Interaural Level Difference Processing in the Lateral Superior Olive and the Inferior Colliculus

Thomas J. Park, Achim Klug, Michael Holinstat, and Benedikt Grothe

1Laboratory of Integrative Neuroscience, Department of Biological Sciences, University of Illinois at Chicago, Chicago, Illinois 60607; and 2Max-Planck Institute of Neurobiology, D-82152 Martinsried, Germany

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Park, Thomas J., Achim Klug, Michael Holinstat, and Benedikt Grothe. Interaural level difference processing in the lateral superior olive and the inferior colliculus. J Neurophysiol 92: 289–301, 2004; 10.1152/jn.00961.2003. Interaural level differences (ILDs) provide salient cues for localizing high-frequency sounds in space, and populations of neurons that are sensitive to ILDs are found at almost every synaptic level from brain stem to cortex. These cells are predominantly excited by stimulation of one ear and predominantly inhibited by stimulation of the other ear, such that the magnitude of their response is determined in large part by the intensities at the 2 ears. However, in many cases ILD sensitivity is also influenced by overall intensity, which challenges the idea of unambiguous ILD coding. We investigated whether ambiguity is reduced from one synaptic level to another for 2 centers in the so-called ILD processing pathway. We recorded from single cells in the free-tailed bat lateral superior olive (LSO), the first station where ILDs are coded, and the central nucleus of the inferior colliculus (ICC), which receives a strong projection from the LSO, as well as convergent projections from many other auditory centers. We assessed effects of overall intensity by comparing ILD functions generated with different fixed intensities to the excitatory ear. LSO cells were characterized by functions that shifted in a systematic manner with increasing intensity to the excitatory ear. In contrast, significantly more ICC cells had functions that were stable across overall sound intensity, indicating that hierarchical transformations increase stability. Furthermore, a population analysis based on proportion of active cells indicated that stability in the ICC was greatly enhanced when overall population activity was considered.

INTRODUCTION

Interaural level differences (ILDs) are salient cues for localizing high-frequency sounds (Erulka 1972; Irvine 1992; Mills 1972). In the CNS there are populations of ILD-sensitive neurons that are excited by stimulation of one ear, and inhibited by stimulation of the other ear. The response magnitude of these cells depends on the strengths of excitation and inhibition, which in turn depend on ILD. Importantly, the particular ILDs that generate maximum and minimum spike counts differ among cells, such that a population of cells encompasses a wide range of sensitivities (Irvine and Gago 1990; Irvine et al. 1996; Park 1998; Sanes and Rubel 1988).

In mammals, ILD-sensitive neurons are found at almost every synaptic level from brain stem to cortex. The first station is the lateral superior olive (LSO) (Boudreau and Tsuchitani 1968; Caird and Klinke 1983; Sanes and Rubel 1988). LSO cells receive a relatively homogeneous input pattern (Sanes 1990) of excitatory inputs from the ipsilateral cochlear nucleus, and inhibitory, glycinergic inputs from the ipsilateral medial nucleus of the trapezoid body, which is driven by the contralateral cochlear nucleus. The LSO sends a strong, excitatory projection to the contralateral central nucleus of the inferior colliculus (ICC), as well as a predominantly inhibitory projection to the ipsilateral ICC (Bruno-Bechtold et al. 1981; Glendenning et al. 1992; Saint Marie and Baker 1990). As with the LSO, there are many cells in the ICC that are sensitive to ILD (Irvine and Gago 1990; Pollak et al. 1986; Semple and Kitzes 1987). However, compared with LSO cells, ICC cells have more variable input patterns, involving many lower nuclei (Irvine 1996), and ILD sensitivity is established through various circuits in addition to the excitatory input from LSO (Covey et al. 1996; Faingold et al. 1993; Klug et al. 1995; Li and Kelly 1992; Vater et al. 1992).

At the ears, ILD remains stable across a wide range of overall intensity. However, ILD-sensitive cells in the ICC (and auditory cortex) show substantial variability in sensitivity across overall intensity (Irvine and Gago 1990; Irvine et al. 1996; Semple and Kitzes 1987). Far less is known about the effects of overall intensity on LSO cells, or how those effects might be modified from LSO to ICC. Only a few studies in the LSO have tested different overall intensities, but these studies tested only a few cells (Boudreau and Tsuchitani 1970; Sanes 1990; Tollin and Yin 2002), or they did not quantify the effects on ILD sensitivity (Park et al. 1997), therefore not allowing for a population statistic. Our first goal was to fill this gap by quantifying and comparing data from LSO and ICC cells from the same species. Our second goal was to perform population analyses, based on overall activity, to determine the merits of such a coding strategy for reducing variability across overall intensities. The impetus for the population analyses comes from recent investigations that support a critical role for such a strategy in interaural time-difference coding (Brand et al. 2002; McAlpine et al. 2001).

METHODS

The animals used in the study were 28 Mexican free-tailed bats (Tadarida mexicana brasiliensis). Mexican free-tailed bats are high-frequency specialists that presumably rely heavily on ILD processing for sound localization (Grothe and Park 2000), and free-field measures indicate that these animals experience ILDs in the range of about ±35

Address for reprint requests and other correspondence: T. Park, University of Illinois at Chicago, Laboratory of Integrative Neuroscience, Department of Biological Sciences, 840 W. Taylor St., Chicago, IL 60607 (E-mail: TPark@uic.edu).

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Acoustic stimuli and data acquisition

When a cell was encountered, its characteristic frequency and threshold were audiovisually determined to set stimulus parameters subsequently controlled by computer. The characteristic frequency (CF) was defined as the frequency that elicited responses at the lowest sound intensity to which a cell was sensitive. Threshold was estimated to the closest 5-dB increment (e.g., 5, 10, 15 dB SPL), such that threshold estimates were presumably accurate to within 2.5 dB. Subsequent data collection included testing at the estimated threshold level, as well as levels above and below in 5- or 10-dB increments. Binaural stimuli were then presented to determine whether a cell was monaural or binaural, and if it was binaural, whether it was excitatory/inhibitory (EI) or excitatory/excitatory (EE). Cells were operationally classified in the present study as ILD-sensitive, EI type, if CF tones at one ear suppressed responses evoked by CF tones at the other ear by more than 50% when the stimuli were presented simultaneously (in the LSO, excitation was driven by the ipsilateral ear, and in the ICC, excitation was driven by the contralateral ear).

Stimuli were 60-ms pure tones with sigmoidal rise and fall times of 0.2 ms. Sinewaves from a Wavetek function generator (model 136) were shaped into tone bursts with an analog switch (Restek Model 15). Stimulus presentations were controlled by a Restek Model 45 Real Time Clock, which also timed spike events for the peristimulus time (PST) histograms and raster plots. A 24-bit digital interface NuBus card (National Instruments DIO-24) and a digital distributor (Restek model 99) connected a Power Macintosh 7300/180 computer to the Restek equipment and a 2-channel digital attenuator (Wilsonics, model PATT). The output of each independently controlled channel of the attenuator was sent to 2 Bruel & Kjær 1/8 in. microphones used as ear phones fitted with probe tubes (5 mm diameter) that were placed in the funnel of each pinna. Maximum sound intensity was 80 dB SPL measured 0.5 cm from the opening of the probe tubes. Sound pressure and the frequency response of each earphone were measured with a 1/4 in. Bruel & Kjær microphone. Each earphone showed less than ±3 dB variability for the frequency range usually used (15–80 kHz) and intensities between the earphones did not vary more than ±3 dB at any of those frequencies. Stimuli were presented at a rate of 4/s. For fundamentals between 10 and 50 kHz and 74 dB SPL, all harmonics were ≥35 dB less intense than the fundamental. For higher frequencies the harmonics were even lower. Acoustic isolation between the ears was better than 40 dB, and was determined empirically during the course of the experiments using monaural cells: stimuli were presented to the ear opposite of the ear driving the cell, and the intensity was increased until spikes were evoked, presumably by cross talk.

Rate-intensity and ILD functions were constructed for each cell to establish its response characteristics to monaural and binaural stimulation. Rate-intensity functions were generated by monaural stimulation of the excitatory ear, usually with intensities from about 10 dB below to 50 dB above threshold, in 5- or 10-dB steps. ILD functions were generated by fixing the sound intensity at the excitatory ear and varying the intensity at the inhibitory ear, usually from 20–40 dB below to 20–40 dB above the intensity at the excitatory ear, in 5- or 10-dB steps. For both the rate-intensity and ILD functions, each stimulus was presented 20 times in pseudorandom order.

RESULTS

We studied 30 LSO neurons and 111 ICC neurons that were sensitive to ILDs (EI type). For the LSO cells, the ipsilateral ear evoked excitation, whereas for the ICC cells, the contralateral ear evoked excitation. For convenience, we refer to the ear evoking excitation as the “excitatory ear,” and the ear evoking inhibition as the “inhibitory ear,” regardless of the source of inhibition, or at what synaptic level it affected the measured response. The characteristic frequencies of the LSO cells...
ranged from 8.3 to 81.3 kHz (mean = 33.7 kHz, SD = 13.8), and for the ICC cells, from 10.4 to 54.0 kHz (mean = 25.2 kHz, SD = 6.0).

In the sections below, we first describe some of the basic monaural and binaural response properties of the cells in our samples, focusing on rate–intensity functions, and binaural ILD functions measured when the intensity to the excitatory ear was fixed at 20 dB above each cell’s threshold. We then describe the effects of variations in the intensity at the excitatory ear on ILD sensitivity, and how responses differ between the LSO and the ICC. Finally we present population analyses for both the LSO and ICC.

**Rate–intensity and ILD functions**

We assessed monaural, excitatory rate–intensity functions, and binaural ILD functions for each cell. An example rate–intensity function from one of the LSO cells is shown in Fig. 1A. The data were generated by presenting intensities to the excitatory ear from −10 to 40 dB SPL. For this cell, spike counts increased with increasing intensity and then reached a plateau.

Within both the LSO and ICC cell populations, rate–intensity functions varied from cell to cell. In both populations there were cells with functions that reached a plateau, or that increased with intensity across the entire range of intensities that we presented (Fig. 1B, left inset). There were also cells with nonmonotonic functions that initially increased in spike count with intensity, and then decreased at higher intensities (Fig. 1B, right inset). To compare the LSO and ICC populations, we derived a quantitative measure of nonmonotonicity from each cell’s rate–intensity function based on the percentage reduction in spike count between that at peak and that at the highest intensity tested, and the resulting distributions are shown in Fig. 1, B and C. A comparison between the 2 populations showed that the ICC cells had significantly greater nonmonotonicity values \([t = 2.70 \text{ (df = 139); } P < .01]\).

An example ILD function is shown in Fig. 2A, which came from the same LSO cell whose rate–intensity data are shown in Fig. 1A. The ILD function was derived by presenting tones with a fixed intensity of 20 dB SPL to the excitatory ear, and variable intensities, from −10 to +40 dB SPL, to the inhibitory ear. For low contralateral intensities, spike counts were similar to those evoked by excitatory stimulation alone at 20 dB SPL (arrow on the rate–intensity function in Fig. 1A). However, higher contralateral intensities progressively inhibited spikes.

ILD sensitivity varied among cells in both LSO and ICC populations. To characterize ILD sensitivity, we used ILD functions generated with an intensity to the excitatory ear fixed at 20 dB above threshold, and calculated the 50% point from each cell’s ILD function. The 50% point reflects the ILD corresponding to the spike count halfway between the minimum and maximum response (i.e., the 50% point of the dynamic range). The 2 example ILD functions shown as insets in Fig. 2B illustrate the variability we observed among cells (50% points are indicated by dashed lines). The curve on the left has a 50% point that corresponds to a positive ILD, indicating a higher intensity at the inhibitory ear compared with the excitatory ear. The distributions of 50% points for the LSO and ICC cell populations are shown in Fig. 2, B and C, respectively. Both populations show a wide distribution of 50% points, corresponding to most of the biologically relevant range of ILDs that this species would experience in the free field (±35 dB). The 2 distributions did not differ significantly \([t = 1.424 \text{ (df = 139); } P = .157]\).

**Effects of intensity at the excitatory ear on ILD sensitivity**

The ILD sensitivity data presented above were derived using a single, standard intensity related to the threshold for the
effects that we observed. In the paragraphs below, we give examples of LSO and ICC cells that illustrate the main types of intensity to the excitatory ear. Figure 3 shows data from the inhibitory ear. Each function was derived using a different intensity to the excitatory ear constant while varying the intensity at the inhibitory ear. For this cell, each of the inhibitory rate–intensity functions shows maximum spike counts for the lowest inhibitory intensities tested, and minimum spike counts for highest inhibitory intensities tested, as one might expect. Differences in maximum spike counts across the 3 functions were also as one might expect: the curve generated with the highest excitatory intensity tested (30 dB SPL) had the highest maximum spike count. An important feature of these curves is that they do not remain parallel to one another across inhibitory intensities. Rather, they show a moderate degree of convergence at higher inhibitory intensities. In other words, whereas greater intensities at the excitatory ear increased maximum spike counts across the functions, greater intensities at the inhibitory ear generated convergent spike counts, regardless of the maximum spike counts. The third panel in Fig. 3A shows the same binaural data as described above, but replotted such that the x-axis is expressed in ILD rather than intensity at the inhibitory ear. This panel illustrates that some ILDs generate similar spike counts regardless of the intensity at the excitatory ear (e.g., 0, -10, -20 dB), whereas other ILDs generate different spike counts for different intensities at the excitatory ear (e.g., +10, +20, +30 dB). The fourth panel in Fig. 3A shows the same ILD functions, normalized to each function’s peak spike count. For this cell, the normalized ILD curves shifted to the left, toward more positive ILDs, as the intensity to the excitatory ear was incrementally increased. A similar pattern of responses was displayed by the LSO cell in Fig. 3B.

In contrast to the cells described above, the LSO neuron in Fig. 3C had an excitatory rate–intensity function that was nonmonotonic (first panel). Thus the excitatory intensities used to generate the inhibitory rate–intensity functions shown in Fig. 3C correspond to a portion of the cell’s excitatory rate–intensity function where spike counts decreased with increasing intensity. As a result, the maximum spike counts of the inhibitory rate–intensity functions also decreased from curve to curve, as the intensity to the excitatory ear was increased, which is the opposite pattern from that of the cells in Figs. 3, A and B. Despite this obvious difference, there were 2 other features that these 3 LSO cells had in common. The first was the convergence of inhibitory rate–intensity functions with increasing intensities at the inhibitory ear (second panel for each cell). The second common feature was a shift in the normalized ILD functions toward more positive ILDs, as the intensity to the excitatory ear was incrementally increased (last panel for each cell).

Effects of intensity at the excitatory ear on ILD sensitivity: ICC cells

Data from 3 example ICC cells are shown in Fig. 3, D–F. The ICC cells in panels D and E had monotonically increasing...
excitatory rate–intensity function, whereas the cell in panel F had a nonmonotonic excitatory rate–intensity function. Note that the nonmonotonic cell in panel F showed a prominent increase in spike counts for certain binaural stimuli (Fig. 3F, second panel). This type of binaural enhancement has been described in detail in previous reports (Park and Pollak 1993; Semple and Kitzes 1993). For the present study, an important feature illustrated by the inhibitory rate–intensity functions of the 3 ICC cells in Fig. 3 (second panels), is the relatively small degree of convergence among curves, compared with that observed for the 3 LSO cells. The ICC cells show an incremental shift in their inhibitory rate–intensity curves, such that curves generated with greater intensities to the excitatory ear were shifted to the right, toward higher intensities at the inhibitory ear. In other words, when the intensity to the excitatory ear was increased, a similar increase in intensity at the inhibitory ear was required to achieve a similar degree of spike suppression. Replotting the data in terms of ILD (third panels) shows that the curves, which were not highly convergent for absolute intensity at the inhibitory ear, were indeed convergent (Fig. 3, D and E), or even overlapping (Fig. 3F) when plotted as a function of ILD. Finally, the normalized ILD functions for these ICC cells (fourth panels) show a high degree of overlap across different intensities to the excitatory ear.

The 2 main differences between the LSO and ICC cells in Fig. 3 were the degree of convergence of ILD functions when spike count was plotted against intensity at the inhibitory ear, and the stability of the normalized ILD functions. A quantitative analysis of these effects is presented in the following section of the results.

FIG. 3. Data from 3 LSO cells (A–C) and 3 ICC cells (D–F) illustrating the main ways in which cells’ binaural responses were affected by increases in the intensity at the excitatory ear. There are 4 panels for each cell (from left to right): the excitatory rate–intensity function, a set of inhibitory rate–intensity functions, a set of spike count–based ILD functions, and a set of normalized ILD functions. Arrows on the excitatory rate–intensity functions indicate the spike counts for monaural stimulation at the excitatory intensities used to generate the corresponding binaural functions (symbols on the arrows indicate corresponding binaural functions).
Quantitative differences between the LSO and ICC populations

To quantify convergence of inhibitory rate–intensity curves (e.g., the curves in Fig. 3, second panels), we calculated the range of inhibitory SPLs that reduced spike rate to an arbitrarily selected low value (10% of the maximum rate) across a given cell’s inhibitory rate–intensity curves. A narrow range reflects a higher degree of spike count convergence than does a wide range. The examples in Fig. 3 suggest that this range is smaller among LSO cells compared with ICC cells, and a comparison of the LSO and ICC populations confirmed that the average range of inhibitory SPLs that reduced spike rate to 10% was significantly smaller for the LSO cells [t = 2.799 (df = 147); P < .01].

The relevance of this result is that it suggests that inhibition acts differently in the LSO and the ICC. For a given LSO cell, there appears to be a particular intensity, or range of intensities, that evokes enough inhibition to suppress most spikes, regardless of the spike count evoked by the excitatory ear. On the other hand, in the ICC, the strength of inhibition appears to increase more incrementally, such that increases in the intensity to the excitatory ear necessitate similar increases in intensity at the inhibitory ear to maintain a criterion level of spike suppression.

The examples in Fig. 3 further suggest that the different ways in which inhibition acts in the LSO and the ICC causes normalized ILD functions to systematically shift in many LSO cells, but to maintain more stability in ICC cells across different intensities to the excitatory ear. We next turn to the issue of quantifying the effects of intensity at the excitatory ear on the magnitude and direction of changes in the ILD functions.

To calculate a quantitative index of change in ILD sensitivity as a function of change in intensity at the excitatory ear for each cell, we took the ratio of shift in 50% points of the ILD functions (in dB), over the range of excitatory intensities tested (in dB), a calculation similar to that made by Irvine and Gago (1990) for EI cells in the ICC of the cat. Thus for a cell whose 50% points did not change, the value of this ratio would be 0. For a cell whose 50% points changed by 10 dB for each 10 dB increment change in intensity at the excitatory ear, the value would be 1. For the example LSO cell in Fig. 3A, the 50% points of the 3 normalized ILD functions in the fourth panel shifted from an ILD of −8.5 to +11 as the intensity to the excitatory ear was increased from 10 to 20 to 30 dB SPL. Thus the shift in 50% points was 19.5 dB, over a 20-dB range of excitatory intensities, giving a ratio value of 0.975. The other LSO cells, in Fig. 3, B and C, had values of 0.58 and 0.77. In contrast, the 3 ICC cells, in Fig. 3, D–F, had smaller values of 0.20, 0.10, and 0.05, respectively. The distributions of ratio values for the LSO and ICC populations are shown in Fig. 4A. Compared with the LSO population, the ICC cells showed significantly less variability in 50% points because of changes in the intensity at the excitatory ear [t = 4.201 (df = 139); P < 0.001].

There is no a priori criterion for classifying a cell’s ILD sensitivity as definitively variant or invariant. However, in previous studies (e.g., Irvine and Gago 1990), ratio values < 0.4 were qualitatively judged to be invariant based on visual inspection of the curves. For our LSO population, only 10% of the cells (3 of 30) fit this criterion for invariance. In contrast, when we applied the same criteria to the ICC cells, we found that 54% of the cells (60 of 111) fit the criterion for invariance.

Both LSO and ICC populations included cells with 50% point ILDs that were not classified as invariant. Those cells had 50% points that shifted either systematically to the left (Fig. 3, A–C), or systematically to the right, or in a nonsystematic way. The proportion of cells whose 50% points shifted systematically to the left, right, and nonsystematically (labeled Mixed) are presented in Fig. 4B. The distribution for the LSO cell population shows that the majority of cells (73%, 22 of 30) had 50% points that shifted systematically to the left, toward positive ILDs, as did the example LSO cells in Fig. 3. In contrast, a much smaller proportion of ICC cells (18%, 20 of 111) had 50% points that shifted systematically to the left. The ICC population also included a substantial proportion of cells (19%) with 50% points that shifted nonsystematically (Mixed). Both populations included only a small portion of cells with 50% points that shifted systematically to the right, toward more negative ILDs.

Next we wanted to determine whether there was a relationship between the way in which increasing intensity to the excitatory ear affected monaural rate–intensity functions, and the way in which it affected ILD functions. The idea is that some cells show monotonically increasing spike counts along their rate–intensity functions, and the presumption for these cells is that the net strength of excitation increases with intensity. For cells that show an initial increase in spike count followed by a decline, the presumption is that the net strength of excitation decreases with intensity (attributed to increasing...
inhibition elicited by the same ear) for the range of intensities corresponding to declining spike counts (Pollak and Park 1993). Thus it may be that cells with monotonic excitatory rate–intensity functions could have ILD functions that show different effects from increasing the intensity at the excitatory ear compared with cells with nonmonotonic excitatory rate–intensity functions. To analyze the effects of nonmonotonicity on ILD sensitivity, we divided the cells into 2 categories. In one category, we included cells whose ILD functions were generated with excitatory intensities corresponding to monotonically increasing portions of their rate–intensity functions (e.g., Fig. 3, A, B, D, and E). In the other category, we included cells whose ILD functions were generated with excitatory intensities corresponding to a nonmonotonic portion of their rate–intensity functions (e.g., Fig. 3, C and F). The open boxes on the bars in Fig. 4B indicate cells categorized as nonmonotonic. For the LSO, the cells that showed the characteristic shift to the left included cells with monotonic rate–intensity functions, as well as cells with nonmonotonic rate–intensity functions. Similarly, in the ICC, the group of cells classified as having stable ILD functions across excitatory intensities included cells with monotonic, as well as cells with nonmonotonic, rate–intensity functions. Within the ICC population we compared the proportion of cells with nonmonotonic rate–intensity functions in the stable group, and the combined nonstable groups, and we found that the variables of nonmonotonicity and stability were not dependent \( \chi^2 = 3.46 \text{ (df = 1); } P = 0.063 \). This result suggests that nonmonotonicity of rate–intensity functions does not play a significant role in the stability of ILD functions across different excitatory intensities.

In the analysis above we focused on normalized ILD functions, as have a number of previous studies (Irvine and Gago 1990; Irvine et al. 1996; Wenstrup et al. 1988). However, there is no definitive evidence for, or against, the notion that the nervous system performs a normalization process, and there are previous studies that have focused on raw spike count data (Semple and Kitzes 1987). Thus we repeated the above analysis using raw ILD spike count data, and instead of using 50% point ILDs to characterize the effects of overall intensity, we used a criterion spike count. For each cell the criterion spike count was determined as the 50% point of the ILD function with the lowest peak spike count. For example, in Fig. 3A (third panel), the function with the lowest peak spike count is depicted with open circle symbols. The peak spike count of this curve is 80 spikes, so the criterion spike count used for this cell was 40 spikes. The ILDs corresponding to 40 spikes for each of the 3 spike count ILD functions were 8.5, 8.0, and 5.0 dB, which yielded a ratio value of 0.175 (the criterion point shifted 0.175 dB ILD per 1 dB SPL increase in intensity to the excitatory ear), which means that, according to the classification scheme described earlier, this cell is classified as invariant. Note that the previous analysis, based on normalized ILD functions, resulted in classifying the same cell as not invariant. There were also examples of conflicting outcomes from the 2 analyses in the opposite direction, where cells had normalized ILD functions that were classified as invariant, but spike count–based ILD functions that were classified as not invariant (e.g., the ICC cell in Fig. 3E). However, for the populations of LSO and ICC cells (Fig. 5), the spike count–based analysis supported 3 of the main findings of the analysis made on normalized ILD functions: 1) Compared with the LSO population, the ICC cells showed significantly less variability in 50% points because of changes in the intensity at the excitatory ear (Fig. 5A) \( J = 3.360 \text{ (df = 139); } P < .01 \); 2) the criterion points for the majority of LSO cells shifted systematically to the left, toward more positive ILDs (Fig. 5B); and 3) a greater proportion of ICC cells had criterion points that were classified as invariant (36% of ICC cells vs. 20% of LSO cells).

**Effects of changes in average binaural intensity**

The ILD functions in our study were generated by presenting a constant intensity to the excitatory ear, and various intensities to the inhibitory ear, and thus far we have displayed the ILD functions accordingly. This method of analysis is useful because it allows a direct assessment of the influence arising from one ear on the activity evoked from the other. However, in real-world listening conditions, as a sound moves in azimuth, the increase in the intensity at one ear occurs at the same time as a reduction in intensity at the other ear. A technique that more closely approximates this situation involves presenting stimuli at a constant average binaural intensity (ABI) for each ILD function. In this procedure, the intensity is simultaneously varied at both ears—increasing at one ear and decreasing at the other ear. Semple and Kitzes (1987) presented data for ICC cells using both assessment techniques (ABI and constant intensity at the excitatory ear) for both EI cells and binaurally excited cells (EE cells). They found that the majority of EI cells were influenced by both ILD and ABI. They also indi-
cated that in some instances the direction and magnitude of shift in ILD functions with overall intensity were very similar for the 2 techniques, whereas in other instances they were not.

To distinguish the effects of ILD and ABI for the cell populations in the present study, ILD functions were replotted such that each point represents a combination of excitatory and inhibitory intensities that are symmetrical around a constant ABI. Thus at a given ILD, variability arising from changes in ABI can be evaluated across functions (Irving and Gago 1993; Semple and Kitzes 1987).

For our data, we were able to construct ILD functions for 3 or more ABIs for 29 of the LSO cells and 104 of the ICC cells. The data in Fig. 6 are from some of the cells for which we had the largest number of ABI-based curves (cells with original data sets that included 5 or more ILD functions taken with different constant intensities at the excitatory ear). Shown for each cell are the excitatory rate–intensity function (left), a set of ILD functions taken with different constant intensities at the excitatory ear (center), and a set of replotted ILD functions based on ABIs (right). For each of the LSO cells (Fig. 6, A–C), the criterion points on the ILD functions taken with different constant intensities at the excitatory ear shift to the left, as described earlier. Leftward shifts can also be observed for the ABI-based ILD functions at almost any given spike rate for each of the 3 LSO cells (except at positive ILDs for the cell in Fig. 6C). An additional, related feature observable from the ABI-based functions is that spike counts at most ILDs declined with increasing ABI (Fig. 6, A–C, right panels). In contrast, the 3 ICC cells presented in Fig. 6, D–F showed different response patterns. For the ILD functions taken with different constant intensities at the excitatory ear (center panels), criterion points showed less variability compared with those of the LSO cells, as described earlier. The ABI-based functions of the ICC cells also differed from those of the LSO cells. For the ICC cells, spike counts at most ILDs either increased or first increased and then decreased with increasing ABI. Note that the ICC cell in Fig. 6E had ILD functions that peaked near 0 dB ILD, displaying a nonmonotonic response to ILD. This type of response in ICC cells has been described in detail by Semple and Kitzes (1987).

The cells in Fig. 6 were among those for which we had the largest number of ABI-based curves. However, we had ≥3 curves for the majority of the cells, from which we extracted an index of how increasing the ABI affected responses to ILD. For each cell, we took the change in spike count per dB change in ABI at 0 dB ILD, and from those values, we determined the direction of change for each cell (“Decrease” as in Fig. 6, A–C, “Increase” as in Fig. 6D, and “Mixed” as in Fig. 6, E and F). The results from the LSO and ICC cell populations are presented in Fig. 7. Figure 7A shows the distributions of change in spike count per dB change in ABI. The values for LSO cells and ICC cells did not differ significantly, indicating that ABI influences cells in both populations to a similar extent. On the other hand, there were prominent differences in the distributions of direction of change between the LSO and ICC [$\chi^2 = 12.44 (df = 2); P < .01$]. As shown in Fig. 7B, the predominant pattern for the LSO cells was a decrease in spike count with increasing ABI at 0 dB ILD, as was the case for the example cells in Fig. 6, A–C. For the ICC cells, the predominant pattern was a mixed response of increases and decreases with increasing ABI, as was the case for the example cells in Fig. 6, E and F. We interpret these results to mean that both LSO cells and ICC cells are influenced by ABI to a similar, substantial degree, but that the influences of ILD are different for the 2 populations.

Population coding

The results presented above indicate that, compared with the LSO, the ICC had a larger proportion of cells with invariant ILD functions across different excitatory intensities. However, even in the ICC, many of the cells were still classified as showing substantial variability (46% when normalized ILD functions were used, 64% when raw spike count ILD functions were used). Thus many individual neurons did not code ILDs invariantly across intensity at the excitatory ear. We next turn to the question of how population responses changed with differences in excitatory intensity. We approached this question in 2 ways. In one analysis we focused on changes in total spike counts, summed across cells, for different ILDs and different excitatory intensities. In a second analysis we as-

FIG. 6. ILD functions plotted in terms of average binaural intensity (ABI) for 3 LSO cells (A–C) and 3 ICC cells (D–F). There are 3 panels for each cell (from left to right): the excitatory rate–intensity function, a set of spike count–based ILD functions with constant intensities at the excitatory ear, and a set of spike count–based ILD functions with constant ABIs. Arrows on the rate–intensity functions indicate the spike counts for monaural stimulation at the excitatory intensities used to generate the corresponding binaural functions (symbols on the arrows indicate corresponding binaural).

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sessed changes in the proportions of cells responding at ≥50% on the dynamic range of their ILD curves across ILDs for different excitatory intensities.

The curves in Fig. 8 were derived from 13 LSO cells (A and C), and 35 ICC cells (B and D) for which we had ILD functions that were generated with intensities at the excitatory ear of 20, 30, and 40 dB SPL. Figure 8, A and B show the summed spike counts for all 13 LSO cells and all 35 ICC cells, respectively, at each ILD. For both populations, the functions differ, indicating that summed spike counts are substantially affected by the intensity at the excitatory ear.

Figure 8, C and D show a similar analysis as the one described above, except that the independent variable was the proportion of cells responding at 50% on the dynamic range of their ILD curves or greater. For this measure, the dynamic parts of the functions in Fig. 8C, from the LSO cells, show a systematic shift toward positive ILDs with increases in intensity at the excitatory ear. This indicates that, at most ILDs, fewer LSO cells respond at ≥50% as the intensity to the excitatory ear is increased, which is consistent with the characteristic leftward shifts observed in the normalized ILD functions of individual LSO cells (Fig. 3, A–C, right panels). As mentioned in a previous section, the leftward shift in ILD functions appears to be related to the observation that for most LSO cells, there is a range of intensities at the inhibitory ear that evokes enough inhibition to suppress most spikes, regardless of the spike count evoked by the excitatory ear. Thus when spike count is plotted as a function of intensity at the inhibitory ear, curves generated with different excitatory intensities converge, but when normalized spike counts are plotted as a function of ILD, the curves shift leftward (Fig. 3).

The functions for the ICC cells in Fig. 8D show less variability, which may be attributable, in part, to the greater proportion of individual ICC cells that show relative invariance to the intensity at the excitatory ear. There may also be a net canceling effect among the relatively large number of ICC cells that have a high degree of variability, but that shift in a nonsystematic manner (cells categorized as having a “mixed” effect in Fig. 4B). To quantify the variability among functions, we calculated the coefficient of variance for points on the dynamic portions of the curves, from +20 to −20 dB ILD. We found that the average coefficient of variance was significantly lower for points on the curves from ICC cells compared with those from LSO cells [t = 2.222 (df = 12); P < 0.05].

Discussion

The main finding of the present study was that, compared with LSO cells, significantly more ICC cells had ILD sensitivities that were invariant to changes in sound intensity at the excitatory ear.

The LSO cells that we studied were characterized by ILD functions that shifted systematically in response to increasing intensities at the excitatory ear. There are very few previous data that have assessed LSO responses at different overall intensities. However, Boudreau and Tsuchitani (1968) tested 12 LSO cells from cat in a procedure where they adjusted the intensity to the excitatory ear to evoke one spike, and then they increased the intensity to the inhibitory ear until the spike was inhibited. This procedure was repeated across a variety of excitatory intensities. The authors concluded that stimulation at the inhibitory ear was usually less efficient compared with stimulation at the excitatory ear. In a subsequent manuscript, the same authors (Boudreau and Tsuchitani 1970) presented data from an LSO cell tested at a variety of binaural levels (their Fig. 39). They used a different stimulus paradigm from that used in the present study (they held the inhibitory intensity constant and varied the excitatory intensity). However, plotting their data in a format consistent with ours revealed that ILD functions shifted systematically to the left, with 50% points shifting 0.7 dB per dB change in the intensity at the excitatory ear, which is similar to the average shift we observed for the LSO cells in the present study (0.79 dB per dB change in the intensity at the excitatory ear). In another study on cat LSO cells, Tollin and Yin (2002) reported that 6 out of 6 cells tested with pure tones or noise showed leftward shifts in the 50% points of their ILD functions. Interestingly, the same study reported that 7 of 9 cells tested with virtual space stimuli showed shifts in the opposite direction, to the right. Virtual space stimuli were noise bursts synthesized to reproduce over earphones the sound pressure waveforms that would be produced in the ears by free field sounds.

A previous study on 73 LSO cells in the mustache bat (Park et al. 1997) focused on changes in the ILD of complete inhibition across different intensities to the excitatory ear. The ILD of complete inhibition is the ILD at which spikes are first completely inhibited as the intensity to the inhibitory ear is incrementally increased. That report showed that the ILD of complete inhibition was significantly less variable across different intensities to the excitatory ear compared with the 50% point ILD. We did not use the ILD of complete inhibition criterion in the present analysis because many ICC cells do not reach complete inhibition (Oswald et al. 1999). Although the article on mustache bat LSO cells focused on the ILD of complete inhibition, the same study reported an average shift in...
50% points of 0.7 dB per dB change in the intensity at the excitatory ear, which is similar to the average shift we observed for the LSO cells in the present study (0.79 dB per dB change in the intensity at the excitatory ear). The article on mustache bat LSO cells did not present data on the direction of 50% point shifts. However, we went back to the original data from that study and determined that the majority of cells (66 of 73) had 50% points that shifted to the left, as did the majority of the LSO cells in the present study.

The ICC receives a direct, excitatory projection from the contralateral LSO, as well as a direct inhibitory projection from the ipsilateral LSO. The ICC also receives many other projections, both excitatory and inhibitory, from virtually every other brain stem auditory center, as well as commissural and descending projections, all of which provide opportunities to modify LSO inputs, as well as to create novel response properties (Covey et al. 1996; Faingold et al. 1993; Klug et al. 1995; Li and Kelly 1992; Vater et al. 1992). Our present results suggest that one function of the ICC is to increase the stability of ILD sensitivity across different overall intensities. However, we point out that, even though the ICC had a significantly greater proportion of cells whose ILD sensitivity was invariant across excitatory intensities compared with the LSO, there were still many ICC cells in our sample whose ILD sensitivity was not invariant.

At the ears, ILDs are invariant across a wide range of absolute intensities. Likewise, our percept of a sound’s location based on ILD also appears to be invariant across a wide range of absolute intensities (Inoue 2001). Thus the idea of neurons in the central auditory system that code ILD independently from absolute intensity is appealing. This type of neuron has been described in the ICC (Aitkin et al. 1984; Grothe et al. 1996; Irvine and Gago 1990; Semple and Kitzes 1987; present report), and Irvine and Gago (1990) suggested that ILD coding may be predominantly accomplished by these cells. However, a problem with this scenario is that neurons with an ILD sensitivity that is invariant to overall intensity make up only a subset of ILD-sensitive cells. In the present study, we found that only one-third to one-half (depending on the analysis technique) of ICC cells had ILD functions that were invariant with changes in intensity at the excitatory ear. An even lower proportion of cells with invariant ILD functions were reported for the ICC of the cat (Irvine and Gago 1990) and the gerbil (Semple and Kitzes 1987), and, from free-field studies measuring spatial receptive fields in the big brown bat (Grothe et al. 1996), and cat (Aitkin et al. 1984).

The question becomes, if ILD coding is predominantly accomplished by the cells whose ILD sensitivity is invariant with absolute intensity, then what is the functional role of the majority of ILD-sensitive cells whose sensitivity is not invariant to absolute intensity? One possibility is that the ILD sensitivity of these cells is not related to ILD processing, per se, but rather it might be an epiphenomenon, related to the way in which these cells process other stimulus features. For example, a scenario such as this has been suggested to explain interaural time difference (ITD) sensitivity in the bat medial superior olive (MSO) (Grothe and Park 1998). Binaural cells in the bat MSO are sensitive to the same range of ITDs as are MSO cells in animals with larger heads (e.g., cats and monkeys), but the bat’s head is too small to generate ITDs in this range. Thus in the free field, bats would not experience ITDs that would be useful for sound localization. However, the same circuitry that generates sensitivity to ITD also generates sensitivity to amplitude modulation (AM) rates that the bats would frequently encounter (Grothe et al. 1997). Thus it appears that ITD sensitivity in bat MSO cells may be an epiphenomenon of binaural temporal processing of amplitude modulations.

There is also evidence that the ILD sensitivity of some ICC neurons may be an epiphenomenon of processing non-ILD–related stimulus features. For example, the same inhibitory input that suppresses spikes at some ILDs also plays a major role in temporal processing of stimulus features not necessarily related to ILD (Klug et al. 1999; Koch and Grothe 1998; Oswald et al. 1999). Also, the underlying circuits that generate ILD sensitivity are suggestive of subpopulations of cells that might be involved in different functions. There are 3 different circuits that generate ILD sensitivity in the ICC (Covey et al. 1996; Faingold et al. 1993; Kelly and Li 1997; Klug et al. 1995; Park and Pollak 1994; Vater et al. 1992). One circuit involves the direct excitatory projection from the LSO. Another involves a combination of excitatory inputs from the LSO, and GABAergic, inhibitory inputs not from the LSO. A third circuit involves integrating monaural inputs from both ears, and does not involve the LSO. Thus there is at least some theoretical basis for the idea of subpopulations of ILD-sensitive cells that might be involved in different functions (the cells whose sensitivity is invariant across absolute intensity may play a dominant role in ILD coding, whereas other subpopulations may participate in coding other stimulus features). However, the idea of a subpopulation of cells with stable ILD sensitivities that are independent from other stimulus parameters becomes extremely complex when one considers recent findings that the ILD sensitivity and/or spatial receptive fields of many cells are affected not only by absolute intensity, but also by a variety of stimulus parameters, including spectrum (Aitkin and Martin 1987; Grothe et al. 1996; Irvine and Gago 1990), duration (Oswald et al. 1999), and spatial patterning (Grothe et al. 1996, 1997; Koch and Grothe 1997, 2000). One wonders how many cells would still show ILD sensitivity independent of all other stimulus features if we were to test cells by varying each of these parameters.

Another possibility, suggested by Irvine and Gago (1990), is that the cells whose ILD sensitivity varies with absolute intensity are, in fact, incorporated into the population code for ILD, despite their variability (although the authors did not suggest how this might work). Our data appear to support this possibility, given that the net output from the populations of cells we tested appear to be surprisingly stable across absolute intensity (Fig. 8), suggesting that ILD sensitivity at the population level is much more invariant across absolute intensity than at a single-neuron level.

Interestingly, recent findings suggest that spatial processing of low-frequency sounds using ITDs might also involve a population code. For decades it has been taken for granted that ITDs are represented in a topographic manner, creating an azimuthal space map (Jeffress 1948; Joris et al. 1998). In fact, such a coding strategy has been found in the avian nucleus laminaris (Carr and Konishi 1988, 1990). There, single cells have ITD functions with individual “best ITDs” that are within the physiologically relevant range, and their ITD functions are stable across changes in stimulus intensity (Pena et al. 1996). However, this might not be the case in the mammalian auditory
system. Recent studies (guinea pig ICC: McAlpine et al. 1996, 2001; and gerbil MSO: Brand et al. 2002) reported that, for cells with similar best frequencies, the peaks of ITD functions were biased to ITDs where the contralateral ear leads the ipsilateral ear, and the steepest part of the slope (the maximum in the first derivative) was within the physiologically relevant range of ITDs, mostly close to zero ITD. Consequently, the largest change in population response rate with spatial position takes place just ipsilateral to the midline. These findings suggest a population code where overall activity, not a topographic space map, reflects ITD.

The population statistics of the ILD data in our study (Fig. 8) suggest a similar strategy to that described above for ITD coding. For the ICC cells, the population functions based on number of cells responding showed the largest changes near the midline, with little variation between functions from overall intensity. It is intriguing to speculate that ITD and ILD processing at the level of the ICC may share a common coding strategy based on overall population activity, especially considering that the lower brain stem circuits for encoding the 2 cues are very different.

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