The ability of inferior colliculus neurons to signal differences in interaural delay

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Communicated by William T. Newsome, Stanford University School of Medicine, Stanford, CA, September 27, 2001 (received for review April 27, 2001)

Sound localization in humans depends largely on interaural time delay (ITD). The ability to discriminate differences in ITD is highly accurate. ITD discrimination (Δ ITD) thresholds, under some circumstances, are as low as 10–20 μs. It has been assumed that thresholds this low could only be obtained if the outputs from many neurons were combined. Here we use Receiver Operating Characteristic analysis to compute neuronal Δ ITD thresholds from 53 cells in the inferior colliculus in guinea pigs. The Δ ITD thresholds of single neurons range from several hundreds of μs down to 20–30 μs. The lowest single-cell thresholds are comparable to human thresholds determined with similar stimuli. This finding suggests that the highly accurate sound localization of human observers is consistent with the resolution of single cells and need not reflect the combined activity of many neurons.

The question of whether the finest sensory discrimination thresholds reflect single-cell resolution or are accomplished by ensembles of neurons has wide implications for our understanding of the relationship between sensory functions and their neuronal substrates. In the study of vision it has become increasingly clear that psychophysical thresholds are not beyond the capabilities of single cells (1, 2), even in cases where spatial discrimination thresholds correspond to positional differences smaller than the diameter of single photoreceptors (3, 4). Somatosensory thresholds may also be accounted for on the basis of single neurons (5, 6). The accuracy of sound localization, on the other hand, has proved difficult to attribute to single neurons. In the case of sound localization, the time difference between the two ears [interaural time delay (ITD)] at discrimination threshold is about 10–20 μs (7–9). It has been widely assumed that discrimination thresholds this low could only be achieved if the responses from many cells were combined (10–15). This view has been challenged on the basis of computer simulations (16). These simulations, which made use of Receiver Operating Characteristic (ROC) analysis, were based on the assumption that the response variability conforms to a Poisson distribution. Although this may be an appropriate assumption for an average neuron, because of considerable intercell differences any given neuron may differ markedly from Poisson variability.

It has long been realized that the sensitivity with which a change in stimulus can be detected is as crucially dependent on the variability in the response to a constant stimulus as on the magnitude of the change in response when the stimulus is changed; this concept has been codified as Signal Detection Theory (17). Thus it is as important, when determining the sensitivity of neurons to changes in ITD (Δ ITD thresholds), that the variability in response as an individual stimulus is repeated is measured, as well as the change in response when stimulus ITD is changed. This, unfortunately, requires a large number of repeats and is, perhaps, one reason why this has not hitherto been attempted. If it is assumed that the spiking of neurons is a memory-less point-process, where the occurrence of a spike at any instant has no influence on the probability of a spike occurring at any other time, then the spike process can be termed a (nonhomogeneous) Poisson process and the probability of counting a given number of spikes in any time interval can be described by a Poisson distribution (18). This assumption is largely valid at the level of the auditory nerve (ignoring refractory effects), but becomes increasingly less certain as the auditory system is ascended and more complex processing occurs. It is therefore vital that, in addition to the mean rate, the distribution of neural firing counts to repeated stimulation is measured.

The earlier computer simulations (16) used published mean rate responses, assumed a Poisson distribution, and could thus be criticized for not using the true variability of the neurons being modeled; in this paper we aim to remedy that defect. Additionally, the responses modeled were obtained from binaural beat stimuli, which are pure tones with an interaural frequency difference of typically 1 Hz and duration of at least a second. The interaural phase difference slowly sweeps through 360° during the period of the beat so an estimate of the ITD tuning curve can be obtained. This estimate is considered to yield ITD tuning curves similar to those obtained by using static tones where interaural time delay is varied (19, 20). However, there are many instances of neural responses to the ITD of static tones that do not match the sensitivities revealed by dynamic stimuli like binaural beats (e.g., ref. 21); at the very least, binaural beat stimuli may cause the amplitude of the response to differ. When spike counts obey a Poisson distribution, the variance is proportional to the mean and so the absolute response levels may affect the estimated discrimination thresholds. Thus, using binaural beat responses may provide a different estimate of sensitivity than short, static tones.

To circumvent these problems, we here use actual neuronal responses to 100 repeats of static tones (i.e., constant ITD throughout each stimulus presentation) to measure Δ ITD thresholds in 53 neurons in the inferior colliculus (IC) of guinea pigs. ROC analysis using spike count distributions based on the actual neural responses are used so that no assumptions are necessary about the nature of the response variability in the IC. Our results demonstrate that the lowest neuronal thresholds are quite close to psychophysical thresholds. It is possible, therefore, that the psychophysical threshold may simply reflect the limit of the most accurate neuron without any pooling being involved.

Methods and Stimuli

Recordings were made in the right IC of 15 pigmented guinea pigs weighing 335–507 g. Animals were anaesthetized with urethane (1.3 g/kg i.p.) and Hypnorm (Janssen; 0.2 ml i.m.), premedicated with Atropine sulfate (0.06 mg/kg s.c.). Further doses of Hypnorm (0.2 ml i.m.) were given on indication by pedal withdrawal reflex. A tracheotomy was performed, and core temperature was maintained at 38°C. The animals were mounted

Abbreviations: ITD, interaural time delay; ROC, Receiver Operating Characteristic; IC, inferior colliculus; BF, best frequency.

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 www.pnas.org/cgi/doi/10.1073/pnas.241513998

in a stereotaxic frame inside a sound-attenuating room. Hollow plastic speculae with sealed-in loudspeakers replaced the ear bars. All experiments were carried out in accordance with the United Kingdom Animals (Scientific Procedures) Act of 1986.

Extracellular action potentials were recorded with tungsten electrodes (22). All stimuli were digitally synthesized at a 100 kHz sampling rate and were output through a waveform reconstruction filter set at 25 kHz. ITD functions were obtained by delaying, or advancing, the fine structure of the signal to the right ear while keeping the signal to the left ear fixed. Signals were gated on and off simultaneously in the two ears with rise/fall times of 2 ms. The signals were tone bursts (of 50 ms or 400 ms duration) at the neuron's best frequency (BF) and at 20 dB above rate threshold. ITD functions were obtained over ±1.5 cycles of BF in 0.1 cycle steps by using 50 repeats (Fig. 1*A*, open symbols). A fine-grained analysis (0.01 cycle steps) was performed from the trough to the peak of the slope through zero ITD with 100 repeats (Fig. 1 *A*, filled symbols, and *B*). A single repeat consisted of the full range of ITDs presented in pseudorandom order. The BFs of cells reported were approximately evenly distributed between 72 and 1185 Hz. No attempt was made to determine ITD sensitivity if the BF was much above 1000 Hz, because past experience strongly indicates that this would be unlikely to succeed.

Results

The average response as a function of ITD for a representative IC neuron is shown in Fig. 1*A*. The responses, which vary cyclically, undergo large changes over narrow portions of each cycle. The filled symbols show a detailed mapping, sampled at 0.01 cycle intervals, of the steeply sloping region of the ITD function that crosses zero ITD (midline azimuthal positions). This neuron was stimulated at 400 Hz; therefore, 0.01 of a cycle is equal to 25 μs. As can be seen from the expanded ITD function in Fig. 1*B*, ITD differences of 25 μs can elicit clear differences in average response.

The ability of a neuron to signal small changes in ITD is determined not only by the steepness of the ITD curve, however, but also by the variability of the response. The reliability (i.e., percent correct response) with which an ideal observer can detect ITD differences was estimated by using ROC analyses (17). ROC analyses determine the probability of differentiating two stimuli on the basis of the response distributions elicited by the two stimuli. This is comparable to using a *t* test [or d′ analysis (17)] to determine the statistical significance of the difference between two means. Unlike a *t* test (or d′), however, ROC analysis does not require any assumptions regarding the nature of the distributions. The application of ROC analysis to neuronal responses has been described (23). Fig. 1*C* shows percent correct ITD discrimination as a function of Δ ITD. From these data, Δ ITD thresholds were computed by determining the Δ ITD giving 75% correct performance.

Fig. 2*A* shows the distribution of Δ ITD thresholds for 53 neurons. The Δ ITD thresholds show a wide distribution, varying from 31 μs to well above 230 μs. The arrows indicate psychophysical Δ ITD thresholds for human observers determined by using 50-ms stimuli (replotted from ref. 24). Fig. 2*B* shows Δ ITD thresholds plotted against tone frequency (filled symbols). Clearly there is a tendency for thresholds to decrease with increasing frequency (slope of regression line = −0.84; r = −0.66). The best neural thresholds are only slightly greater than the corresponding human psychophysical thresholds, and the decrease in neural threshold with increasing frequency is in general agreement with psychophysical performance in human observers (indicated with open symbols; from ref. 24). It is clear from both figures that the most sensitive neurons are not abnormal outliers.

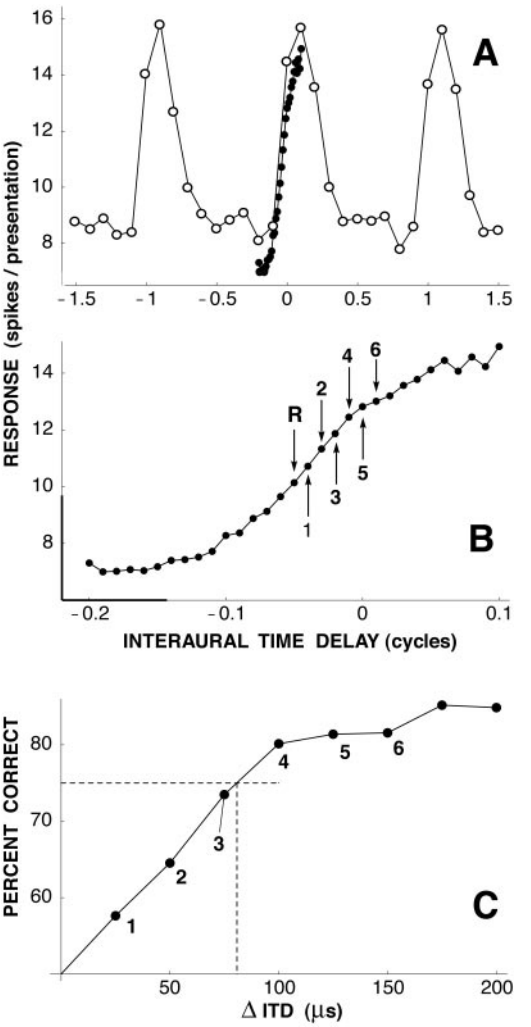

Fig. 1. (*A*) Mean response from a single neuron as a function of ITD over three cycles (open symbols) sampled at 0.1 cycle intervals (50 presentations per interval). Also shown is a detailed measurement (filled symbols) of the steepest part of the ITD curve covering a range of 0.3 cycles sampled at 0.01 cycle intervals around zero ITD (100 presentations per interval). Positive ITD values signify that the stimulus to the contralateral ear was leading. (*B*) An expanded view of the detailed ITD curve replotted from *A*. Percent correct ITD discrimination was estimated by using the ROC technique. The values were obtained from the data underlying the curve shown in *B* by selecting a reference stimulus (indicated by R) and comparing the response to this stimulus with the distributions obtained with stimuli marked 1, 2, 3, 4, etc. (*C*) Percent correct discrimination response as a function of Δ ITD. As expected, the percent correct performance increased with Δ ITD. The threshold was defined as the Δ ITD value where the curve crosses the 75% level. For the neuron in this example the Δ ITD threshold was 81 μs.

One factor that may affect the comparison between single cells and psychophysics is the presence of long-term variability. Psychophysical thresholds are determined, typically, by making comparisons between two stimuli presented close together in time. In the present experiments the stimuli were presented in a pseudorandom sequence extending over several minutes with each ITD presented 100 times. The ROC analysis assigns equal significance to responses that occur close together as to those that are separated by extended periods of time. The existence of slow response fluctuations, or long-term variability, is well documented (23, 25–27). To estimate the effect of these slow fluctuations on our neuronal thresholds, we carried out a pairwise comparison in which the response to the *n*th presen-

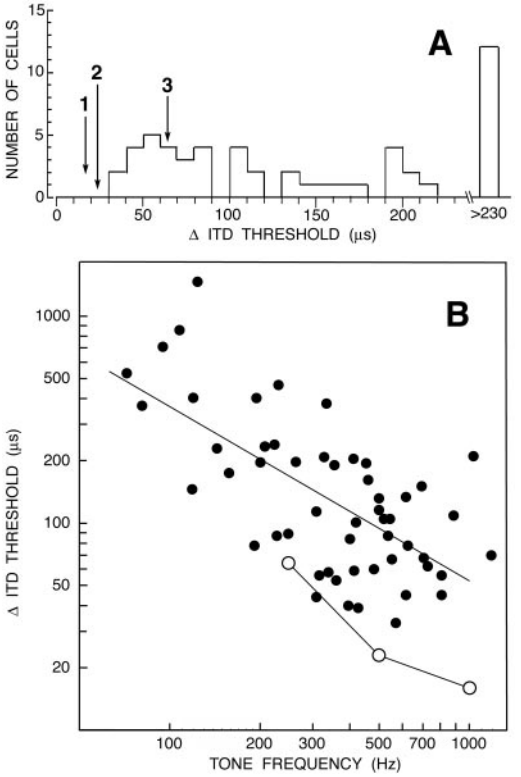

Fig. 2. (*A*) Distribution of Δ ITD thresholds for 53 IC neurons estimated by using the ROC method. All Δ ITD thresholds were obtained by using 100 repetitions of 50-ms-duration stimuli presented at 20 dB above response threshold, sampled at 0.01 cycle intervals. The arrows indicate human Δ ITD thresholds for 50-ms-duration tones at 50 dB SPL (Sound Pressure Level; from ref. 24): (arrow 1) 16 μs for 1,000 Hz; (arrow 2) 23 μs for 500 Hz; and (arrow 3) 65 μs for 250 Hz. The best frequency of the neurons ranged from 72 to 1,185 Hz. (*B*) Log–log plot of thresholds against actual tone frequency (note that some neurons were tested at a frequency lower than the best frequency). A regression line (solid line; slope = −0.84) has been fitted to the data underscoring the tendency for thresholds to decrease with increasing frequency (correlation $r = -0.66$). Open circles mark human thresholds for 50-ms stimuli (from ref. 24).

tation of one stimulus was compared with the response to the *n*th presentation of another (see Fig. 3 legend for further details). For the vast majority of neurons, reducing the variability in this manner did not alter the threshold. In a few cells, however—including that with the lowest threshold—there was a threshold reduction of about 20%. The percent correct as a function of Δ ITD for our most sensitive neuron, responding to stimuli of 400 ms duration, is shown in Fig. 3*C*. Results obtained both with the conventional ROC method (filled circles), and those based on pairwise comparison (open circles), are shown. The Δ ITD thresholds under the two cases were 21 μs and 17 μs, respectively. By comparison, human Δ ITD thresholds for 400-ms stimuli, depending on rise-time and individual differences, range from 14 to 24 μs (from figure 4 of ref. 24). Thus, this neuron's threshold fell within the range of the variability of human observers.

Discussion

The goal of this study was to examine whether the extremely low Δ ITD thresholds of human observers is reflected in the behavior of single neurons, or whether it necessitates pooled responses from many neurons. If we make the reasonable assumption that the behavioral threshold reflects the performance of neurons having the greatest acuity then we would expect the psychophys-

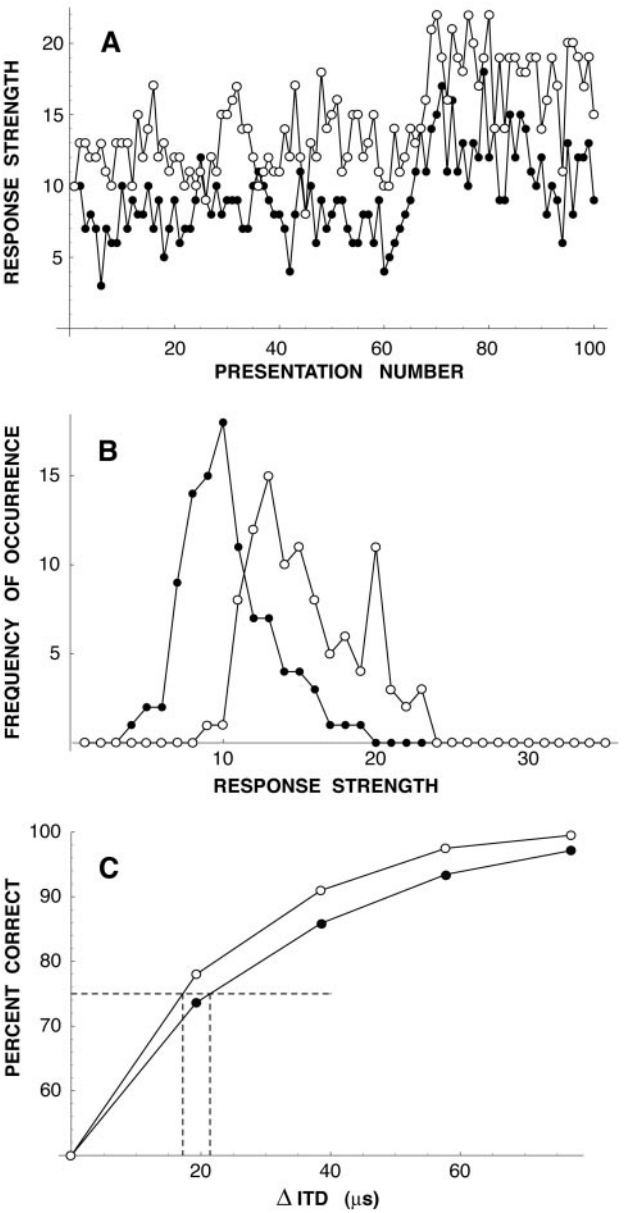

Fig. 3. (*A*) Responses to 100 presentations of each of two stimuli differing in ITD by 0.07 cycles: $ITD_1 = -0.04$ cycles (filled symbols) and $ITD_2 = 0.03$ cycles (open symbols). The neuron was stimulated at 536 Hz; therefore, 0.07 cycles = 131 μs. When pairwise comparisons were made to minimize the effect of long-term variability, it was found that ITD_1 gave the larger response in 96 of the 100 presentations. Thus, an ideal observer would be correct 96% of the time by consistently choosing the higher response. (Stimulus duration 400 ms repeated every 1,600 ms at 20 dB SPL above threshold.) (*B*) The same data have been compiled into frequency of occurrence distributions (i.e., the kinds of distributions on which ROC analyses are based). Filled and open symbols denote the distributions of responses to ITD_1 and ITD_2, respectively. ROC analysis based on these distributions gave 88% correct response. The difference between 88% obtained by using ROC analysis and 96% obtained by pairwise comparisons is attributable to long-term variability. (*C*) Percent correct performance determined as a function of Δ ITD for the neuron in our sample with the lowest threshold. Open symbols show the results of pairwise comparisons (which reduce long-term variability) and filled symbols represent results of conventional ROC analysis (which includes long-term variability). The horizontal dashed line marks the 75% correct level. The two dashed vertical lines mark the Δ ITD values where the curves cross the 75% level—i.e., the Δ ITD thresholds. Reducing the influence of the long-term variability in this case reduced the Δ ITD threshold from 21 to 17 μs. (This neuron was stimulated at 20 dB above threshold with a 519 Hz tone. The stimulus duration was 400 ms repeated every 1,600 ms; the stimulus was presented 100 times.)

ical thresholds to lie in the lower tails of the distribution of neural thresholds. Fig. 2 shows that guinea pig neural thresholds are slightly higher than human psychophysical thresholds. This discrepancy may represent a species difference, as discussed below, or may be the result of our trying to estimate the tail of a distribution with insufficient observations (53 cells spread evenly over BFs between 72 and 1,185 Hz). In either case, we feel that the agreement is sufficiently close for us to conclude that neurons probably exist that have sufficiently low thresholds to account for behavioral thresholds, and, consequently, that pooling of the responses from many neurons may not be required. This conclusion is in agreement with earlier computer simulations based on responses to binaural beat stimuli (16).

Our conclusion involves an across-species comparison. Human observers show very low Δ ITD thresholds and thus, optimally, we would have examined ITD discriminability at the level of single neurons in humans; however, this is not possible. Instead, we might have compared our guinea pig neuronal thresholds to behavioral thresholds in the same species, although, unfortunately, we are not aware of any study in which behavioral Δ ITD thresholds have been determined in this animal. However, for guinea pig behavioral thresholds to invalidate our conclusions, these thresholds would have to be (markedly) lower than those of humans, which is unlikely because behavioral thresholds for free-field localization of broad-band stimuli in animals are mostly much larger than those of human observers (28). It seems more likely that behavioral thresholds in guinea pigs are higher than those in humans and thus are higher than the single-cell thresholds that we have measured. If so, it may be that the information carried by the lowest-threshold guinea pig IC neurons is lost or underused. In this case one might speculate that interspecies differences in behavioral Δ ITD thresholds may be determined more by the ability of different species to use the information carried by the most accurate neurons than by the thresholds of these neurons themselves.

If human neural sensitivity were better than that of guinea pigs, we would have to invoke a similar argument about loss or underutilization of information. If, on the other hand, human neural sensitivity were *worse* than that of guinea pigs, then we would have to invoke pooling to explain human psychophysical sensitivity. Consistent binaural physiology across a wide range of laboratory animals (29) suggests that neuronal Δ ITD thresholds in humans and guinea pigs may be similar. The shapes of ITD functions and the positions of their peaks have been obtained in the IC, in response to both tones and noise, in cat, rabbit, kangaroo rat, and barn owl, as well as guinea pig (29), and are very similar across these species. Additionally, although guinea pigs are small animals, they have large bullae, an adaptation that allows them to hear low frequencies. Thus the comparison between human and guinea pig is not invalidated by their having very different audiograms. These arguments, though, do not address the trial to trial *variability* in firing rate that, as we have here demonstrated, is an important determinant of ITD discriminability. There are no across-species comparisons that can be made here because there are no previous reports of these measurements for ITD discrimination. One component of the variability is likely to be the accuracy with which the auditory waveform is transmitted to the input of the ITD-sensitive coincidence-detector mechanism in the Medial Superior Olive (MSO). The closest we can get to this comparison is at the level of the auditory nerve (which is a single synapse away from the MSO): here the accuracy of phase locking is approximately the same for both cat (30) and guinea pig (31) up to about 800 Hz, where the guinea pig synchronization index begins to decline about an octave lower than that of cat. However, the guinea pig synchronization index does not become negligible until about 2 kHz, again an octave below that of cat. Although there are a number of ways in which the variability of ITD representation could be altered between auditory nerve and IC, at least in the auditory nerve the accuracy of representation is similar in two very different species over most of the range of frequencies that we have studied.

Because phase-locking at the auditory nerve is approximately constant across the range of frequencies that we have used, we can, with a couple of assumptions, make predictions about the shape of the Δ ITD threshold versus frequency curve (Fig. 2*B*). It is generally accepted that ITD responses at the IC are, to a large extent, a reflection of coincidence-detection between spike trains derived from the stimulus presented to each ear (11–15, 19–21, 29). If we assume that the inputs to the coincidence detectors have similar phase locking to that in the auditory nerve, and that the variability at the output of these coincidence detectors is related to the phase-locking at the input, then the variability (for a fixed firing rate) will be independent of stimulus frequency. However, the slope of the ITD function (and hence the change in firing rate for a given Δ ITD) will be inversely proportional to stimulus frequency. Because log–log plots show power relationships as straight lines, we would expect that the slope of a log–log plot of Δ ITD threshold as a function of frequency would be -1 up to the point at which phase-locking declines. The data shown in Fig. 2*B* come close to this. Because we did not attempt to measure ITD sensitivity for cells with BFs much above 1 kHz, because they generally show poor modulation of the ITD function, there is an implicit increase in Δ ITD threshold somewhere close to the maximum frequency shown, comparable with human psychophysics.

Low-frequency IC units show responses that demonstrate convergence from cells in both medial (MSO) and lateral superior olive (LSO; ref. 32). It would be interesting to know whether ITD sensitivity were different for responses deriving originally from different nuclei. It is likely that units with a peak near 0 IPD in the ITD function (peak units) receive afferent projections from MSO, whereas those with a trough near zero (trough units) receive projections from LSO. However, with only a single frequency ITD function it is not possible to determine unambiguously whether a unit is a peak or trough. To be completely unambiguous, ITD functions are needed at a range of frequencies. These data were not gathered because recording time was limited to the data specific to ITD thresholds. Given that, almost by definition, trough units will yield a large best interaural phase value compared with peak units, however, our sample population can be segregated accordingly. We have done this and looked at the ITD functions of all units with long best IPDs. Although a few are probably trough units, members of our sample more commonly showed intermediate properties (possibly reflecting influences such as convergence and divergence) in accordance with the results of previous studies of IC behavior (32). Thus, although we do not have the data to address the question of afferent input directly, it is likely that trough units form a minority in our sample and, hence, the majority of our units were most likely innervated from the MSO.

Although comparisons across species raise concern, given that previous studies have argued strongly that pooling of responses from many neurons is required to achieve the very low psychophysical Δ ITD thresholds in humans (10–15), the demonstration that *any* auditory neurons in *any* species have thresholds comparable to those of human psychophysics is significant. The demonstration refutes the notion that human Δ ITD thresholds are beyond the resolution of single neurons, irrespective of species.

Our findings should not be taken to indicate that ITD discrimination involves only a single cell. On the contrary, given that

the stimuli are of suprathreshold intensity and that ambiguities need to be resolved (e.g., sound level differences need to be differentiated from ITD differences), it would be surprising if only a single neuron were involved in the task. Instead, these results show that it may not be *necessary* to combine the responses from many neurons to achieve the astonishingly high accuracy of human ITD discrimination. Whether psychophysical ITD discrimination actually reflects the limit of the most accurate neuron has yet to be determined, although our data lend credence to this possibility.

We are indebted to Carl Hansen of Pictopia.com of Emeryville, CA, for writing perl-scripts.

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