Binaural interactions in the auditory midbrain with bilateral electric stimulation of the cochlea

by

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Abstract

Bilateral cochlear implantation seeks to restore the advantages of binaural hearing to the profoundly deaf by giving them access to binaural cues normally important for accurate sound localization and speech reception in noise. This thesis characterizes binaural interactions in auditory neurons using a cat model of bilateral cochlear implants. Single neuron responses in the inferior colliculus (IC), the main nucleus of the auditory midbrain, were studied using electric stimulation of bilaterally implanted intracochlear electrode arrays. Neural tuning to interaural timing difference (ITD) was emphasized since it is an important binaural cue and is well represented in IC neural responses. Stimulation parameters were explored in an effort to find stimuli that might result in the best ITD sensitivity for clinical use.

The majority of IC neurons were found to be sensitive to ITD with low-rate constant-amplitude pulse trains. Electric ITD tuning was often as sharp as that with acoustic stimulation in normal-hearing animals, but many neurons had dynamic ranges of ITD sensitivity limited to a few decibels. Consistent with behavioral results in bilaterally implanted humans, neural ITD discrimination thresholds degraded with increasing pulse rates above 100 pulses per second (pps).

Since cochlear implants typically encode sounds by amplitude modulation (AM) of pulse-train carriers, ITD tuning of IC neurons was also studied using AM pulse trains. Many IC neurons were sensitive to ITD in both the amplitude envelope and temporal fine structure of the AM stimulus. Sensitivity to envelope ITD generally improved with increasing modulation frequency up to 160 Hz. However, the best sensitivity was to fine structure ITD of a moderate-rate (1000 pps) AM pulse train.

These results show that bilateral electric stimulation can produce normal ITD tuning in IC neurons and suggest that the interaural timing of current pulses should be accurately controlled if one hopes to design a bilateral cochlear implant processing strategy that provides salient ITD cues. In additional experiments, we found that evoked potentials may be clinically useful for assigning frequency-channel mappings in bilateral implant recipients, such as pediatric patients, for which existing psychophysical methods of matching interaural electrodes are unavailable.

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Chapter 1

Introduction

A cochlear implant is a sensory prosthesis that elicits hearing sensation in individuals with profound sensorineural hearing loss. It bypasses the mechanisms of the external, middle, and inner ears by directly stimulating the auditory nerve with electric current via electrodes implanted in the scala tympani of the cochlea. Contemporary clinical cochlear implant devices are successful in restoring hearing sensation and drastically improving speech discrimination in most post-lingually deafened adults. The majority of individuals with the latest speech processors are able to score 80% or better on high-context sentences with only auditory cues (NIH Consensus Statement, (1995)). Their hearing is still impaired, however, and many cochlear implant users struggle to hear in certain situations on a daily basis. This is especially the case when there are multiple competing sound sources in real environments, such as in a busy restaurant. One possible solution is to implant both ears instead of just one so that cochlear implant users might take advantage of spatial information available when listening with two ears.

Binaural hearing has several advantages over monaural hearing. One benefit comes from having an additional sensory organ to deliver redundant information about an acoustic stimulus which can improve performance even when the signals at each ear are identical. The greatest advantages of binaural hearing, however, are often realized when the signals at each ear differ. Accurate localization of sounds in the horizontal plane is based primarily on interaural timing differences (ITDs) for sounds containing low-frequency energy and on interaural level differences (ILDs) for high-frequency sounds (Wightman and Kistler, 1992; Macpherson and Middlebrooks, 2002). Another key advantage, known as “spatial unmasking”, is also observed for both the detection of sounds (Saberi et al., 1991; Gilkey and Good, 1995) and speech intelligibility in the presence of spatially separated noise (Cherry, 1953) or competing talkers (Hawley et al., 1999). Spatial unmasking improvements in speech intelligibility are based on two components of roughly equal importance (Zurek, 1993). First, a purely acoustic component occurs because having two ears increases the odds that the position of one of
them will provide a better signal-to-noise ratio (S/N) and the listener can simply attend to the “better ear”. An example of this occurs when a target talker is directly in front of the listener and a competing noise 90° to the side. In this scenario, the acoustic shadow of the head, which baffles mostly high frequencies, results in the acoustic signal at the ear opposite the noise will have a higher S/N than at the ear closest to the noise. The other contributor to spatial unmasking relies on binaural interactions in the auditory CNS, especially at low frequencies, and is thought to be related to the neural processing of ITD cues (Colburn and Durlach, 1978; Zurek, 1993; Colburn, 1995). This fundamentally binaural aspect is especially important in the many real-world situations where the target speech and masker are spatially separated, but there is not an advantageous S/N at either ear (Hawley et al., 1999). For example when a target talker is directly in front of a listener and a competing talker is 45° to the side, there is not much of a head shadow for the competing talker from this intermediate angle, but there are still advantages that can obtained with binaural comparison of the signals at the two ears.

Poor performance with a single cochlear implant led to the implantation of a second device in the other ear of a handful of implant patients (Balkany et al., 1988; Pelizzone et al., 1990; Green et al., 1992; Lawson et al., 1998; Long et al., 2003). While the motivation of bilateral implantation in these cases was not to deliver binaural advantages per se, many of these subjects reported a fused sound image when stimulated bilaterally which could be lateralized with the introduction of ILDs. Lateralization by and sensitivity to ITD in these users was generally poor with ITD detection thresholds greatly exceeding those with acoustic stimuli in healthy ears.

More recently, several research groups have implanted subjects with identical or similar devices in each ear, often in the same surgical procedure with the aim of studying any resulting binaural advantages that they might receive (van Hoesel and Clark, 1997; Gantz et al., 2002; Muller et al., 2002; Schon et al., 2002; Tyler et al., 2002; van Hoesel and Tyler, 2003). Most of the reports from these groups address speech reception levels with and without bilateral stimulation under various speech-noise configurations using clinical and research speech processors. In tests with spatially separated speech and noise, nearly all subjects have shown improved speech scores with bilateral stimulation, usually performing near the level of the better ear alone. Thus most of the advantages
with bilateral implants thus far can be attributed to the head-shadow effect and not to processing of binaural cues. The research group in Germany has reported significant advantages with bilateral implants beyond the head-shadow effect (Schon et al., 2002), but these advantages can be attributed primarily to binaural summation since the acoustic signals at the microphones for each ear were nearly identical.

Studies of sound localization show much better performance with bilateral over monolateral stimulation in bilaterally implanted cochlear implant subjects (van Hoesel et al., 2002; van Hoesel and Tyler, 2003; Poon, 2006). Sensitivity to ILD and ITD on pitch matched electrodes with unmodulated pulse trains often shows discrimination of the smallest ILD (~0.1-0.2 dB) allowed by the implant system of many users (Lawson et al., 1998; van Hoesel and Tyler, 2003) and ITD discrimination thresholds as low as 50 µs and as high as several milliseconds depending on the pulse rate and electrode pair (Lawson et al., 1998; van Hoesel and Tyler, 2003) with the best thresholds at the lowest pulse rates (50 pps) (van Hoesel and Tyler, 2003). In comparison, discrimination of ITD for acoustic stimuli in normal-hearing subjects is better and more robust with JNDs of 10-50 µs depending on the stimulus (Klumpp and Eady, 1956; Yost et al., 1971).

This thesis addresses fundamental questions related to the effective coding of binaural information with bilateral cochlear implants, with particular focus on ITD, since ITD discrimination has been relatively poor with bilateral implant subjects to date. A cat model of bilateral cochlear implants was used and responses of ITD sensitive neurons in the inferior colliculus (IC), the main nucleus of the auditory midbrain, were studied to find stimulus parameters that might limit ITD tuning. Additionally, a method using evoked potentials for assigning frequency-channel mappings in bilateral implant recipients was tested and validated in the cat model. The results presented in this thesis are important for their clinical significance and also because they offer new insights to the neural mechanisms of binaural hearing.

While many IC neurons are sensitive to ITD, the first place in the auditory system where ITD-sensitivity originates is the superior olivary complex (SOC). Two principal nuclei, both sensitive to ITD, are contained in the SOC. Neurons in the medial superior olive (MSO) receive primarily low-frequency excitatory inputs from the cochlear nuclei of each side. MSO neurons act as coincidence detectors and respond best at a particular
ITD, usually when the stimulus is nearly in phase at the two ears (Goldberg and Brown, 1969; Yin and Chan, 1990). Neurons in the lateral superior olive (LSO) receive excitatory inputs from the ipsilateral ear via the ipsilateral cochlear nucleus and inhibitory inputs from the contralateral ear via the ipsilateral medial nucleus of the trapezoid body (MNTB). LSO cells are predominantly high-frequency, though low-frequencies are represented as well, and are primarily sensitive to ILD. LSO neurons also show sensitivity to ITD and typically respond best when the amplitude envelope of a stimulus is out of phase at the two ears (Joris and Yin, 1995). Neurons in the MSO and LSO send direct and indirect projections to the central nucleus of the IC. Consequently, binaural responses of IC neurons resemble those in the MSO, LSO, and also a cross between their responses (Yin and Kuwada, 1983b; Batra et al., 1993; McAlpine et al., 1998). The ITD tuning of IC neurons with electric stimulation is investigated in Chapters 2 and 3. Responses in the IC are the focus in this thesis because of the convergence of MSO- and LSO-like responses and also because of the orderly tonotopic arrangement of the IC (Merzenich and Reid, 1974).

Chapter 2 uses constant-amplitude pulse trains as the electric stimulus, and looks at ITD sensitivity in single IC neurons. Pulse trains were used since cochlear implants typically use fixed-rate trains of current pulses in each channel. Electric ITD tuning characteristics were measured and compared with those obtained in previous studies with acoustic stimulation in normal-hearing cats. ITD tuning as a function of pulse rate was also measured, and neural ITD discrimination thresholds were estimated using detection theoretic methods (Green and Swets, 1966). In general, ITD discrimination thresholds were best at low pulse rates (< 100 pps) and degraded with increasing pulse rates. This finding is consistent with reported behavioral ITD discrimination thresholds in bilaterally implanted human subjects (van Hoesel and Tyler, 2003; Poon, 2006).

Since cochlear implants typically encode sounds in the amplitude modulations (AM) of fixed-rate current pulses (Wilson et al., 1991), Chapter 3 compares the ITD tuning of single IC neurons to ITD contained in either the amplitude envelope or fine temporal structure of more complex electric stimuli. Sinusoidal AM pulse trains were used as the stimulus and ITD was independently manipulated in the AM (envelope) and the carrier pulses (fine structure). Introduction of AM restored sustained responses to
high-rate pulse trains in most neurons. Results show that the majority of IC neurons are sensitive to envelope ITD (ITD_{env}), though selectivity to ITD_{env} is generally poorer than selectivity to ITD with low-rate constant-amplitude pulse trains (Chapter 2). About half of neurons sensitive to ITD_{env} were also shown to be sensitive to fine structure ITD (ITD_{fs}) using 1000 pps carrier pulses. In neurons that showed sensitivity to ITD_{fs}, tuning was comparable to that with to ITD with low-rate constant-amplitude pulse trains and significantly better than tuning to ITD_{env} over the range of modulation frequencies tested. This result is significant because clinically available cochlear implant sound processors do not control for the interaural timing of carrier pulses.

Results with a small number of bilateral cochlear implant subjects suggest that the ability of bilaterally-implanted patients to discriminate ITD depends on a match between the cochlear positions of the stimulating electrode pairs in the two ears (Long et al., 2003; Wilson et al., 2003). Chapter 4 tests a method using evoked potentials, first proposed by Pelizzone and colleagues (Pelizzone et al., 1990), to find interaural electrode matches. The binaural interaction component (BIC) of the electrically-evoked auditory brainstem response (EABR) was used to measure the strength of binaural interaction between stimuli in the two ears, with the idea that stimulating in matched cochlear locations would maximize binaural interactions. Results show that the BIC amplitude is maximal for interaural electrode pairs in the same cochlear position. Neural activation patterns along the tonotopic axis of the IC were also recorded and show that better aligned activation patterns correlated with BIC amplitude. These results suggest that evoked potentials may be clinically useful for assigning frequency-channel mappings in bilateral implant recipients, such as pediatric patients, for which existing psychophysical methods of matching interaural electrodes are unavailable.
Chapter 2

Sensitivity to Interaural Time Differences in the Inferior Colliculus with Bilateral Cochlear Implants: Constant-Amplitude Pulse Trains

Abstract

Bilateral cochlear implantation attempts to increase performance over a monaural prosthesis by harnessing the binaural processing of the auditory system. Interaural time difference (ITD) is a major binaural cue and many neurons in the inferior colliculus (IC) are sensitive to ITD. We investigated ITD tuning in IC neurons of anesthetized cats stimulated with trains of electric current pulses delivered via bilaterally implanted intracochlear electrodes. We found that the majority of IC neurons are sensitive to ITD and that electric ITD tuning can be as sharp as that with acoustic stimulation in normal-hearing animals. The sharpness of ITD tuning and the degree of rate-modulation within the naturally occurring range of ITD depended on stimulus intensity in most IC neurons. Some units had a dynamic range of ITD sensitivity as low as 1-5 dB. We also found that neural ITD sensitivity was best at pulse rates below ~100 pps and decreased with increasing pulse rate. This rate limitation is consistent with behavioral ITD discrimination in bilaterally implanted individuals.
Introduction

The auditory system is wired such that having two ears has many functional advantages over a single ear, including improved speech reception in noise and more accurate sound localization. Despite this, tens of thousands of people have been treated for deafness by implanting a cochlear prosthesis at a single ear. These cochlear implant users often have good speech reception in quiet, but their speech understanding drops precipitously in the presence of competing sounds common in the everyday acoustic world. More recently, cochlear implant candidates are increasingly being implanted in both ears with the goals of improved speech intelligibility in noise and better sound localization. A key issue facing the design of bilateral cochlear implant systems is how acoustic information should be encoded into electric stimuli so that patients obtain a maximal benefit. We studied neurophysiological responses in the auditory midbrain of bilaterally implanted cats in order to identify stimulus configurations for effective delivery of binaural information. The primary focus is on interaural time difference (ITD) because ITD is the dominant cue used for the azimuthal localization of sounds containing low-frequency energy (Wightman and Kistler, 1992; Macpherson and Middlebrooks, 2002), and because binaural advantages in speech intelligibility in noise depend largely on the target and interferer having distinct ITDs (Zurek, 1993).

Studies in bilaterally implanted subjects show significant improvements in sound localization and speech intelligibility in spatially separated noise with bilateral over monolateral stimulation (Muller et al., 2002; Schon et al., 2002; van Hoesel et al., 2002; van Hoesel and Tyler, 2003). Direct tests of sensitivity to interaural level differences (ILD), show relatively good ILD discrimination thresholds that can be as low as the smallest ILD (~0.1-0.2 dB) allowed by clinical implant systems (Lawson et al., 1998; Long et al., 2003; van Hoesel and Tyler, 2003). ITD discrimination thresholds are more variable across subjects, and range from 50 µs (rare) to several milliseconds depending on the subject, pulse rate, and electrode pair tested (Lawson et al., 1998; van Hoesel and Tyler, 2003; Wilson et al., 2003). In comparison, discrimination of ITD for acoustic stimuli in normal-hearing subjects is better and more consistent across subjects, with JNDS of 10-20 µs for clicks (Klumpp and Eady, 1956; Yost et al., 1971).
The auditory brainstem contains nuclei specialized for the processing of ITD. Neural activity originating from both ears converges in the superior olivary complex (SOC). In this brainstem structure, there are two principal nuclei in which neurons are sensitive to ITD in different frequency ranges. Neurons in the medial superior olive (MSO) receive primarily low-frequency excitatory inputs from spherical bushy cells in the ventral cochlear nuclei in both sides. MSO neurons act as coincidence detectors and respond best at a particular ITD when inputs from each side arrive simultaneously (Goldberg and Brown, 1969; Yin and Chan, 1990). Neurons in the lateral superior olive (LSO) receive excitatory inputs from the ipsilateral ear via the ipsilateral cochlear nucleus and inhibitory inputs from the contralateral ear via the ipsilateral cochlear nucleus and the ipsilateral medial nucleus of the trapezoid body (MNTB). LSO cells are predominantly high-frequency and typically respond best when a stimulus is out of phase at the two ears (Joris and Yin, 1995). Both MSO and LSO neurons have direct and indirect projections to the IC. Neurons in the IC have ITD tuning that can resemble that in the MSO and LSO, and can also exhibit a cross between the two types (Yin and Kuwada, 1983b; Batra et al., 1993; McAlpine et al., 1998).

In the present study, we investigated the ITD sensitivity of IC neurons to electric pulse trains delivered via bilaterally implanted intracochlear electrodes. We found that the majority of neurons in the central nucleus are sensitive to ITD, with tuning as sharp as that seen with acoustic stimulation in normal-hearing animals. Some neurons exhibited ITD tuning over only a limited range of intensity. Neural ITD sensitivity sharply degraded at increasing pulse rates above 100 pps. Preliminary reports have been presented previously (Smith and Delgutte, 2003a, b; Smith and Delgutte, 2005b).
Methods

Subjects and Deafening

All surgical and experimental procedures followed the regulations set by NIH and were approved by the MEEI IACC. Healthy adult cats of either sex were deafened by co-administration of kanamycin (300 mg/kg subcutaneous) and ethacrynic acid (25 mg/kg intravenous, (Xu et al., 1993) 7-14 days prior to cochlear implantation and electrophysiological recordings.

Surgery

On the day of the experiment, after induction of anesthesia by Dial in urethane (75 mg/kg), a tracheal canula was inserted; skin and muscles overlying the back and top of the skull were reflected. Ear canals were transected for insertion of a closed acoustic system. Tympanic bullae were opened to allow access to the round-window for placement of intracochlear electrodes. Part of the skull overlying the occipital cortex was removed to allow for partial aspiration of cortical tissue and access to the bony tentorium and IC. The part of the tentorium overlying the IC was drilled for better access to the dorsal-lateral surface of the IC. Throughout all procedures, animals were given supplementary doses of anesthesia to maintain an areflexic state and vital signs were monitored.

Cochlear implantation and electrode configurations

Stimulating electrodes were surgically implanted into each cochlea through the exposed round window. The electrodes were either custom-made Pt/Ir ball electrodes (0.45 mm diameter), or 8-contact electrode arrays with 0.75 mm spacing (Cochlear Corp., ring-type contacts with 0.45 mm diameter). Particular care was taken to achieve the same insertion depth on both sides. In all experiments, we used a wide bipolar configuration (~5mm between electrodes), with the active electrode inserted ~5mm into the scala tympani and the return electrode (either another Pt/Ir ball or the most basal contact of the array) just inside the round window. This electrode configuration is similar to the monopolar configuration commonly used in clinical devices in that it produces a broad
pattern of excitation, but decreases the distance between the active and return electrodes thus reducing stimulus artifact measured at the recording electrodes (Litvak et al., 2003).

Effectiveness of the deafening protocol was assessed by measuring auditory brainstem response (ABR) thresholds to acoustic clicks in each ear. Calibrated acoustic assemblies comprising an electrodynamic speaker and a probe-tube microphone were inserted into the cut ends of each ear canal to form a closed system. Condensation clicks (100 µs) were delivered via these acoustic systems, and ABR thresholds measured in both ears. ABR was measured between vertex and ear bar using a small screw inserted into the skull. In all experiments, no acoustic ABR response was seen up to the highest intensity tested (110 dB SPL peak).

**Single-unit recordings and cancellation of stimulus artifact**

Single-unit activity in the IC was recorded using either parylene-insulated tungsten stereotrodes (Microprobe, ~2 MΩ impedance), or 16-channel silicon probes (NeuroNexus Technologies, 100 or 150 µm linear spacing, 177 µm² site area). Recording electrodes were advanced through the IC along one of two possible trajectories. The standard trajectory ran from dorsolateral to ventromedial, in the coronal plane tilted 45º off the sagittal plane so as to record activity from a set of neurons covering a highly-reproducible range of CFs (Merzenich and Reid, 1974; Snyder et al., 1990). The alternate electrode trajectory ran from dorsal to ventral in the coronal and parasagittal planes and is referred to as the 0º trajectory. The 0º trajectory was used in an effort to sample more neurons in the lateral part of the inferior colliculus where the majority of ascending projections from the MSO are located (Aitkin and Schuck, 1985; Oliver et al., 2003).

Stimulus artifact (the electric potential seen at the recording electrode directly resulting from current passing between the stimulating electrodes) was typically much larger than the single-unit activity. Recordings were made simultaneously from at least two sites, only one of which sampled the activity of the neuron of interest. Since stimulus artifact was present on both channels, it could be minimized by filtering and subtracting the reference channel (which only contains artifact) from the neuron channel with an adaptive filter. Real-time artifact cancellation was achieved using a least-mean-
square adaptive filter (Widrow et al., 1975), implemented in software running on a DSP board.

After online artifact cancellation, spikes from well-isolated single units were amplified and detected with a custom-built discriminator. Spike times were measured by a custom-built timer with a resolution of 1 µs, then processed and displayed by computer. All spike times were stored to disk for post-hoc analyses.

**Stimulus generation and delivery**

All stimuli were generated by a pair of 16-bit digital-to-analog converters (D/A) at a sampling rate of 100 kHz. Stimulus levels were set by custom-built attenuators having a resolution of 0.1 dB. Attenuated outputs of the D/A converters were delivered to the intracochlear electrodes via a pair of custom-built high-bandwidth (40 kHz), optically-isolated, constant-current sources. All electric stimuli were made up of 100 µs biphasic current pulses (cathodic-anodic, 50 µs/phase).

The search stimulus consisted of a sequence of three current pulses with a 100 ms interval between each pulse. The first two pulses were delivered monaurally to each ear in turn and the last pulse was binaural. The search stimulus was repeated at a rate of 2/s at an intensity suprathreshold to neurons near the recording electrode (as assessed by local field potentials). Once a single neuron was well isolated, its threshold was measured with monaural and binaural pulses. Following this preliminary characterization of the unit, ITD sensitivity was studied.

**ITD stimuli**

Both static and dynamic ITD stimuli were used to assess ITD tuning with 40 pps pulse trains. For static ITD stimuli, the 300 ms stimulus was repeated 10 times with a 200 ms gap between trials (dot raster display of response is shown in Fig. 2.1A). Stimuli with dynamic ITDs are commonly used to efficiently study ITD sensitivity in single units (Kuwada et al., 1979). In our study, dynamic stimuli had an ITD that changed with each pulse in the pulse train starting at -1000 µs and going to +1000 µs and then back to -1000 µs in 100 µs steps (Fig. 2.1B, dotted line shows evolution of dynamic ITD throughout the stimulus). Each forward and reverse sweep of the dynamic ITD stimulus was 1050 ms in
duration. It was repeated 20 times without any gap between repeats for a total duration of 21 s and 40 presentations of each ITD step.

Data Analysis

Spike times were processed to compute PST histograms and rate-ITD curves. For static ITD stimuli, response rates were computed for each ITD step in an ITD sequence, by windowing the response over the 300 ms of the stimulus in each trial. For the dynamic stimulus, spikes were gated so that spikes originating from a given stimulus pulse were assigned to its ITD. Since the pulse rate was 40 pps, the windows were the 25 ms between each pulse. Spikes were assigned to immediately preceding pulses.

Modulation depth (MD) was computed for rate-ITD curves where MD is defined:

$$MD = \frac{\max(rate) - \min(rate)}{\max(rate)}$$

Units were classified as being ITD sensitive if the MD of its rate-ITD curve was at least 0.5 at an intensity that evoked a minimum firing rate of 10 spikes/s (40 pps stimulus).

Rate-ITD curves were fit with several equations based on Gaussian and sigmoid functions. The Gaussian functions had the form:

$$rate(ITD) = Ae^{\left(-\frac{2\sqrt{\ln2}(ITD-ITD_{best})^2}{HW}\right)} + B$$

with the parameters ITD_{best}, HW, A, and B (best ITD, halfwidth, scale factor, and DC offset respectively). Positive values of A were used for peak-shaped ITD curves (Fig. 2.4A) and negative values for trough-shaped tuning (Fig. 2.4B). Monotonic-shaped ITD tuning was fit with a sigmoid function (Fig. 2.4C) that had the form:

$$rate(ITD) = \frac{A}{1 + e^{-\left(\frac{ITD-ITD_{MS}}{\tau}\right)}} + B$$

with the parameters ITD_{MS}, \tau, A, and B (ITD of maximum slope, steepness, scale factor, and DC offset). Responses with biphasic-shaped tuning (Fig. 2.4D) were fit with the following function that is the difference of two Gaussian functions:

$$rate(ITD) = A \left[ e^{\left(-\frac{(ITD-ITD_{MS}-D)^2}{D}\right)} - e^{\left(-\frac{(ITD-ITD_{MS}+D)^2}{D}\right)} \right] + B$$
with the parameters ITD\textsubscript{MS}, D, A, and B (ITD of maximum slope, width and distance between two Gaussians, scale factor, DC offset).

We used several measures to compare the ITD tuning characteristics of different neurons. These included best ITD (ITD\textsubscript{best}), halfwidth (HW), maximum slope, ITD of maximum slope (ITD\textsubscript{MS}), halfrise, physiological modulation range (PMR), and physiological modulation depth (PMD). These measures were obtained directly or calculated based on the fits to individual rate-ITD tuning curves. Since many of the fitted functions were symmetric, ITD\textsubscript{MS} was defined as the ITD closest to 0 with the maximum slope. Halfrise was defined as the width of the rate-ITD curve between 25\% and 75\% normalized response, centered on ITD\textsubscript{MS}. Physiological modulation range (PMR) was defined as the range of rates within the physiological range of ITD. Physiological modulation depth (PMD) is the physiological modulation range divided by the maximum discharge rate (at any ITD).

**Neural Discrimination**

ITD discrimination of single neurons was quantified by expressing the difference in spike counts elicited by stimuli at two different ITDs in units of their combined standard deviation. The metric of neural discrimination used was a slightly modified version of standard separation (Sakitt, 1973), or $D$, and was defined as:

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

where $\mu_{\text{ITD}}$ and $\mu_{\text{ITD+\text{\Delta ITD}}}$ are the means of the spike counts and $\sigma_{\text{ITD}}$ and $\sigma_{\text{ITD+\text{\Delta ITD}}}$ their respective standard deviations. We replaced the geometric mean of variances in the original definition of $D$ with the arithmetic mean to avoid problems when the mean and variance of the spike counts are 0 for one of the ITDs. Standard separation is analogous to $d'$ which is often used to quantify discrimination in psychophysical studies (Green and Swets, 1966). The just noticeable difference (JND), for a given ITD was defined as the $\Delta$ITD needed for the standard separation to reach a value of 1 (and corresponds to $\sim$76\% correct in a two-interval discrimination task).
Results

Results are based on responses of 140 IC neurons to bilateral electric stimulation of the cochlea in 21 deafened cats. We first describe the basic responses of IC neurons as a function of ITD for pulse-train stimuli and then look at the influence of stimulus intensity, interaural level difference (ILD), and stimulus pulse rate on ITD tuning. We then make estimates of neural ITD discrimination thresholds for single neurons and compare them with behavioral thresholds from human bilateral cochlear implant subjects (van Hoesel and Tyler, 2003; Poon, 2006).

Comparison of responses to static and dynamic ITD stimuli

Of the 140 neurons studied, 121 were classified as ITD sensitive (MD ≥ 0.5). The basic stimulus was a fixed-rate pulse train (40 pps) with either a static or dynamic ITD. ITD was typically varied from -1000 µs to +1000 µs (positive ITD values indicate a contralateral leading stimulus) in 100 µs steps. A larger range of ITD (e.g. ±2000 µs) was occasionally used for neurons with relatively broad ITD tuning. The dynamic stimulus allowed for rapid characterization of the ITD tuning function. Example spiking patterns from one neuron in response to static and dynamic ITD stimuli are shown in Fig. 2.1 (static ITD – Fig. 2.1A; dynamic ITD – Fig2.1B). The spike raster display for the static ITD stimulus shows that spikes are tightly time-locked to the individual stimulus pulses. The shapes of the rate-ITD tuning curves derived from the responses to the two different stimuli are very similar suggesting that dynamic ITD has little affect on ITD tuning shape.

Fig. 2.2A shows rate-ITD curves from eight neurons and compares results using static and dynamic ITD stimuli. For most neurons, the shapes of the rate-ITD curves are similar for both stimulus types. However, there are obvious differences in overall spike rate for some of the neurons. Fig. 2.2B shows ITD$_{best}$ from 27 neurons with peak- or trough-shaped tuning with measures obtained with static ITD stimuli plotted against those with dynamic ITD stimuli. A similar comparison is made for the width of ITD tuning in Fig. 2.2C, which shows ITD halfwidth (same neurons as in Fig. 2.2B). While best ITD (ITD$_{best}$) are similar for the two stimuli, halfwidths are generally wider with
static than with dynamic stimuli (with 21/27 points on the right side of the equality line). Differences between ITD functions measured in these two fashions may arise because of the difference in duration of the stimuli and/or the dynamic nature of the ITD. Some neurons showed rapid adaptation to a stimulus and thus the continuous dynamic stimulus might elicit a lower spike rate. Alternatively, the dynamic nature of the dynamic ITD stimulus may intrinsically evoke a stronger peak spike rate and sharper tuning (Spitzer and Semple, 1991, 1998).

**Synchrony and entrainment of firing**

Spikes were generally highly time-locked to the stimulus pulses as can be seen in the dot raster display in Figure 2.1A. Spike latency and jitter were analyzed for all responses to static ITD stimuli in 40 neurons (1154 measurements). Consistent with a previous study of IC neural responses to electric stimulation of the cochlea in acutely deafened animals (Shepherd et al., 1999), mean spike latency was typically between 5-10 ms (Fig. 2.3A). The absence of many longer latency responses suggests that the neurons studied were indeed from the central nucleus of the IC. There was a slight inverse correlation between spike latency and spike rate ($r = -0.17, p < 0.001$, Fig. 2.3C). Spike jitter (standard deviation of spike latencies in one measurement) was typically low ($\mu = 0.88$ ms, Fig. 2.3B) and there was also a slight inverse correlation between spike jitter and spike rate ($r = -0.14, p < 0.001$, Fig. 2.3D).

**Stereotyped ITD tuning shapes**

To better quantify the ITD tuning of IC rate responses to electric stimulation, we fit each of four response shapes to the measured rate-ITD curves (peak, trough, monotonic, and biphasic). Based on these least-squares fits, rate-ITD response curves were assigned to one of the four response shapes corresponding to the best fit. A fifth group was made up of responses that were not well fit by any of the stereotyped shapes and typically had multiple peaks. For each ITD sensitive neuron, ITD curves were measured using the dynamic ITD stimulus at 40 pps. Since ITD tuning often changed with intensity, comparisons across neurons were made at a standard intensity. This intensity was the lowest intensity that elicited a spike rate greater than 0.5 spikes/pulse.
for at least one ITD value. Fig. 2.4A-D shows the four response shapes (see Methods for equations). Fig. 2.4E-H shows rate-ITD functions, normalized and shifted so that they are centered at 0 with a width of 1, for each ITD type. This was done for each neuron and shows how well the stereotyped functions are able to capture the shape of the actual rate-ITD curves. At the standard intensity, the majority of neurons (80/121) had peak ITD tuning. The ITD tuning of the remaining neurons were roughly evenly split between trough (12/121), monotonic (10/121), biphasic (9/121), and multi-peaked (10/121) ITD tuning.

Summary statistics of ITD tuning

ITD tuning characteristics were calculated for our population of neurons with electric stimulation at the standard intensity. ITD_{best} and halfwidth were calculated from rate-ITD fits for all peak and trough neurons (N = 92). Distribution of ITD_{best} is shown as black bars in Fig. 2.5A. The majority (68/92) of units’ ITD_{best} falls within the natural range of ITD for cat (approximately +/- 350 µs) and there is a clear contralateral bias to the distribution (mean = 161 µs, σ = 335 µs, and 86% of ITD_{best} > 0). When compared to data from IC neurons in acoustically stimulated cats (shown as black lines, N=166, broadband noise) (Hancock and Delgutte, 2004), both distributions have a clear contralateral bias for ITD_{best}, but the acoustic data have a mean ITD_{best} that is much further from 0 and the spread in the distribution is much wider (mean = 252 µs, σ = 607 µs). A two-sample Kolmogorov-Smirnov test shows that the electric and acoustic ITD_{best} distributions are significantly different (p < 0.01). This difference may arise from the electric population consisting of neurons at a wide range of electrode depths, and thus a putative wide range of CFs, while the acoustic population only contains of low-CF neurons (<3 kHz).

Distribution of halfwidths for electric stimulation is shown in Fig. 2.5B and had a mean of 691 µs. Distributions of halfwidth for electric and acoustic stimulation were not significantly different (p=0.68). This is important since ITD selectivity appears to be as sharp with electric pulses as with acoustic broadband noise despite differences in stimuli and neuronal sampling.
Since ITD$_{\text{best}}$ and halfwidth were only defined for peak and trough neurons, we also looked at ITD$_{\text{MS}}$, halfrise, and physiological modulation depth. This allowed the inclusion of monotonic and biphasic responses together with the peak and trough. ITD$_{\text{MS}}$ is where the greatest change in rate for a given change in ITD occurs and therefore where sensitivity is greatest. Fig. 2.5C shows the distribution of ITD$_{\text{MS}}$ for electric stimulation in black bars. The ITD$_{\text{MS}}$ of the majority of characterized neurons (93/111) was within the natural range of ITD with a mean of -70 µs and standard deviation of 311 µs. Comparing this distribution with that from acoustic stimulation (red lines), the distributions are significantly different ($p < 0.01$). Indeed, the electric distribution has a slight ipsilateral bias while the acoustic distribution is more closely centered on zero. Also the electric distribution is narrower than the acoustic distribution.

Halfrise measures the width over which the ITD curve rises from 25% to 75% of its maximum response. For peak and trough neurons, halfrise was about 0.4 times the halfwidth. The distribution of halfrise for the population of characterized neurons (N = 111) is shown in Fig. 2.5D and has a mean of 293 µs. Distributions of electric and acoustic (shown in black) halfrise were not significantly different ($p=0.072$), just as there were not significant differences for halfwidth.

Physiological modulation depth (PMD) was calculated from the fits to each neuron’s rate-ITD curve at the standard intensity. The PMD is the range of discharge rates within the physiological range of ITD divided by the maximum rate for a given rate-ITD curve. Fig. 2.5E shows the distribution of PMD for electric stimulation in black bars. The mean PMD was 0.70 and more than half of neurons had at least an 80% change in discharge rate within the physiological range of ITD. When compared to acoustic stimulation (shown in red), the distribution of PMD is very similar. Since intensity can have a large effect on PMD with electric stimulation (see next section), the similarity between electric and acoustic PMD may depend on the choice of standard intensity.

When the ITD tuning characteristics of neurons’ rate-ITD curves are compared across response shapes (see Fig. 2.6A), peak-shaped responses are on average more sharply tuned to ITD than the other three response shapes and would be expected to have lower ITD JNDs. This is indicated in Fig. 2.6A in the lower left-hand corner by narrower tuning (low halfrise) and ITD$_{\text{MS}}$ near 0 µs ITD.
It is remarkable how similar ITD tuning is in IC neurons stimulated with electric current in the cochlear or with acoustic sound. The only significant differences are in the distributions of ITD<sub>best</sub> and ITD<sub>MS</sub>, though these differences are small compared to the widths of the distributions. With electric stimulation, neurons tend to have a tighter ITD<sub>best</sub> distribution closer to 0 µs ITD. Since acoustically, ITD<sub>best</sub> inversely correlates with CF, differences between acoustic and electric ITD tuning may be a consequence of recording from different ranges of CFs.

*Trends with electrode depth*

Since CF could not be directly measured in neurons from deafened animals, ITD tuning characteristics were analyzed as a function of electrode depth, which closely correlates with CF in the dorso-ventral electrode penetrations (Snyder et al., 1990). All electrode penetrations were either 45 degrees off the sagital plane (standard trajectory) or parallel to it going from posterior to ventral (alternate trajectory). The standard angle was chosen so that the electrode would travel parallel to the tonotopic axis of the central nucleus of the inferior colliculus (ICC). As depth of the electrode increased, so should the characteristic frequency (CF) of the neurons (Merzenich and Reid, 1974; Snyder et al., 1990), with low-CF neurons at the dorsal-lateral edge of the ICC and high-CF neurons at deeper depths (towards ventral-medial). Although CF is expected to increase at a smaller rate with the alternate trajectory (0°) than with the standard trajectory (45°), separate analysis did not show any obvious difference between the two trajectories, so the two sets of data were combined.

We found no significant correlation of ITD<sub>best</sub>, halfwidth, max slope, halfrise, and PMD with electrode depth ($r^2 < 0.01$ and $p > 0.35$ for all ITD characteristics). Fig. 2.6B-C shows ITD<sub>best</sub> and halfwidth as a function of electrode depth for peak and tough shaped responses. For acoustic stimulation, there is an inverse correlation for ITD<sub>best</sub> and halfwidth in low-frequency ITD-sensitive IC neurons and a positive correlation of ITD<sub>best</sub> with halfwidth (McAlpine et al., 2001). While there is no obvious trend for ITD<sub>best</sub> and halfwidth with IC depth with electric stimulation, the peak of the ITD<sub>MS</sub> distribution is near 0 for both types of stimulation (Fig. 2.5B). There is also no clear segregation of unit types as may have been expected given the idea that binaural inputs to low-CF units
come from the MSO and give rise to peak-type) responses while binaural inputs to higher-CF units come from the LSO and give rise to trough-type responses (Batra et al., 1997).

**Influence of overall intensity**

Thus far, all rate-ITD responses were measured at the standard intensity, which was usually 1-2 dB above threshold. Many neurons were studied over a range of intensities and it was found that stimulus intensity could have a large effect on rate-ITD tuning. Fig. 2.7 shows ITD curves for nine different neurons over a range of stimulus intensities. The neurons shown in the top row (Fig. 2.7A-C) had peak shaped ITD tuning at levels just above threshold; as intensity increased, ITD tuning broadened and eventually saturated at 7, 1.5, and 2.6 dB above threshold respectively. The middle row (Fig. 2.7D-F) shows rate-ITD curves for three more neurons that had peak-shaped tuning at low intensities that broadened with increasing intensity. However, unlike the neurons in the top row, these neurons did not fully saturate at any of the intensities tested. The bottom row (Fig. 2.7G-I) shows three neurons that did not show decreased tuning with increasing intensity over the range of intensities tested.

Not only did the sharpness of ITD tuning change with intensity for many neurons, but often the shape of the ITD tuning curve could change with intensity as seen for the unit in Fig. 2.7D. Fig. 2.8A shows the evolution of ITD tuning shape for 99 neurons that were studied at a minimum of 3 intensities. At the lowest intensities (just above threshold), most neurons (78%) had peak-shape responses, while 12% had biphasic-, 8% had trough-, and only 2% had monotonic-shaped responses. At mid levels, the number of peak-shaped neurons decreased, with the largest gains going to biphasic-shaped neurons which jumped to 30% of the population. The proportions of trough- and monotonic-shaped neurons also increased somewhat at mid intensities to 16% and 9% respectively. At the highest levels (without saturating the response) the largest change was an increase in trough-shaped responses with about equal decreases in peak-shaped responses. The proportion of ITD tuning shapes at high intensities was about evenly split between peak-, trough-, and biphasic-shapes at 36%, 22%, and 30% respectively and then ~11% monotonic-shaped.
For neurons that remained peak-shaped over a range of intensities, \( \text{ITD}_{\text{best}} \) showed no significant or consistent change. However, this same group showed a general increase in halfwidth with increases in intensity. We can consider a larger number of neurons if we look at \( \text{ITD}_{\text{MS}} \) and halfrise which can be measured regardless of ITD tuning shape. A straight line was fit to plots of these features as a function of intensity for each neuron using linear regression. Fig. 2.8B shows the distribution of the slopes of the regression lines (in \( \text{ITD}_{\text{MS}} \) per dB) for neurons whose \( \text{ITD}_{\text{MS}} \) were positive (increasing response with increasing ITD). The mean change in \( \text{ITD}_{\text{MS}} \) was \(-84 \mu s/dB\) and about 76\% of neurons had the location of \( \text{ITD}_{\text{MS}} \) move towards more ipsilateral leading stimuli. Fig. 2.8C shows the change in halfrise per dB change in intensity for 93 neurons. The mean change is \(+42 \mu s/dB\) and about 73\% of neurons show an increase in halfrise with increasing intensity. This is consistent with the observation of widening ITD tuning seen in peak-only responses with increasing intensity.

Plots of physiological modulation range (PMR) of ITD tuning, as a function of intensity, show somewhat different patterns. For neurons that clearly saturated at higher intensities, PMR typically increased with intensity up to a certain point and then decreased towards zero at the saturation intensity. PMR for these neurons is shown in Fig. 2.8D where the horizontal axis is in dB re the intensity where PMR was maximal. Fig. 2.8E shows PMR versus intensity for neurons that had a PMR peak but did not completely saturate at the levels tested. The remaining neurons shown in Fig. 2.8F had increasing or no change in PMR with increasing intensity. It is unknown whether the PMR of these neurons would decrease at intensities higher than those tested. This analysis shows that slightly over half of all neurons (32/58) had limited dynamic ranges (first two categories, Fig. 2.8D-E) in their ITD tuning for the range of intensities tested.

*Effect of interaural level differences (ILD)*

Since naturally occurring binaural stimuli include interaural differences in intensity as well as in time, the effect of interaural level difference (ILD) on ITD tuning was studied for some cells. Typically, within a small range of ILD, ITD tuning remained well defined, but there were shifts in \( \text{ITD}_{\text{best}} \). Fig. 2.9A shows normalized rate-ITD curves for an example single unit at a range of ILDs (from -3 to +3 dB). While tuning
width remains nearly constant, ITD_{best} shifts towards more contralateral leading values (more positive ITD) with increasing intensity in the contralateral ear (Fig. 2.9B). A straight line fit to the data points has a slope of about 60 µs/dB. Fig. 2.9C shows ITD_{best} versus ILD for 16 units which had peak shaped ITD tuning. 11/16 units had negative slopes and 5/16 had positive slopes. The average magnitude of the slope was 42 µs/dB. Fig. 2.9D is a scatter plot of ITD_{best} versus ILD slopes as a function of ITD_{best} at an ILD of 0 dB. There is a significant inverse correlation between slope and ITD_{best} (r = -0.67, p < 0.005). This also seen in Fig. 2.9C as ITD_{best} tends to go towards 0 at more positive ILDs (greater intensity at contralateral ear).

**Neural discrimination thresholds**

The standard stimulus in this study was a 40 pps pulse train with either a static or dynamic ITD. A range of pulse rates (40-320 pps) was presented with static ITDs to 8 neurons to examine the effect of stimulus pulse rate on the ITD sensitivity of IC neurons. Results from an example neuron are shown in Fig. 2.10A. As the pulse rate increases, responses no longer occur over the entire stimulus duration and become increasingly limited to the stimulus onset. The shape of ITD tuning curves is maintained at higher stimulation rates but the overall firing rate is lower (Fig. 2.10B).

In an effort to compare ITD sensitivity with electric cochlear stimulation between single neurons in our cat preparation and human behavior, neural detection thresholds were estimated based on single neuron responses. The standard separation (Sakitt, 1973) was computed between each point in an ITD sequence and 0 µs ITD. This analysis was used to estimate the detection threshold in single units based on the spike rate statistics of individual trials. Standard separation is plotted as a function of ITD for the example neuron in Fig. 2.10C. The just noticeable difference (JND), is the ITD closest to 0 that reaches a standard separation of 1. For the neuron displayed in Fig. 2.10, the ITD JNDs at 40, 80, 160, and 320 pps are approximately 118, 250, 460, and 620 µs respectively.

The mean ITD discrimination thresholds for 8 single neurons are shown as a function of stimulus rate in Fig. 2.11A. At 40 and 80 pps, mean neural ITD JNDs were about 150 µs. At higher stimulus rates, the ITD needed to produce a significant change in the firing rate of a neuron increases. The mean ITD JNDs at 160 and 320 pps were 300
and 500 µs respectively. The relative contribution of onset and sustained responses at different pulse rates was characterized by splitting responses into two time segments and calculating ITD JNDs. Discrimination thresholds based on the first 50 ms of the response (onset) and the remaining 250 ms of the response (sustained) are plotted with thresholds based on the full response in Fig. 2.11B. As a function of pulse rate, thresholds from the onset response are roughly flat while thresholds from the sustained response are good at 40-80 pps but get progressively worse at 160 and 320 pps. Comparison of thresholds based on the onset and sustained responses with those based on the full response shows that at 40 pps, thresholds are dominated by the sustained response, while at 320 pps, thresholds are dominated by the onset response.

Since sustained responses are responsible for the lower ITD JNDs observed with lower-rate pulse trains, we also analyzed the contribution of each pulse in a 40 pps pulse train to the discrimination threshold. Since spikes were tightly locked to each stimulus pulse, this was achieved by windowing the response between each pulse. Fig. 2.11C shows ITD JNDs for 22 neurons as a function of the number of pulses in a 40 pps pulse train. Mean ITD discrimination thresholds dropped linearly on a log-log scale, with mean thresholds decreasing from ~500 µs for one pulse to ~100 µs for 12 pulses. The dotted line in Fig. 2.11C shows the best ITD JND of any single neuron, over the 22 neurons tested, as a function of the number of pulses. The best thresholds were about a factor of 5 times better than the mean thresholds, with the best ITD JND decreasing from ~100 µs for one pulse to ~20 µs for 12 pulses.

All of the ITD discrimination thresholds up to this point were calculated from a reference ITD of 0 µs. Fig. 2.11D plots the mean ITD JND at 40 pps as a function of reference ITD (N = 22 neurons). Between reference ITDs of -300 to +300 µs, the ITD JND is roughly constant, while for greater reference ITDs, thresholds slowly get worse. This result is consistent with the earlier finding that the distribution of ITD_{MS} is centered near 0 µs ITD and has a standard deviation of ~300 µs.

Effect of different interaural electrode pairings on ITD tuning

In a few neurons, the effect of an offset in the cochlear place of stimulation between the two ears on ITD tuning was studied. Choice of interaural electrode pairings
has been shown to be important in human behavioral tests of ITD discrimination (Long et al., 2003), with pitch-matched electrodes generally showing the lowest ITD JNDs. For this section, bipolar stimulation was used in animals implanted with the 8-contact Nucleus intracochlear electrode arrays. In bipolar electrode configuration, the return electrode is always 1 contact along the array basal to the active electrode (0.75 mm spacing). The cochlear place of stimulation and stimulus intensity were fixed in one ear while the place of stimulation in the other ear was varied and tested at several stimulus intensities. ITD tuning was characterized in 5 neurons at interaural electrode offsets between ±2 electrodes. Fig. 2.12A shows rate-ITD curves for an example neuron at different interaural electrode offsets. There is good ITD tuning at offsets of -1 and 0, but ITD tuning is flat at wider offsets in either direction. The maximum slope of the fitted rate-ITD curves was used in this case to characterize of degree of ITD tuning. Large values of maximum slope indicate sharp ITD tuning and small values indicate poor ITD tuning. Fig. 2.12B shows the maximum slope of each rate-ITD curve from Fig. 2.12A and confirms that ITD tuning degrades at increasing interaural electrode offsets for this neuron. While the results from this neuron show a significant effect of interaural electrode offset on ITD tuning, the other neurons showed less of an effect. Fig. 12C shows the mean maximum slope as a function of interaural electrode offset across all 5 neurons tested. Overall, there is little effect of interaural electrode offset on ITD tuning. This is partly because peaks in the maximum slope occur at different electrode offsets for different neurons, but also because most of the neurons were capable of showing significant ITD tuning at various interaural electrode offsets when the intensity of the varied ear was properly adjusted. Across all neurons, a two-way ANOVA showed no significant effect of electrode offset on maximum slope ($p = 0.099$), but a significant effect of the neuron on maximum slope ($p < 0.001$).
Discussion

This is the first neurophysiological study of ITD sensitivity with bilateral cochlear implants. Our main finding is that ITD sensitivity of IC neurons with electric stimulation was in many ways similar to that with acoustic stimulation despite the lack of cochlear processing with electric stimulation. This result is encouraging for the prospect of restoring the benefits of ITD for bilaterally implanted individuals.

Comparison of ITD tuning with electric and acoustic stimulation

Most studies of the ITD sensitivity of IC neurons with acoustic stimulation have focused on low-CF neurons in the central nucleus of the IC (Rose et al., 1966; Kuwada et al., 1979; Kuwada and Yin, 1983; Yin and Kuwada, 1983b, a; Yin et al., 1986; Kuwada et al., 1987; Palmer et al., 1990; McAlpine et al., 1996; McAlpine et al., 1998; McAlpine et al., 2001; Shackleton et al., 2003). Some studies have focused on the sensitivity of high-CF neurons to envelope ITD (Yin et al., 1984; Caird and Klinke, 1987; Batra et al., 1993; Griffin et al., 2005). In this study, with electric stimulation, neurons with a putative wide range of CFs were recorded from. This may explain the differences in the distributions of ITD<sub>best</sub> and ITD<sub>MS</sub> with acoustic and electric stimulation (Fig. 2.5A-B). Despite the different sampling of neurons, the distributions of halfwidth, halfrise, and physiological modulation depth found with electric stimulation are remarkably similar to those with acoustic stimulation (Fig. 2.5C-E). Mean ITD<sub>best</sub> and halfwidth are both inversely correlated with CF in the IC of normal-hearing animals (McAlpine et al., 2001; Hancock and Delgutte, 2004). These trends are lacking with pulsatile electric stimulation (Fig. 2.6B-C), possibly as a result of bypassing the mechanisms of the cochlea that provide its sharp frequency tuning. The mean ITD<sub>best</sub> inverse correlation observed in normal-hearing animals may reflect the influence of cochlear delays, which are also inversely correlated with CF, in the normal system (Shamma et al., 1989; Joris et al., 2004).

ITD tuning characteristics were remarkably homogenous throughout the IC with electric stimulation, regardless of the electrode depth along the tonotopic axis of the IC. This suggests that differences in binaural processing between low- and high-CF neurons
seen with acoustic hearing, such as broader ITD tuning and loss of sensitivity to fine structure ITD in high-CF neurons, may be primarily influenced by differences in cochlear processing and not by differences in neural mechanisms. This was predicted by an early model of ITD sensitivity (Colburn and Esquissaud, 1976) and is also supported by more recent psychophysical and physiological studies using “transposed stimuli” (Bernstein and Trahiotis, 2002; Griffin et al., 2005).

ITD tuning was found to be highly sensitive to overall stimulus intensity with electric stimulation. Intensity steps as small as 1 dB were often sufficient to dramatically change the shape and reduce the tuning of rate-ITD curves in individual neurons (Figs. 2.7 and 2.8). In contrast, stimulation with low-frequency acoustic tones shows robust ITD tuning over 40 dB, with only slight shifts in ITD\(_{\text{best}}\) (Kuwada and Yin, 1983; Fitzpatrick et al., 2005), though acoustic clicks can show large changes in ITD tuning with intensity (Carney and Yin, 1989). This difference may arise as early as the auditory nerve, where the dynamic range of single-fiber responses is between 15-40 dB for acoustic pure tones (Sachs and Abbas, 1974) whereas with electric pulse trains and sinusoids, the dynamic range is between 1-4 dB (Moxon, 1967; van den Honert and Stypulkowski, 1987b; Javel and Shepherd, 2000). It is difficult to know whether this reduction in dynamic range would have an impact on behavioral ITD sensitivity. A large reduction in the dynamic range of ITD tuning with clicks, an acoustic stimulus that is very similar to our current pulses, has been reported in IC neurons (Carney and Yin, 1989). However, clicks are one of the best stimuli for behavioral ITD discrimination in normal-hearing humans (Klumpp and Eady, 1956; Yost et al., 1971), suggesting that a large dynamic range in single IC neurons may not be behaviorally essential. Perhaps only a small subpopulation of neurons with good ITD tuning is required for good behavior ITD sensitivity over the full range of stimulus intensities. Such a requirement could be met by a fixed subpopulation of IC neurons with large dynamic ranges (Fig. 2.7G-J) or by a changing subpopulation of neurons at the flanking edges of the neural excitation pattern that only have good ITD tuning at intensities near threshold.

In this study, we also found that ITD tuning depends on ILD. Small changes in ILD resulted in systematic ITD\(_{\text{best}}\) shifts and were expressed in terms of a time-intensity trading ratio (\(\Delta\text{ITD}_{\text{best}}/\Delta\text{ILD}\)). Time-intensity trading ratios have also been characterized
in low-CF neurons with pure tone stimulation in normal-hearing animals (Yin and Kuwada, 1983a), where ILD caused a mean change in magnitude of mean interaural delay of 5.8 µs/dB with binaural beat tones. In another study of the IC (Caird and Klinke, 1987), high-frequency neurons had mean time-intensity trading ratios of 91 µs/dB when stimulated with CF tone bursts and 40 µs/dB when stimulated with clicks. For electric stimulation with pulses, we found a mean time-intensity trading ratio of 42 µs/dB, which is most consistent with acoustic stimulation of high-CF neurons with clicks.

Effect of pulse rate on IC responses

Neural ITD JNDs generally started to degrade with increasing pulse rates above 100 pps (Figs. 2.10 and 2.11A-B). Pulse rate had little effect on the ITD tuning characteristics ITD_{best} and halfwidth, but higher pulse rates largely resulted in a suppression of the overall response. A stimulus rate limitation (pulse rates and frequencies above 100-300 Hz) on the sustained and phase-locked responses of neurons in the IC, seems to be a common observation in anesthetized animals with electric stimulation (Snyder et al., 1991; Snyder et al., 1995), but is not observed in the auditory nerve (Moxon, 1967; van den Honert and Stypulkowski, 1987b; Parkins, 1989). Stimulation with pure tones in normal-hearing animals does not show a similar limitation with increasing frequency.

Comparison of neural ITD discrimination with human psychophysics

While inter-subject variability in psychophysical data with cochlear implant subjects makes it difficult to compare absolute performance, several trends in the ITD discrimination threshold data for single IC neurons can be compared to behavioral results in bilaterally implanted human subjects. Neural ITD JNDs generally degraded with increasing pulse rates above 100 pps (up to 320 pps tested, Fig. 2.11A). This trend has also been observed psychophysically in human subjects (van Hoesel and Tyler, 2003; Poon, 2006), where higher pulse rates have been studied. By analyzing different portions of the neural response, we showed that, at lower pulse rates (<100 pps), the ITD JND is
dominated by information provided by the sustained portion of the response (Fig. 2.11B). In contrast, at the highest rate tested (320 pps), neurons did not respond in a sustained fashion, and only the response just following the stimulus onset contributed to the ITD JND. Similarly, behavioral ITD discrimination thresholds of 50 pps stimuli improve with an increasing number of pulses in the stimulus, while ITD discrimination of 800 pps is completely based on the stimulus onset (Poon, 2006). Finally, the contribution of successive pulses in the standard 40 pps pulse train stimulus was shown to decrease neural ITD JNDs linearly on a log-log axis (Fig. 2.11C). On a log-log scale, the slope of this decrease is approximately -0.5 (inverse square root), which is the theoretical change predicted by perfect integration of equal ITD information from each pulse due to reduction in the variance. The same trend was also observed at 50 pps in the human behavioral data previously mentioned (Poon, 2006).

It is remarkable that these trends in ITD discrimination are so similar between the physiology and psychophysics despite many differences between our animal model and human subjects. There are also many similarities in the ITD tuning seen in the IC with electric and acoustic stimulation. Despite this, there is still a large gap in the performance of normal-hearing and bilaterally implanted human subjects. The best neural ITD JNDs were on the order of 20 µs, while ITD JNDs in best human subjects are usually on the order of 100 µs and can be much larger in other subjects. The animals used in this study represent the best case scenario in terms of neural survival and normal binaural experience. On the contrary, the human subjects used in the behavioral studies have varying amounts of acoustic experience, duration of deafness, and experience with bilateral implants. Also, the clinical sound processors used on a daily basis by cochlear implant subjects do not preserve the fine timing of the acoustic signal normally important for ITD. These differences in experience may underlie the difference in absolute ITD discrimination thresholds. Future studies should address the issues of experience on binaural processing.

**Implications for ITD coding with bilateral cochlear implants**

Our results indicate that single IC neurons in acutely deafened animals are sensitive to ITD with electric stimulation and have ITD tuning that is as selective as with
acoustic stimulation. However, good ITD tuning with electric stimulation was limited to pulse rates below 100 pps, due to a decrease in sustained neural firing at higher rates, and in some neurons, a small range of stimulus intensities. Issues that are not addressed in this chapter that are relevant to clinical applications of bilateral cochlear implants, include the use of more complex and realistic stimuli (see Chapter 3), interactions between neighboring electrodes, and the long-term effects of deafness and bilateral stimulation on the auditory CNS.
Figures

2.1 Responses to static and dynamic ITD stimuli in the same neuron show similar ITD tuning.
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2.12 Effect of interaural electrode offsets on ITD tuning.
Fig. 1. Responses to static and dynamic ITD stimuli from the same neuron.

Fig. 2.1. Responses to static and dynamic ITD stimuli in the same neuron show similar ITD tuning. Left panels are spike raster displays for example responses to static and dynamic ITD stimuli. The panels to the right of each spike raster show the mean spike rate for each ITD step. (A) Static ITD stimulus. Each row in the spike raster is a different ITD step which is repeated 10 times. The pulse rate is 40 pps and spikes are tightly time-locked to the individual stimulus pulses. (B) Dynamic ITD stimulus. The dashed line in the spike raster shows instantaneous values of ITD as it sweeps periodically between -1000 µs and +1000 µs. Dots indicate spikes and are associated with an ITD based on windowing the spike times with the stimulus pulses.
Fig. 2.2. Comparison of ITD tuning with static and dynamic ITDs. (A) Rate-ITD tuning for static ITD (solid black lines) and dynamic ITD (dashed red lines) stimuli measured in eight different single neurons (different subpanels). (B) Pairwise comparison of ITD$_{\text{best}}$ in neurons with peak-shaped ITD tuning for static- and dynamic-ITD stimuli ($n = 29$ neurons). Mean ITD$_{\text{best}}$ ratio = 1.04 ± 0.53 and distributions are not significantly different ($t$-test, $p = 0.74$). (C) Pairwise comparison of halfwidth in neurons with peak-shaped ITD tuning for static- and dynamic-ITD stimuli ($n = 29$ neurons). Mean halfwidth ratio = 0.75 ± 0.33, and 23/29 (79%) have ratios < 1.
Fig. 2.3. Spike latency and jitter. (A) Mean spike latency for all pulses in static ITD stimuli at 40 pps (1154 measurements in 40 neurons). Most responses have latencies between 5-10 ms. (B) Spike jitter (standard deviation of spike latency for the same neuron and stimulus) is low with electric stimulation (mean = 0.88 µs). (C) Firing rate and spike latency are inversely correlated \( r = -0.17, p < 0.001 \). (D) Firing rate and spike jitter are also inversely correlated \( r = -0.14, p < 0.001 \).
Fig. 2.4. Standard shapes of rate-ITD functions and data fits. 

(A-D) Idealized response shapes are shown with metrics to describe ITD tuning. Shading indicates the physiological range of ITD naturally occurring for a cat. For each functional type the physiological modulation depth and $\text{ITD}_{\text{MS}}$ is shown. For peak and trough functions “ITD$_{\text{best}}$” and “halfwidth” are also defined. (A) A positive Gaussian function is used to represent peak shape responses, the example function shown has a best ITD of 300 $\mu$s, halfwidth of 600 $\mu$s, and physiological modulation depth of 80%. (B) A negative Gaussian function is used to characterize trough type response shapes. (C) A sigmoid function is used to characterize monotonic ITD tuning. (D) The difference of two Gaussian functions is used to describe biphasic ITD tuning (see Methods for equations). (E-H) show the ITD functions of all classified neurons (one trace per neuron). Response shapes are scaled and shifted in both response amplitude and ITD to show the degree of fit to the designated ITD tuning shape.
Fig. 2.5. Distributions of ITD_{best}, ITD_{MS}, halfwidth, and physiological modulation depth for electric pulses (N = 92, 111 for ITD_{MS}) and acoustic broadband noise (N = 166) stimulation. ITD_{best} and ITD_{MS} distributions are significantly different between electric and acoustic stimulation ($p < 0.01$). The distributions of halfwidth and halfrise are not significantly different between electric and acoustic stimulation ($p = 0.58$, $p = 0.07$). Comparison of physiological modulation depth shows that most of a neurons dynamic range is relevant for real ITD coding in this population of neurons. (Distributions compared with the two-sample Kolmogorov-Smirnov test.)
Fig. 2.6. ITD tuning characteristics across tuning shape and location in the IC. (A) Peak shaped responses tend to have smaller ITD_{MS} and halfrise than all other response shapes. Crosses show mean and standard deviations for each response shape. (B-C) Unlike with acoustic stimulation, there are no trends of ITD tuning characteristics with position along the tonotopic axis of the IC. In acoustically stimulated cats, CF systematically increases with electrode depth. (B) ITD_{best} as a function of electrode depth. With acoustic stimulation, there is a significant inverse correlation of ITD_{best} and CF for low-frequency neurons. (C) ITD tuning halfwidth as a function of electrode depth. For acoustic stimulation, halfwidth is largely determined by the frequency selectivity of the neuron and the effective periodicity of the stimulus and there is a very strong inverse correlation of halfwidth and CF.
Fig. 2.7. Influence of stimulus intensity on ITD tuning. Numbers on curves indicate intensity in units of dB re threshold. Neurons in A-C have saturating rate-ITD curves, in D-F ITD tuning broadens and physiological modulation range decreases at higher intensities, G-I neurons have good ITD tuning over all intensities tested above a particular level.
Fig. 2.8. Changes in ITD tuning characteristics with overall stimulus intensity. (A) Fraction of ITD tuning shapes over the population of neurons as a function of stimulus intensity. (B) Distribution of changes in ITD of maximum slope (ΔITD_{MS}) with intensity for neurons with positive maximum slopes. (C) Distribution of changes in halfrise with intensity. Panels D-F: physiological modulation range (PMR) as a function of stimulus intensity (dB re peak in PMR function). (D) PMR for neurons that completely saturated at higher intensities. (E) PMR for neurons that partially saturated at the highest intensities tested. (F) PMR for neurons that did not saturate at highest intensities tested.
Fig. 2.9. Effect of interaural level difference (ILD) on ITD tuning. (A) ITD tuning in a single neuron as a function of ILD. (B) ITD\textsubscript{best} as a function of ILD for the neuron in panel A. (C) ITD\textsubscript{best} as a function of ILD for 16 neurons. 11/16 functions have negative slopes when fit with a straight line. (D) ITD\textsubscript{best} at 0 dB ILD plotted against fitted slope of ITD\textsubscript{best} vs. ILD functions (∆ITD\textsubscript{best}/∆ILD).
Fig. 2.10. ITD sensitivity as a function of pulse rate for an example neuron. (A) Dot-raster display shows responses to pulse train stimulus at different rates. At highest rates response is mostly limited to the stimulus onset (stimulus duration is 300 ms). (B) ITD tuning is summarized here as rate-ITD curves for each stimulus rate (bars give standard deviation based on trial counts). (C) Standard separation (D) from 0 µs ITD. ITD just noticeable difference (JND) is where D=1 (dotted line).
Fig. 2.11. Neural ITD discrimination thresholds. (A) The ITD JND from 0 µs is given for 8 single neurons tested at 40, 80, 160, and 320 pps (thin black lines). Mean JNDs across neurons increase with pulse rate (thick red line). (B) The first 50 ms of the response (onset response) is analyzed separately from the remaining 250 ms of the response (sustained response). ITD JNDs from the onset response are roughly independent of pulse rate while ITD JNDs for the sustained response degrades at higher pulse rates. The ITD JND at 320 pps is entirely from the onset response. (C) ITD thresholds are shown as a function of the number of stimulus pulses in a 40 pps pulse train by windowing the responses of a 300 ms pulse train. Mean ITD JNDs drop linearly on a log log scale. The dotted line shows the lower envelope of the ITD thresholds from individual neurons (N=22). (D) ITD JNDs as a function of reference ITD. Mean thresholds are best within the physiological range of ITD (±300 µs) and get worse at increasing ITD offsets. The lower envelope of JNDs from individual neurons is roughly constant ~10-20 µs for a much larger range of reference ITDs.
Fig. 2.12. Effect of interaural electrode offsets on ITD tuning. (A) Example ITD tuning for one neuron that has sharp ITD tuning for matched interaural electrode pairs and flat ITD tuning at increasing interaural electrode offsets. (B) Maximum slope of rate-gaussian-fitted ITD curves from panel A. (C) Mean maximum-slope of rate-ITD functions for 5 different neurons at interaural electrode offsets of ±2 electrodes.
Chapter 3

Neural sensitivity to ITD in the envelope and fine time structure for electric stimulation with bilateral cochlear implants

Abstract

Bilateral cochlear implantation seeks to improve electric hearing by taking advantage of the binaural processing of the central auditory system. Cochlear implants typically encode sound in each spectral channel by amplitude modulating (AM) a fixed-rate pulse train. We investigated the sensitivity of neurons in the inferior colliculus to interaural time differences (ITD) with AM pulse trains. ITD was introduced independently to the AM and/or carrier pulses in order to measure the relative efficacy of envelope and fine structure for delivering ITD information. We found that many IC cells are sensitive to ITD in both the envelope (ITD_{env}) and fine structure (ITD_{fs}) depending on the modulation frequency and carrier rate of the stimulus. ITD_{env} sensitivity generally improved with increasing modulation frequency up to the maximum modulation frequency that elicited a sustained response in each neuron (tested up to 160 Hz). ITD_{fs} sensitivity was relatively sharp for a 1000 pps and non-existent at 5000 pps. Neural tuning to ITD_{env} and ITD_{fs} was found to be highly separable in neurons sensitive to both stimulus dimensions. Overall, the best ITD sensitivity was found for ITD contained in the fine structure of a moderate rate AM pulse train (1000 pps). These results suggest that the interaural timing of current pulses should be accurately controlled and the pulse rate may need to be limited in order to design a bilateral cochlear implant processing strategy that provides salient ITD cues.
Introduction

Cochlear implantation is a widely used treatment for sensorineural deafness with tens of thousands of children and adults implanted worldwide. While most cochlear implant users have been implanted in one ear, the number of individuals implanted on both sides has steadily increased over the past few years, with the intention of restoring the advantages of binaural hearing. However, commercially available cochlear implant sound processors have not been designed with binaural hearing in mind.

Binaural advantages for normal listeners include accurate localization of sound sources in the horizontal plane and improved speech reception in background noise. The acoustic cues that lead to these advantages are a direct result of the physical separation of the two ears about the head and include interaural time differences (ITD) and interaural level differences (ILD). This study focuses on ITD and addresses issues of ITD coding with bilateral cochlear implants by studying the sensitivity of neurons to ITD using electric stimulation in an animal model. The stimuli used in this study are amplitude-modulated (AM) pulse trains. This stimulus was chosen since it is more like the type of stimulation that are used clinically as compared to constant-amplitude pulse trains that were studied in Chapter 2.

Cochlear implant sound processors typically split sound into multiple frequency bands and then use the filtered signals in each band to determine the amplitude of current pulses delivered to tonotopically arranged cochlear electrodes. The CIS (continuous interleaved stimulation) strategy uses the amplitude envelope of the filtered sound signal in each channel to amplitude modulate a fixed-rate pulse train, which is temporally interleaved with the pulse trains in other channels (Wilson et al., 1991). In the majority of clinically available processing strategies, the temporal fine structure of the original sound signal is discarded and the amplitude envelope is preserved and delivered to the cochlea via the implanted electrodes. Thus the only ITD cues available to users of bilateral cochlear implants are contained in the envelope. While envelope cues in a limited number of bands (e.g. 6-12) are sufficient for good speech understanding in favorable acoustic environments (high SNR) (Shannon et al., 1995), they are not generally sufficient for good speech reception in noise, for pitch perception, nor for lateralization of
low-frequency sounds (Henning, 1974; Henning and Ashton, 1981; Smith et al., 2002; Qin and Oxenham, 2003).

ITD-sensitive neural responses originate in the auditory brainstem. Neurons in the medial superior olive (MSO) and lateral superior olive (LSO) create ITD tuning from convergent inputs from the contralateral and ipsilateral ears. While MSO neurons analyze low-frequency sounds and are primarily sensitive to ITD (Goldberg and Brown, 1969; Yin and Chan, 1990), LSO neurons are predominantly high-frequency and are sensitive to interaural level differences (ILD) and ITD in the amplitude envelope of AM tones (Joris and Yin, 1995). Both MSO and LSO neurons have direct and indirect projections to the IC. Neurons in the IC have ITD tuning that can resemble that in the MSO and LSO, and can also exhibit a cross between the two types (Yin and Kuwada, 1983b; Batra et al., 1993; McAlpine et al., 1998). Stimulation with broadband noise shows that ITD sensitive IC neurons with low-CFs (< 1 kHz) are primarily sensitive to ITD_{fs} and neurons with high-CFs (> 3 kHz) are primarily sensitive to ITD_{env}, with a transition region in between (Joris, 2003).

A key question addressed in this chapter is determining the relative neural sensitivity to ITD in the amplitude envelope (ITD_{env}) versus the temporal fine structure (ITD_{fs}) with electric stimulation. Since ITD_{fs} is perceptually more salient than ITD_{env} with acoustic hearing (Wightman and Kistler, 1992; Macpherson and Middlebrooks, 2002) and since electric stimulation of the cochlea elicits precise temporal responses in the auditory system (Moxon, 1967; van den Honert and Stypulkowski, 1987a; Javel and Shepherd, 2000), our hypothesis is that ITD-sensitive neurons should be more sharply tuned to ITD_{fs} than to ITD_{env} with electric stimulation.

In the present study, we investigated the ITD sensitivity of IC neurons to AM pulse trains delivered via bilaterally implanted intracochlear electrodes. We found that the majority of neurons in the central nucleus of IC are sensitive to ITD_{env} with ITD tuning similar to that seen with acoustic stimulation in normal-hearing animals with AM tones. We also found that many neurons were sensitive to ITD_{fs} at a moderate pulse rate (1000 pps) and that this tuning was sharper than that for ITD_{env}. Preliminary reports have been presented previously (Smith and Delgutte, 2003a, b; Smith and Delgutte, 2005b; Smith and Delgutte, 2005a).
Methods

Subjects and Deafening

All surgical and experimental procedures followed the regulations set by NIH and were approved by the MEEI IACC. Healthy adult cats of either sex were deafened by co-administration of kanamycin (300 mg/kg subcutaneous) and ethacrynic acid (25 mg/kg intravenous, (Xu et al., 1993) 7-14 days prior to cochlear implantation and electrophysiological recordings.

Surgery

On the day of the experiment, after induction of anesthesia by Dial in urethane (75 mg/kg), a tracheal canula was inserted; skin and muscles overlying the back and top of the skull were reflected. Ear canals were transected for insertion of a closed acoustic system. Tympanic bullae were opened to allow access to the round-window for placement of intracochlear electrodes. Part of the skull overlying the occipital cortex was removed to allow for partial aspiration of cortical tissue and access to the bony tentorium and IC. The part of the tentorium overlying the IC was drilled for better access to the dorsal-lateral surface of the IC. Throughout all procedures, animals were given supplementary doses of anesthesia to maintain an areflexic state and vital signs were monitored.

Cochlear implantation and electrode configurations

Stimulating electrodes were surgically implanted into each cochlea through the exposed round window. The electrodes were either custom-made Pt/Ir ball electrodes (0.45 mm diameter), or 8-contact electrode arrays with 0.75 mm spacing (Cochlear Corp., ring-type contacts with 0.45 mm diameter). Particular care was taken to achieve the same insertion depth on both sides. In all experiments, we used a wide bipolar configuration (~5mm between electrodes), with the active electrode inserted ~5mm into the scala tympani and the return electrode (either another Pt/Ir ball or the most basal contact of the array) just inside the round window. This electrode configuration is similar to the monopolar configuration commonly used in clinical devices in that it produces a broad
pattern of excitation, but decreases the distance between the active and return electrodes thus reducing stimulus artifact measured at the recording electrodes (Litvak et al., 2003).

Effectiveness of the deafening protocol was assessed by measuring auditory brainstem response (ABR) thresholds to acoustic clicks in each ear. Calibrated acoustic assemblies comprising an electrodynamic speaker and a probe-tube microphone were inserted into the cut ends of each ear canal to form a closed system. Condensation clicks (100 µs) were delivered via these acoustic systems, and ABR thresholds measured in both ears. ABR was measured between vertex and ear bar using a small screw inserted into the skull. In all experiments, no acoustic ABR response was seen up to the highest intensity tested (110 dB SPL peak).

**Single-unit recordings and cancellation of stimulus artifact**

Single-unit activity in the IC was recorded using either parylene-insulated tungsten stereotrodes (Microprobe, ~2 MΩ impedance), or 16-channel silicon probes (NeuroNexus Technologies, 100 or 150 µm linear spacing, 177 µm² site area). Recording electrodes were advanced through the IC along one of two possible trajectories. The standard trajectory ran from dorsolateral to ventromedial, in the coronal plane tilted 45º off the sagittal plane so as to record activity from a set of neurons covering a highly-reproducible range of CFs (Merzenich and Reid, 1974; Snyder et al., 1990). The alternate electrode trajectory ran from dorsal to ventral in the coronal and parasagittal planes and is referred to as the 0º trajectory. The 0º trajectory was used in an effort to sample more neurons in the lateral part of the inferior colliculus where the majority of ascending projections from the MSO are located (Aitkin and Schuck, 1985; Oliver et al., 2003).

Stimulus artifact (the electric potential seen at the recording electrode directly resulting from current passing between the stimulating electrodes) was typically much larger than the single-unit activity. Recordings were made simultaneously from at least two sites, only one of which sampled the activity of the neuron of interest. Since stimulus artifact was present on both channels, it could be minimized by filtering and subtracting the reference channel (which only contains artifact) from the neuron channel with an adaptive filter. Real-time artifact cancellation was achieved using a least-mean-
square adaptive filter (Widrow et al., 1975), implemented in software running on a DSP board.

After online artifact cancellation, spikes from well-isolated single units were amplified and detected with a custom-built discriminator. Spike times were measured by a custom-built timer with a resolution of 1 μs, then processed and displayed by computer. All spike times were stored to disk for post-hoc analyses.

**Stimulus generation and delivery**

All stimuli were generated by a pair of 16-bit digital-to-analog converters (D/A) at a sampling rate of 100 kHz. Stimulus levels were set by custom-built attenuators having a resolution of 0.1 dB. Attenuated outputs of the D/A converters were delivered to the intracochlear electrodes via a pair of custom-built high-bandwidth (40 kHz), optically-isolated, constant-current sources. All electric stimuli were made up of 100 μs biphasic current pulses (cathodic-anodic, 50 μs/phase).

The search stimulus consisted of a sequence of three current pulses with a 100 ms interval between each pulse. The first two pulses were delivered monaurally to each ear in turn and the last pulse was binaural. The search stimulus was repeated at a rate of 2/s at an intensity suprathreshold to neurons near the recording electrode (as assessed by local field potentials). Once a single neuron was well isolated, its threshold was measured with monaural and binaural pulses. Following this preliminary characterization of the unit, ITD sensitivity was studied.

**Basic ITD sensitivity**

The basic ITD sensitivity was assessed in each neuron with constant-amplitude pulse trains at 40 pps (see Chapter 2). ITD tuning was determined to be either peak-, trough-, monotonic-, or biphasic- shaped by finding the best fit of ITD functions to four stereotyped ITD tuning shapes. Halfrise, ITD of maximum slope (ITD_{MS}), and physiological modulation depth (PMD) were determined from the fits. This information was used for further analyses in the current study to compare the basic ITD tuning properties of two subpopulations of neurons.
AM pulse trains

Stimuli were made up of pulse trains at a rate of either 1000 pulses per second (pps) or 5000 pps. Pulse trains were then amplitude modulated with a sinusoidal waveform between 10-200 Hz ($f_{mod}$) at 100% modulation depth. The standard stimulus was a 40 Hz / 1000 pps AM pulse train. Stimuli with dynamic ITDs were used to efficiently study envelope ITD tuning in single units (Yin et al., 1984). Dynamic ITD was imposed in the envelope of AM stimuli by increasing $f_{mod}$ in the contralateral ear by 1 Hz (Fig. 3.1A). We refer to this stimulus the “binaural modulation beat” (BMB) and it has an interaural phase difference in the amplitude envelope (IPD$_{env}$) that takes all possible values from -0.5 to +0.5 cycles over the 1 sec beat period (Fig. 3.1C). The BMB stimulus was 3 seconds in duration and was repeated 10 times for each measurement. The interaural timing of the carrier pulses was controlled independently and is shown for ITD$_{fs}$ = 0 (synchronized carrier) in Fig. 3.1B. In some cases, ITD$_{fs}$ tuning was tested simultaneously with ITD$_{env}$ by statically introducing ITD$_{fs}$ to the BMB stimulus on successive stimulus presentations.

Data analysis

Spike times were processed to compute PST histograms and IPD$_{env}$ functions. A PST histogram for 10 presentation of a 10 Hz, 3 s BMB is shown in Fig. 3.1D and shows the instantaneous firing rate of the neuron every 25 ms averaged over the 10 stimulus presentations. IPD$_{env}$ functions were taken from 2 cycles of the modulation beat (from 500-2500 ms of the BMB stimulus). The two cycles from the PST histogram were averaged together (so the IPD$_{env}$ function is effectively made up of 20 cycles of the modulation beat). Finally a three-point smoothing kernel with values [0.25 0.5 0.25] was circularly convolved with the IPD$_{env}$ function. The IPD$_{env}$ function derived from the PST histogram of Fig. 3.1D is shown in Fig. 3.1E. The IPD$_{env}$ function can also be expressed in terms of ITD$_{env}$ by multiplying the IPD values by the period of $f_{mod}$. ITD$_{fs}$ functions were measured by presenting the BMB stimulus at several ITD$_{fs}$ steps and measuring spike rate from the resulting IPD$_{env}$ curves at a fixed value of IPD$_{env}$ (typically 0).

Sensitivity to ITD was quantified by computing the vector strength (Goldberg and Brown, 1969) of the IPD$_{env}$ and ITD$_{fs}$ functions. The vector strength takes on a value
between 0 and 1 and indicates how unevenly the spike rate is distributed around the full cycle of IPD. Vector strength is significant (\(p < 0.01\)) if the Rayleigh coefficient (\(nVS^2\), where \(n = \) the number of spikes and VS is the vector strength) exceeds a value of 13.8 (Mardia and Jupp, 2000). Neurons with IPD functions that have significant vector strength are considered to be ITD sensitive.

**Neural Discrimination**

ITD discrimination of single neurons was quantified by expressing the difference in spike counts elicited by stimuli at two different ITDs in units of their combined standard deviation. The metric of neural discrimination used was a slightly modified version of standard separation (Sakitt, 1973), or \(D\), and was defined as:

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

where \(\mu_{\text{ITD}}\) and \(\mu_{\text{ITD}+\Delta\text{ITD}}\) are the means of the spike counts and \(\sigma_{\text{ITD}}\) and \(\sigma_{\text{ITD}+\Delta\text{ITD}}\) their respective standard deviations. We replaced the geometric mean of variance in the original definition of \(D\) with the arithmetic mean of the variance to avoid problems when the mean and variance of the spike counts are 0 for one of the ITDs. Standard separation is analogous to \(d'\) which is often used to quantify discrimination in psychophysical studies (Green and Swets, 1966). The just noticeable difference (JND), for a given ITD was defined as the \(\Delta\text{ITD}\) needed for the standard separation to reach a value of 1 (and corresponds to \(~76\%\) correct in a two-interval discrimination task).
Results

Results are based on responses of 47 IC neurons to bilateral electric stimulation of the cochlea with amplitude modulated (AM) pulse trains in 17 deafened cats. All neurons studied were well isolated single units. While most IC neurons only exhibited onset discharges to constant-amplitude pulse trains at rates > 300 pps, low-frequency AM (< 300 Hz) restored sustained firing at moderate and high pulse rates (1000 and 5000 pps). ITD was introduced to AM and carrier pulses independently in order to test the hypothesis that neuronal selectivity would be greater for ITD in the temporal fine structure (ITD_{fs}) than for ITD in the amplitude envelope (ITD_{env}) as is generally the case for neurons in normal hearing animals (Yin et al., 1984; Batra et al., 1993; Griffin et al., 2005). Neural sensitivity to ITD in the envelope (ITD_{env}) and fine structure (ITD_{fs}) were characterized at several intensities, modulation frequencies, and pulse rates. Estimates of ITD discrimination thresholds for single neurons were made to further compare the effects of different stimuli.

The breakdown of the number of neurons sensitive to each type of ITD is summarized in Table 3.1. Of the 47 neurons studied, 46 responded throughout the duration of amplitude modulated (AM) stimuli (typically probed with a 1000 pps carrier and 10-40 Hz AM). Of the 46 neurons that responded to AM stimuli, 35 were sensitive to ITD delivered in the amplitude envelope. 31/35 ITD_{env} sensitive neurons were tested for additional ITD sensitivity in the fine structure at a carrier rate of 1000 pps. 17/31 neurons were sensitive to both ITD_{env} and ITD_{fs}, while the remaining 14/31 neurons were only sensitive to ITD_{env}. Seven neurons that showed good ITD_{fs} tuning at 1000 pps were also tested at 5000 pps. Only 1/7 of these neurons exhibited any significant ITD_{fs} sensitivity at this higher rate.

Envelope ITD Sensitivity

Neurons with sustained responses to AM stimuli were first tested for sensitivity to ITD_{env}. By using a dynamic ITD_{env} stimulus (binaural modulation beat), the ITD_{env} tuning of a cell was quickly assessed and several ITD tuning characteristics were
measured (vector strength, best IPD, halfwidth, etc.) Only responses that had a significant vector strength ($p < 0.01$) were considered sensitive to ITD$_{env}$.

Fig. 3.2 shows ITD$_{env}$ tuning characteristics for the 33 ITD$_{env}$ sensitive neurons tested with AM pulse trains with a 1000 pps carrier and $f_{mod} = 40$ Hz. These stimulus parameters were the most often tested since neurons in the IC often respond well to 40 Hz AM. The distribution of vector strengths for these measurements is shown in Fig. 3.2A. Vector strength varies widely amongst ITD$_{env}$ sensitive neurons with a mean of 0.51 and standard deviation of 0.28. The distribution of best IPD$_{env}$ is clustered tightly near 0 cycles as shown in Fig. 3.2B. Positive best IPD$_{env}$ indicates a contralateral leading envelope. The mean best IPD$_{env}$ is 0.05 cycles and the standard deviation is 0.16 cycles.

The halfwidth of each ITD$_{env}$ tuning curve was estimated by fitting a Gaussian function to the IPD$_{env}$ curve ($halfwidth = 2\sigma \sqrt{2 \ln 2}$). The distribution of halfwidths is shown in Fig. 3.2C on a logarithmic scale and has a geometric mean of 3.5 ms or 0.14 cycles. The mean halfwidth is much larger than the ±350 µs range of ITDs naturally encountered by a cat and would presumably lead to poor ITD$_{env}$ discrimination based on the average IC neuron at this low modulation frequency.

Neural ITD discrimination thresholds, or just noticeable differences (JNDs), were estimated for single-units using the procedures described in the METHODS. Briefly, spike count statistics at each ITD step were used to determine the smallest ITD step from 0 that could be detected by an ideal observer. ITD$_{env}$ JNDs were obtained for 31/33 neurons (2/33 had immeasurable ITD$_{env}$ JNDs). The distribution of ITD$_{env}$ JNDs is shown in Fig. 3.2D on a logarithmic scale. The geometric mean of the distribution (excluding the 2 neurons with immeasurable JNDs) is 1.3 ms, with the best ITD$_{env}$ JNDs near 400 µs.

**Effect of modulation frequency and carrier rate on ITD$_{env}$ sensitivity**

ITD$_{env}$ tuning was tested as a function of modulation frequency ($f_{mod}$) between 20 and 160 Hz. Fig. 3.3A shows IPD$_{env}$ tuning curves for an example neuron over the full range of modulation frequencies regularly tested in this study. In this example, the carrier rate is 1000 pps. The data points are fitted with a Gaussian function (shown in red) which is used to estimate the halfwidth of each IPD$_{env}$ curve. Fig. 3.3B shows the
rate modulation transfer function (rMTF) for this neuron as derived from the peak of each IPD$_{env}$ curve. The rMTF shows that this neuron responds best to BMB stimuli at $f_{mod}$ between 80-120 Hz. The vector strength is shown in Fig. 3.3C and is significant for all $f_{mod}$ tested except for 20 Hz where the response was low. Halfwidths in units of IPD$_{env}$ cycles (Fig. 3.3D) are relatively stable as a function of $f_{mod}$ with values between 0.05-0.10 cycles. Halfwidth decreases with increasing $f_{mod}$ when expressed in units of µs (ITD$_{env}$) as shown in Fig. 3.3E. IPD$_{best}$ remains roughly constant with values near 0 cycles at all values of $f_{mod}$ tested (Fig. 3.3F). Fig. 3.3G shows neural ITD$_{env}$ JNDs as a function of $f_{mod}$. The dotted red line shows half of the modulation period, which is the upper limit of possible ITD$_{env}$ JNDs. For the neuron in Fig. 3.3, ITD$_{env}$ JNDs were only measurable from 80 to 120 Hz, where this particular neuron had the strongest response, and were ~500 µs.

We studied the effect of $f_{mod}$ on ITD$_{env}$ tuning in 15 neurons at a pulse rate of 1000 pps and in 11 neurons at a pulse rate of 5000 pps. Fig. 3.4A-C shows the population data for ITD$_{env}$ halfwidths, ITD$_{env}$ JNDs, and rMTF as a function of $f_{mod}$ from 20-160 Hz. The top and middle rows show single-neuron data for stimuli with pulse rates of 1000 pps and 5000 pps respectively. The bottom row shows population mean data and allows for a direct comparison of the two pulse rates tested. ITD$_{env}$ halfwidth decreased regularly with increases in $f_{mod}$. This was true for nearly all neurons between 20 and 80 Hz and for most neurons up to 160 Hz. The population mean data (Fig. 3.4A, bottom panel) shows that there is not an obvious difference in ITD$_{env}$ halfwidth when 1000 pps and 5000 pps carrier rates are compared. Halfwidths for each neuron are nearly proportional to the modulation period. The red dotted line in bottom panel of Fig. 3.4A is $\kappa f_{mod}$, where $\kappa$ is a proportionality constant, and is about the same slope as the halfwidth curves.

Neural ITD$_{env}$ JNDs were estimated from each neuron’s ITD$_{env}$ tuning curves as a function of $f_{mod}$. The dotted red line in each panel of Fig. 3.4B is $1/(2* f_{mod})$ which was the maximum measurable ITD at each value of $f_{mod}$. Immeasurable JNDs are not plotted. In general, the neural JND decreased with increasing $f_{mod}$. The bottom panel of Fig. 3.4B shows the geometric mean data for the population and compares the two carrier rates. Immeasurable JNDs are excluded from the calculation (geometric mean). For the 1000 pps carrier (solid black line), the mean ITD$_{env}$ JND drops steadily with increasing $f_{mod}$.
from 20 Hz to 160 Hz. For the 5000 pps carrier, ITD_{env} JNDs are similar to those at 1000 pps for \( f_{\text{mod}} \) from 20-80 Hz, but above 80 Hz, the mean ITD_{env} JNDs are flat for the 5000 pps carrier unlike the decreasing values for the 1000 pps carrier. This was unexpected since the mean ITD_{env} halfwidths were not significantly different between the two carrier rates at each \( f_{\text{mod}} \). The peak discharge rate for each ITD_{env} tuning curve varied with \( f_{\text{mod}} \) for each neuron as shown in Fig. 3.4C. Across the population, each neuron’s best \( f_{\text{mod}} \) varied as well. The bottom row of Fig. 3.4C shows that for both carrier rates, the population mean rMTF is bandpass with best modulation frequencies between 40 and 60 Hz. The amplitude of the population rMTF is greater for the 1000 pps carrier due to wider individual rMTFs. This difference is greater at higher modulation frequencies where there is a sharper dropoff in the population rMTF for 5000 pps. Poorer ITD_{env} JNDs at higher values of \( f_{\text{mod}} \) for the 5000 pps carrier rate is probably a direct result of lower firing rates at higher \( f_{\text{mod}} \). Another difference emerges between the two carrier rates when the proportion of measurable ITD_{env} JNDs is analyzed (Fig. 3.5). For the 1000 pps carrier, the proportion of neurons with measurable ITD_{env} JNDs is about 70% across the full range of \( f_{\text{mod}} \) tested. For the 5000 pps carrier, the proportion of neurons with measurable ITD_{env} JNDs is close to 70% from 20-80 Hz but drops regularly at higher \( f_{\text{mod}} \) and is only about 30% at \( f_{\text{mod}} = 160 \) Hz. This is most likely a result of the neural population having a lower lowpass corner frequency at 5000 pps than at 1000 pps.

**Effect of stimulus intensity on envelope ITD tuning**

In 12 neurons, ITD_{env} tuning was studied for several stimulus intensities with the standard AM stimulus parameters (carrier rate = 1000 pps, \( f_{\text{mod}} = 40 \) Hz). Intensity (current) was varied equally in both ears in identical dB steps. Fig. 3.6A shows ITD_{env} tuning curves for an example neuron at 5 different suprathreshold intensities. With increasing intensity, the peak firing rate increases and ITD_{env} tuning broadens. Also, the peak of the ITD_{env} function shifts towards more contralateral leading ITD_{env}. This shift results in a stable location of the steep slope of the function near 0 despite widening with increasing intensity. These trends are better appreciated by looking at changes over the population of neurons tested at multiple stimulus intensities. Fig. 3.6B shows the peak rates from the ITD_{env} curves as a function of intensity re threshold for all 12 neurons. As
expected, the discharge rates increase with increasing intensity at most intensity steps. Linear regression (dashed red line) shows significant positive correlation between intensity and peak spike rate ($r = 0.57, p < 0.0001$). Fig. 3.6C shows best IPD$_{env}$ for each neuron as a function of intensity. Like the example neuron in Fig. 3.6A, IPD$_{env}$ shifts towards more negative values (ipsilateral leading) for the majority of neurons. Linear regression reveals a negative correlation between intensity and best IPD$_{env}$ across the population ($r = -0.36, p < 0.05$). ITD$_{env}$ halfwidth increases for most neurons as shown in Fig. 3.6D, and the correlation is significant ($r = 0.55, p < 0.001$). Neural ITD$_{env}$ JNDs are shown for each neuron as a function of intensity in Fig. 3.6E. While there is no significant correlation for the population data ($r = -0.15; p = 0.42$) due to the wide variation in ITD$_{env}$ JND magnitude across neurons, ITD$_{env}$ JNDs seem to improve (decrease) with increasing intensity for most individual neurons. To quantify this observation, a straight line was fit to the data for each neuron with measurable JNDs. Across the population, the mean slope was about $-0.19 \mu s/\text{dB} (\sigma = 0.17)$ indicating that, on average, ITD$_{env}$ JNDs decrease with increasing intensity (this was the case for 8/9 neurons with measurable JNDs). It is interesting that despite broadening in the ITD$_{env}$ functions, neural thresholds generally improved with increasing stimulus intensity, presumably due to increased firing rates.

**ITD sensitivity to the temporal fine structure**

Sensitivity to ITDs in the temporal fine structure (ITD$_{fs}$) was measured simultaneously with ITD$_{env}$ sensitivity by introducing static ITD steps in the carrier of the dynamic ITD$_{env}$ stimulus. Tests of ITD$_{fs}$ sensitivity were always made at $f_{\text{mod}} = 40$ Hz and most frequently at a carrier rate of 1000 pps. Fig. 3.7A shows IPD$_{env}$ curves for an example neuron at 10 different IPD$_{fs}$ steps covering the 1000 µs period of the carrier pulse rate. This neuron is sensitive to ITDs introduced to both the amplitude envelope and temporal fine structure of the stimulus. This neuron responds well at ITD$_{fs}$ between -100 and +200 µs and IPD$_{env}$ near 0 cycles. These curves can be combined into a 2-dimensional plot of discharge rate against IPD$_{env}$ and IPD$_{fs}$ as shown in Fig. 3.7B. In this display spike rate for each IPD$_{env}$-IPD$_{fs}$ combination is indicated by the color of the square. ITD$_{fs}$ tuning curves can be derived from this plot by taking the columns and
converting IPD\textsubscript{fs} into ITD\textsubscript{fs} by scaling the axis by the carrier period. Fig. 3.7C shows the ITD\textsubscript{fs} tuning curve for IPD\textsubscript{env} = 0 cycles derived from the previously described data. The halfwidth of this ITD\textsubscript{fs} curve is 284 \(\mu\text{s}\) (from fitted Gaussian). It is interesting that, while IPD tuning is narrower in the modulation dimension, \textit{ITD} tuning is narrower in the carrier dimension due to the large difference in period duration between modulation and carrier (25 ms and 1 ms respectively).

A total of 31 ITD\textsubscript{env}-sensitive IC neurons were tested for sensitivity to ITD\textsubscript{fs} at a carrier rate of 1000 pps. Roughly half of the neurons (17/31) showed significant ITD\textsubscript{fs} tuning \((p < 0.01,\text{ as assessed with the Rayleigh coefficient of the IPD\textsubscript{fs} vector strength})\). For these 17 neurons, we measured ITD\textsubscript{fs} halfwidth and estimated ITD\textsubscript{fs} JNDS. A histogram of ITD\textsubscript{fs} halfwidths for the population is shown in Fig. 3.8A. ITD\textsubscript{fs}-sensitive neurons are shown in open bars and the closed bar to the right indicates the remaining neurons that were not sensitive to ITD\textsubscript{fs} at this carrier rate. The mean ITD\textsubscript{fs} halfwidth, for ITD\textsubscript{fs}-sensitive neurons, was about 250 \(\mu\text{s}\), which is much narrower than the \(\sim 690 \mu\text{s}\) mean halfwidth observed for low-rate constant-amplitude pulse trains (Chapter 2). Fig. 3.8B plots the mean ITD\textsubscript{fs} halfwidth and the mean ITD\textsubscript{env} halfwidths as a function of \(f_{\text{mod}}\) for the entire dataset. ITD\textsubscript{fs} tuning for the standard stimulus is significantly narrower, when present, than ITD\textsubscript{env} tuning over the range of \(f_{\text{mod}}\) tested. A histogram of ITD\textsubscript{fs} JNDS (from a reference ITD\textsubscript{fs} of 0 \(\mu\text{s}\)) for the population is shown in Fig. 3.8C. The mean ITD\textsubscript{fs} JND for ITD\textsubscript{fs}-sensitive neurons is about 100 \(\mu\text{s}\) which is comparable to the mean ITD JND for low-rate constant-amplitude pulse trains (see Chapter 2). Fig. 3.8D compares the mean ITD\textsubscript{fs} JND with the mean ITD\textsubscript{env} JNDS as a function of \(f_{\text{mod}}\) (Fig. 3.4C). As was the case with ITD tuning width, mean ITD\textsubscript{fs} JNDS are significantly lower than ITD\textsubscript{env} JNDS over the range of \(f_{\text{mod}}\) tested.

\textit{Relating ITD\textsubscript{fs} tuning to ITD tuning with low-rate, constant-amplitude pulse trains}

Why is only a subset of neurons sensitive to ITD\textsubscript{fs}, while most binaural neurons are sensitive to ITD\textsubscript{env}? We investigated possible differences between the ITD\textsubscript{fs}-sensitive and -insensitive neurons to test the hypothesis that ITD\textsubscript{fs}-sensitive neurons are in general more sharply tuned to ITD than ITD\textsubscript{fs}-insensitive neurons. The ITD tuning characteristics of each neuron were previously characterized using a low-rate, constant-
amplitude pulse train (40 pps) in Chapter 2. Basic ITD tuning characteristics include ITD of maximum slope (ITD_{MS}), halfrise (width of the rate-ITD function about ITD_{MS} between 25% and 75% normalized spike rate), and physiological modulation depth (PMD; normalized change in spike rate within the physiological range of ITD for the cat). These basic ITD tuning characteristics, as well as ITD_{env} halfwidth and electrode depth were compared between ITD_{fs}-sensitive (N = 16) and ITD_{fs}-insensitive neurons (N = 15) with two-sample t-tests. Table 3.2 shows the means and standard deviations for each property. On average, ITD_{fs} sensitive neurons have narrower halfrise, ITD_{MS} closer to 0 (and within the natural range of ITD), and higher PMD than ITD_{fs} insensitive neurons, consistent with the hypothesis that this subset of neurons is more sharply tuned. ITD_{fs}-sensitive neurons also tended to have significantly narrower ITD_{env} halfwidth and were recorded at shallower electrode depths than ITD_{fs} insensitive neurons, indicating that these were lower CF neurons. Fig. 3.9 shows basic ITD halfrise plotted against ITD_{env} halfwidth for the population of neurons. ITD_{fs}-sensitive neurons are shown as blue filled symbols and ITD_{fs}-insensitive neurons are shown as red open symbols. Different symbol shapes indicate the different basic ITD tuning shapes (see Chapter 2), and there is no apparent effect of ITD response type on ITD_{fs}-sensitivity. Although there is no significant correlation between basic ITD halfrise and ITD_{env} halfwidth, the combination of these two metrics provides a clear segregation of ITD_{fs}-sensitive versus ITD_{fs}-insensitive neurons, with ITD_{fs}-sensitive neurons clustered in the lower left corner of the plot. ITD_{fs}-sensitive neurons with larger basic ITD halfrise tended to have smaller ITD_{env} halfwidth and those with larger ITD_{env} halfwidth tended to have smaller basic ITD halfrise. Earlier we demonstrated that increases in stimulus intensity increased the ITD_{env} halfwidth. There may be a similar change in ITD_{fs} halfwidth, though this was not explicitly tested. The apparent tradeoff between basic ITD halfrise and ITD_{env} halfwidth requirements for ITD_{fs} sensitivity illustrated in Fig. 3.9 may be related to such an effect of stimulus intensity on ITD_{fs} tuning width. Overall, these analyses support the hypothesis that ITD_{fs}-sensitive neurons are fundamentally more sharply tuned to ITD.

**ITD_{fs} tuning at high carrier rates**
In a small number of ITD\textsubscript{fs} sensitive neurons, the effect of using a higher pulse rate on ITD\textsubscript{fs} tuning was tested. The standard stimulus had a carrier rate of 1000 pps and therefore a period of 1000 µs. The higher pulse rate was 5000 pps with a corresponding period of 200 µs. In order for there to be any tuning to ITD\textsubscript{fs} with the 5000 pps stimulus, the tuning would have to be very sharp in order to see modulation of the response within the ±100 µs possible range of ITD\textsubscript{fs}. Fig. 3.10A shows the ITD\textsubscript{env}-ITD\textsubscript{fs} tuning display for an example neuron at the standard 1000 pps carrier rate with $f_{\text{mod}} = 40$ Hz. ITD\textsubscript{fs} tuning is relatively sharp for this neuron (halfwidth = 108 µs, vector strength = 0.85) and the best ITD\textsubscript{fs} is near 0 µs. When the carrier rate is increased to 5000 pps (Fig. 3.10B), ITD\textsubscript{env} tuning curves at each ITD\textsubscript{fs} step are very similar, indicating that ITD\textsubscript{fs} tuning is essentially eliminated (vector strength = 0.02 and is no longer significant). The effect of carrier rate on ITD\textsubscript{fs} tuning was tested in 7 neurons with good ITD\textsubscript{fs} tuning at 1000 pps and in each case ITD\textsubscript{fs} tuning was eliminated or severely reduced with the 5000 pps carrier. The mean vector strength for 1000 pps stimuli was 0.68 while for 5000 pps it was only 0.13 (6/7 of the vector strength measures for the 5000 pps carrier were not significant, $p < 0.01$ criterion).

*Separability of ITD\textsubscript{env} and ITD\textsubscript{fs} tuning*

The joint ITD\textsubscript{env}-ITD\textsubscript{fs} tuning of neurons sensitive to both stimulus dimensions (e.g. Figs. 3.7B and 3.10A) was analyzed with singular value decomposition (SVD) to assess their separability (Pena and Konishi, 2001). SVD was used to transform the joint ITD\textsubscript{env}-ITD\textsubscript{fs} tuning matrix of each neuron to the form $U\Lambda V^T$, where $\Lambda$ is a diagonal matrix of singular values and $U$ and $V$ are sets of orthogonal vectors. The SVD of a completely separable response will only have one non-zero term (the first diagonal term) in $\Lambda$, and the original response can be perfectly reconstructed from the multiplication of two vectors (in this case representing the independent sensitivity to ITD\textsubscript{env} and ITD\textsubscript{fs}). By analyzing the relative magnitude of each singular value ($\lambda(n)^2 / \sum_i \lambda(i)^2$, where $\lambda(n)$ is the $n$-th diagonal term of $\Lambda$), the fractional power of the response space captured by each singular value is obtained. SVD analysis was performed on 16 ITD\textsubscript{fs} sensitive neurons and the mean fractional power of the first singular value was 87.9 ± 5.7% (Fig. 3.11A). This indicates that a purely multiplicative model, with independent ITD\textsubscript{env} and
ITD_{fs} tunings, should be able to account for about 88% of the variance in the joint ITD_{env}-ITD_{fs} tuning space. By setting all singular values to zero except for the first term ($\lambda(1)$), predicted ITD_{env}-ITD_{fs} tuning with a purely multiplicative model, which assumes perfect separability of ITD_{env} and ITD_{fs} sensitivity, was compared to the actual data (Fig. 3.11B). Across the population, the correlation between the SVD prediction and the measured data is high ($r^2 = 0.867$), further indicating a high separability between ITD_{env} and ITD_{fs} tuning.

**Whole waveform ITD sensitivity for AM stimuli**

All previous measures of ITD sensitivity involved independent manipulations of envelope and fine structure ITD. We also tested sensitivity to ITD shifts in the entire waveform of AM pulse trains in order to verify the relative tuning to ITD_{env} versus ITD_{fs} measured with the dynamic stimulus. Fig. 3.12A shows the dynamically derived ITD_{env} tuning curve (ITD_{fs} = 0 µs) from -5000 µs to +5000 µs for the neuron used for Fig. 3.10A. Since the carrier rate is 1000 pps and has a period of 1000 µs, the ITD_{fs} curve for this neuron over the range of -5000 µs to +5000 µs is the same as the ITD_{fs} curve in Fig. 3.10A repeated every 1000 µs. This is shown in Fig. 3.12B and when compared to Fig. 3.12A illustrates how much sharper the ITD_{fs} tuning is than ITD_{env} tuning. Whole waveform ITD (ITD_{wav}) tuning was also measured with static ITD stimuli for this neuron (Fig. 3.12C). The shape of the ITD_{wav} curve is very close to the product of the ITD_{env} and ITD_{fs} curves. The response peaks every 1000 µs as did the ITD_{fs} curve, but only over a range of ITDs of about the same width and shape as the ITD_{env} curve. The envelope of the ITD_{wav} curve is more symmetric about 0 than the ITD_{env} curve. This may be because the ITD_{env} curve was measured dynamically. Within the range of relevant ITDs for a cat or a human, the ITD sensitivity of this neuron is clearly dominated by its sensitivity to ITD_{fs}.

Responses to the ITD_{wav} stimulus can also be derived from the 2-dimensional ITD_{env}-ITD_{fs} display, since this matrix fully describes the response to every combination of envelope and fine structure ITD. For the example neuron in Fig. 3.12, this space (shown in Fig. 3.10A) is highly separable in the ITD_{env} and ITD_{fs} dimensions (fractional power of first singular component = 97.3%), thus the multiplication of the ITD_{env} and
ITD$_{fs}$ tuning curves gives a good prediction. A more complex ITD$_{env}$-ITD$_{fs}$ space is shown for another neuron in Fig. 3.13$B$. Since the ITD$_{env}$-ITD$_{fs}$ tuning is less separable for this neuron (fractional power of first singular component = 84.6%), we expect that the ITD$_{wav}$ tuning of this neuron will not be as well predicted from the individual ITD$_{env}$ and ITD$_{fs}$ curves as for the neuron in Fig. 3.10. Fig. 3.13$A$ and $C$ show the ITD$_{env}$ and ITD$_{fs}$ curves for this neuron. The predicted ITD$_{wav}$ curve from multiplication of the ITD$_{env}$ and ITD$_{fs}$ curves is shown in Fig. 3.13$E$. The measured ITD$_{wav}$ curve is shown in Fig. 3.13$F$ as black points and is more closely matched by the prediction from sampling the joint ITD$_{env}$-ITD$_{fs}$ tuning space (Fig. 3.13$D$) than the prediction from the multiplication of ITD$_{env}$ and ITD$_{fs}$ curves (Fig. 3.13$E$).
Discussion

We studied single-neuron responses to amplitude-modulated trains of electric current pulses in the IC of anesthetized cats with bilateral cochlear implants. Sensitivity to envelope ITD was found to be similar in many respects to that seen with acoustic stimulation. The halfwidth of ITD_{env} curves decreased with increasing modulation frequency such that halfwidth was nearly constant when expressed in units of modulation phase. Neurons that had the best sensitivity to ITDs in low-rate constant-amplitude pulse trains were also likely to be sensitive to ITD_{fs} with a 1000 pps carrier. Neural ITD_{fs} selectivity was relatively sharp when compared to ITD_{env} for 1000 pps carriers, but was eliminated at the high carrier rate of 5000 pps. This is similar to acoustic stimulation where neural sensitivity to ITD_{fs} in the IC drops rapidly above 1500 Hz (Yin et al., 1984; Joris, 2003) and ITD_{env} JNDs to sinusoidal AM tones are poorer than sensitivity to pure tones of the same frequency (Griffin et al., 2005).

Sensitivity to envelope ITD

The majority of neurons in the IC were sensitive to ITD_{env} at modulation frequencies that elicited a sustained response. The decrease in ITD_{env} halfwidth with increasing f_{mod} was consistent with constant IPD_{env} halfwidth over the range of f_{mod} tested (20-160 Hz). A similar result has been seen in high-frequency neurons of the IC of the awake rabbit using acoustic stimulation with SAM tones over a higher range of f_{mod} (300-700 Hz) (Batra et al., 1993). Although we did not observe a significant change in ITD_{env} halfwidth between carrier rates of 1000 and 5000 pps for the range of f_{mod} tested, there were significantly poorer ITD_{env} JNDs using the 5000 pps carrier for f_{mod} > 80 Hz, because firing rates were lower. Although using a higher carrier rate increases the upper limit of f_{mod} that can be delivered with a cochlear implant, this result suggests a possible degradation in the representation of AM with higher carrier rates.

We found that using a higher f_{mod} leads to sharper ITD_{env} tuning and smaller ITD_{env} JNDs. Although values of f_{mod} above 160 Hz were not systematically tested, previous studies suggest that there is a limit near 200-300 Hz above which most IC neurons would have a much diminished sustained response (Snyder et al., 1995; Snyder
et al., 2000), similar to the rate limit seen in Chapter 2 with constant-amplitude pulse trains. Employing values of $f_{mod}$ much greater than those tested in this study may not lead to better ITD$_{env}$ sensitivity for this reason. Since ITD$_{env}$ halfwidth seems to be directly related to the width of each cycle of the amplitude envelope, temporal sharpening of the envelope might decrease ITD$_{env}$ halfwidth, while avoiding possible rate limits that result in mostly onset responses in the IC. Temporal sharpening of the amplitude envelope would be similar to “transposed stimuli” used in acoustic studies of binaural hearing, where better behavioral (Bernstein and Trahiotis, 2002) and neural (Griffin et al., 2005) ITD$_{env}$ discrimination thresholds are achieved by using a halfwave-rectified sinusoid to AM a high-frequency sinusoidal carrier.

**Sensitivity to fine structure ITD**

While stimulation with an unmodulated 1000 pps pulse train carrier elicited predominantly onset responses in IC neurons, low-frequency AM of the carrier restored sustained responses. Despite a general lack of phase locking to the 1000 pps carrier, many IC neurons were sensitive to ITD$_{fs}$ at this carrier rate when AM was imposed upon the stimulus. This finding indicates that the processing of ITD$_{fs}$ is likely occurring at a level lower than the IC (such as the SOC), as has been suggested in previous studies of acoustic stimulation with AM tones in high-frequency neurons (Yin et al., 1984; Batra et al., 1993), and that the lower limit of phase locking arises after ITD$_{fs}$ computation. The ranges of ITD$_{fs}$ halfwidths and neural JNDs are consistent with the values obtained in the best neurons in Chapter 2 for low-rate (40 pps) constant-amplitude pulse trains. Likewise, neurons that were sensitive to ITD$_{fs}$ tended to have narrow ITD halfwidths for low-rate constant amplitude pulse trains, while neurons that were insensitive to ITD$_{fs}$ had broader ITD tuning. Unlike acoustic stimulation, where phase locking degrades at frequencies above ~1500 Hz (Johnson, 1980; Joris et al., 1994), electric stimulation can show significant phase locking in the auditory nerve for 5000 pps (Litvak et al., 2003). The general loss of ITD$_{fs}$ sensitivity observed in the present study at the higher carrier rate (5000 pps) may be the result of the relatively short (200 µs) period of the carrier when compared to typical ITD halfwidth of IC neurons, or alternatively may reflect limited phase locking, beyond the auditory nerve, in the binaural circuit that processes
ITD. This loss of ITD<sub>fs</sub> sensitivity with high frequency stimulation is also seen with acoustic hearing. However, with electric stimulation, this effect was observed within individual neurons since electric stimulation allows an arbitrary stimulus to be delivered to the same CF region, whereas in normal-hearing animals, this effect is seen by comparing responses across neurons of different CFs, since there is a tight coupling of a neuron’s CF and the frequency of the fine structure of an acoustic stimulus.

Are envelope and fine-structure ITD sensitivities based on different mechanisms?

The result that IPD<sub>env</sub> halfwidths are nearly constant for a given neuron over a wide range of <i>f</i><sub>mod</sub> supports the notion that ITD<sub>env</sub> sensitivity may have more to do with the instantaneous intensities of the stimulus at each ear rather than the interaural timing of the amplitude envelopes. In Chapter 2, we showed that the rate of a constant-amplitude pulse train did not have a large effect on the halfwidth of ITD tuning, but here with AM pulse trains, increasing <i>f</i><sub>mod</sub> greatly decreased the halfwidth of ITD<sub>env</sub> tuning such that the IPD<sub>env</sub> halfwidth was roughly constant (in units of cycles). There is also a lack of correlation between neurons’ ITD tuning properties (e.g. halfrise) with low-rate constant amplitude pulse trains and ITD<sub>env</sub> tuning with AM pulse trains. On the other hand, ITD sensitivity with low-rate pulse trains resembles the ITD<sub>fs</sub> tuning in this study, suggesting that they are based on the same or similar mechanism. Another line of evidence supporting the notion of distinct ITD mechanisms is the high separability of ITD<sub>env</sub> and ITD<sub>fs</sub> tuning (Fig. 3.11) and the results of whole waveform ITD curves for ITD<sub>fs</sub> sensitive neurons (Figs. 3.12 and 3.13). As a first-order approximation, there is an independent relationship of envelope and fine structure ITD sensitivity in these responses.

Comparison with behavioral data from bilaterally implanted human subjects

Published reports of psychophysical ITD JNDs for AM stimuli in bilaterally implanted human subjects are scarce. In one study (van Hoesel and Tyler, 2003), ITD JNDs were measured in a single subject with a 800 pps carrier and 50 Hz AM (6.8 dB modulation depth). For this subject the ITD<sub>env</sub> JND was 290 µs and the ITD<sub>wav</sub> JND was 120 µs (ITD<sub>fs</sub> was not tested). Two additional subjects were tested for ITD<sub>wav</sub> only and had JNDs of 160 and 130 µs. All three subjects had immeasurable ITD JNDs to constant
amplitude pulse trains at 800 pps. Thus, behaviorally, AM was required at this pulse rate for measurable ITD sensitivity. This is qualitatively similar to our neural results in cat IC. In Chapter 2, we found that ITD sensitivity in the sustained responses degraded with increasing pulse rates and here we show that the addition of AM restores ITD sensitivity to the carrier pulses at 1000 pps by reviving sustained responses.

Possible bilateral implant processing strategy for a clinical device

Given the range of modulation frequencies and carrier rates tested, the best ITD sensitivity seen in this study was for ITD contained in the fine structure of an AM pulse train at 1000 pps. This is an important result since most clinical cochlear implants do not control the fine timing of their current pulses. Fig. 3.14 shows an example of the type of strategy that would maintain ITDs in the fine structure. This contrasts with a conventional cochlear implant processor, which would have good representation of the amplitude envelope of the filtered signal in each channel, but lose the temporal information in the fine structure. First the sound is split into multiple frequency channels by a bank of bandpass filters. Then, in each channel, the timing and amplitude of the current pulses are determined by zero-crossings and the amplitude envelope respectively. The exact procedure used for this figure was a moving window (duration equal to the reciprocal of the center frequency of the channel). In each window, a pulse is output at a time corresponding to the maximum in the derivative of the filtered signal and the pulse amplitude is determined by the value of the amplitude envelope of the filtered signal at this same time point. The output is shown for a bilateral device in blue and red when the input is the vowel /æ/. The acoustic signal to the left ear (blue) leads the signal to the right ear (red) by 200 µs. Notice that the output pulses of the implant processor preserve the ITD of the original signals. A bilateral processing strategy similar to the one shown in Fig. 3.14 has been described previously by van Hoesel and Tyler (2003), but differs from ours in that it uses the timing of the peak of the amplitude envelope in each channel for the timing of the current pulses.

A possible drawback of such a strategy is that there will occasionally be temporally overlapping current pulses in different channels. It is not clear how often this would occur or even whether this would be a problem. If such interactions are
detrimental, then electrode designs and configurations that minimize current field interactions might become important. Alternatively, pulse collisions could be minimized by designing an algorithm that avoids collisions by giving priority to particular channels (like low-frequency channels or those with more energy). Also, the maximum sustained pulse rate in any one channel should be limited based on the result that neuron sensitive to ITD$_{fs}$ in a 1000 pps carrier were not sensitive to ITD$_{fs}$ in a 5000 pps carrier (a rate limit was not imposed for Fig. 3.14).

**Conclusion**

The neural responses in this study show tuning to envelope ITD similar to that seen in normal-hearing animals using AM tones. Over the range of modulation frequencies tested (up to 160 Hz), IC neurons are more sharply tuned to ITD in the fine time structure rather than the amplitude envelope of 1000 pps AM pulse trains, though fine structure ITD sensitivity is eliminated at a higher carrier rate of 5000 pps. Based on these single neuron results, we predict that the best behavioral ITD discrimination thresholds for AM pulsatile electric stimuli will be for whole waveform ITDs in an AM stimulus with a carrier rate $\leq$ 1000 pps. Our results further suggest that a bilateral cochlear implant strategy that successfully conveys ITD cues should control the precise timing of current pulses based on the fine timing of the sound sources at each ear. Further benefit from improved sensitivity to envelope ITD may potentially be achieved by temporally sharpening the amplitude envelope as with “transposed stimuli” (van de Par and Kohlrausch, 1997; Bernstein and Trahiotis, 2002), though with the possible side effect of distorting speech information.
Tables and figures

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</table>

Table 3.1. Number of neurons responsive to AM stimuli and sensitive to ITD. Each successive column is a subset from the “yes” row of the previous column.
|                        | Basic Halfrise (µs) | Basic $|\text{ITD}_{\text{ms}}| (µs)$ | Physiological Modulation Depth (%) | ITD$_{\text{env}}$ Halfwidth (ms) | Electrode depth (µm) |
|------------------------|---------------------|-------------------------------|----------------------------------|----------------------------------|-----------------------|
| ITD$_{fs}$ sensitive (16) | 160 ± 99.7          | 145 ± 175                     | 84.8 ± 21.7                      | 2.89 ± 1.14                      | 2213 ± 740            |
| ITD$_{fs}$ insensitive (15) | 436 ± 292           | 398 ± 372                     | 51.3 ± 27.4                      | 5.42 ± 3.09                      | 2711 ± 563            |
| Significance ($P$)     | < 0.01 (**)         | < 0.05 (*)                    | < 0.001 (***))                   | < 0.01 (**)                      | < 0.05 (*)            |

Numbers are means ± standard deviations. $P$ values are from two-sample $t$-tests comparing properties of ITD$_{fs}$ sensitive and insensitive units.

Table 3.2. Difference in basic ITD tuning between ITD$_{fs}$ sensitive and insensitive neurons.
Fig. 3.1. Binaural modulation beat (BMB) stimulus and example responses. (A) The modulation frequency in the contralateral ear is 1 Hz greater than that in the ipsilateral ear to create a dynamic ITD\textsubscript{env} that traverses the full range of IPD\textsubscript{env} between -0.5 and 0.5 cycles every second. For illustrative purposes the modulation frequencies shown here are relatively low (11 Hz for the contralateral ear and 10 Hz for the ipsilateral ear). (B) Zoomed in (5 ms) view of stimulus waveforms shows that the carrier pulses are synchronized (ITD\textsubscript{fs} = 0 µs). (C) IPD\textsubscript{env} as a function of time for the modulation beat stimulus. (D) PST histogram of the spiking of a neuron to 10 presentations of the stimulus. Since the spike rate changes with time (and thus IPD\textsubscript{env}), this neuron is sensitive to IPD\textsubscript{env} in the stimulus (see panel E).
Fig. 3.2. Population ITD_{env} tuning for the standard BMB stimulus (pulse rate = 1000 pps, $f_{mod} = 40$ Hz). (A) Distribution of vector strength. (B) Distribution of best IPD_{env}. (C) Distribution of ITD_{env} halfwidths. (D) Distribution of single-unit neural ITD_{env} JNDs (from a reference of 0 ms) for 31/33 neurons. 2 neurons had immeasurable JNDs and are shown to the right of the distribution.
Fig. 3.3. ITD\textsubscript{env} tuning at multiple modulation frequencies for an example neuron. (A) IPD\textsubscript{env} tuning curves for each value of \( f_{\text{mod}} \). Blue dots show measured data and red curves are Gaussian fit. The vertical dimension is spike rate and the scale is fixed from plot to plot. (B) rMTF. (C) Vector strength. (D) ITD\textsubscript{env} halfwidth in units of cycles of the modulation period. (E) ITD\textsubscript{env} halfwidth in units of \( \mu \text{s} \). (F) Best IPD\textsubscript{env}. (G) Estimated ITD\textsubscript{env} JNDS. Red dotted line indicates half of the modulation period, which is the upper limit of measurable ITD\textsubscript{env} JNDS. Immeasurable JNDS are shown as ‘x’.
Fig. 3.4. Effect of modulation frequency and pulse rate on envelope ITD tuning. **Top row:** single neuron data \((N = 15)\) for carrier = 1000 pps. **Middle row:** single neuron data \((N = 11)\) for carrier = 5000 pps. **Bottom row:** mean values for the population comparing carrier rates (solid black lines are 1000 pps and dashed magenta lines are 5000 pps). (A) ITD\(_{\text{env}}\) halfwidth as a function of modulation frequency. The dotted red line in the bottom panel is \(\kappa f_{\text{mod}}\). (B) ITD\(_{\text{env}}\) JNDs as a function of modulation frequency. Red dotted lines show immeasurable values. Population mean JNDs only include measurable JNDs from single neurons. See Fig. 3.5 for the proportion of measurable JNDs at each modulation frequency. (C) Rate modulation transfer functions given in units of normalized spike rate.
Fig. 3.5. Proportion of neurons with measurable JNDs at different modulation frequencies.
Fig. 3.6. Effect of stimulus intensity on envelope ITD tuning. (A) ITD<sub>env</sub> functions for an example neuron at several stimulus intensities (units are dB re threshold). Stimulus is a binaural modulation beat with a 1000 pps carrier and 40 Hz AM. Panels B-D: ITD<sub>env</sub> tuning characteristics of 7 neurons over a range of stimulus intensities. Thin black lines show data from individual neurons and the red dashed lines are linear fits to the population data. (B) Peak spike rate as a function of stimulus intensity. (C) Best IPD<sub>env</sub> as a function of stimulus intensity. (D) ITD<sub>env</sub> halfwidth as a function of stimulus intensity. (E) ITD<sub>env</sub> JNDS as a function of stimulus intensity.
Fig. 3.7. Sensitivity to fine structure ITD. (A) IPD$_{\text{env}}$ tuning curves at successive ITD$_{fs}$ steps. (B) Joint IPD$_{\text{env}}$-IPD$_{fs}$ tuning space. (C) ITD$_{fs}$ tuning at IPD$_{\text{env}} = 0$. 


Fig. 3.8. Population ITD<sub>fs</sub> sensitivity. (A) Distribution of ITD<sub>fs</sub> halfwidths. ITD<sub>fs</sub> sensitive neurons are shown in solid black bars. ITD<sub>fs</sub> insensitive neurons are shown in the open red bar to the right of the distribution. (B) Comparison of envelope and fine structure halfwidths at 1000 pps. (C) Distribution of neural ITD<sub>fs</sub> JNDs derived from single neurons. The shading of the bars follows the convention in panel A. (D) Comparison of envelope and fine structure ITD JNDs at 1000 pps.
Fig. 3.9. Correlation of various ITD tuning properties and ITDfs sensitivity. Halfrise of ITD tuning with 40 pps constant-amplitude pulse trains (Chapter 2) is plotted against ITDenv halfwidth for ITDfs sensitive and insensitive neurons. ITD tuning shape (as determined from ITD tuning curve with 40 pps constant-amplitude pulse trains, Chapter 2) is shown by the shape of the symbol. Blue filled symbols are ITDfs sensitive neurons and red open symbols are ITDfs insensitive neurons.
Fig. 3.10. Effect of carrier rate on ITD$_{fs}$ tuning. (A) ITD tuning for a neuron at a pulse rate of 1000 pps ($f_{mod} = 40$ Hz). Subpanels follow the organization of Fig. 3.7. (B) ITD tuning for the same neurons at a pulse rate of 5000 pps ($f_{mod} = 40$ Hz).
Fig. 3.11. Separability of ITD$_{env}$-ITD$_{fs}$ tuning. (A) Fractional power of singular values from 16 neurons sensitive to ITD in the envelope and fine structure of 1000 pps, 40 Hz AM stimulus. (B) Comparison of measured spike rates from joint ITD$_{env}$-ITD$_{fs}$ tuning spaces with predictions from the SVD multiplicative model, which assumes perfect separability by only using the first singular value to reconstruct the data.
Fig. 3.12. Sensitivity to ITD in the whole waveform. Panels A-C show tuning to ITD in different parts of a 1000 pps, 40 Hz AM stimulus in the same neurons. (A) ITD\textsubscript{env} tuning for ITD\textsubscript{fs} fixed at 0. (B) ITD\textsubscript{fs} tuning for ITD\textsubscript{env} fixed at 0. (C) Tuning to ITD in the whole waveform (ITD\textsubscript{wav}).
Fig. 3.13. Whole waveform ITD tuning for a neuron with less separable ITD\textsubscript{env}-ITD\textsubscript{fs} tuning. (A) ITD\textsubscript{env} tuning at ITD\textsubscript{fs} = 0. (B) Joint display of ITD\textsubscript{env}-ITD\textsubscript{fs} tuning. (C) ITD\textsubscript{fs} tuning at ITD\textsubscript{env} = 0. (D) Prediction of ITD\textsubscript{wav} tuning from dynamically measured ITD\textsubscript{env}-ITD\textsubscript{fs} display (panel B). (E) Prediction of ITD\textsubscript{wav} tuning from multiplication of ITD\textsubscript{env} and ITD\textsubscript{fs} tuning (from panels A and C). (F) Explicitly measured ITD\textsubscript{wav} tuning (black points) superimposed on predictions from ITD\textsubscript{env} and ITD\textsubscript{fs} tuning curves (green line) and joint ITD\textsubscript{env}-ITD\textsubscript{fs} tuning space (red line).
Fig. 3.14. Possible processing scheme that preserves fine timing cues. The “pulse generator” uses the maximum derivative of the filtered signal in each channel for the timing of each pulse. The example shown here for the vowel /æ/ has a 200 µs ITD that can be seen in the magnified views (right panels) of the input signal and output pulses for EL2.
Chapter 4

Using Evoked Potentials to Match Interaural Electrode Pairs with Bilateral Cochlear Implants

Abstract

Bilateral cochlear implantation seeks to restore the advantages of binaural hearing to the profoundly deaf by giving them access to binaural cues normally important for accurate sound localization and speech reception in noise. Psychophysical data suggest that a key issue for the implementation of a successful binaural prosthesis is the ability to match the cochlear positions of stimulation channels in each ear. This may not only be important for binaural hearing, but also for the fusion of speech information across ears. We used a cat model of bilateral cochlear implants with 8-electrode arrays implanted in each cochlea. The arrays allowed the cochlear location of stimulation to be independently varied in each ear in order to test how binaural interactions change with interaural electrode separation. The binaural interaction component (BIC) of the electrically-evoked auditory brainstem response was used as an assay of binaural processing. BIC amplitude peaked for interaural electrode pairs at the same relative cochlear position and dropped with increasing cochlear separation in either direction. To test the hypothesis that BIC amplitude peaks when electrodes from the two sides activate the same neural population, we measured multi-unit neural activity along the tonotopic gradient of the inferior colliculus (IC) with 16-channel recording probes and determined the spatial pattern of IC activation for each stimulating electrode. We found that the interaural electrode pairings that produced the best aligned IC activation were also those that yielded maximum BIC amplitude. These results suggest that ABR measurements may provide a method for assigning frequency-channel mappings in bilateral implant recipients, such as pediatric patients, for which psychophysical measures of pitch ranking or binaural fusion are unavailable.
Introduction

Cochlear prostheses are increasingly being implanted in both ears of some patients instead of the more standard implantation on one side. This is being done with the hope of improving the hearing performance of users of cochlear implants by taking advantage of binaural cues important in normal hearing individuals for localization of sound sources and speech reception in noise. Beyond traditional binaural advantages due to binaural difference cues and the head shadow effect, some bilateral cochlear implant users have better speech reception with the addition of redundant or complementary information across the ears (Schon et al., 2002; Long et al., 2004). This effect, often referred to as binaural summation, highlights the ability of the auditory system to combine information across the ears.

A hallmark of the auditory system is the tonotopic arrangement that begins in the cochlea and persists through its ascending pathways to the primary auditory cortex. This organization is also maintained in the early connections between auditory neurons from the two sides of the head. The characteristic frequencies (CFs) of binaural neurons for monaural stimulation of the two ears are highly correlated in the medial superior olive (Guinan et al., 1972; Yin and Chan, 1990), lateral superior olive (Boudreau and Tsuchitani, 1968), and the IC (Kuwada et al., 1984; Qiu et al., 2003). One issue with bilateral cochlear implants is the correct assignment of analysis frequency bands to stimulus channels along the electrode arrays in each ear so that bilaterally delivered information is properly aligned once it converges on the binaural neurons of the auditory CNS. Such an alignment may be important for both binaural hearing and the fusion of speech information across ears.

Potential benefits of having closely matched frequency-place assignments across the ears include improved speech reception and better sound localization. It has been shown that shifting or warping of the natural frequency-place map is detrimental to speech reception with both unilateral cochlear implants (Baskent and Shannon, 2004) and simulations of cochlear implants in normal-hearing subjects (Dorman et al., 1997; Shannon et al., 1998; Baskent and Shannon, 2003). While subjects can often adapt to shifts in the frequency-place map over time (Rosen et al., 1999), simulations of bilateral
implants in normal-hearing subjects (Siciliano et al., 2006) suggest that an offset between frequency-place maps in the two ears are not only detrimental to speech reception, but are also difficult to adapt to. Improvements over time in these simulations were consistent with listeners adopting a strategy that ignored one ear. Behavioral results in a bilaterally implanted human subject suggest that sensitivity to interaural time differences (ITDs) is best for interaural electrode pairs that excite the same tonotopic region of the auditory nerve (Long et al., 2003). Similarly, acoustic sensitivity to ITD in the envelope of SAM tones is also best when the location of stimulation is the same in each cochlea, by matching the carrier frequencies delivered to the two ears (Nuetzel and Hafter, 1981). It is likely that the binaural improvements for speech reception in noise, that exist for acoustic hearing (Cherry, 1953) and depend on differences in ITD between the target and masker (Zurek, 1993), also require a frequency-aligned convergence of information between the two ears.

One of the first studies of a patient with bilateral cochlear implants (Pelizzone et al., 1990), showed binaural interactions in the evoked responses with binaural stimulation. Pelizzone and colleagues hypothesized that the binaural interaction component (BIC) of the electrically-evoked auditory brainstem response (EABR) should be greatest when auditory nerve fibers from comparable regions in the two ears are stimulated. They proposed that this could provide a way to symmetrically position cochlear implants in each ear. This chapter develops and investigates such a method by measuring evoked potentials with different interaural electrode pairs in bilaterally implanted cats and testing whether BIC amplitude is greatest for matched interaural electrode pairs. This non-invasive method could in principle work in humans, so it has potential clinical usefulness. We also used an invasive measure of neural activity along the tonotopic axis of the IC to more directly measure the neural population excited by each individual stimulus electrode and make interaural electrode assignments based on the alignment of the response peaks. This second measure is used to test the results of the evoked potential method. Preliminary results have been presented (Smith and Delgutte, 2003b, 2006).
Methods

Subjects and Deafening

All surgical and experimental procedures followed the regulations set by NIH and were approved by the MEEI IACC. Healthy adult cats of either sex were deafened by co-administration of kanamycin (300 mg/kg subcutaneous) and ethacrynic acid (25 mg/kg intravenous, (Xu et al., 1993) 7-14 days prior to cochlear implantation and electrophysiological recordings.

Surgery

On the day of the experiment, after induction of anesthesia by Dial in urethane (75 mg/kg), a tracheal canula was inserted; skin and muscles overlying the back and top of the skull were reflected. Ear canals were transected for insertion of a closed acoustic system. Tympanic bullae were opened to allow access to the round-window for placement of intracochlear electrodes. Part of the skull overlying the occipital cortex was removed to allow for partial aspiration of cortical tissue and access to the bony tentorium and IC. The part of the tentorium overlying the IC was drilled for better access to the dorsal-lateral surface of the IC. Throughout all procedures, animals were given supplementary doses of anesthesia to maintain an areflexic state and vital signs were monitored.

Cochlear implantation and electrode configurations

Stimulating electrodes were surgically implanted into each cochlea through the exposed round window. The electrodes were 8-contact electrode arrays with 0.75 mm spacing (Cochlear Corp., ring-type contacts with 0.45 mm diameter). The contacts of the arrays were numbered 1-8, from apical to basal. Particular care was taken to achieve the same insertion depth on both sides as observed by an operating microscope. Depth of insertion was 5-6 mm depending on the animal and the most basal contact (#8) was typically just at the round window. Absorbent cotton spears were placed lateral to each electrode array and used to push the array against the modiolus.
Several intracochlear electrode configurations were used in this study including monopolar (MP), bipolar (BP), bipolar plus one (BP+1), and wide bipolar (WBP) electrode configurations. For all configurations there was an active electrode and a return electrode between which the stimulus current was passed. The active electrode was always one of the intracochlear electrodes on the implanted array and only the only difference between electrode configurations is the location of the return electrode. For monopolar configuration, the return electrode was a needle electrode in the neck muscle. For bipolar configuration, the return electrode was also one of the intracochlear electrodes and was always one contact basal of the active electrode. Bipolar plus one is similar to bipolar configuration except that the return electrode was two contacts basal of the active electrode. For wide bipolar configuration, the return electrode was the most basal electrode (electrode #8) of the intracochlear array and was at the round window. Although there was always a pair of electrodes for each stimulus configuration in each ear, only the position of the active electrode (the most apical of the pair) is reported since the location of the return electrode is given by the configuration type. For example, when intracochlear electrodes #2 and #3 are used as the active and return electrodes respectively, this is simply referred to as bipolar stimulation at electrode #2 (BP 2).

Effectiveness of the deafening protocol was assessed by measuring auditory brainstem response (ABR) thresholds to acoustic clicks in each ear. Calibrated acoustic assemblies comprising an electrodynamic speaker and a probe-tube microphone were inserted into the cut ends of each ear canal to form a closed system. Condensation clicks (100 µs) were delivered via these acoustic systems, and ABR thresholds measured in both ears. ABR was measured between vertex and ear bar using a small screw inserted into the skull. In all experiments, acoustic ABR threshold was immeasurable since no response was seen up to the highest intensity tested (110 dB SPL peak).

*Stimulus generation and delivery*

All stimuli were generated by a pair of 16-bit digital-to-analog converters (D/A) at a sampling rate of 100 kHz. Stimulus levels were set by custom-built attenuators having a resolution of 0.1 dB. Attenuated outputs of the D/A converters were delivered to the intracochlear electrodes via a pair of custom-built high-bandwidth (40 kHz),
optically-isolated, constant-current sources. All electric stimuli were made up of 100 µs biphasic current pulses (cathodic-anodic, 50 µs/phase).

**EABR measurements**

The electrically-evoked auditory brainstem response (EABR) was measured by recording the voltage between a screw placed at the vertex of the skull and the earbars of the stereotaxic device and averaging the response over 500 stimulus presentations. The stimulus consisted of single biphasic pulses (50 µs/phase, 21/s) with alternating polarity on each stimulus presentation. The alternating polarity allows for the stimulus artifact, which reverses polarity with the stimulus, to be mostly averaged out from the neural response, which does not reverse polarity with the stimulus. Evoked potentials were amplified (60 dB) and bandpass filtered (cutoff frequencies of 100 Hz and 10 kHz). The resulting signal was digitized at a sampling rate of 20 kHz and the average waveform (500 responses) was saved to disk. In post-processing, EABR waveforms were digitally filtered twice (once forward and once reversed) with a 31st order FIR bandpass filter (300 Hz and 3 kHz cutoffs) so that no net delay was added to the signal. The amplitude of Wave 4 was measured for binaural and monaural EABR waveforms by measuring the voltage between the preceding trough and peak of Wave 4 (as indicated by triangles in Fig. 4.1A-C). Wave 4 amplitude was measured as a function of pulse amplitude for each intracochlear stimulating electrode in bipolar and monopolar configurations and hereafter will be referred to as EABR amplitude. We also calculated the binaural interaction component (BIC) of the EABR by subtracting the sum of the monaural EABR responses from the binaural EABR response (Fig. 4.1). The BIC consists of a single biphasic wave and its amplitude was measured between the preceding trough and the following peak as shown in Fig. 4.1D.

**Inferior Colliculus recordings**

Neural activity was recorded simultaneously at multiple locations in the IC using 16-channel silicon probes (NeuroNexus Technologies, 100 or 150 µm linear spacing, 177 µm² site area). The recording probe was advanced through the exposed IC from dorsolateral to ventromedial, in the coronal plane tilted 45° off the sagittal plane so as to
record activity from neurons covering a highly-reproducible, wide range of CFs (Merzenich and Reid, 1974; Snyder et al., 1990). Neural responses to single biphasic current pulses (50 µs/phase) were recorded simultaneously from all 16 channels by saving the raw waveforms of the signals at each probe site to disk at a sampling rate of 20 kHz.

Isolation of neural activity at different sites across the 16-site recording probe varied depending on the position of the array in the IC. While most sites exhibited fairly uniform local field potentials and multi-unit responses, it was not uncommon for 2-4 sites (depending on the exact position of the probe) to show well-isolated activity from single-units. In order to obtain a more uniform neural response quality across sites, responses to 10 stimulus presentations were averaged for each site, de-emphasizing the larger voltage excursions from possible single-unit activity. The average response was then lowpass filtered at 3kHz and the RMS amplitude was calculated for a 10 ms window, beginning 2.5 ms after the stimulus (Fig. 4.2A). Fig. 4.2A shows filtered average response waveforms for an example recording at one site as a function of stimulus intensity. This neural activity is a combination of multi-unit activity (> 300 Hz) and local field potentials (< 300 Hz). The corresponding RMS amplitudes, as calculated from the response waveforms, are shown in the right panel (Fig. 4.2B) and show monotonic growth with increasing intensity.

Neural activation patterns along the tonotopic axis of IC were assessed by plotting neural response for a constant intensity stimulus as a function of IC depth (i.e. probe site). The precise location of the response peak was estimated by convolving the spatial profile with a 3-point triangular kernel [.25 .5 .25] and then interpolating the curve with a cubic spline and picking the maximum of the fitted curve. The alignment of neural activation patterns elicited by different intracochlear electrodes was compared by measuring the physical distance between response peaks from their respective spatial profile.
Results

Results are based on evoked recordings in 7 of the 21 deafened cats with bilateral cochlear implants that were used in the experiments from Chapters 2 and 3. In this subset of animals, the effect of interaural electrode pairing was studied on the BIC waveform. Parallel recordings at a minimum of 16 sites along the tonotopic axis of IC were made in four of these animals in order to characterize the place and shape of neural activation in the auditory CNS with different intracochlear stimulating electrodes. Best interaural electrode pairings were determined with the evoked responses by finding the interaural electrode pairs that produced the largest BIC amplitude given equivalent strength stimuli. Interaural electrode pairings were also assigned based on the degree of alignment of neural activation patterns in the IC for individual stimulus electrodes. Interaural pairings determined with both methods are compared as is the correlation between BIC amplitude and the distance between IC response peaks.

Evoked Potentials

Effects of overall stimulus level and interaural level difference on EABR and BIC amplitudes

EABR amplitude-level functions always grew monotonically regardless of electrode position in the scala tympani and electrode configuration (e.g. bipolar, monopolar, wide bipolar). While thresholds varied between electrodes and animals, with the more apical electrode generally having lower thresholds, the slope of the EABR amplitude-level functions only depended on electrode configuration, not on distance along the cochlear partition. Responses in bipolar configurations generally had EABR amplitude-level functions with shallower slopes while the slopes for monopolar electrode configurations were about twice steeper (Fig. 4.3B). Binaural EABR and BIC amplitudes show similar growth with intensity as monaural EABR responses (Fig. 4.3A).

EABR responses were also measured as a function of interaural level difference (ILD). For these measurements the mean binaural level was held constant by changing the level in each ear in equal dB steps in opposite directions. While monaural EABR
amplitudes follow the intensity at each ear, the BIC amplitude is maximal for a given ILD and falls for ILDs in either direction (Fig. 4.3C). The ILD that produces the maximum BIC amplitude generally corresponded to intensities at each ear that produced similar monaural EABR amplitudes, typically a fixed number of dB above threshold. Thus the BIC amplitude peaks when the stimuli at each ear are at the same “effective” intensity. With acoustic stimulation in humans, the BIC amplitude peaks for click stimuli that are centered in the head (Furst et al., 1985; Riedel and Kollmeier, 2002). For clicks that are presented simultaneously (ITD = 0 μs), this occurs when they are the same level at both ears (ILD = 0 dB).

Finding the BIC amplitude for binaurally balanced stimuli

Since the BIC amplitude is highly dependent on the intensity at each ear, we needed to find a way to make fair comparisons of BIC amplitude across different interaural electrode pairings. Since monaural stimuli that produce equal amplitude EABR are assumed to have the same “effective” stimulus strength, we first found stimulus intensities that elicited the same monaural EABR amplitude and used these intensities in each ear to measure the BIC. The procedure for finding binaurally balanced stimuli is shown in Fig. 4.4A for an example interaural electrode pair. The intensities for each ear were first picked by looking at the monaural EABR amplitude-level functions and finding the stimulus intensity that evoked an EABR amplitude between 1.5-2.0 μV. One ear was designated the “fixed” ear and its intensity was held constant during subsequent EABR measurements while the intensity in the opposite ear (“varied” ear) was varied over a small range of intensities (usually five 0.5 dB steps covering a range of 2 dB) around the intensity estimated to evoke a similar EABR amplitude. For the example in Fig. 4.4A, the right ear intensity is fixed at 5 dB re 1 mA and the right EABR amplitude is constant. In this example, the left ear intensity is varied from 7 to 9 dB re 1 mA and the left EABR amplitude increases incrementally with intensity. Unlike the case when the mean binaural level is fixed, for which BIC functions peak at a given ILD, here the BIC increases with increasing level in the varied ear since the mean binaural level is also increasing. The intensity at which the monaural EABR functions cross is assumed to be the intensity for the “varied” ear that matches the effective stimulus strength of the
“fixed” ear. Monaural EABR and BIC amplitudes are interpolated by linear regression (solid lines in Fig. 4.4A) and the BIC amplitude is estimated at the matching intensity of 7.9 dB (purple arrow). This procedure was repeated for five different electrodes in the “varied” ear while the electrode and stimulus level in the “fixed” ear was unchanged in order to measure BIC amplitude as a function of interaural electrode offset. Fig. 4.4B plots the BIC amplitude for all five pairings between electrode #3 in the “fixed” ear and the five electrodes in the “varied” ear. This curve is called a BIC-electrode function. For the example in Fig. 4.4B, the BIC amplitude is maximal for electrode #3 in the “varied” ear which corresponds to an interaural electrode offset of 0 electrodes. In total, 26 BIC-electrode functions were measured in 7 animals as summarized in Table 4.1. Across the dataset of BIC-electrode curves, the mean monaural EABR amplitude ± one standard deviation was 1.72 ± 0.22 µV.

Changes in BIC amplitude with interaural electrode offset

The BIC amplitude was measured for various interaural electrode pairings to test the hypothesis that “matched” interaural electrode pairs would produce greater BIC amplitude than “unmatched” pairings. BIC amplitude was measured for stimulation at a constant cochlear position and stimulus intensity in one (“fixed”) ear while the cochlear position was varied along the intracochlear array in the other (“varied”) ear. Stimulus intensity in the “varied” ear was varied for each cochlear position tested so as to keep monaural EABR amplitude constant as explained in the previous section, and the BIC amplitude for that position was estimated for a balanced stimulus. BIC-electrode functions (as in Fig. 4.4B) were constructed from the estimated BIC amplitudes for each “fixed” ear configuration.

The entire set of measured BIC-electrode functions are shown superimposed in Fig. 4.5A with BIC amplitude normalized so that each function peaks at 1. Each panel shows the measured BIC-electrode function for a given fixed active electrode in the array. Black lines indicate individual BIC-electrode function while the thick purple lines show the mean function for each fixed cochlear site of stimulation. In general, the location of the BIC-electrode peak is highly dependent on the cochlear location of stimulation for the “fixed” ear. The peak usually occurs for interaural electrode pairings
with the same number, which corresponds to electrodes at the same approximate insertion depth. Fig. 4.5B shows all BIC-electrode curves as a function of interaural electrode offset. Most of the curves peak at zero and the mean curve (thick purple line) is fairly symmetric. A histogram of the interaural electrode offset of the BIC peak is shown in Fig. 4.5C. A large majority of curves (20/26) peak at an interaural electrode offset of 0. In no case does the offset exceed the distance of ± 1 interaural electrode.

A breakdown of BIC-electrode data for all animals is shown in Table 4.1. All best interaural electrode matches based on the peak of BIC-electrode curves are in agreement for 4/6 animals, representing 14/25 BIC-electrode curves (animal #24 omitted since only one BIC-electrode curve was measured). Consistent offset in each animal is to be expected since the spacing of electrodes on each intracochlear array is fixed at 0.75 mm and the electrode array is relatively rigid. For the first of the two remaining animals (#30), 6/7 measurements were consistent. In the second animal (#34), 3/4 measurements indicate different interaural electrode alignments that could differ by 2 electrodes. The inconsistent interaural electrode offsets in this animal may be due to errors in the BIC-electrode measurements or in actual differences in the best offset. Asymmetries in implantation (such as with bent array in one ear) or cross-turn activation of the auditory nerve are possible reasons for differing offsets at different electrodes in the same animal. Overall, the electrode offsets estimated by maximizing the BIC are highly consistent in each animal.

Comparison of Bipolar and Monopolar BIC selectivity

The previous analysis grouped all BIC-electrode functions together regardless of electrode configuration. Here we compare the selectivity of BIC-electrode functions for bipolar and monopolar electrode configurations to test the hypothesis that bipolar stimulation will exhibit more selective BIC-electrode functions. The second column of Table 4.1 lists the electrode configurations tested in each animal. Selectivity of BIC-electrode functions is analyzed by plotting normalized BIC-amplitude as a function of the absolute value of the cochlear distance from the peak in the BIC-amplitude curves shown in Fig. 4.5B (i.e. BIC-electrode curves are shifted so that they peak at an offset of 0). Fig. 4.6A and 4.6B show the decrease in BIC amplitude with increased interaural electrode
offset for bipolar and monopolar stimulation respectively. On average, BIC amplitude is 50% of the peak value at an offset of about 2 electrodes (~1.5 mm cochlear distance) for both bipolar and monopolar stimulation. Contrary to the hypothesis, a 2-way ANOVA reveals that decreases in BIC amplitude are not significantly different for the two configurations \( (p = 0.16) \) as shown in a comparison plot in Fig. 4.6C. This result suggests that at the stimulus intensities tested, bipolar and monopolar stimulation produce similarly selective binaural neural activity.

**Inferior Colliculus Recordings**

Topographic neural response patterns elicited by the various intracochlear electrodes were measured along the tonotopic axis of the IC in 4 of the 7 animals studied with evoked potentials. This was done to directly test the hypothesis that matched interaural electrode pairs as assessed by the BIC methods activate aligned neural populations. Fig. 4.7A shows the orientation of the 16-channel recording probe in the IC, and the presumed tonotopic organization in the central nucleus of the IC with low- to high-CF neurons arranged from dorsal-lateral to ventral-medial (Merzenich and Reid, 1974). In one normal-hearing animal, acoustic response maps were measured for pure tones with log-spaced frequencies presented at several intensity steps. The acoustic response maps were recorded (16 sites at a time) as a function of depth from the surface of the IC and CF was estimated at each location as shown in Fig. 4.7B. More than 16 total sites were sampled by moving the probe to multiple depths. As expected from similar measurements for this trajectory in the IC (Merzenich and Reid, 1974; Snyder et al., 1990; Snyder et al., 2004), CF progresses monotonically as a function of depth and covers the entire range of hearing over a 5 mm range.

For electric stimulation, the recording probe was fixed at a single position relatively deep in the IC and responses at each of the 16 probe sites were characterized. Example neural spatial response patterns are shown in Fig. 4.7C for bipolar stimulation of the contralateral ear. Each panel shows the spatial response pattern for electric stimulation at a single cochlear position. From left to right, the panels progress from the most apical stimulation (BP 1) to the most basal stimulation (BP 7). Within each panel, color indicates the magnitude of the neural response as a function of IC depth (horizontal
axis) and stimulus intensity (vertical axis). Two qualitative observations can be made from these example neural response patterns. First, as stimulus intensity increases the width of the response pattern increases, indicating a broadening of the neural population excited by the more intense stimuli. Second, basalward shifts in the cochlear position of stimulation produces neural response patterns with loci at deeper locations in the IC, consistent with the tonotopic map.

The location of the peak of the neural response patterns was used to quantify the relative position of the response along tonotopic axis of IC. For a given stimulus configuration, a peak was estimated from its associated neural response pattern by analyzing the response at the same stimulus intensity used during the BIC measurements. Fig. 4.8A shows the smoothed spatial profiles at fixed intensities derived from the spatial response patterns shown in Fig. 4.7C. The stimulus intensities used are those from the BIC-electrode curves and are indicated by horizontal white lines in Fig. 4.7C. The locations of the activation peaks from this example (Fig. 4.8B) show a systematic progression of neural excitation to increased depths in the IC for more basal stimulation of the cochlea.

**Alignment of IC activation patterns**

The location of the peak response of IC activation patterns was used to compare neural activation patterns produced by different interaural electrode pairs. The distance between the response peaks from each electrode for a given interaural pair measures the degree of alignment between their respective neural activation patterns and is referred to as the “neural distance”. Fig. 4.9A shows examples of how the neural distance is measured between the neural activation patterns from stimulation in one cochlear location in the “fixed”/ipsilateral ear and from several cochlear locations in the “varied”/contralateral ear. The neural distance is plotted as a function of stimulus electrode in the “varied” ear for this example in Fig. 4.9B. The electrode number in the “fixed” ear (BP 2) is indicated by the red arrow. Best interaural electrode matches can be correspond by to the minimum of the neural distance function. For this particular example, the neural distance is minimal when the “varied” electrode is BP 2.
Width of neural activation patterns with bipolar and monopolar stimulation

The finding that stimulation with bipolar and monopolar configurations lead to equally sharp drops in BIC amplitude with increasing interaural electrode offset was unexpected. This result suggests that the spatial width of excitation with bipolar and monopolar stimulation may be comparable in binaural neurons at the intensities employed in the evoked potential portion of this study. Neural response patterns recorded in the IC of 3 animals were used to further test this notion, providing a more direct method for measuring the actual width of neural activation in the auditory CNS. Responses to monaural stimulation were recorded at multiple sites along the tonotopic axis of the IC at several stimulus intensities as previously shown in Fig. 4.7C for bipolar stimulation. The peak response amplitude and the width of the response at half the peak amplitude (i.e. halfwidth) were determined as a function of stimulus intensity. Fig. 4.10A shows the mean peak response amplitude versus intensity for bipolar and monopolar stimulation. The monopolar response curve has a greater slope (about twice as steep) than the bipolar response curve consistent with the EABR results discussed previously (see Fig. 4.3B). However, mean halfwidths are comparable for bipolar and monopolar stimulation for intensities up to 5 dB above threshold (Fig. 4.10B). For intensities greater than 5 dB, halfwidth is greater for monopolar than bipolar stimulation. Halfwidth is also plotted as a function of the peak response amplitude in Fig. 4.10C in an effort to correct for the difference in growth of responses as a function of intensity. This analysis shows that, over the range of response amplitudes that overlap between bipolar and monopolar stimulation, the widths of the responses are comparable. Percent changes in response amplitude and halfwidth between bipolar and monopolar configurations using the same active electrode and in the same animal are shown in the lower panels (D-F) of Fig. 4.10. Solid lines show mean percent changes and dotted lines indicate ±1 standard deviation. Positive changes indicate that the values for monopolar stimulation are greater than for bipolar stimulation. Fig. 4.10D shows that, as intensity increases, monopolar stimulation results in proportionally more response than bipolar stimulation. Fig. 4.10E confirms that the width of response pattern is only significantly greater for monopolar stimulation at intensities above 5 dB, but not at lower intensities. There is no significant change in response width between monopolar and bipolar stimulation when plotted as a function of
peak response amplitude (Fig. 4.10F). These results indicate that, while the widths of neural response patterns with monopolar stimulation are greater than those with bipolar stimulation for intensities much above threshold, widths are comparable at lower intensities and are not significantly different when differences in dynamic range are taken into account.

**Comparison of evoked responses and IC neural activation patterns**

The distance between neural activation peaks was measured for all of the interaural electrode pairings tested with evoked potentials for 4/7 of the animals in this study. Fig. 4.11A shows the BIC-electrode function for the same example configuration shown in Fig. 4.9. The neural distance function from Fig. 4.9B is replotted in Fig. 4.11B with the vertical axis inverted. The shapes of the BIC-electrode curve and the corresponding neural distance function in Figs. 4.11A-B are strikingly similar. The maximum BIC amplitude and the minimum neural distance both occur at the same place and thus an interaural electrode match based on either measurement would be the same (electrode #2 in the “varied” ear).

The relationship between interaural electrode alignments seen with evoked potentials and neural activation patterns in the IC is examined by plotting normalized BIC amplitude against neural distance measured with the same stimulus configurations in the same animals (Fig. 4.11C). Note that Fig. 4.11A and B contribute five points to Fig. 4.11C. Across the entire set of data, normalized BIC amplitude and neural distance are negatively correlated (r = -0.74), with normalized BIC amplitude tending to be large when neural distance is small. Nearly 60% of the variance can be accounted for by a decaying exponential fit to the data ($r^2 = 0.58$, $BIC = .86e^{-\text{nd}^{.580} + .09}$), where $nd$ is the neural distance in µm.

Fig. 4.11D shows the difference between interaural electrode matches based on maximum BIC amplitude and minimum neural distance. The matched interaural pairs are in agreement for the majority of cases tested with both methods (11/16 fixed electrodes in 4 animals). The difference between interaural electrode matches with the two methods never exceeded 2 electrodes (1.5 mm in the cochlea).
Discussion

This study investigated a novel method, first suggested by Pelizzone and colleagues (1990), of using evoked potentials for finding the relative positions of bilaterally implanted intracochlear electrodes and for assigning interaural electrode matches. The binaural interaction component (BIC) of the electric auditory brainstem response (EABR) was found to be maximal for stimuli presented at interaural pairs of electrodes in the same intracochlear position when stimulus strength was balanced. Neural response maps in the inferior colliculus support the hypothesis that BIC-matched interaural electrode pairs stimulate maximally aligned populations of binaural neurons in the auditory CNS.

Variability of thresholds and using EABR amplitude to match stimulus strength

An important aspect of measuring meaningful BIC-electrode curves in this study was using stimuli that had similar effective stimulus strengths at each intracochlear electrode. This is not trivial with cochlear implants since thresholds vary widely between electrodes and ears. Variability of threshold is presumably due primarily to the different positioning of the stimulating electrodes relative to the excitable neural elements. In these experiments, the intracochlear electrode array was often repositioned if initial tests of threshold were deemed too high. This was done by pushing the array closer to the modiolus with cotton that filled the space towards the lateral wall of the scala tympani and resulted in lowered thresholds. We assumed that stimuli presented at different cochlear positions have the same effective stimulus strength when they evoke the same Wave 4 amplitude in the EABR. While it is not known whether this results in perceptually loudness-balanced stimuli, it was effective for getting consistent results in the BIC-electrode measurements.

Topographic neural response maps in the IC

Simultaneous neural activity across multiple sites along the tonotopic axis of IC and auditory cortex has been previously measured in response to cochlear implant stimulation in a single ear (Bierer and Middlebrooks, 2002; Middlebrooks and Bierer,
In these studies, the normalized spike-rate of multi-unit activity was used to define spatial activation patterns with various intracochlear electrode positions and configurations. For the data presented here, we used RMS amplitude to assess the response strength of both local field potentials and synchronous multi-unit activity at each site. Using RMS amplitude of the averaged response resulted in more consistent measurements across recording sites that were less influenced by well-isolated single-neurons present at a minority of the probe sites. This analysis was also chosen since it captures the continuous increases in response amplitude with increasing stimulus intensity that result from the synchronous activity of many neurons (see Fig. 4.2). Since the IC has a prominent tonotopic organization, this metric was appropriate for characterizing the place and spread of neural activity with different intracochlear stimulating electrodes. However, recordings of multi-units and local field potentials did not show significant modulation with ITD, while ITD sensitivity was seen in the majority of well-isolated IC single-units (Chapter 2). Thus this metric was good for the purpose of comparing spatial activity patterns in the IC, but not for characterizing ITD tuning of IC neurons.

One limitation of our approach is that the spatial resolution of the recording probe was restricted to 100-150 µm. In practice, the location of the peak response could be estimated with greater spatial precision by piecewise cubic spline interpolation of the spatial response profile. A simplification made in the comparison of neural activation patterns across ears is that only the relative locations of the response peaks were taken into account, and not the shapes of the response patterns. Consideration of the shape of the response patterns may be important for irregular shaped or asymmetric response patterns sometimes observed in our raw data.

**Comparisons of bipolar and monopolar stimulation**

A surprising result was the comparable selectivity of BIC-electrode curves with bipolar and monopolar stimulation. Physiological studies of the effects of electrode configuration have almost universally reported that monopolar stimulation is relatively broad and provides less spatial selectivity in its activation patterns when compared to bipolar stimulation (van den Honert and Stypulkowski, 1987a; Kral et al., 1998; Rebscher
et al., 2001; Bierer and Middlebrooks, 2002; Snyder et al., 2004). Perhaps our result differs from previous studies because we used the BIC measurement in a manner that characterizes the selectivity of binaural interactions, while previous reports measured activation patterns elicited by monaural stimulation. These studies typically compared widths of excitation between different electrode configurations at a fixed level above threshold (e.g. 6 dB). When analyzed in this way, our monaural IC data also show broader activation patterns with monopolar stimulation than with bipolar stimulation. However, when spatial width of excitation is plotted against peak response amplitude (Fig. 4.11C), both electrode configurations show similar spreads of activity over the range of overlapping peak amplitudes for the two configurations. This suggests that the critical difference between studies is not binaural versus monaural stimulation, but our compensation for the difference in the growth of neural excitation with stimulus intensity between bipolar and monopolar stimulation. It may be that stimulus configurations and intensities that produce extremely broad excitation, as often seen in physiological experiments, would result in an uncomfortably loud percept and thus would be avoided by clinical implant settings.

We commonly saw a sudden, rapid expansion of the width of excitation in the IC at higher intensities (> 5 dB re threshold) with monopolar stimulation (Fig. 4.11B). This was not observed with bipolar stimulation, which maintained relatively good spatial tuning over the range of intensities tested. This difference may provide an explanation of psychophysical results in cochlear implant subjects showing that decreases in speech reception at high levels are more common with monopolar than bipolar stimulation (Franck et al., 2003).

Potential use in human subjects

Existing methods that have been used to match interaural electrodes include the psychophysical tests of pitch ranking (van Hoesel and Clark, 1997; Long et al., 2003) and binaural fusion (Eddington, 2005). These are subjective measurements that may not always predict interaural electrode pairs with the best ITD JNDS (Long et al., 2003) and are impractical in pediatric recipients of bilateral cochlear implants. Another potential
method is the use of radiographic imaging to measure the exact location of each electrode (Kos et al., 2005).

Our results with evoked potentials and neural response patterns in the IC suggest that evoked potentials can effectively be used to find the relative position of bilaterally implanted intracochlear electrode arrays. The method based on BIC amplitude to find interaural electrode matches in human subjects needs to be tested in adults where comparisons can be made with psychophysical methods. The existence of a BIC has already been reported in one bilateral implant subject (Pelizzone et al., 1990), so the method should be feasible in humans. In a study of normal-hearing newborns, the BIC waveform was detectable in over half of the babies tested with acoustic clicks (Furst et al., 2004) suggesting that the required binaural brainstem circuits are in place at birth and that BIC amplitude might also be useful in matching interaural electrodes in bilaterally implanted infants (as young as 9-12 months). This would assist in the assignment of frequency-electrode maps so that stimulation in each ear is tonotopically aligned, which potentially could improve the proper development of spatial hearing in the congenitally deaf.
Table and figures

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<table>
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<th>Animal number</th>
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Table 4.1. Breakdown of BIC-electrode data. BP = bipolar, WBP = wide bipolar, MP = monopolar.
Fig. 4.1. Measuring the binaural interaction component (BIC). The first three panels (A-C) show EABR waveforms for binaural and monaural stimulation with single biphasic current pulses. Waves 2, 3, and 4 are seen, but wave 1 is obscured since the first 1 ms of the EABR waveforms contain residual stimulus artifact. Triangles show the negative and positive peaks used to measure the peak-peak amplitudes of each response. The bottom panel (D) shows the BIC waveform, which is computed by subtracting the sum of the monaural evoked responses from the binaural response.
Fig. 4.2. Example response waveforms from one site of IC activation pattern. RMS amplitudes of average response waveforms are used to characterize the magnitude of the neural response at one location as a function of level. (A) Average response waveforms from one site in the IC for bipolar stimulation of the contralateral ear. Analysis window is 10 ms in duration and starts 2.5 ms after the stimulus pulse. (B) Summary of RMS amplitude as a function of stimulus intensity.
Fig. 4.3. Effects of stimulus intensity on evoked responses. (A) Mean EABR amplitude-level functions for bipolar stimulation across all animals and electrodes. Increasing stimulus intensity results in greater binaural EABR, monaural EABR, and BIC amplitudes (intensity given in dB re monaural EABR threshold). (B) Mean monaural EABR amplitude-level functions for bipolar and monopolar stimulation. Bipolar stimulation has a more gradual EABR amplitude-level function than monopolar stimulation which is about twice as steep. (C) Mean normalized BIC amplitude across all animals as a function of interaural intensity difference (the 0 dB point for each individual curve is set to where monaural EABR amplitudes are equal). BIC amplitude peaks at an ILD of 0 dB.
Fig. 4.4. Estimating the BIC amplitude for intensity-matched interaural electrodes. (A) Monaural EABR and BIC amplitudes are measured for a fixed intensity in the right ear (5 dB re 1 mA) and a range of intensities in the left ear (points fit with linear regression). The left and right ear intensities are considered “matched” when they evoke the same monaural EABR amplitude (7.9 dB in left ear, dashed line). The BIC amplitude for this interaural electrode pair is estimated for the matched intensity (purple arrow). The noise floor of the measurements is indicated by gray shading. (B) BIC amplitude as a function of the active electrode in the left ear (right ear fixed at BP 3). The BIC amplitude measured in panel A was for the interaural electrode pair right BP 3 and left BP 4 and is shown by the purple point. The same procedure was repeated for 5 different bipolar electrode locations in the left ear and make up the BIC-electrode curve in panel B.
Fig. 4.5. Effect of interaural electrode offset on BIC amplitude.  
(A) Complete set of BIC-electrode functions measured in the 7 animals (BIC amplitude normalized). Curves are sorted into panels according to the location of the active electrode in the fixed ear (red contact and red arrow). Thin black lines indicate each individual BIC-electrode curve and thick purple lines are the mean normalized BIC-amplitude for each fixed electrode location.  
(B) All BIC-electrode functions superimposed and plotted as a function of interaural electrode offset (varied electrode – fixed electrode).  
(C) Locations of BIC-electrode peaks. 20/26 functions peak at an interaural electrode offset of 0. The greatest offset is ± 1 electrode.
Fig. 4.6. Comparison of BIC-offset falloff with bipolar and monopolar stimulation. Panels A-B: thin black lines are individual BIC-offset curves, thick lines are mean values. Curves are shifted so that BIC peak is at 0. (A) Bipolar stimulation. (B) Monopolar stimulation. (C) Comparison of bipolar (red solid line) and monopolar (blue dashed line) stimulation (vertical bars indicate ±1 standard deviation). There is not a significant difference between the BIC-offset falloff data for bipolar versus monopolar stimulation ($p = 0.16$, 2-way ANOVA).
Fig. 4.7. Neural response patterns in the Inferior Colliculus. (A) The recording probe is advanced into the IC in the coronal plane, 45° from vertical so that the trajectory is from dorsolateral to ventromedial, parallel to the tonotopic arrangement of CFs in the central nucleus of the IC. With this electrode trajectory, low-CF neurons are located at shallow depths from the surface of the IC and high-CF neurons are deeper. (B) CF as a function of electrode depth for one probe penetration (3 probe positions) in a normal-hearing animal. (C) Plots of neural response amplitude as a function of position in the IC and stimulus intensity. Each panel shows the neural response pattern for a different bipolar electrode location in the contralateral ear. White horizontal lines indicate stimulus intensities that elicited equal-amplitude EABR amplitudes.
Fig. 4.8. Location of neural activation patterns are quantified by peak of response. (A) Example spatial profiles from the neural response patterns shown in Fig. 4.7C (bipolar stimulation). Spatial response profiles show response amplitude (normalized in figure) versus probe depth in the IC. The stimulus intensity for each spatial response is shown in Fig. 4.7C as white horizontal lines. Curves are smoothed and interpolated with a cubic spline. (B) Location of response peak in the IC as a function of intracochlear electrode.
Fig. 4.9. Determining interaural electrode matches from IC neural responses patterns. (A) Each panel shows the spatial response in the right IC for monaural stimulation of each ear (bipolar configuration). Stimulation in the right/ipsilateral cochlea is fixed at BP 2 and varies in the left/contralateral ear for each panel. The distance is calculated between the peaks of the right and left responses for each interaural pairing. (B) The distance between response peaks is called the “neural distance” and is shown as a function of the varied electrode in the left ear (location of fixed electrode in right ear indicated by red arrow). The neural distance is minimal at BP 2 in the varied ear.
Fig. 4.10. Comparison of neural response patterns for bipolar and monopolar electrode configurations. Panels A–C show mean values, computed across all electrodes and animals, for bipolar (red solid lines) and monopolar (blue dashed lines) stimulation. (A) Peak amplitude of neural activation patterns versus stimulus intensity. (B) Halfwidth of neural activation patterns versus stimulus intensity. (C) Halfwidth versus peak amplitude of neural activation patterns. Panels D–F show mean percent change (solid lines) from bipolar to monopolar stimulation (dotted lines indicate ±1 standard deviation). (D) Change in peak amplitude of neural activation pattern versus stimulus intensity. (E) Change in halfwidth of neural activation pattern versus stimulus intensity. (F) Change in halfwidth versus peak amplitude of neural activation pattern.
Fig. 4.11. Comparison of interaural electrode matching methods. (A) Example BIC-electrode curve, fixed electrode is BP 2 (indicated by red arrow). (B) Flipped neural distance function for same animal and configuration as in panel A (flipped version of Fig. 4.9C). (C) Normalized BIC amplitude versus neural distance for all data points measured in the same animals and same configurations. Comparison includes data from 4 animals and 16 fixed electrodes. Data is fit with a decaying exponential ($r^2 = 0.58$, space constant = 700 µm) (D) Histogram of differences in interaural electrode matches between measurement methods. 11/16 matches are in agreement between the two methods.
Chapter 5

Conclusions

Summary of results

The primary goal of this thesis was to study the ITD tuning of neurons in the auditory midbrain with bilateral electric stimulation of the cochlea, with particular focus on stimulus parameters that might limit ITD sensitivity. Both constant-amplitude and amplitude modulated (AM) pulse trains were used as stimuli and responses were compared to those in normal hearing animals with pure tones, clicks, and AM acoustic stimuli. Neural ITD discrimination thresholds were estimated using detection theoretic methods and used to compare the neural ITD sensitivity with recent psychophysical results in bilaterally implanted human subjects. The findings relating to stimulus parameters that effect ITD tuning are a useful guide for future cochlear implant processing strategies optimized for binaural hearing. A secondary focus of this thesis was to investigate a non-invasive method, using evoked potentials, for finding the relative cochlear position of interaural electrode pairs. This method has potential clinical use for assigning frequency-channel mappings in bilateral implant recipients, such as pediatric patients, for which existing psychophysical methods of matching interaural electrodes are impractical.

In Chapter 2, the sensitivity of inferior colliculus (IC) neurons to ITD with low-rate constant-amplitude pulse trains was studied. Electric ITD tuning characteristics were measured and compared with those obtained in previous studies in normal-hearing animals. We found that most IC neurons are tuned to ITD with electric stimulation and that they are as selective to ITD as low-frequency IC neurons with acoustic stimulation. For many neurons, ITD tuning was most selective at stimulus intensities near threshold and could change dramatically with intensity. Neural ITD discrimination was found to be best for lower pulse rates that elicited sustained responses (typically < 100 pps), and was poorer for higher pulse rates that produced onset responses. These results suggest that degraded ITD discrimination at higher pulse rates seen in bilaterally implanted human subjects (van Hoesel and Tyler, 2003), may be the result of subjects’ inability to access
ongoing ITD cues in the stimulus as recently suggested by Poon (2006). However, studies in unanesthetized animals are needed to verify that the rate limitation observed in our preparation is not a consequence of anesthesia.

The relative sensitivity of IC neurons to ITD in the amplitude envelope and temporal fine structure of AM pulse trains was studied in Chapter 3. This stimulus was used since sounds are coded by AM of pulse trains in most cochlear implant processors. We found that envelope ITD tuning is generally broader than ITD tuning to low-rate unmodulated pulses or to fine structure ITD of a 1000 pps AM stimulus. ITD$_{env}$ halfwidths decrease with increasing modulation frequency over the range of modulation frequencies tested (20-160 Hz), but broaden with increasing stimulus intensity. We also found that ITD$_{fs}$ tuning is much sharper than ITD$_{env}$ tuning, but is not preserved at a high carrier rate (5000 pps). These results, with AM pulse trains indicate that the best ITD sensitivity in IC neurons, with complex electric stimuli is for ITD in rate-limited carrier pulses ($\leq$ 1000 pps). Since clinical sound processors for cochlear implants do not control for the fine timing of the current pulses, these results have important implications for the future design of binaural cochlear implant sound processors. Based on our results, a strategy that is specifically designed for binaural hearing and bases the timing of the current pulses on the timing of the acoustic signal is described in Chapter 3.

**Model and underlying mechanisms**

We developed a phenomenological model that captures many of the trends in the ITD tuning of IC neurons with electric stimulation. The goal of creating this model was to better understand the possible underlying mechanisms that shape responses in the IC to stimuli with ITD. The model consists of a series of stages that convert the electric current waveforms delivered to each ear into a signal representing the firing probability of a single IC neuron. By varying ITD in ways similar to the experiments in Chapters 2 and 3, rate-ITD functions are derived by integrating the spike probability with respect to time to get the expected spike rate at each ITD.

Fig. 5.1 shows a schematic of model for ITD sensitivity. Parameter values used are given in Table 5.1. First a hard threshold is applied to the input currents at each ear. This is achieved by subtracting a constant threshold value from the input waveform and
then setting all negative values to zero. The resulting waveform is then convolved with an excitatory post-synaptic potential (EPSP) of the form: $\alpha_e t e^{-t/\tau_e}$, where $\alpha_e$ is a scale factor, $t$ is time, and $\tau_e$ is the time constant. This convolution step is akin to low-pass filtering and serves to add temporal jitter and limit phase locking at high pulse rates. Up to this point, the model is identical for each ear. In order to model the best ITD of a neuron’s response, a delay (characteristic delay) is added to the output of the contralateral ear. Next the signals from each ear are multiplied as an approximation of coincidence detection between the two ears. The output of the multiplication stage then splits into two parallel branches. The first branch is excitatory and goes directly into a summation stage representing synaptic integration in the IC. The signal in the second branch is delayed (synaptic, 1 ms) and is convolved with an inhibitory post-synaptic potential (IPSP) of the form: $-\alpha_i t e^{-t/\tau_i}$, where $\alpha_i$ is a scale factor, and $\tau_i$ is the time constant. Convolving with a negative function makes the second branch inhibitory. The two branches are finally summed and halfwave rectified to obtain the probability of a spike. The inhibitory branch of the model serves to limit sustained spiking at high pulse rates. Possible anatomical substrates for an ITD sensitive inhibitory input to the IC, include inhibitory projections from the dorsal nucleus of the lateral leminscus (Brugge et al., 1970; Adams and Mugnaini, 1984) and intrinsic inhibitory connections within the IC (Oliver et al., 1994). These final stages of the model, with the interaction of short excitation with delayed, long-lasting inhibition, is similar to an existing model of IC responses to acoustic AM stimuli (Nelson and Carney, 2004).

The model captures several aspects of the data, including: (1) reduction in sustained responses to constant-amplitude pulses with increasing in pulse rate, (2) restoration of sustained responses to high-rate pulse trains by low-frequency AM, (3) decrease in $\text{ITD}_{\text{env}}$ halfwidth with increasing modulation frequency, (4) increase in $\text{ITD}_{\text{env}}$ halfwidth with increasing stimulus intensity, (5) sharper tuning to fine structure ITD than envelope ITD, and (6) loss of fine structure ITD tuning at high pulse rates.

In the following examples of model responses to different electric stimuli, the peak stimulus intensity is expressed in decibels relative to the model threshold. So if an
AM pulse train stimulus is 1 dB re threshold, then only the positive peaks of the amplitude envelope exceed threshold.

Fig. 5.2 shows the model response for constant-amplitude pulse trains with an ITD equal to the characteristic delay in the model (stimulus ITD = ITD_{best}) for different pulse rates at 1 dB re threshold. These are plots of the spike probability as a function of time, and resemble PST histograms of actual IC responses. The first five panels show the output of the model at pulse rates ranging from 40 pps to 1000 pps. For 40 pps and 160 pps, the outputs are sustained and locked to the individual stimulus pulses. For 320 pps, the output remains locked to the individual stimulus pulse, but only the onset has a high-probability, while the sustained portion has a low-probability throughout the remainder of the stimulus. For 500 pps and 1000 pps, the output consists of only a single onset transient where the spike probability is greater than zero. The last panel shows the output for 1000 pps when 40 Hz sinusoidal AM is applied to the pulse train. Low-frequency AM restores sustained portions of the output that are now phase-locked to the 40 Hz amplitude peaks of the stimulus. The key element of the model that creates a transition between sustained and onset-only responses is the delayed inhibition after the multiplication. Since the time constant of the inhibition (τ_i = 2 ms) is an order of magnitude longer than that for the excitation (τ_e = 0.1 ms), the inhibition builds up and overlaps the excitation at unmodulated pulse rates above 200 pps, while at lower rates, the inhibition and excitation are interleaved in time and have little interaction. The balance between excitation and inhibition also impose a similar limit on modulation frequencies that will elicit sustained responses to AM stimuli.

Envelope ITD functions derived from the model were calculated as a function of modulation frequency (Fig. 5.3A) and overall intensity (Fig. 5.3B) for AM pulse trains at 1000 pps. Consistent with the results in Chapter 3, ITD_{env} halfwidth decreases with increasing modulation frequency (Fig. 5.3C) and increases with increasing stimulus intensity (Fig. 5.3D). In the model, the width and shape of ITD_{env} tuning is primarily dependent on the width and shape of suprathreshold peaks from each AM cycle. By increasing the modulation frequency, the width of the suprathreshold portion of the modulation narrows and thus ITD_{env} halfwidth narrows. Similarly, by increasing the stimulus intensity, more of each peak in the AM is suprathreshold and thus the
suprathreshold portion widens and the ITD\textsubscript{env} halfwidth increases. The sharpest ITD\textsubscript{env} tuning occurs in the model, and approaches fine structure ITD tuning, when only a single pulse in each cycle of the AM is suprathreshold. This is most likely to occur for higher modulation frequencies and low stimulus intensities.

Finally, whole waveform ITD curves from the model are shown for 40 Hz AM pulse trains at 1000 pps and 5000 pps in Figs. 5.4A and B respectively. Stimulus intensity for both cases is 1 dB re threshold. For the 1000 pps carrier (Fig. 5.4A), ITD tuning to the fine structure creates a 1000 µs periodicity in the ITD function that is much narrower than the wide ITD tuning to the envelope that gives the function its overall shape. For the 5000 pps carrier (Fig. 5.4B), fine structure ITD tuning is lost, and only ITD tuning to the envelope remains. These results are consistent with those seen in the neural data in Chapter 3. In the model, fine structure ITD tuning is lost at 5000 pps because of lowpass filtering by the EPSP ($\tau_e = 0.1$ ms) before the multiplication step.

In Chapter 3, we showed that tuning to ITD\textsubscript{env} and ITD\textsubscript{fs} are highly separable and suggested that there might be two independent mechanisms responsible for this phenomenon. The model gives some insight into which underlying factors might contribute to tuning to ITD\textsubscript{env} and ITD\textsubscript{fs}. In the model, the width and shape of envelope ITD tuning with AM pulse trains is primarily controlled by the width and shape of each cycle of the stimulus AM that exceed threshold. For fine structure ITD tuning with constant-amplitude or AM pulses, it is the width of the EPSP, or temporal jitter before binaural coincidence detection, that determines the width of ITD tuning in the model. These two factors interact in a multiplicative fashion, and thus result in ITD\textsubscript{env} and ITD\textsubscript{fs} separability in the model.

Aspects of the data that are not captured by the model include: (1) saturation of ITD functions (with constant-amplitude pulse trains) at high stimulus intensities, (2) shifts in best ITD with changes in overall intensity and ILD, (3) decreases in firing rate over time due to adaptation, (4) changes in spike latency with intensity, and (5) stochastic responses. Most of these limitations could be dealt with by more carefully modeling responses to electric stimulation observed in the auditory nerve. The threshold stage of our model could be replaced by a more complex stage consisting of a dynamic threshold,
latency as a function of intensity, and stochastic spiking. For our purposes, however, the simple threshold suffices to capture the desired aspects of the data.

Though relatively simple, this model accounts for many aspects of the temporal response patterns and the ITD tuning of the neural data. The model is useful for understanding the basic mechanisms that possibly underlie neural ITD sensitivity with electric stimulation and can be used to predict responses to stimuli not tested in vivo. One limitation of the model in its current form is that it does not make predictions of discrimination thresholds. Since the model is deterministic, it only predicts mean discharge rate and not variance. This could be resolved by adding a stochastic spiking element to the model to introduce noise.

Relation to human behavioral results

While many of the trends in the neural ITD discrimination thresholds found in this thesis are consistent with behavioral thresholds in bilateral cochlear implant subjects, nothing in our results specifically predicts the difference in ITD JNDS between acoustic and electric hearing observed psychophysically. We showed that the ITD selectivity of IC neurons can be as sharp with electric stimulation as that reported with acoustic stimulation, but bilateral cochlear implant users have yet to experience ITD sensitivity comparable to that with normal hearing. This thesis addressed the ITD tuning of single-neurons in an acutely-deafened animal preparation. While ITD sensitivity of single IC neurons with electric stimulation was comparable to acoustic stimulation, the population code across neurons may be severely distorted. This is a difficult problem to solve since we do not know what neural code results in perception. If one assumes a labeled-line model of lateralization (Colburn, 1995; Stern and Trahiotis, 1995), where binaural percepts are derived from the pattern of activity across “neurons” that are typically arranged in a matrix of internal delay and CF, then distortions in the arrangement of ITD_{best} and CF in the population code could be detrimental to ITD detection thresholds. Alternatively, models of binaural interaction that compare the overall balance of hemispheric neural activity between the two sides (von Békésy, 1930; van Bergeijk, 1962; Colburn and Latimer, 1978; McAlpine et al., 2001), would be less susceptible to
distortions in the organization of ITD tuning in the IC, but depend more upon a contralateral bias in the distribution of ITD$_{\text{best}}$ (see Chapter 2).

Unexplained deficiencies in behavioral ITD discrimination with electric hearing may also be the result of differences between our animal model and bilaterally implanted human subjects. Animals studied in our experiments had normal hearing until they were acutely deafened for 1-2 weeks, were stimulated with an auditory prosthesis for less than 48 hours, and were anesthetized throughout all recordings and electric stimulation. In contrast, human subjects tested in psychophysical experiments have varying degrees of normal binaural experience, duration of deafness before implantation, and experience with bilateral implants (usually with clinical processors not optimized for binaural hearing). Future studies that address the possible effects of anesthesia, auditory deprivation, binaural experience during development, and experience with a binaural prosthesis (that provides behaviorally relevant ITD cues) on binaural interactions in the auditory CNS may give further insights into the electric-acoustic gap in behavioral ITD thresholds in human subjects.
Fig. 5.1. Phenomenological model of electric ITD tuning. Operations are shown in circles and include convolution (*), multiplication (×), and summation (∑).
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\tau_e$</td>
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</tr>
<tr>
<td>$\tau_i$</td>
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</tr>
<tr>
<td>$\alpha_e/\alpha_i$</td>
<td>1.25</td>
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<tr>
<td>synaptic delay</td>
<td>1 ms</td>
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</tbody>
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Table 5.1. Parameter values used in the phenomenological model of ITD tuning.
Fig. 5.2. Temporal response patterns of model as a function of pulse rate. All stimuli are 300 ms in duration, the peak intensity is 1 dB re model threshold, and the ITD equals the characteristic delay of the model (ITD_{best}). The bottom right panel shows the effect of AM on the response to a 1000 pps pulse train.
Fig. 5.3. Dependence of model ITD\(_{\text{env}}\) halfwidths on modulation frequency and stimulus intensity. Stimulus intensity is expressed in units of dB peak current re model threshold. (A) ITD\(_{\text{env}}\) tuning for a 1000 pps AM stimulus at three modulation frequencies (1 dB re threshold). (B) ITD\(_{\text{env}}\) tuning for a 1000 pps, 80 Hz AM stimulus at three stimulus intensities. (C) ITD\(_{\text{env}}\) halfwidth decreases with increasing modulation frequency (from panel A). (D) ITD\(_{\text{env}}\) halfwidth increases with increasing stimulus intensity (from panel B).
Fig. 5.4. Model exhibits narrower tuning to ITD$_{fs}$ than ITD$_{env}$ at 1000 pps, 40 Hz AM. (A) Model ITD$_{wav}$ tuning for 1000 pps, 40 Hz AM stimulus at 1 dB re threshold. Narrow peaks in ITD$_{wav}$ function have 1000 µs periodicity and come sensitivity to ITD$_{fs}$. (B) Model ITD$_{wav}$ tuning for 5000 pps, 40 Hz AM stimulus at 1 dB re threshold. In comparison to panel A, sensitivity to ITD$_{fs}$ is mostly lost and only tuning to ITD$_{env}$ remains.
References


