decreasing SIPI fraction (Fig. 10a–c) is consistent with this mechanism, since the extra pulse is moved temporally closer to the preceding pulse as the SIPI fraction decreases. This mechanism is also consistent with the stronger effect of SIPIs observed at higher base rates (Fig. 3) since, for a given SIPI fraction, the interval between the two pulses forming a SIPI (in μsec) decreases with increasing base rate. Additionally, this mechanism is consistent with the similar effects observed with the level-increment stimuli (Fig. 11), since this would provide even less time for I_{KLVA} shunting to initiate. The suppression of firing rates with SIPIs observed in a minority of neurons (e.g., Fig 2c) could arise through inhibitory inputs from neurons that show increased firing with SIPIs. Such inhibitory inputs could come either from inhibitory interneurons in the IC or from ascending projections, e.g., from the dorsal nucleus of the lateral lemniscus (DNLL) or the ipsilateral lateral superior olive (LSO). Thus, a mechanism involving I_{KLVA} currents is broadly consistent with our findings, although it is not known at what stage(s) in the auditory brainstem these currents would produce the SIPI effect. Other nonlinear membrane channels frequently expressed in the ITD circuit (such as hyperpolarization-activated current I_h) may also play a role.

Effect of SIPI Rate and Amplitude Modulation

The responses of IC neurons to high-rate pulse trains with SIPIs were similar to responses to low-rate,

isochronous pulse trains, with respect to both ITD sensitivity (Fig. 6) and the dependence of firing rates on stimulation rate (Fig. 5). Only a small fraction of neurons (e.g., neuron D in Fig. 5) showed large differences in the responses to the two stimuli. Because ITD sensitivity to isochronous pulse trains degrades for pulse rates above 200–300 pps in most IC neurons (Smith & Delgutte 2007; Chung et al. 2016), we expect that ITD sensitivity to short-IPI stimuli would also degrade for SIPI rates ≥ 200 –300 pps. Although this prediction was not directly tested, we did observe clear suppression of firing rates in many neurons when the SIPI rate was increased from 100 to 200 pps (Fig. 10f). Since changes in firing rate from introducing SIPIs can partially predict ITD sensitivity (Fig. 6e), the suppression of firing rates at higher SIPI rates suggests that ITD sensitivity may also degrade.

There were strong similarities between the responses to SIPI stimuli and level-increment stimuli. Even a 2-dB increase in pulse amplitude produced similar increases in firing rate as an extra pulse forming a SIPI (Fig. 11). These sparse level increments could be considered an extreme form of amplitude modulation (AM). Sinusoidal AM of high-rate, isochronous pulse trains has been shown to increase synchronized firing and improve ITD sensitivity in about half of IC neurons (Smith and Delgutte 2008). However, Hancock et al. (2017) found that electric pulse trains with sinusoidally AM are not very effective stimuli for IC neurons in anesthetized cats. Most neurons respond better to modulation waveforms with long intervals of silence and brief high-amplitude segments. Studies of IC neurons with high-carrier-frequency AM tones in normal hearing animals found greater ITD sensitivity with envelope shapes that contain steeper slopes than sinusoids such as transposed tones (Griffin et al. 2005) or square waves (Dietz et al. 2016). Studies of perceptual ITD sensitivity in both normal hearing and CI subjects also show better performance for modulation waveforms with short attack times and low-duty cycles rather than with sinusoidal modulations (Normal hearing: Bernstein and Trahiotis 2002; Klein-Hennig et al. 2011; CI: Laback et al. 2011).

Comparison with Perceptual Data from CI Users

The present neurophysiological results from the rabbit IC closely parallel results from a study of perceptual ITD sensitivity with SIPI stimuli in human CI users (Srinivasan et al. 2018). Specifically, Srinivasan et al. showed that introducing SIPIs to a 1000-pps isochronous pulse train improved ITD-based left/right discrimination performance in seven of eight bilaterally implanted listeners. The largest improvements in performance were observed for low SIPI rates and short SIPI fractions, where the

performance was comparable to that for jittered pulse trains (Laback and Majdak 2008). The monotonic improvement in performance with decreasing SIPI fraction (Fig. 3 in Srinivasan et al. 2018) is consistent with the increasing trend in neural firing rates (Fig. 10b) and the correlation between increased firing rate and improved ITD sensitivity (Fig. 6e). Regarding the effect of SIPI rate, a steep drop in left/right discrimination performance occurred between 100 and 200 pps (their Fig. 4), paralleling the decrease in firing rate observed in many IC neurons (our Fig. 10b).

In a separate experiment, Srinivasan et al. (2018) showed that incrementing the amplitude of occasional pulses by 3 dB in a 1000-pps isochronous stimulus produced improvements in left/right discrimination performance comparable to those of introducing SIPIs. This parallels our finding that incrementing the level of occasional pulses by as little as 2 dB produced similar increases in firing rate as introducing SIPIs. However, the perceptual effects of SIPI and level increments were not identical in that increments but not SIPIs produced an increase in loudness even though the two stimuli have the same total energy when the increment is 3 dB. The lack of an effect of SIPIs on loudness is intriguing because SIPIs increased firing rate in a majority of IC neurons and loudness has long been assumed to be related to the total neural activity evoked by a sound (e.g., Fletcher and Munson 1933). However, it is possible that the neurons that contribute to loudness form a distinct subset from neurons for which SIPIs increase firing rates and improve ITD sensitivity. For example, Shofner and Dye (1989) have shown that regular-firing chopper neurons in the ventral cochlear nucleus convey more information about sound level than primary-like neurons. Since primary-like response patterns are recorded from bushy cells, which form the main excitatory projection to the MSO, while chopper patterns are recorded from stellate cells, which do not participate in brainstem binaural circuits, the findings of Shofner and Dye (1989) are consistent with the notion of separate neural populations for loudness and binaural processing.

Role of Spike Timing

In addition to increasing firing rates, SIPIs elicited spikes with precise latencies (Fig. 4), and our coincidence detection analysis demonstrated that these synchronized spikes can be especially sensitive to ITD (Figs. 7, 8 and 9). The strong background activity often present in the IC of unanesthetized rabbits can “mask” the ITD information available in synchronized spikes when sensitivity is quantified by the overall firing rate (Chung et al. 2016). The cross-correlation analysis of Chung et al. (2016) utilized stimulus information to extract synchronized spikes,

whereas our analysis used only information from two input spike trains irrespective of the stimulus. Coincidence analysis was most effective at improving ITD sensitivity when the two inputs to the CD had matched firing rates, temporal response patterns, and ITD tuning, as shown by the idealized case when the two inputs were selected from responses of one neuron to different trials of the same stimulus (Fig. 8). Coincidence analysis could still improve ITD sensitivity when the two inputs to the CD came from different neurons and therefore differed in statistical properties (Fig. 9), although the ITD sensitivity at the CD output was more typically intermediate between the sensitivities of the two input neurons when neuron pairs were selected at random. Coincidence detection of spikes from multiple neurons combined with a Hebbian-type mechanism to select the most effective combinations of inputs could serve as a general mechanism to optimize the extraction of ITD information in the presence of non-synchronized spiking.

The extent to which higher auditory centers extract spike timing information is unknown, but coincidence detection is a common dendritic computation throughout the brain (London and Häusser 2005). In normal hearing animals, the first spike latencies of most auditory cortical neurons to tone stimuli have standard deviations (jitter) below 1 ms, comparable to those of auditory nerve fibers (Heil and Irvine 1997), suggesting cortical neurons may have the temporal precision required for coincidence detection. Although the ability of neurons to phase lock to acoustic stimuli tends to degrade along the ascending auditory pathway (Joris et al. 2004), synchronized responses to click trains have been observed at rates > 100 Hz in both the auditory thalamus (Bartlett and Wang 2007) and auditory cortex (Lu et al. 2001) of awake marmosets. Synchronized responses to electric pulse trains have also been observed up to ~100 Hz in the auditory cortex of deaf marmosets with cochlear implants (Johnson et al. 2017). This limit is near the upper cutoff of the SIPI effect with respect to SIPI rate (Fig. 10f). Thus, it is plausible that neurons central to the IC could extract ITD information present in the synchronized firings of IC neurons via a coincidence mechanism.

Implications for CI Stimulation Strategies

Our results support the idea that SIPIs could be incorporated in a CI stimulation strategy to improve perceptual ITD sensitivity while still maintaining the high rates of stimulation important for transmitting speech information (Loizou et al. 2000). Both jittering the timing of pulses in high-rate pulse trains (Laback and Majdak 2008) and introducing SIPIs (Srinivasan et al. 2018) have been shown to improve perceptual ITD sensitivity in CI users. A jittered pulse train will contain SIPIs at random times, but placing

SIPIs at specific times may avoid distorting the envelope representation of speech. For example, SIPIs could be placed in the peaks or on the rising edges of the amplitude modulations at the fundamental frequency of voicing. Similar benefits for ITD processing might also be obtained by incrementing the amplitudes of selected pulses in modulated pulse trains, but, unlike SIPIs, amplitude increments have the disadvantage of altering the loudness of constant-amplitude pulse trains and might also distort the perception of the envelope modulations important for speech (Srinivasan et al. 2018).

Adding SIPIs or level increments can be thought of as a form of envelope enhancement that presents an alternative to directly coding the temporal fine structure, which has been proposed to improve ITD sensitivity with limited success so far (van Hoesel and Tyler 2003; van Hoesel et al. 2008; Riss et al. 2008, 2014). An extreme form of envelope enhancement is the Fundamental Asynchronous Stimulus Timing strategy (“FAST”), a variable pulse rate strategy that only places pulses at the peak of envelope modulations (Smith et al. 2014). This strategy uses low pulse rates by design, so the question remains whether representing the full envelope shape with a high-rate pulse train while emphasizing envelope peaks with SIPIs would improve speech perception over a low-rate strategy like FAST. Mixed-rate strategies using temporal fine structure on apical channels and amplitude modulation of a high-rate carrier in basal channels can also improve ITD discrimination, but lead to slightly lower speech recognition scores relative to a standard continuous interleaved sampling strategy (Churchill et al. 2014). SIPIs or level increments could possibly be combined with this mixed strategy in the basal channels.

This work is a first investigation into the feasibility of using SIPIs to improve neural and perceptual ITD sensitivities with CIs. Future work will test whether the effects of SIPIs observed with constant-amplitude pulse trains also occur with AM pulse trains. It will also be important to investigate how SIPIs interact with the existing envelope representation as produced by CI processors with speech inputs. There are other concerns as well, such as how SIPIs could be incorporated into a multi-electrode strategy. If SIPIs can enhance the ITD sensitivity of CI subjects without degrading speech reception, then a SIPI strategy could significantly increase the benefit of bilateral CIs.

ACKNOWLEDGEMENTS

We thank Camille Shaw and Melissa McKinnon for technical assistance, Michael Kaplan for advice regarding cochlear implantation, and Cochlear Ltd. for providing the cochlear implants.

Funding Information This work was supported by NIH grants R01 DC00575 (BD), P30 DC005209, and F31 DC014873 (BDB) and the Hearing Health Foundation (Emerging Research Grant, YC).

COMPLIANCE WITH ETHICAL STANDARDS

Conflict of Interest The authors declare that they have no conflicts of interest.

REFERENCES

- ARONOFF JM, YOON Y-S, FREED DJ, VERMIGLIO AJ, PAL I, SOLI SD (2010) The use of interaural time and level difference cues by bilateral cochlear implant users. *J Acoust Soc Am* 127:EL87–EL92
- BARNES-DAVIES M, BARKER MC, OSMANI F, FORSYTHE ID (2004) Kv1 currents mediate a gradient of principal neuron excitability across the tonotopic axis in the rat lateral superior olive. *Eur J Neurosci* 19:325–333
- BARTLETT EL, WANG X (2007) Neural representations of temporally modulated signals in the auditory thalamus of awake primates. *J Neurophysiol* 97:1005–1017
- BERNSTEIN LR, TRAHOTIS C (2002) Enhancing sensitivity to interaural delays at high frequencies by using “transposed stimuli”. *J Acoust Soc Am* 112:1026
- BREW HM, FORSYTHE ID (1995) Two voltage-dependent K⁺ conductances with complementary functions in postsynaptic integration at a central auditory synapse. *J Neurosci* 15:8011–8022
- CAO X-J, SHATADAL S, OERTEL D (2007) Voltage-sensitive conductances of bushy cells of the mammalian ventral cochlear nucleus. *J Neurophysiol* 97:3961–3975
- CHUNG Y, DELGUTTE B, COLBURN HS (2015) Modeling binaural responses in the auditory brainstem to electric stimulation of the auditory nerve. *J Assoc Res Otolaryngol* 16:135–158
- CHUNG Y, HANCOCK KE, DELGUTTE B (2016) Neural coding of interaural time differences with bilateral cochlear implants in unanesthetized rabbits. *J Neurosci* 36:5520–5531
- CHUNG Y, HANCOCK KE, NAM S-I, DELGUTTE B (2014) Coding of electric pulse trains presented through cochlear implants in the auditory midbrain of awake rabbit: comparison with anesthetized preparations. *J Neurosci* 34:218–231
- CHURCHILL TH, KAN A, GOUELL MJ, LITOVSKY RY (2014) Spatial hearing benefits demonstrated with presentation of acoustic temporal fine structure cues in bilateral cochlear implant listeners. *J Acoust Soc Am* 136:1246–1256
- COLBURN HS, CHUNG Y, ZHOU Y, BRUGHERA A (2009) Models of brainstem responses to bilateral electrical stimulation. *J Assoc Res Otolaryngol* 10:91–110
- COLBURN HS, HAN YA, CULOTTA CP (1990) Coincidence model of MSO responses. *Hear Res* 49:335–346
- DEMING WE (1943) STATISTICAL ADJUSTMENT OF DATA. JOHN WILEY & SONS, NEW YORK
- DIETZ M, WANG L, GREENBERG D, McALPINE D (2016) Sensitivity to interaural time differences conveyed in the stimulus envelope: estimating inputs of binaural neurons through the temporal analysis of spike trains. *J Assoc Res Otolaryngol* 17:313–330
- FLETCHER H, MUNSON WA (1933) Loudness, its definition, measurement and calculation. *Bell Labs Tech J* 12:377–430
- FRANKEN TP, BREMEN P, JORIS PX (2014) Coincidence detection in the medial superior olive: mechanistic implications of an analysis of

- input spiking patterns. *Front Neural Circuits* 8:42
- GOLDBERG J, BROWN P (1969) Response of binaural neurons of dog superior olivary complex to dichotic tonal stimuli: some physiological mechanisms of sound localization. *J Neurophysiol* 32:613–636
- GRIFFIN SJ, BERNSTEIN LR, INGHAM NJ, McALPINE D (2005) Neural sensitivity to interaural envelope delays in the inferior colliculus of the guinea pig. *J Neurophysiol* 93:3463–3478
- HAFTER E, BUELL T (1990) Restarting the adapted binaural system. *J Acoust Soc Am* 88:806–812
- HANCOCK KE, CHUNG Y, DELGUTTE B (2013) Congenital and prolonged adult-onset deafness cause distinct degradations in neural ITD coding with bilateral cochlear implants. *J Assoc Res Otolaryngol* 14:393–411
- HANCOCK KE, CHUNG Y, DELGUTTE B (2012) Neural ITD coding with bilateral cochlear implants: effect of binaurally coherent jitter. *J Neurophysiol* 108:714–728
- HANCOCK KE, CHUNG Y, MCKINNEY MF, DELGUTTE B (2017) Temporal envelope coding by inferior colliculus neurons with cochlear implant stimulation. *J Assoc Res Otolaryngol* 18:771–788
- HANCOCK KE, NOEL V, RUGO DK, DELGUTTE B (2010) Neural coding of interaural time differences with bilateral cochlear implants: effects of congenital deafness. *J Neurosci* 30:14068–14079
- HEIL P, IRVINE DR (1997) First-spike timing of auditory-nerve fibers and comparison with auditory cortex. *J Neurophysiol* 78:2438–2454
- JACKSON JE (1991) A user's guide to principal components. John Wiley & Sons, Inc., Hoboken
- JOHNSON LA, DELLA SANTINA CC, WANG X (2017) Representations of Time-Varying Cochlear Implant Stimulation in Auditory Cortex of Awake Marmosets (*Callithrix jacchus*). *J Neurosci* 37:7008–7022
- JORIS P, SCHREINER C, REES A (2004) Neural processing of amplitude-modulated sounds. *Physiol Rev* 84:541–577
- KAN A, LITOVSKY RY, GOUELL MJ (2015) Effects of interaural pitch matching and auditory image centering on binaural sensitivity in cochlear implant users. *Ear Hear* 36:e62–e68
- KAN A, STOELEB C, LITOVSKY RY, GOUELL MJ (2013) Effect of mismatched place-of-stimulation on binaural fusion and lateralization in bilateral cochlear-implant users. *J Acoust Soc Am* 134:2923–2936
- KLEIN-HENNIG M, DIETZ M, HOHMANN V, EWERT SD (2011) The influence of different segments of the ongoing envelope on sensitivity to interaural time delays. *J Acoust Soc Am* 129:3856–3872
- KUIPER NH (1960) Tests concerning random points on a circle. *Indag Math* 63:38–47
- LABACK B, EGGER K, MAJDAK P (2015) Perception and coding of interaural time differences with bilateral cochlear implants. *Hear Res* 322:138–150
- LABACK B, MAJDAK P (2008) Binaural jitter improves interaural time-difference sensitivity of cochlear implant users at high pulse rates. *Proc Natl Acad Sci U S A* 105:814–817
- LABACK B, MAJDAK P, BAUMGARTNER W-D (2007) Lateralization discrimination of interaural time delays in four-pulse sequences in electric and acoustic hearing. *J Acoust Soc Am* 121:2182–2191
- LABACK B, ZIMMERMANN I, MAJDAK P, BAUMGARTNER WD, POK SM (2011) Effects of envelope shape on interaural envelope delay sensitivity in acoustic and electric hearing. *J Acoust Soc Am* 130:1515–1529
- LITOVSKY RY, GOUELL MJ, GODAR S, GRIECO-CALUB T, JONES GL, GARADAT SN, AGRAWAL S, KAN A, TODD A, HESS C, MISURELLI S (2012) Studies on bilateral cochlear implants at the University of Wisconsin's Binaural Hearing and Speech Laboratory. *J Am Acad Audiol* 23:476–494
- LITVAK L, DELGUTTE B, EDDINGTON D (2001) Auditory nerve fiber responses to electric stimulation: modulated and unmodulated pulse trains. *J Acoust Soc Am* 110:368–379
- LOIZOU PC, POROY O, DORMAN M (2000) The effect of parametric variations of cochlear implant processors on speech understanding. *J Acoust Soc Am* 108:790–802
- LONDON M, HÄUSSER M (2005) Dendritic computation. *Annu Rev Neurosci* 28:503–532
- LONG CJ, EDDINGTON DK, COLBURN HS, RABINOWITZ WM (2003) Binaural sensitivity as a function of interaural electrode position with a bilateral cochlear implant user. *J Acoust Soc Am* 114:1565–1574
- LU T, LIANG L, WANG X (2001) Temporal and rate representations of time-varying signals in the auditory cortex of awake primates. *Nat Neurosci* 4:1131–1138
- MANIS PB, MARX SO (1991) Outward currents in isolated ventral cochlear nucleus neurons. *J Neurosci* 11:2865–2880
- MATHEWS PJ, JERCOG PE, RINZEL J, SCOTT LL, GOLDING NL (2010) Control of submillisecond synaptic timing in binaural coincidence detectors by K(v)1 channels. *Nat Neurosci* 13:601–609
- MO Z-L, ADAMSON CL, DAVIS RL (2002) Dendrotoxin-sensitive K(+) currents contribute to accommodation in murine spiral ganglion neurons. *J Physiol* 542:763–778
- POON BB, EDDINGTON DK, NOEL V, COLBURN HS (2009) Sensitivity to interaural time difference with bilateral cochlear implants: development over time and effect of interaural electrode spacing. *J Acoust Soc Am* 126:806–815
- RISS D, ARNOLDNER C, BAUMGARTNER W-D, KAIDER A, HAMZAVI JS (2008) A new fine structure speech coding strategy: speech perception at a reduced number of channels. *Otol Neurotol* 29:784–788
- RISS D, HAMZAVI J, BLINER M ET AL (2014) FS4, FS4-p, and FSP: a 4-month crossover study of 3 fine structure sound-coding strategies. *Ear Hear* 35:e272–e281
- ROTHMAN JS, MANIS PB (2003) Differential expression of three distinct potassium currents in the ventral cochlear nucleus. *J Neurophysiol* 89:3070–3082
- SCOTT LL, MATHEWS PJ, GOLDING NL (2005) Posthearing developmental refinement of temporal processing in principal neurons of the medial superior olive. *J Neurosci* 25:7887–7895
- SEEBER BU, FASTL H (2008) Localization cues with bilateral cochlear implants. *J Acoust Soc Am* 123:1030–1042
- SHEK J, WEN G, WISNIEWSKI H (1986) Atlas of the rabbit brain and spinal cord. S. Karger AG, Staten Island, NY
- SHOFNER WP, DYE RH JR (1989) Statistical and receiver operating characteristic analysis of empirical spike-count distributions: quantifying the ability of cochlear nucleus units to signal intensity changes. *J Acoust Soc Am* 86:2172–2184
- SIVARAMAKRISHNAN S, OLIVER DL (2001) Distinct K currents result in physiologically distinct cell types in the inferior colliculus of the rat. *J Neurosci* 21:2861–2877
- SMITH PH (1995) Structural and functional differences distinguish principal from nonprincipal cells in the guinea pig MSO slice. *J Neurophysiol* 73:1653–1667
- SMITH ZM, DELGUTTE B (2007) Sensitivity to interaural time differences in the inferior colliculus with bilateral cochlear implants. *J Neurosci* 27:6740–6750
- SMITH ZM, DELGUTTE B (2008) Sensitivity of inferior colliculus neurons to interaural time differences in the envelope versus the fine structure with bilateral cochlear implants. *J Neurophysiol* 99:2390–2407
- SMITH ZM, KAN A, JONES HG, BUHR-LAWLER M, GODAR SP, LITOVSKY RY (2014) Hearing better with interaural time differences and bilateral cochlear implants. *J Acoust Soc Am* 135:2190–2191
- SRINIVASAN S, LABACK B, MAJDAK P, DELGUTTE B (2018) Introducing short interpulse intervals in high-rate pulse trains enhances binaural timing sensitivity in electric hearing. *J Assoc Res Otolaryngol* 19:301–315
- SVIRSKIS G, KOTAK V, SANES DH, RINZEL J (2002) Enhancement of signal-to-noise ratio and phase locking for small inputs by a low-threshold outward current in auditory neurons. *J Neurosci* 22:11019–11025

- SVIRSKIS G, KOTAK V, SANES DH, RINZEL J (2004) Sodium along with low-threshold potassium currents enhance coincidence detection of subthreshold noisy signals in MSO neurons. *J Neurophysiol* 91:2465–2473
- TILLEIN J, HUBKA P, SYED E, HARTMANN R, ENGEL AK, KRAL A (2010) Cortical representation of interaural time difference in congenital deafness. *Cereb Cortex* 20:492–506
- TIRKO NN, RYUGO DK (2012) Synaptic plasticity in the medial superior olive of hearing, deaf, and cochlear-implanted cats. *J Comp Neurol* 520:2202–2217
- VAN HOESEL R, BÖHM M, PESCH J, VANDALI A, BATTMER RD, LENARZ T (2008) Binaural speech unmasking and localization in noise with bilateral cochlear implants using envelope and fine-timing based strategies. *J Acoust Soc Am* 123:2249–2263
- VAN HOESEL RJM (2007) Sensitivity to binaural timing in bilateral cochlear implant users. *J Acoust Soc Am* 121:2192–2206
- VAN HOESEL RJM (2008) Observer weighting of level and timing cues in bilateral cochlear implant users. *J Acoust Soc Am* 124:3861–3872
- VAN HOESEL RJM (2012) Contrasting benefits from contralateral implants and hearing aids in cochlear implant users. *Hear Res* 288:100–113
- VAN HOESEL RJM, JONES GL, LITOVSKY RY (2009) Interaural time-delay sensitivity in bilateral cochlear implant users: effects of pulse rate, modulation rate, and place of stimulation. *J Assoc Res Otolaryngol* 10:557–567
- VAN HOESEL RJM, TYLER RS (2003) Speech perception, localization, and lateralization with bilateral cochlear implants. *J Acoust Soc Am* 113:1617–1630
- WANG GI, DELGUTTE B (2012) Sensitivity of cochlear nucleus neurons to spatio-temporal changes in auditory nerve activity. *J Neurophysiol* 108:3172–3195