Neural Coding of Interaural Time Differences with Bilateral Cochlear Implants in Unanesthetized Rabbits

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Although bilateral cochlear implants (CIs) provide improvements in sound localization and speech perception in noise over unilateral CIs, bilateral CI users' sensitivity to interaural time differences (ITDs) is still poorer than normal. In particular, ITD sensitivity of most CI users degrades with increasing stimulation rate and is lacking at the high carrier pulse rates used in CI processors to deliver speech information. To gain a better understanding of the neural basis for this degradation, we characterized ITD tuning of single neurons in the inferior colliculus (IC) for pulse train stimuli in an unanesthetized rabbit model of bilateral CIs. Approximately 73% of IC neurons showed significant ITD sensitivity in their overall firing rates. On average, ITD sensitivity was best for pulse rates near 80–160 pulses per second (pps) and degraded for both lower and higher pulse rates. The degradation in ITD sensitivity at low pulse rates was caused by strong, unsynchronized background activity that masked stimulus-driven responses in many neurons. Selecting synchronized responses by temporal windowing revealed ITD sensitivity in these neurons. With temporal windowing, both the fraction of ITD-sensitive neurons and the degree of ITD sensitivity decreased monotonically with increasing pulse rate. To compare neural ITD sensitivity to human performance in ITD discrimination, neural just-noticeable differences (JNDs) in ITD were computed using signal detection theory. Using temporal windowing at lower pulse rates, and overall firing rate at higher pulse rates, neural ITD JNDs were within the range of perceptual JNDs in human CI users over a wide range of pulse rates.

Key words: binaural hearing; cochlear implant; inferior colliculus; interaural time difference; temporal coding

Significance Statement

Many profoundly deaf people wearing cochlear implants (CIs) still face challenges in everyday situations, such as understanding conversations in noise. Even with CIs in both ears, they have difficulty making full use of subtle differences in the sounds reaching the two ears [interaural time difference (ITD)] to identify where the sound is coming from. This problem is especially acute at the high stimulation rates used in clinical CI processors. This study provides a better understanding of ITD processing with bilateral CIs and shows a parallel between human performance in ITD discrimination and neural responses in the auditory midbrain. The present study is the first report on binaural properties of auditory neurons with CIs in unanesthetized animals.

Introduction

Bilateral cochlear implants (CIs) are an increasingly common treatment for severe to profound hearing loss with the goal of

providing binaural benefits enjoyed by normal-hearing listeners. Although bilateral CIs provide benefits for sound localization and speech reception in noise (for review, van Hoesel, 2012), binaural performance of bilateral CI users is still well below that of normal-hearing listeners. Binaural benefits from bilateral CIs largely result from the listeners' ability to use interaural level differences (ILDs) for sound localization (Grantham et al., 2008; Seeber and Fastl, 2008) and to take advantage of the acoustic head shadow to attend to the ear with the most favorable signal-to-noise ratio in noisy environments (Litovsky et al., 2006; Ricketts et al., 2006). Bilateral CI users' sensitivity to interaural time differences (ITDs) is highly dependent on the subject and stimulus waveform, and poorer than in normal-hearing subjects on the average (for review, Laback et al., 2015; Kan and Litovsky, 2015).

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A major limiting factor on ITD sensitivity for bilateral CI listeners is the rate of stimulation. ITD discrimination thresholds for constant-amplitude pulse trains degrade with increasing pulse rate above 100–200 pulses per second (pps) even in good-performing bilateral CI listeners (van Hoesel, 2007; van Hoesel et al., 2009), and ITD sensitivity is altogether lacking at the high carrier pulse rates used in CI processors to deliver speech information. The neural mechanisms underlying this degradation in ITD sensitivity are unclear. Studies in animal models of bilateral CIs (Smith and Delgutte, 2007, 2008; Hancock et al., 2010, 2013) have shown that although ITD sensitivity of inferior colliculus (IC) neurons in acutely deafened animals can be as good as in normal-hearing animals at low pulse rates, this sensitivity degrades at higher pulse rates, where most neurons respond only to stimulus onset, and additional degradations occur in congenitally deaf animals. However, the dependence of neural ITD sensitivity on pulse rate has not been quantified in a way that can be directly compared to perceptual ITD discrimination thresholds of CI listeners. Moreover, the previous neurophysiological studies were performed in anesthetized animals. We show that IC neurons in unanesthetized rabbit exhibit greater sustained responses and enhanced temporal coding of high-rate pulse trains compared with results from anesthetized preparations (Chung et al., 2014). Similar effects of anesthesia have been reported in the auditory cortex with CI stimulation (Johnson et al., 2011; Kirby and Middlebrooks, 2012). Moreover, ITD tuning of IC neurons in normal-hearing rabbits can be altered by barbiturate anesthesia (Kuwada et al., 1989).

We characterized the ITD sensitivity of IC neurons in an unanesthetized rabbit model of bilateral CIs over a wide range of pulse rates. We used signal detection theory to compute neural just-noticeable differences (JNDs) in ITD that could be directly compared with ITD thresholds in CI users. ITD sensitivity was observed at higher pulse rates in the unanesthetized rabbit compared with results from anesthetized preparations. However, at low pulse rates, strong background activity masked stimulus-driven responses in many neurons. Selecting synchronized responses by temporal windowing revealed ITD sensitivity in these neurons. With temporal windowing, the dependence of neural ITD JNDs on pulse rate was consistent with perceptual data from human CI users over a wide range of pulse rates. To our knowledge, these are the first data from unanesthetized animals on neural ITD coding with CIs.

Materials and Methods

Animals

Four female Dutch-belted rabbits were used for single-unit recordings from the IC. All animals were deafened and underwent bilateral cochlear implantation as adults (8–12 months). All procedures were approved by the animal care and use committee of Massachusetts Eye and Ear.

Surgical procedures

Methods for chronic cochlear implantation and recordings from single units in the IC of unanesthetized rabbits were as described in a previous report (Chung et al., 2014). Anesthesia for all surgeries was induced with xylazine (6 mg/kg, s.c.) followed by ketamine (35–44 mg/kg, i.m.). For prolonged surgeries such as cochlear implantation, a surgical level of anesthesia was maintained by isoflurane mixed with oxygen (2.5%) delivered via a facemask (0.8 l/min).

The rabbits underwent three surgical procedures: a first one to affix a stainless-steel cylinder and brass bar to the skull, a second one to implant intracochlear electrode arrays bilaterally, and a third one to make a small craniotomy to access the IC. In the first surgery, a stainless-steel cylinder and brass head bar were affixed to the skull using stainless-steel screws and dental acrylic (Jet Denture Repair; Lang Dental). After the rabbit

Table 1. Summary of deafness history in the rabbits

	Age in months at deafening and implantation	Duration of deafness in days at training/recording sessions	Number of training/recording sessions
A62	8	20–182	38
A71	12	11–182	52
B05	8	16–173	71
B07	10	20–304	53

recovered, surgery for cochlear implantation was performed. A bullectomy was made to expose the round window, which was then enlarged. Distilled water (5–10 μ m) was injected into the cochlea through the round window to deafen the ear by causing hypotonic stress to the organ of Corti (Ebert et al., 2004). An eight-contact electrode array (Z60274 for three rabbits, HL8 for one rabbit; Cochlear) was inserted into the cochlea. Success of cochlear implantation was verified by measuring the electrically evoked auditory brainstem response (EABR) to biphasic current pulses (50 μ s/phase) delivered between the most apical and the most basal electrodes in the intracochlear array. EABR thresholds were usually in the range of –16 to –12 dB re 1 mA. The efficacy of deafening was confirmed by the absence of auditory brainstem response to 100 μ s acoustic clicks at 100 dB peak SPL.

After recovery from cochlear implantation surgery (1–2 weeks), rabbits were habituated to the experimental setup until they could sit quietly for 2–3 h with the head clamped by the headpost while receiving electric stimulation through the cochlear implants. After 1–2 weeks of habituation, the animals underwent a third procedure to make a small (~2 mm diameter) craniotomy 10.5 mm posterior and 3 mm lateral to bregma. The exposed area was covered with a topical antibiotic (Bacitracin) and sealed with dental impression material (Reprosil; Dentsply). Single-unit recording sessions started after 2–3 d of recovery and continued for 6–10 months (Table 1). In some animals, the craniotomy had to be enlarged one or more times to reach the IC, which was identified by background entrainment to the search stimuli. In these cases, data collection started after a longer period from the deafening and implantation. Rabbits were monitored on a closed-circuit video system throughout the 2 h recording sessions and only received auditory stimulation through their CIs during the recording sessions.

Electrophysiological methods

Single-unit recordings. Recording electrodes were advanced with a remote-controlled microdrive (Kopf model 650; David Kopf Instruments) in a dorsoventral direction through the occipital cortex up to the IC. In early experiments, epoxy-insulated tungsten electrodes (A-M Systems) were used to record single-unit activity. Signals from the electrode were preamplified (Axoprobe 1A; Molecular Devices), bandpass filtered (1–3 kHz), and sampled at 100 kHz using a 12 bit analog-to-digital (A/D) converter (PXI-6123; National Instruments). The stimulus artifact was removed by gating out a short interval (0.3–0.5 ms) after each stimulus pulse.

In later experiments, we used four-contact polyimide-insulated platinum/iridium linear microelectrode arrays (150 μ m spacing between contacts, 12.5 μ m site diameter; MicroProbes). Recordings were made differentially between one contact showing clear spike activity and a local reference obtained by averaging the signals from the three remaining contacts. This method greatly reduced the amplitude and duration of the stimulus artifact. Signals from the recording electrodes were acquired by a unity gain headstage (HST/16050; Plexon) and then filtered (100–8000 Hz) and amplified (PBX2; Plexon). The conditioned signals were sampled at 100 kHz using the 12 bit A/D converter. The stimulus artifact was removed by a gate-and-interpolate technique (Heffer and Fallon, 2008).

Histological processing. In the last recording session from two rabbits, electrolytic lesions were made to mark the borders of the region showing multiunit activity in response to CI stimulation while the animal was under deep anesthesia (xylazine, 6 mg/kg, s.c.; 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 then transferred to 25% sucrose solution for several days. Coronal sections (80 μm) were cut with a freezing microtome, mounted on slides, and stained with azure thionin. Borders of IC regions were identified by comparing the sections with images from an atlas of the rabbit brain (Shek et al., 1986). All identified lesions were located within the central nucleus.

Stimuli. Electric pulse train stimuli were generated using 16 bit digital-to-analog converters (PXI-6221; National Instruments) 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. This wide bipolar electrode configuration stimulates auditory neurons over the entire length of the tonotopic axis while reducing stimulus artifact relative to monopolar stimulation (Litvak et al., 2001).

The stimulus used to search for single units was a sequence of three biphasic pulses presented alternately to both ears (diotically), the left ear, and the right ear. The interval between consecutive pulses in the triplet was 100 ms, and the silent interval between triplets was 200 ms. Upon isolating a single unit, we first measured responses to the search stimulus as a function of stimulus level (varied in 1 or 2 dB steps) to determine the threshold to each pulse. All subsequent measurements used 300 ms periodic trains of biphasic pulses (50 μs /phase) presented every 600 ms. To assess the range of effective pulse rates, responses to diotic pulse trains were measured for pulse rates ranging from 20 to 1280 pps in half-octave steps. Stimuli were usually presented at 1–6 dB above the single-pulse diotic threshold. Pulse rates were presented in random order and each rate was repeated 8–12 times.

ITD sensitivity was then characterized. In early experiments, ITD sensitivity was tested at a pulse rate that evoked a strong synchronized response. ITD was varied from -2000 to $+2000$ μs in 200 or 400 μs steps, where contralateral-leading ITDs are positive. ITD was selected randomly on each stimulus presentation, and each ITD was presented 8–12 times. If time permitted, this measurement was repeated at other pulse rates (typically two or three pulse rates). In later experiments, pulse rates ranging from 20 to 640 pps in 1 octave steps and ITDs ranging from -2000 to $+2000$ μs in 200 or 400 μs steps were interleaved randomly. Each ITD–pulse rate combination was presented 10 times. For both measurement paradigms, stimuli were usually presented at 1–6 dB above the single-pulse diotic threshold with zero ILD in current levels (as verified with a current monitor). If there was no response to a diotic pulse, the lower of the contralateral and ipsilateral thresholds was used.

Data analysis

Neural ITD sensitivity and JNDs. ITD tuning curves were obtained by averaging the firing rates for each ITD over the entire stimulus duration (0–300 ms) and across all stimulus presentations. We also computed a “background” firing rate by counting spikes over a 200 ms window extending from 100 ms after the stimulus offset to the onset of the next stimulus. The background firing rate was averaged over all ITDs and pulse rates to obtain a proxy for spontaneous activity.

Two metrics of ITD sensitivity were derived from the tuning curves. The ITD signal-to-total variance ratio (STVR) is a metric based on analysis of variance (Hancock et al., 2010). It represents the fraction of the variance in neural spike counts due to variation in ITD relative to random variability across stimulus trials. It ranges from zero, indicating no ITD sensitivity, to one, indicating perfectly reliable ITD coding (meaning the spike counts vary with ITD and are identical on every trial for each ITD). Neural responses were considered to be ITD sensitive when the STVR was significantly greater than zero (F test, $p < 0.01$).

To compare neural ITD sensitivity to human performance in ITD discrimination, we used signal detection theory to estimate the neural just-noticeable difference in ITD (Shackleton et al., 2003; Smith and Delgutte, 2007). To smooth out noise in ITD tuning curves that might result in artifactually small JNDs, these curves were fitted with a cubic spline using the MATLAB function *fit* with smoothing parameter $p = 1.125 \times 10^{-6}$ (MathWorks). Both the mean and the variance of the spike count were spline fitted. Then, a modified standard separation,

Figure 1. Template for ITD curve fitting. The sum (blue) of a Gaussian (red) and a sigmoid function (green) was fit to each ITD tuning curve. Parameters of the template (A – D ; for the equation, see Materials and Methods) and metrics used to characterize ITD tuning are shown.

D , from the reference ITD was calculated from the spline curves as follows:

$$D_{\text{ITD,ITD}+\Delta\text{ITD}} = \frac{|\mu_{\text{ITD}} - \mu_{\text{ITD}+\Delta\text{ITD}}|}{\sqrt{(\sigma_{\text{ITD}}^2 + \sigma_{\text{ITD}+\Delta\text{ITD}}^2)/2}},$$

where μ_{ITD} is the mean spike count (from the cubic spline) at the reference ITD, $\mu_{\text{ITD}+\Delta\text{ITD}}$ is the mean spike count at the test ITD, and σ_{ITD} and $\sigma_{\text{ITD}+\Delta\text{ITD}}$ are their respective standard deviations (also from the cubic spline). The JND is defined as the ΔITD , where $D = 1$. The reference ITD was chosen by an exhaustive search over the range ± 300 μs to minimize the JND. This range approximates the “physiologically relevant” range of ITDs in rabbit (Day et al., 2012). If a neuron did not respond to the pulse train or the standard separation did not reach 1 within the range of ITDs tested, the ITD JND was undefined (unmeasurable).

Shapes of ITD tuning curves. To characterize their shapes, ITD tuning curves were fit with the sum of Gaussian and sigmoid functions of following form (Fig. 1):

$$\text{Rate}(\text{ITD}) = A \cdot 2^{-\left(\frac{\text{ITD} - B}{C/2}\right)^2} + \frac{D}{1 + 3^{-2\left(\frac{\text{ITD} - B}{C}\right)}} + E,$$

where B determines the center of both the Gaussian and sigmoid functions, C represents the half-width of the Gaussian function and the half-rise of the sigmoid function, and A , D , and E are scaling factors. The data were fit to the templates using the MATLAB function *lsqcurvefit* (MathWorks). Fitted curves were categorized into one of four shapes: monotonic, peak, trough, and other (unclassified). Specifically, a curve was classified as peak type if the firing rate fell by $>20\%$ of the rate range (the difference between maximum and minimum firing rates) on both sides of the maximum. Similarly, a curve was considered a trough type if the rate rose by $>20\%$ of range on both sides of the minimum. A curve that fell from maximum by at least 20% of range on only one side was classified as monotonic. ITD curves that were poorly fit ($r^2 < 0.75$) by the template were left as unclassified. These were typically curves with multiples peaks or troughs. Because this analysis was only applied to cases with significant ITD STVR, flat ITD tuning curves were excluded.

Extraction of synchronized responses. To characterize the synchronization of spikes to the stimulus pulses, we used a method based on cross-correlation (Hancock et al., 2013; Chung et al., 2014). For each pulse rate, the stimulus pulse train was cross-correlated with the spike train and a histogram constructed using a 0.1 ms bin width. A perfectly synchronized response would yield a single peak at the spike latency in the cross-correlogram. To assess the statistical significance of cross-correlogram peaks, we computed cross-correlograms for random spike trains containing the same number of spikes as the data, but uniformly distributed

Figure 2. Responses of an example neuron illustrating typical ITD sensitivity. **A–C**, Temporal discharge patterns (dot rasters) as a function of ITD at three different pulse rates. Alternating colors indicate blocks of stimulus trials at different ITDs. Stimulus pulse trains are shown at the top. **D**, Firing rate versus ITD curves for different pulse rates. **E**, ITD STVR as a function of pulse rate. Filled dots represent statistical significance ($p < 0.01$). **F**, Neural ITD JND as a function of pulse rate. UM, Unmeasurable.

over the stimulus duration (excluding the artifact gating windows). This computation was repeated for 5000 random spike trains, and a confidence bound was defined as the 99.5th percentile ($p = 0.005$) of these synthetic cross-correlograms. A correlogram peak was regarded as significant when the average of two consecutive bins exceeded the confidence bound.

The cross-correlograms were used to separate synchronized spikes from unsynchronized spikes and thereby define a synchronized firing rate for each ITD. The area of each significant correlogram peak lying above the average firing rate was converted to units of firing rate (spikes per second) for comparison with overall firing rates. The synchronized firing rates obtained by this method were used to compute an ITD STVR and a JND based on synchronized responses only.

Single-unit recordings from anesthetized cats

We collected new data from the ICs of three anesthetized cats and reanalyzed data from five cats used previously (Hancock et al., 2013) to allow quantitative comparison with the unanesthetized rabbit data at the neural population level. All eight cats were adults with normal auditory development that were deafened with ototoxic drugs and then received cochlear implants bilaterally at the beginning of the neurophysiological experiment.

The surgical procedure for deafening and implantation of cats were as described in previous reports (Smith and Delgutte, 2007; Hancock et al., 2010, 2013). The cats were deafened by injection of kanamycin (300 mg/kg, s.c.) followed after 30 min by ethacrynic acid (25 mg/kg, i.v.; Xu et al., 1993). Effectiveness of deafening was verified by the absence of auditory brainstem response to 100 μ s acoustic clicks up to 100 dB peak SPL (Hancock et al., 2010). The neurophysiological experiment took place either 1–2 weeks ($n = 6$) or 6 months ($n = 2$) after deafening. Cats were anesthetized with a combination of urethane (300 mg/kg, i.p.) and either diallyl barbituric acid (75 mg/kg, i.p.) or sodium pentobarbital (37 mg/kg, i.p.). Tympanic bullae were opened bilaterally to expose the round window. A small cochleostomy was made, and eight-contact electrode arrays (Cochlear Ltd., Z60274) were inserted bilaterally. An opening was made in the skull, and the dorsal surface of the IC was exposed by aspi-

rating the overlying cerebral cortex and removing part of the bony tentorium.

Aside from the use of anesthesia in cat, all stimulation protocols, recording procedures, and methods for data analysis were the same in the two species, except for minor differences. Single-unit recordings in cat were made using 16-site multichannel electrodes (Neuronexus). The recordings were typically made differentially between adjacent electrodes in the array to minimize stimulus artifact and local field potentials.

Results

We recorded from 184 single units in the IC of four bilaterally deafened and implanted unanesthetized rabbits. The single-unit recordings were made 26–304 d after implantation (Table 1). Approximately 73% of the IC neurons in which ITD tuning curves were measured for at least two different pulse rates showed significant ITD sensitivity in their overall firing rates based on an analysis of variance ($p < 0.01$).

Responses to periodic electric pulse trains were measured as a function of both pulse rate (from 20 to 640 pps) and ITD (over $\pm 2000 \mu$ s). Responses of two example neurons are shown in Figures 2 and 3. The neuron in Figure 2 illustrates the sigmoidal ITD tuning with preference for contralateral-leading ITDs that is commonly observed. Electrical pulses presented at a rate of 20 pps generate short-latency, tightly synchronized action potentials against a background of evoked, but, unsynchronized spiking (Fig. 2A). At 80 pps, the ongoing response is comprised mainly of tightly synchronized spikes occurring with clear contralateral-leading preference (Fig. 2B). At 320 pps, the excitatory response is largely limited to the onset and is followed by suppression of background activity during the stimulus (Fig. 2C). For all three rates (Fig. 2A–C), strong background activity is observed during the silent period between

Figure 3. A–F, Responses of an example neuron illustrating highly sharp ITD tuning. The panel layout is the same as in Figure 2.

stimuli. ITD tuning curves (Fig. 2D) show preference for contralateral-leading ITDs for all pulse rates up to 160 pps. However, both the maximum firing rate and the modulation depth of the ITD tuning curve depend on the pulse rate. ITD sensitivity measured by the STVR (see Materials and Methods) is highest at 80–112 pps and falls on both sides of this maximum but remains significant up to 320 pps ($p < 0.01$; Fig. 2E). To compare neural ITD sensitivity to human performance, we also calculated neural ITD JNDs based on overall firing rates (see Materials and Methods). The JNDs in this neuron are $\sim 250 \mu$ s at low rates and increase to $\sim 800 \mu$ s at 320 pps (Fig. 2F). The JND was unmeasurable for 640 pps.

Figure 3 shows results from another example neuron with a very different response pattern. This neuron shows synchronized responses for ITDs near +400 μ s and little or no response to other ITDs at 20, 80, and 320 pps (Fig. 3A–C) with minimal background activity. ITD tuning curves sharply peak at +400 μ s for all pulse rates, although the peak height depends on the pulse rate (Fig. 3D). ITD STVRs are high (>0.7) and statistically significant ($p < 0.01$) for the entire range of pulse rates tested (Fig. 3E). Correspondingly, the ITD JNDs are very low ($<100 \mu$ s) over the entire range of pulse rates (Fig. 3F).

Shapes of ITD tuning curves and ITD tuning metrics

We used a flexible template, the sum of Gaussian and sigmoid functions, to fit the ITD tuning curves with statistically significant STVRs and classify them into four basic shapes (for details, see Materials and Methods). Only ITD tuning curves measured with pulse rates up to 160 pps were used for this analysis because at higher pulse rates, the ITD curves become periodic within the $\pm 2000 \mu$ s range of ITDs tested. A periodic curve implies that the firing rate at the beginning and end of each period must be the same, which precludes fitting a monotonic template. Figure 4 shows example ITD tuning curves for each of the four shapes: monotonic (Fig. 4A), peak (B), trough (C), and unclassified (D).

The ITD tuning curve in Figure 4D had significant ITD sensitivity (STVR, 0.41; $p < 0.001$) but was poorly fit by the template ($r^2 = 0.56$), so it was left unclassified.

Figure 4E shows the distribution of ITD tuning shapes across the 113 neurons that showed significant ITD sensitivity to at least one pulse rate of ≤ 160 pps. When significant ITD sensitivity was observed at multiple pulse rates, the ITD tuning curve with the highest STVR was selected. The monotonic tuning curve is the most common shape (38%), followed by peak (32%) and trough (10%) types. Twenty percent of the units were not well fit by the template.

Figure 4F shows how the distribution of tuning shapes varies with pulse rate for all neurons with significant ITD sensitivity at each pulse rate. For 20 and 40 pps, 40–50% of the neurons have monotonic ITD tuning curves. With increasing pulse rate, the peak shape becomes increasingly common, until it becomes the most common type at 80 and 160 pps. Trough type is the least common at all pulse rates. The difference in shape distributions across pulse rates just misses significance (χ^2 test, $p = 0.057$).

ITD tuning metrics were derived from the fitted curves (Fig. 1). The best ITD (ITD_{best}) was calculated from peak types only. If a neuron showed different tuning shapes depending on the pulse rate, all unique shapes were selected. The distribution of ITD_{best} (Fig. 5A) shows a weak contralateral bias (58% of $ITD_{best} > 0$). This trend is, however, not statistically significant (mean, 99 μ s; t test, $p = 0.08$). The lack of a strong contralateral bias may arise because Figure 5A excludes the monotonic shapes. Seventy-nine percent of monotonic types showed contralateral preference, which is well above chance ($p < 0.001$, binomial test). For peak-type tuning curves, the half-width of ITD tuning (the range of ITDs over which firing rate is $\geq 50\%$ of maximum) has a broad distribution ranging from near 0 to over 2000 μ s with a median of 960 μ s (Fig. 5B). For monotonic and peak types, the half-rise (the range be-

Figure 4. *A–C*, Examples of ITD tuning curves with monotonic, peak, and trough shapes. *D*, An example of an ITD tuning curve with a significant ITD sensitivity (STVR, 0.41; $p < 0.001$) but poor fit to the template ($r^2 = 0.56$). *E*, Distribution of ITD tuning shapes. Analysis was limited to units with statistically significant ITD STVRs. Twenty percent of ITD-sensitive neurons are poorly fit by the template. For the neurons that are well fit to the template, monotonic is the most common shape, followed by peak and trough shapes. *F*, Distribution of ITD tuning curve shapes depends on pulse rates.

tween the ITDs where the firing rate reaches 25 and 75% of maximum) has a broad, highly skewed distribution with a median of 480 μ s (Fig. 5C). Finally, the ITD of maximum slope (ITD_{MS}), where the firing rate is most sensitive to changes in ITD, was determined for all ITD tuning shapes, except unclassified. ITD_{MS} is broadly distributed with a mean near zero (-77μ s; t test, $p = 0.23$), consistent with results from normal-hearing animals (McAlpine et al., 2001; Fig. 5D).

Effect of duration of deafness on background activity and ITD sensitivity

A previous study in anesthetized cats reported that the distributions of ITD tuning metrics among IC neurons depended on the duration of deafness (Hancock et al., 2013). The distributions of half widths and ITD_{MS} were broader in cats that were deafened ~ 6 months before the electrophysiological recordings than in cats that were deafened just 1 week before recordings, and the best ITD distribution in the long-term deafened cats lacked the contralateral bias that was present in both acutely deafened and normal-hearing animals. In addition, spontaneous activity was higher in the long-term deafened cats (Shepherd et al., 1999; Hancock et al., 2013).

Neural recordings from our rabbits were made 26–304 d after implantation (which is also the duration of deafness since deafening occurred just before implantation), thereby offering an

opportunity to track changes in ITD sensitivity and spontaneous activity over time. A complication is that the deafened rabbits were not completely deprived of auditory experience since they received electric stimulation through their CI during the 2 h recording sessions. A detailed history of deafness and electric stimulation for each animal is presented in Table 1.

Figure 6A shows the background firing rate (measured during the silent intervals between stimuli while recording ITD tuning curves) as a function of the duration of deafness for the three animals that provided the most data. No significant effect of deafness on background activity was observed in two of these animals (A71, Kendall's $\tau = -0.17$, $p = 0.10$; B07, $\tau = -0.03$, $p = 0.73$). However, in the third animal (B05), there was a significant trend for background activity to increase with longer deafness (Kendall's $\tau = 0.21$, $p = 0.01$). The change in background activity in this animal was not due to changes in the effectiveness of the electric stimulation, because thresholds for a single pulse did not change over time (Kendall's $\tau = -0.10$, $p = 0.39$). This animal experienced complete auditory deprivation for 2 months, during which there were no recording sessions, and the median background activity significantly increased from 11.7 spikes/s to 25.2 spikes/s after this period of deprivation (Wilcoxon rank sum test, $p = 0.01$). B07 also experienced a long period of complete auditory deprivation, but only

three neurons were recorded from following the deprivation, precluding any firm conclusion.

We also tested the effect of duration of deafness on the maximum ITD STVR across pulse rates for each neuron (Fig. 6B). A significant decrease in maximum STVR was observed over time in two animals (A71, Kendall's $\tau = -0.38$, $p = 0.03$; B05, $\tau = -0.27$, $p = 0.008$). However, there was no change in the third animal (B07, $\tau = 0.21$, $p = 0.08$).

Finally, we examined the effects of duration of deafness on the ITD tuning metrics. No significant effect of duration of deafness on ITD_{MS} was found for any of the animals (A71, Kendall's $\tau = -0.05$, $p = 0.78$; B05, $\tau = 0.09$, $p = 0.46$; B07, $\tau = 0.17$, $p = 0.23$). A significant decrease in half-rise was observed in one animal (A71, $\tau = -0.35$, $p = 0.01$); however, there was no significant change in half-rise in the other two (B05, $\tau = 0.01$, $p = 0.96$; B07, $\tau = 0.07$, $p = 0.55$). There were not enough data for ITD_{best} and half-width to perform the tests in individual animals. Pooling data across animals, no significant effect of duration of deafness was found for these metrics (ITD_{best}, $\tau = -0.13$, $p = 0.12$; half-width, $\tau = -0.20$, $p = 0.05$).

Together, the results do not provide compelling evidence for an effect of duration of deafness on response properties of IC neurons in our experimental conditions. The most suggestive evidence comes from the animal (B05) that experienced a gap in recording sessions, in which background activity tended to in-

Figure 5. Distributions of ITD_{best} (A), half-width (B), half-rise (C), and ITD_{ms} (D) for all units. Pulse rates that resulted in the best ITD STVR were selected for each unit. Error bars in A and D show mean $\pm$ 1 SD.

crease and ITD sensitivity tended to degrade over time. However, this animal did not show the effect on ITD tuning metrics that were expected based on results in adult-deafened cats with 6 months of auditory deprivation (Hancock et al., 2013).

Temporal coding improves ITD sensitivity at low pulse rates

ITD sensitivity at low pulse rates was often masked by strong background activity unsynchronized to the pulse train. For example, Figure 7A illustrates the temporal response pattern of a neuron that was not ITD sensitive at 20 pps based on overall firing rate (ITD_{STVR} , 0.11; $p = 0.27$). However, each stimulus pulse was followed by short-latency spike activity, and this synchronized activity was stronger for positive (contralateral-leading) ITDs than for very negative ITDs. Apparently, the ITD sensitivity present in the synchronized responses was masked by unsynchronized activity occurring between pulses when the sensitivity was assessed based on overall firing rate. Strong unsynchronized activity between short-latency spikes following each pulse is also observed in the neuron in Figure 2A at 20 pps, although in this case the ITD STVR based on overall firing rate did reach statistical significance. To test whether synchronized responses might contain additional ITD information that is masked in the overall firing rate, we used cross-correlation between the stimulus pulse train and the neural spike train to select the synchronized activity (Hancock et al., 2012, 2013; Chung et al., 2014). Cross-correlograms for the neuron in Figure 7A are shown as a function of ITD in Figure 7B. Robust synchronized activity is evoked by

Figure 6. A, Level of background activity as a function of duration of deafness. B, Maximum STVR as a function of duration of deafness.

pulses with contralateral-leading ITDs as shown by peaks at a latency of ~ 7 ms in the cross-correlograms (Fig. 7B, green shading). The area of the significant cross-correlogram peaks lying above the average firing rate was used to define a “synchronized firing rate.” Figure 7C compares the ITD tuning curve based on synchronized rate with the tuning curve based on overall firing rate (all spikes including both synchronized and unsynchronized spikes). Selecting the synchronized spikes by windowing reveals a preference for contralateral-leading ITDs ($STVR$, 0.65; $p < 0.001$). Additionally, the neural ITD JND based on synchronized spikes is well defined ($747 \mu s$), whereas the JND based on all spikes is unmeasurable.

ITD tuning curves from the neuron in Figure 2 are presented again in Figure 8A, but now with synchronized activity isolated for pulse rates between 20 and 80 pps, where the effect of windowing was most prominent. ITD tuning curves based on synchronized rate show a stronger ITD-dependent modulation than curves based on overall rate. The improvement in ITD STVR through windowing is most prominent at 20 and 40 pps in this neuron, with the STVR increasing from ~ 0.4 to >0.8 (Fig. 8B). At pulse rates of ≥ 320 pps, there is no synchronized activity, and hence the STVR is zero. ITD JNDs based on synchronized spikes (Fig. 8C) are smaller than the JNDs based on all spikes for low pulse rates (20–80 pps), but become unmeasurable at 320 pps,

Figure 7. Selecting pulsed-locked spikes reveals ITD sensitivity at 20 pps in an example neuron. **A**, Temporal discharge patterns of an IC neuron for a 20 pps pulse train at different ITDs. **B**, Cross-correlogram between stimulus pulse trains and neural spikes. Each trace shows the cross-correlogram for one ITD. Gray shading indicates the 99.5% upper confidence bound for a random spike train; correlation peaks exceeding the confidence bound are filled in green. **C**, ITD tuning curves for all spikes and synchronized spikes.

where the JND based on all spikes is still well defined. Thus, in this neuron, ITD is best coded by synchronized rate at low pulse rates and by overall firing rate at higher pulse rates.

Figure 9 compares ITD sensitivity based on synchronized rate versus overall firing rate across the sample of IC neurons. Figure 9A shows the percentage of neurons that are ITD sensitive as a function of pulse rate for all spikes and for synchronized spikes. Isolating synchronized activity reveals ITD sensitivity in more neurons at 20 and 40 pps. Likewise, the mean ITD STVR based on synchronized spikes is higher than the STVR for all spikes for pulse rates up to 160 pps (Fig. 9B). A two-way ANOVA was performed on the arcsine transformed STVRs to make the distribution more closely approximate a Gaussian. There were significant main effects of both pulse rate and windowing ($p < 0.001$ for both effects) and a significant interaction between pulse rate and windowing ($p = 0.007$).

Figure 9C compares neural ITD JNDs based on all spikes and on synchronized spikes. The median ITD JNDs based on overall firing rates are lowest (median, 511 μs) at 160 pps and increase for both lower and higher pulse rates. ITD JNDs for pulse rates below 160 pps are improved by selecting the synchronized spikes. For pulse rates of ≥ 320 pps, ITD JNDs based on synchronized spikes were unmeasurable for over half of the neurons, so that a median could not be determined. In that range, JNDs based on overall firing rate were lower on average than JNDs based on synchronized rate. Thus, the best overall performance is achieved by using the synchronized rate at low pulse rates and the overall rate at high pulse rates.

To compare neural ITD JNDs with perceptual ITD JNDs measured in human CI subjects, we assumed that neural JNDs are

based on synchronized spikes for low rates (< 300 pps) and on all spikes for high pulse rates (> 300 pps). Figure 9D compares the 25th percentile of neural JNDs with median perceptual thresholds from 21 subjects in four studies of human CI users (for details, see the Fig. 9 legend). We chose the 25th percentile empirically to obtain a rough match with average human performance, but the choice of a low percentile is guided by the “lower envelope principle” (Parker and Newsome, 1998, p. 242), which states that performance in perceptual tasks is largely determined by the best-performing neurons. With this choice, neural ITD JNDs from rabbit IC lie within the interquartile range of perceptual JNDs in human bilateral CI users over a broad range of pulse rates (40–640 pps).

Comparison with anesthetized cat

We showed previously that the upper frequency limit of temporal coding of electric pulse trains was underestimated due to the confound of anesthesia (Chung et al., 2014). To test whether ITD sensitivity at high pulse rates is also enhanced in unanesthetized preparations, we compared the pulse rate dependence of neural ITD sensitivity in unanesthetized rabbits with previous results from anesthetized cats. In our previous study, the changes in response observed after

injecting a short-acting anesthetic while recording from single neurons in rabbit IC were consistent with the differences in responses to pulse trains between anesthetized cats and unanesthetized rabbits, suggesting that effects of anesthesia were the major factor underlying these differences in response.

To compare the pulse rate dependence of ITD sensitivity in the two preparations, we used metrics based on all spikes because windowing made little difference for data from anesthetized cats, where spontaneous activity is rarely observed. Figure 10A shows the percentage of IC units showing a statistically significant ITD STVR as a function of pulse rate in both unanesthetized rabbit and anesthetized cat. Analysis was limited to neurons that were tested with at least three pulse rates. More IC neurons were ITD sensitive at low pulse rates (20–40 pps) in anesthetized cat than in unanesthetized rabbit. However, at 160 and 320 pps, more IC units were ITD sensitive in the unanesthetized rabbit. Similarly, mean ITD STVRs based on all spikes were higher at 160 and 320 pps, but lower at 20 pps, in unanesthetized rabbit compared to anesthetized cat (Fig. 10B). A two-way ANOVA of arcsine-transformed STVR showed a significant main effect of pulse rate and a significant interaction between pulse rate and preparation ($p < 0.001$ for both effects), but no main effect of preparation ($p = 0.33$).

Discussion

Pulse rate dependence of ITD sensitivity in unanesthetized preparation

We characterized the ITD sensitivity of IC neurons over a wide range of pulse rates in an unanesthetized rabbit model of bilateral

Figure 8. *A*, Firing rate versus ITD curves based on all spikes (dashed lines) and synchronized spikes (solid lines) for the same neuron as in Figure 2. *B*, ITD STVR as a function of pulse rate for all spikes and synchronized spikes. *C*, ITD JND as a function of pulse rate for all spikes and synchronized spikes.

CI to gain a better understanding of the neural basis for the degradation in perceptual ITD sensitivity observed at high pulse rates in CI users. For pulse rates ≥ 160 pps, neural ITD sensitivity based on overall firing rate was better in unanesthetized rabbit than in anesthetized cat (Fig. 10), and $\sim 25\%$ of IC neurons in unanesthetized rabbit were still ITD sensitive at the highest rate tested (640 pps). These findings extend our previous results (Chung et al., 2014) showing better temporal coding at high stimulation rates in an unanesthetized preparation. However, ITD sensitivity based on overall firing rate was poorer at low pulse rates than at 80–160 pps in unanesthetized rabbit, in contrast to the monotonic decrease in ITD sensitivity with increasing pulse rate observed in anesthetized cat (Fig. 10). Prominent unsynchronized activity occurring between tightly synchronized spikes could mask ITD sensitivity at low pulse rates when it was assessed by overall firing rates (Figs. 2A, 7A). Selecting synchronized activity by windowing uncovered ITD sensitivity at these low pulse rates (Fig. 8). Signal detection theory was used to define neural ITD JNDs that could be compared with human ITD discrimination thresholds. Using synchronized activity for pulse rates < 300 pps and overall firing rate > 300 pps, neural ITD JNDs for the better-performing neurons (25th percentile) lied within the interquartile range of perceptual JNDs for CI users over a wide range of pulse rates (40–640 pps).

Masking of ITD sensitivity by background activity at low pulse rates

The finding that selecting synchronized spikes by temporal windowing can uncover ITD sensitivity masked by unsynchronized activity raises two questions. First, is the masking of ITD sensitivity a phenomenon limited to or worse in the deaf system due to the increase of spontaneous activity resulting from prolonged deafness? Spontaneous activity is known to be upregulated in the auditory midbrain of anesthetized animals after prolonged hear-

Figure 9. *A*, Percentage of IC units showing statistically significant ITD STVR as a function of pulse rate for all spikes and for synchronized spikes only. *B*, Mean ITD STVR versus pulse rate for all spikes and for synchronized spikes only. Error bars represent ± 2 SEs. *C*, ITD JND versus pulse rate for all spikes and for synchronized spikes only from individual neurons. Solid lines represent the median. ITD JNDs are unmeasurable (UM) for more than half of the units for 640 pps based on all spikes, and for 320–640 pps based on synchronized spikes. The sizes of the circles representing UM are proportional to the number of measurements included. Analysis was limited to IC units for which responses were measured using at least three pulse rates. *D*, Comparison of neural ITD JNDs with perceptual ITD JNDs measured in human CI subjects. Perceptual ITD JNDs are from the studies by van Hoesel and Tyler (2003), van Hoesel (2007), van Hoesel et al. (2009), and Egger et al. (2014), adapted from Laback et al. (2015). Two studies were excluded: those by van Hoesel and Clark (1997), because of the overall poor performance of the subjects, and Laback et al. (2007), because of the short duration of stimuli used made the comparison difficult. Error bars represent interquartile range measured in 21 subjects. Neural ITD JNDs are based on pulse-locked spikes for low pulse rates (< 300 pps) and from all spikes for high pulse rates (> 300 pps).

ing loss induced by acoustic trauma (Manzoor et al., 2012; Robertson et al., 2013). At the same time, spontaneous activity of IC neurons is higher in unanesthetized, normal-hearing animals than in anesthetized animals (Kuwada et al., 1989; Tortorolo et al., 2002). Therefore, masking of ITD sensitivity may also occur in normal-hearing animals for stimuli containing long pauses such as low-rate click trains. However, we are not aware of any study of ITD sensitivity in the IC that used click train stimuli in an unanesthetized preparation.

A second question is, can the central auditory system detect the ITD information available in synchronized responses when it

Figure 10. *A*, Percentage of IC units showing statistically significant ITD STVR as a function of pulse rate in unanesthetized rabbit and anesthetized cat. *B*, Mean ITD STVR versus pulse rate. Error bars represent ± 2 SEs. Analysis was limited to IC units that were tested for at least three pulse rates.

is masked by unsynchronized activity? Although pulse rates below 100 pps are rarely used in psychophysical studies of ITD sensitivity with bilateral CIs, one study (van Hoesel and Tyler, 2003) reported ITD JNDs for pulse rates below 100 pps that were similar to or better than JNDs at higher pulse rates. This implies that a neural mechanism exists that can extract the synchronized activity. One possible mechanism is a coincidence detector central to the IC that would receive inputs from two or more IC neurons with similar ITD tuning and would only fire when spikes occur nearly simultaneously in these inputs. By emphasizing the coincident, synchronized spikes over the unsynchronized background activity, such a mechanism should be able to extract the ITD information that is masked in the overall firing rate (Buechel et al., 2016). That coincidence detection emphasizes synchronized activity over unsynchronized activity is well established in several model systems (Han and Colburn, 1993; Rothman et al., 1993; Reyes et al., 1996; Kalluri and Delgutte, 2003).

Effect of duration of deafness

Adult cats that experience a prolonged period of deafness exhibit increased spontaneous activity and substantial changes in ITD tuning in the IC, including a loss of contralateral bias in the best ITD distribution, broader ITD tuning, and a broader distribution of ITD_{MS} compared to acutely deafened cats (Hancock et al., 2013). In principle, our chronic preparation for neural recordings from deafened rabbits with cochlear implants offers an opportunity to track the time course of the changes in response properties resulting from deprivation of auditory experience using a longitudinal design. Nevertheless, we failed to find compelling evidence for an effect of duration of deafness on either background activity or ITD sensitivity in the present experiments. Of course, the large variability in response properties among IC neurons makes the detection of any trend over time challenging when only a few neurons are sampled in each recording session. One of our animals that experienced a ~2 month

period of auditory deprivation did show a trend for background activity to increase and ITD sensitivity to decrease over time. This observation (if confirmed in additional animals) would suggest that electric stimulation during the 2 h recording sessions may be sufficient to avoid severe effects of deprivation of auditory inputs on neural activity. In other words, the very presentation of auditory stimuli necessary to assess ITD sensitivity may alter the operation of the deaf auditory system.

Alternatively, because the earliest recording sessions started about 4 weeks after deafening and implantation, it is possible that loss of sharp ITD tuning primarily occurred shortly after deafening and before the recordings began in the animals that showed no effect of duration of deafness. Rapid changes in strength of inhibition have been observed in the IC and other brainstem auditory nuclei following peripheral deafening (Takesian et al., 2009; Bender and Trussell, 2011). Clearly, additional data obtained with more controlled stimulation schedules will be required to definitively assess the time course of changes in ITD sensitivity and other response properties following the onset of deafness.

Relation to perceptual results in CI users

Most bilateral CI users show a degradation in perceptual ITD sensitivity for pulse rates above 100 pps, with JNDs becoming unmeasurable above 400–800 pps (for review, Laback et al., 2015; Kan and Litovsky, 2015). However, some exceptional listeners can detect ITDs up to 800–1000 pps (Laback et al., 2007; van Hoesel et al., 2009). We found that ITD JNDs of the better-performing neurons (25th percentile) roughly matched perceptual JNDs for the “typical” subject over a wide range of pulse rates when the neural JNDs were based on synchronized activity at low pulse rates (<300 pps) and overall firing rate at higher pulse rates. In addition, some IC neurons had good ITD JNDs up to the highest rates tested (640 pps; Figs. 3*F*, 9*C*). The exceptional performance of some subjects might be explained by their ability to access ITD information conveyed by such highly sensitive neurons more effectively than typical subjects. If so, it would be important to identify the stimulus conditions and electrode configurations most likely to recruit these “star” neurons.

The perceptual limit of ITD sensitivity at high pulse rates is similar in some respects to the limit of monaural rate discrimination in CI users. Most CI listeners can discriminate the rate of periodic pulse trains and rank them based on perceived pitch up to ~300 pps (Moore and Carlyon, 2010). However, a few exceptional subjects can detect changes in pulse rate as high as 900 pps (Townshend et al., 1987; Kong and Carlyon, 2010). A recent report (Ihlefeld et al., 2015) showed a correlation between monaural rate discrimination and ITD discrimination performance in the same subject, supporting the view that temporal coding and ITD sensitivity may be partly dependent on a common neural mechanism.

The degradation in ITD JNDs with increasing pulse rate should be taken into account when designing processing strategies to improve binaural benefits with bilateral CIs. With the continuous interleaved sampling (CIS) strategy, higher carrier pulse rates improve speech reception at least up to ~500 pps (Loizou et al., 2000; Arora et al., 2009), which is above the limit of ITD sensitivity in most CI listeners. Thus, there may be a trade-off between speech reception and binaural benefit when selecting a carrier rate for a CIS strategy. Some experimental processing strategies aim for a compromise between the two goals by delivering low-rate fine structure information to apical electrode

channels while maintaining high carrier rates at the more basal electrodes (Churchill et al., 2014; Riss et al., 2014).

In summary, we found that roughly a quarter of IC neurons in unanesthetized rabbits are sensitive to ITD up to the highest pulse rate tested (640 pps). Although ITD sensitivity at low pulse rates could be masked by unsynchronized activity, selecting synchronized spikes revealed ITD sensitivity in these neurons. The pulse-rate dependence of neural ITD JNDs in unanesthetized rabbit broadly parallels the dependence of perceptual ITD JNDs in human CI listeners over a wide range of pulse rates. Better perceptual ITD sensitivity at high pulse rates might be achieved through devices and strategies that specifically target the neurons most sensitive to ITD.

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