Varying Overall Sound Intensity to the Two Ears Impacts Interaural Level Difference Discrimination Thresholds by Single Neurons in the Lateral Superior Olive

Jeffrey J. Tsai, Kanthaiah Koka, and Daniel J. Tollin
Department of Physiology and Biophysics, University of Colorado Health Sciences Center, Aurora, Colorado

Submitted 13 October 2009; accepted in final form 6 December 2009

Tsai JJ, Koka K, Tollin DJ. Varying overall sound intensity to the two ears impacts interaural level difference discrimination thresholds by single neurons in the lateral superior olive. J Neurophysiol 103: 875–886, 2010. First published December 9, 2009; doi:10.1152/jn.00911.2009. The lateral superior olive (LSO) is one of the earliest sites in the auditory pathway involved in processing acoustical cues to sound location. LSO neurons encode the interaural level difference (ILD) cue to azimuthal location. Here we investigated the effect of variations in the overall stimulus levels of sounds at the two ears on the sensitivity of LSO neurons to small differences in ILDs of pure tones. The neuronal firing rate versus ILD functions were found to depend greatly on the overall stimulus level, typically shifting along the ILD axis toward the excitatory ear and attaining greater maximal firing rates as stimulus level increased. Seventy-five percent of neurons showed significant shifts with changes in overall sound level. The range of ILDs corresponding to best neural acuity for ILDs shifted accordingly. In a simulation using the empirical data, when the overall stimulus level was randomly changed from one trial to the next, the neural discrimination thresholds for ILD, or ILD acuities, were worsened by 50–60% across the population of neurons relative to fixed stimulus levels whether ILD acuity was measured at the azimuthal midline or the ILD pedestal producing the best acuity. The impairment in ILD discrimination was attributed to the increased neural response variance imparted by varying the stimulus level. These results contrast to those observed in psychophysical studies where ILD discrimination thresholds under similar experimental conditions are invariant to overall changes in stimulus level. A simple computational model that incorporated the antagonistic inputs of bilateral LSO nuclei as well as the dorsal nuclei of the lateral lemniscus to the inferior colliculus produced a more robust encoding of ILD even in the setting of roving stimulus level. Testable predictions of this model and comparison to other computational models addressing stimulus invariance were considered.

INTRODUCTION

A remarkable aspect of perception is the relative invariance to large changes in stimulus intensity or level. For example, in auditory perception, sound sources can be accurately localized over an extraordinary range of sound pressure levels (Macpherson and Middlebrooks 2000; Sabin et al. 2004; Vligen and van Opstal 2004). The primary acoustical cue for the location of high-frequency sounds in azimuth is the difference in sound level at the two ears or interaural level difference (ILD). ILD cues result from the joint amplification of sound by the external ear ipsilateral to the source and attenuation of sound at the ear contralateral to the source by the so-called acoustic shadow cast by the head. Based on anatomical, physiological, and behavioral lesion studies, the neurons comprising the lateral superior olive (LSO) of the mammalian brain stem are widely believed to be the first site at which ILDs are extracted (Kavanagh and Kelly 1992; Moore and Caspary 1983; Boudreau and Tsuchitani 1968; see Tollin 2008 for review). Consistent with this, the discharge rates and associated response variability of single LSO neurons permit neural sensitivity, or acuity, to changes in ILD on the order of ~1 dB, which is directly comparable to psychophysical ILD thresholds in humans and cats (Tollin et al. 2008).

Psychophysical studies have demonstrated that ILD discrimination thresholds in humans are invariant with overall stimulus level (Bernstein 2004; Grantham 1984; Hartmann and Constan 2002; Stellmack et al. 2004). That is, ILD discrimination thresholds remain constant at ~1–2 dB even when the overall stimulus level at the two ears varies considerably from interval to interval in each trial in a classical two-alternative forced-choice paradigm. That ILD discrimination thresholds are invariant to these level changes demonstrates that the observers in such studies were basing their decisions on the ILD cue and not the sound level changes at any one ear; the “roving” of overall sound level from interval to interval effectively renders the use of sound level at one ear useless for the task (see Green 1988). This invariance observed in ILD acuity may be a basis for the stimulus-level invariance of sound localization accuracy.

Roving overall stimulus level in psychophysical studies of ILD acuity raises some intriguing questions as to how ILD cues are processed neurally. Any comprehensive model of ILD processing based on empirical studies of ILD encoding by neurons in the auditory system must contend with the psychophysical invariance of ILD acuity with overall level changes. The same is also true for any neural explanation for the level invariance of sound source localization behavior (see Stecker et al. 2005). However, little is known about the effect of changing stimulus level on ILD coding at the level of the LSO, the first site of ILD extraction and representation. In other words, it is not known how ILDs are encoded and ultimately interpreted for sound sources where the stimulus levels are unknown. For a fixed pedestal sound level at the two ears, the discharge rate versus ILD functions in LSO are sigmoidally shaped with the rate changing monotonically with ILD (e.g., Fig. 1A). However, some investigators have noted substantial changes in the rate-ILD functions of LSO neurons when the overall stimulus level at the two ears was changed between experimental blocks (Park et al. 2004; Tollin and Yin 2002). Most prominently, as overall level increased, maximal dis-
charge rate increased and the ILD of the rate-ILD functions corresponding to half the maximum rate typically shifted consistently to an ILD closer to the ipsilateral excitatory ear. This shift in the rate-ILD functions with overall sound level precludes a one-to-one mapping of discharge rate to a fixed value of ILD at all sound levels. Thus the behavioral invariance of ILD acuity cannot have its origin in the responses of single neurons in the LSO. Neither Park et al. (2004) nor Tollin and Yin (2002) examined in detail the consequence of these observations for behavioral sound localization performance. Park et al. (2004) also demonstrated that a higher proportion of ILD sensitive neurons in the central nucleus of the inferior colliculus showed more level-invariant rate-ILD functions than that found in LSO neurons.

The neural acuity of LSO neurons for small changes in ILD has been shown to correlate directly with the local steepness, or slope, of the rate-ILD function (Tollin et al. 2008). The best acuity occurs near, but not at, the ILD corresponding to the half-maximum rate where the rate-ILD slope is maximal. Here we examined the consequences of changing the overall sound level at the two ears for neural ILD acuity in the LSO. Additionally, we calculated the sensitivity of LSO neurons by simulating a roving-stimulus level experiment similarly to psychophysical methods using data from fixed level experiments. We found that neural ILD discrimination thresholds varied substantially when roving the overall stimulus level in contrast to the psychophysical invariance to overall level. To explore how level invariance of ILD coding might emerge, we proposed a general model of ILD coding based on known anatomy that allowed for much more robust ILD encoding with changing stimulus level. Such a mechanism, if present, may account for the invariance of ILD acuity with changes in overall sound level observed psychophysically.

METHODS

Anatomy and physiology

All surgical and experimental procedures complied with the guidelines of the University of Colorado Health Science Center Animal Care and Use Committees and the National Institutes of Health. Specific details of the procedures used here have been described previously (Tollin et al. 2008). In brief, adult cats were anesthetized with a combination of ketamine, acepromazine, and pentobarbital. Pentobarbital is known to have effects on inhibition produced in GABAergic pathways (Barker and Ransom 1978) and may also affect the responses of LSO neurons (Brownell et al. 1979). Both pinnae were cut transversely and removed, and tight-fitting custom-built hollow earpieces were fitted snugly into the external auditory meatus. Middle ear pressure was equalized through small holes drilled in the bullae. The LSO was approached ventrally through small holes in the basioccipital bone. Parylene-coated tungsten microelectrodes (1–2 MΩ, Microprobe, Clarksburg, MD) were advanced ventromedially at an angle of 26–30° into the brain stem by a microdrive (Kopf Model 662, Tujunga, CA) affixed to a micromanipulator that could be remotely advanced from outside the double-walled sound-attenuating chamber (Industrial Acoustics, Bronx, NY). Electrical activity was appropriately amplified and filtered (300–3,000 Hz). Single-unit responses were discriminated with a BAK amplitude-time window discriminator (Model DDIS-1, Mount Airy, MD), and spike times were stored at a precision of 1 μs via a Tucker-Davis Technologies (TDT, Alachua, FL) RV8. Our criteria for the successful isolation of a single neuron were spike waveforms that were largely invariant from spike to spike and had high signal-to-noise ratios.

Acoustic stimuli

All stimuli were generated digitally at 24-bit resolution and converted to analog at a nominal rate of 100 kHz. Overall stimulus level to each ear was independently controlled in 1-dB steps (TDT PAS attenuators) and delivered through an acoustic assembly (1 for each ear) comprising a speaker (TDT EC1), a calibrated probe-tube microphone (Bruel and Kjæer Type 4182, Norcross, GA), and a hollow earpiece that was fitted snugly into the cut end of the auditory meatus and sealed with petroleum jelly. Digital filters that equalized the responses of the acoustical system were applied and typically yielded flat frequency responses within ±2 dB for frequencies <30 kHz.

Once a single unit was isolated, the characteristic frequency (CF), spontaneous activity, and threshold were measured using an automated threshold tracking routine or by measuring a frequency-intensity response area. Sensitivity to ILDs was measured with ≥20 repetitions of a 300-ms duration tone at the CF of the neuron, presented every 500 ms with a linear rise/fall time of 5 ms. ILD was manipulated by holding constant the stimulus level to the ipsilateral ear at 4–25 dB above the ipsilateral-only threshold level in each block of trials while the level of the same stimulus presented to the contralateral ear was varied randomly in 5-dB steps over a range to produce ILDs of ±25 dB. The ipsilateral-only level was varied from block to block over a range of 10–30 dB in steps 5 or 10 dB; the number of levels ranged from 3 to 7 for each neuron and depended on how long the neuron could be held. Discharge rate for each neuron was computed over a fixed 300-ms window beginning at 5 ms.
Data analysis

Descriptive functions were fitted to the discharge rate and the associated SD of the rate (computed over repeated presentations of the stimuli) as a function of ILD. The descriptive functions have no functional biological significance but simply facilitated the analysis of the data and exploration of a larger stimulus space. A nonparametric standard separation metric $D$ (Sakitt 1973), based on detection theory (Green and Swets 1988), was used to calculate neural ILD discrimination thresholds. Details of these procedures were described in Tollin et al. (2008).

The spike discharge rate versus ILD function was fit by a four-parameter sigmoid function of the form

$$y = a + \frac{b}{1 + e^{-x-x_0}}$$

where $x$ is the ILD, $y$ is the discharge rate, and $a$, $b$, $c$, and $d$ are free parameters. The function relating the variance of the discharge rate to the mean rate was a two-parameter power function

$$y = ax^b$$

where $x$ is the discharge rate and $a$ and $b$ are free parameters.

We define here the ILD discrimination threshold, or acuity, as the smallest increment in ILD that corresponded to a metric $D$ of 1

$$D = \left| f\left(x + \frac{\Delta x}{2}\right) - f\left(x - \frac{\Delta x}{2}\right) \right| / \sqrt{\frac{\sigma_x}{2} + \frac{\sigma}{2}}$$

where $f$ is the discharge rate, $x$ and $\Delta x$ are pedestal and increment ILD, respectively, and $\sigma$ is the SD of the discharge rate; the discharge rate and SD were computed directly from the fitted functions as described above in Eqs. 1 and 2. By pedestal ILD, we mean the fixed ILD about which neural acuity for small changes in ILD was measured here. For each stimulus condition (e.g., fixed overall sound level, roving level, etc.), ILD discrimination thresholds were computed for a range of pedestal ILDs between ±25 dB in 0.05- to 0.1-dB increments.

Simulation of roving sound level experiments

In a traditional two-interval two-alternative forced choice (2-AFC) psychophysical task, observers are presented with sounds over headphones that contain two different ILDs (see Bernstein 2004). The ILDs are created by presenting the sound at one ear slightly higher (or lower) than the same sound presented to the opposite ear. In the two intervals of the 2-AFC task, the magnitude of the ILD is the same, but the sign is opposite in each interval. For example, in one interval, the stimuli might contain an ILD of −2 dB (favoring the left ear) and the subsequent interval would contain an ILD of +2 dB (favoring the right ear). The task of the observer would be to indicate in which of the two intervals the sound appeared to favor the left ear (i.e., lateralized to the left side of the head). In this example, the first interval would be the correct answer and the second interval the incorrect answer. During such a psychophysical experiment, the magnitude of the ILD is systematically changed from small magnitudes (i.e., 0 dB ILD), where the observers are forced to guess the correct interval (i.e., 50% correct discrimination), to large magnitudes for which discrimination performance would be expected to approach 100% correct discrimination. A plot of the percentage of correct discriminations as a function of the magnitude of the ILD is called the psychometric function. From this function, which typically increases from ~50 to 100% correct discrimination, the psychophysical ILD discrimination threshold can be determined. Threshold is often taken as the ILD that corresponds to 75% correct discrimination. The method detailed above replicates this task but using the distributions of LSO neuron discharge rates as a function of ILD (see Tollin et al. 2008 for details).

Psychophysical studies have demonstrated that ILD discrimination thresholds in humans measured as just described are invariant with overall stimulus level (Bernstein 2004; Grantham 1984; Hartmann and Constan 2002; Stellmack et al. 2004). That is, ILD discrimination thresholds remain constant at ~1−2 dB even when the overall stimulus level at the two ears varies considerably from interval to interval in each trial in a classical 2-AFC paradigm. The variation of overall stimulus level from one interval to the next is often referred to as “roving” the overall stimulus level. Here we sought to replicate this roving level paradigm, but using the distributions of LSO discharge rates as a function of ILD, to examine whether the acuity for ILD in LSO neurons was also invariant with changes in overall stimulus level. From the discharge rate versus ILD functions measured at multiple overall intensities, we simulated the experiment of roving the overall level from interval to interval by drawing randomly and equally from the samples of discharge rate data collected at each level. It can be shown (see Appendix) that the spike discharge rate in the simulation, $\text{R}_{\text{rov}}$, and the associated across-trial variance of the rate is related to the empirical discharge rates measured in the fixed level conditions from which the simulated data were drawn

$$\langle \text{R}_{\text{rov}} \rangle = \{\mu_k\}$$

$$\text{Var}[\text{R}_{\text{rov}}] = \langle \sigma_k^2 \rangle + \langle \mu_k^2 \rangle - \frac{1}{N} \left( \sum \mu_k \right)^2$$

where $\mu_k$ is the mean and $\sigma_k^2$ is the variance of the discharge rate measured at fixed ipsilateral level $k$, for $k = 1, 2, \ldots, N$; $\langle \rangle$ is the mean operator, and $\text{Var}[\text{]}$ is the variance operator.

This simulation procedure assumes that there was no short-term adaptation or plasticity in the responses of LSO neurons to changing ILDs and/or overall stimulus levels given the long intertrial intervals of 500 ms used here (Park et al. 2008). In support of this assumption, Finlayson and Adam (1997) showed that there was no short-term adaptation in LSO responses provided that interstimulus intervals exceeded 100 ms. Therefore our simulations were expected to capture the real behavior of the neurons without the confound of short-term adaptation. The implications of these assumptions for ILD coding are discussed at length in the DISCUSSION.

Parts of this work were presented at the 30th Midwinter Meeting of the Association of Research in Otolaryngology.

RESULTS

Results are based on recordings from 17 well-isolated LSO neurons in 10 cats where sensitivity to ILDs was measured for at least three or more overall sound intensities. A subset of the data (i.e., from 1 fixed sound level) from 11/17 neurons were reported previously (Tollin et al. 2008). The neurons had CFs between 3 and 32 kHz [21.1 ± 8 (SD) kHz; median = 21.9 kHz] and responses that were characteristic of LSO neurons (Tollin 2008): low spontaneous rates (4.4 ± 7.0 spike/s; median = 1.4 spike/s), chopping poststimulus time histograms to short tone pips with correspondingly small coefficients of variations (CVs) in the distributions of interspike intervals (mean CV = 0.36 ± 0.13, median = 0.35), and excitation by ipsilateral and inhibition by contralateral acoustical stimulation. Eleven neurons were verified histologically to be located in the LSO. The remaining six neurons were included here because both the neural response characteristics and the electrode depth at which they were encountered were consistent with LSO neurons identified in histologically verified experiments. A table of important monaural and binaural response
properties for the 17 neurons used in this paper can be found in the Supplemental Materials. These neurons have properties that are wholly consistent with prior studies of the LSO (Boudreau and Tsuchitani 1968; Park et al. 2004; Sanes and Rubel 1988; Tsuchitani 1982).

Rate-ILD functions of LSO neurons are dependent on overall stimulus level

A typical set of rate-ILD functions (error bars show ±1 SD) recorded from one LSO neuron (CF = 17.4 kHz) at five different ipsilateral stimulus levels are shown in Fig. 1A. Here we define ILDs corresponding to greater stimulus level at the ipsilateral excitatory ear as positive values while greater stimulus levels at the contralateral inhibitory ear produce negative ILDs. Although this convention for ILD is opposite to that used in our prior research (Tollin and Yin 2002; Tollin et al. 2008), it is necessary in this study to be consistent with the ILD definitions of Irvine and Gago (1990) and Park et al. (2004). The solid line through each dataset indicates the best fitted sigmoid function (R² > 0.95 for each fit). Following Irvine and Gago (1990) and Park et al. (2004), we quantified one aspect of the effect of changing overall stimulus level (from 25 to 45 dB SPL in Fig. 1A) on rate-ILD functions by the shift in the ILD corresponding to the half-maximal rate of the ILD function (the discharge rate corresponding to the half-maximal point of the rate-ILD functions, expressed as a ratio of ILD shift, in units of dB/dB) of the magnitude of the shift divided by the range of overall ipsilateral intensities presented.

Neural acuities of LSO neurons for ILDs are sensitive to overall stimulus level

Previous work in our laboratory has shown that the neural discrimination thresholds or acuities of LSO neurons for ILD are determined primarily by the maximal slope of the rate-ILD function (Tollin et al. 2008). The best neural acuity was found to occur near but not exactly at, the ILD corresponding to the half-maximal rate in the rate-ILD functions (the discharge rate variance precludes the best acuity from occurring at the ILD of maximum rate slope) (Tollin et al. 2008). Thus the shifts in the rate-ILD functions as shown in Fig. 1A were hypothesized to result in a change in the range of pedestal ILDs over which the LSO neurons were most sensitive to small changes in ILD. As an example of a test of this hypothesis, Fig. 1B shows the ILD discrimination thresholds as a function of pedestal ILD computed from the empirical rate-ILD data, as described in Methods, for the respective rate-ILD functions shown in Fig. 1A. ILD discrimination threshold is plotted on a logarithmic axis simply to highlight the small discrimination thresholds of this neuron. Regardless of the overall stimulus level, low ILD discrimination thresholds of ~1 dB were achieved by this neuron. However, as expected from the shift in the rate-ILD functions with overall sound level (Fig. 1A), the minimal ILD discrimination thresholds were achieved at different pedestal ILDs for each overall sound level. Thus for a given pedestal ILD, the ILD acuity for this neuron was highly dependent on overall sound level.

In the current study, we focused primarily on the ILD sensitivity at a single pedestal ILD, 0 dB ILD, as this is the ILD about which virtually all the psychophysical measurements of ILD acuity have been made. At 0 dB ILD, neural ILD discrimination thresholds for the neuron in Fig. 1, A and B, decreased from 11.1 dB (95% confidence interval, 8.5–24.4 dB shown by vertical line) for an overall sound level of 25 dB SPL to 1.4 dB (95% confidence interval, 1.2–1.6 dB) for a sound level of 45 dB SPL. In terms of the ILD acuity of this particular LSO neuron about a pedestal ILD of 0 dB, changing overall sound level by a factor of 1.8 changed the ILD discrimination threshold by nearly a factor of 10. Hence ILD discrimination thresh-

1 The online version of this article contains supplemental data.
olds for this LSO neuron were not invariant to overall sound level. Note that the discrimination thresholds may be less or more level invariant if computed at a different pedestal ILD.

Figure 3 shows an example for another LSO neuron (CF = 29.6 kHz). Figure 3A shows the empirical and fitted rate-ILD functions for three different overall levels and the associated SDs (dashed lines, bottom of figure). For this neuron, changing overall sound level had somewhat less effect on the half-maximal ILDs than the neuron in Fig. 1A, shifting by ~5 dB over a 10-dB range of sound levels for a shift index of 0.5. In terms of the ILD discrimination thresholds at the midline, however, Fig. 3B demonstrates that thresholds increased only marginally from 2.2 to 3.1 over this 10-dB range of levels. The vertical lines through each dataset at 0 dB ILD in Fig. 3B show the 95% confidence intervals for discrimination threshold ILD; the confidence intervals overlap in all cases implying that these discrimination thresholds were not significantly affected by changing stimulus level. Thus this neuron appears to be more robust to overall sound level than the example in Fig. 1, at least for a pedestal ILD at 0 dB.

**Randomly roving stimulus level decreases neural acuity for ILD**

Based on rate-ILD functions and associated response variabilities measured for different overall sound levels, we investigated the effect on neural ILD acuity of randomly changing the overall stimulus level, or “roving” the level, from interval to interval in a simulated two-interval, two-alternative forced-choice task. This roving level paradigm is equivalent to randomly and uniformly sampling from data collected at a particular pedestal ILD and different stimulus levels. By repeating this procedure many times at different pedestal ILDs, a roved-level rate-ILD function and associated SD of discharge rates were constructed for each neuron (see METHODS). In addition to the empirical data, Fig. 3A shows the roved-level rate and associated SD computed from the data for one neuron.

From the roved-level data, the ILD discrimination thresholds for each neuron were then computed in the same fashion as for the fixed level conditions described in the preceding text. Figure 1B shows the ILD discrimination threshold function obtained in the roving-level condition. At a pedestal of 0 dB ILD, in the roving-level condition the discrimination threshold was 3.6 dB, an increase of a factor of 2 over the discrimination threshold corresponding to the overall sound level (35 dB SPL) at the midpoint of the level rove (i.e., halfway between 25 and 45 dB). Thus for this neuron, roving overall level impaired neural acuity.

For the neuron shown in Fig. 3, the roved-level rate-ILD function and associated SD are shown as the solid and dashed gray lines, respectively (Fig. 3A). Note that the SD in the roved-level condition is larger than the respective single fixed-level SDs, reflecting the additional response variance due to roving the overall sound level. This particular example was chosen because, unlike the case for the example in Fig. 1, the ILD discrimination thresholds at a pedestal of 0 dB ILD were approximately the same at 2.2, 3.0, and 3.1 dB for overall levels of 25, 30, and 35 dB SPL, respectively. In the roved-level condition, the ILD discrimination threshold at 0 dB increased to 5.3 dB. The vertical lines indicate the 95% confidence intervals based on boot-strapped resampling of the ILD discrimination thresholds at a 0 dB pedestal ILD. Even in this particular case where the individual ILD discrimination thresholds were comparable over different overall levels, roving the level significantly increased the discrimination thresholds.

To compare the ILD discrimination thresholds between the roved and fixed stimulus level conditions, we defined an ILD discrimination threshold ratio, \( T \)
where $\Delta T_{\text{roved}}$ is the ILD discrimination threshold in the roved level condition and $\langle \Delta T_{\text{fixed}} \rangle$ is the mean ILD discrimination threshold averaged over the fixed-level conditions, respectively. A subscript to $T$ indicates the pedestal ILD where the discrimination thresholds were taken. For example, $T_{0dB}$ refers to the pedestal ILD of 0 dB. The values of $T_{0dB}$ for the example neurons in Figs. 1 and 3 were 0.93 and 1.92, respectively. These examples were chosen to reflect a case where roving affected the ILD discrimination thresholds very little (Fig. 1) or quite a lot (Fig. 3).

While psychophysical studies have predominantly measured ILD discrimination threshold at the azimuthal midline (0 dB pedestal ILD), the best (smallest) discrimination threshold ILDs for LSO neurons were often near, but not at, the midline. Tollin et al. (2008) demonstrated that across a population of LSO neurons, the pedestal ILD corresponding to best ILD acuity spanned a large range ($\pm 20$ dB) about the midline. To examine the ILD discrimination threshold at the most dynamic part of the rate-ILD function where acuity is best, we also defined $\Delta T_{\text{offset}}$ (Eq. 5), at a pedestal ILD that is offset from 0 dB, where the offset is the mean of the pedestal ILDs at which the best ILD acuity occurs under the fixed level conditions. For the example neuron in Fig. 1A, the best discrimination thresholds were measured at pedestal ILD of $-13.8$, $-8.9$, $-5.5$, $-0.7$, and $3.8$ dB for stimulus levels $25$, $30$, $35$, $40$, and $45$ dB, respectively. $\Delta T_{\text{offset}}$ for this neuron was determined at the pedestal equal to the mean of these values, $-5.03$ dB. The rationale for this approach was to identify a pedestal ILD at which the neuron is close to its best acuity so that $\Delta T_{\text{offset}}$ serves as a metric of the effect of roving levels on the best (i.e., lowest) ILD discrimination thresholds. For the example neurons in Figs. 1 and 3, $\Delta T_{\text{offset}}$ was $-5.03$ and $-1.82$ dB, respectively. In both cases, the best discrimination threshold ILDs were impaired by roving the overall stimulus level, whereas the discrimination thresholds at 0 dB ILD were impaired only in the neuron in Fig. 3. Again these example neurons were chosen to illustrate the relative extremes of the data.

If randomly roving the stimulus level did not impact the ILD discrimination threshold, then the discrimination threshold ratio $T$ (either $T_{0dB}$ or $T_{\text{offset}}$) would be expected to be distributed with a mean of 1.0. On the other hand, if roving worsened the ILD discrimination thresholds, then $T$ would be $>1.0$. The distribution of $T_{0dB}$ (shown along the ordinate in Fig. 4) for the 17 LSO neurons was significantly $>1.0$ (mean $= 1.47 \pm 0.4$; $t_{(16)} = 4.84$, $P < 0.001$, 2-tailed $t$-test). The distribution of $T_{\text{offset}}$ (shown along the abscissa in Fig. 4) was comparable in magnitude to $T_{0dB}$ and also significantly $>1.0$ (mean $= 1.55 \pm 0.54$, $t_{(16)} = 4.21$, $P < 0.001$, 2-tailed). These results show that roving stimulus level adversely impacted the sensitivity of individual LSO neurons to ILD by $\sim 50$–$60\%$ on average across the population of LSO neurons studied irrespective of the two pedestal ILDs where discrimination thresholds were measured. All 17 neurons had $T_{\text{offset}} > 1.0$ (Fig. 4), whereas all but 1 had $T_{0dB} > 1.0$. Together these results demonstrate that at the level of the LSO, the acuity of individual neurons to small changes in ILD were not invariant with respect to changes in the overall stimulus level, in contrast to the level invariance observed in psychophysical data.

**Subtraction model for overall level-invariant ILD acuity**

We propose here a simple model for ILD processing that might account for the discrepancy between psychophysical observations (level invariance) and neural responses in the LSO nucleus (level variant). The model is motivated by anatomical studies demonstrating strong excitatory projections from the LSO to the contralateral inferior colliculus (IC) and dorsal nucleus of the lateral lemniscus (DNLL) and a predominantly inhibitory projection to the ipsilateral IC and DNLL (Brunso-Bechtold et al. 1981; Glendenning et al. 1992; Saint Marie and Baker 1990). Here ipsi- and contralateral refer to the side of the IC relative to the LSO and/or DNLL providing the input. Figure 5 shows a schematic of this ascending anatomy from LSO to IC, including the DNLL.

Physiological studies have shown that ILD-sensitive neurons in the IC do not merely recapitulate the responses of LSO neurons to the ILD cue; rather evidence indicates that inhibitory projections to the IC from a variety of sources contribute to shaping responses of many IC neurons to ILDs (Kelly and Li 1997; Park et al. 2004; Pollak et al. 2002; Tollin and Yin 2002). These studies suggest that inputs to the IC from both ipsilateral (Fig. 5, projection B) and contralateral (Fig. 5, projection A) LSO and/or DNLL (Fig. 5, projection C) nuclei are important for ILD processing. An additional motivation for exploring the consequences of this particular circuitry was based on the observations of Park et al. (2004), who demonstrated that ILD-sensitive neurons in the IC are much more level tolerant than neurons in the LSO. The anatomical inputs to the IC directly from the contralateral LSO (projection A) and from inhibitory sources (projections B and C) that are also themselves ILD-sensitive (inset responses B and C) like the ipsilateral LSO and the contralateral DNLL may play a role in establishing the improved level tolerance at the IC. There are several additional ascending pathways that are not shown in
DNLL (DNLLL) and left IC. The increased activity in the left input signals, one from the contralateral LSO (Fig. 5, LSOR) opposite direction. We propose that at the level of the IC, these similarly-tuned neurons in the contralateral LSO but in the (Figs. 1 and 3), will also generate a comparable shift in (without changing the stimulus ILD), while causing a shift in in Fig. 5. Our conjecture is that a change in stimulus level (e.g., LSOR) and the contralateral DNLL (e.g., DNLLR) and/or indirectly via the contralateral DNLL or contralateral IC (not shown) as in Fig. 5. The rate-ILD functions of corresponding pairs of LSO and anti-neurons were then subtracted from each other to give the rate-ILD function of a presumed IC neuron (see dashed line, Fig. 5, top left inset). ILD discrimination thresholds were then computed from these modeled IC rate-ILD functions and associated response variances to generate output for both fixed-level stimuli and roved-level conditions.

As an example, Fig. 3C shows the ILD discrimination threshold versus pedestal ILD functions based on the subtraction model outlined here for each of the three overall sound levels tested for that particular neuron plus the results of the roving-level condition. For the fixed-level conditions, the subtraction-model discrimination threshold ILDs were only marginally improved relative to the empirical data shown in Fig. 3B. However, in the roving-level condition, discrimination threshold ILDs were greatly improved relative to the empirical data (Fig. 3B) and fell within the range of discrimination threshold ILDs for the fixed-level cases (Fig. 3C). Thus for this example neuron, the subtraction model produced a largely level-invariant acuity for ILD from inputs that were not themselves level invariant (Fig. 3, A and B).

Figure 6 compares the discrimination threshold ratios (Eq. 5) of our subtraction model for each of the 17 LSO neurons to those obtained empirically (the values of $T_{offset}$ in Fig. 4). If the subtraction model neither improved nor impaired the ILD discrimination thresholds under the stimulus level roving condition, then the data in Fig. 6 would have been expected to fall along the positive diagonal. Notably, the model produced discrimination threshold ratios that fell below the diagonal, indicating that the subtraction model output was more level invariant (Fig. 6, horizontal dashed line). Indeed, for the LSO neurons as a group, the model output was level invariant [null hypothesis $T_{offset}$ (model) = 1; mean = 0.972, $t_{(16)}$ = −1.56, $P = 0.14$]. Thus our subtraction model, based on known anatomical connections, vastly reduced the ambiguity introduced by roving stimulus levels, in concordance with the greater invariance in responses observed psychophysically and also physiologically at the level of the IC.

**Figure 5.** Neural circuit of the subtraction model of ILD coding. A schematic of the ascending connections from LSO to inferior colliculus (IC) on one side, depicting a simplified set of both excitatory and inhibitory feedforward connections from the LSO (bilaterally) and the dorsal nucleus of the lateral lemniscus (DNLL). The curves shown next to each of the LSO nuclei illustrate stereotyped rate-ILD functions of LSO cells. Because the inhibitory and excitatory inputs to the 2 LSO nuclei are complementary, their responses are mirror images ($A$ and $B$). The ILD sensitivity at the DNLL contralateral (DNLLL) to the IC of interest is also shown ($C$). Our model assumes that the responses from the LSO and/or contralateral DNLL are differentiated at the level of the IC, producing a response curve shown as the dotted line (top left).
FIG. 6. Neural ILD discrimination threshold ratios, $T_{\text{thresh}}$, calculated from the subtraction model of ILD processing illustrated in Fig. 5 are compared with those from the empirical LSO data. The diagonal dotted line shows line of equality. It is apparent that model discrimination threshold ratios differ from empirical LSO data and are clustered around unity, indicating that the difference model effectively produces level invariant ILD coding from inputs that themselves are not level invariant.

**D I S C U S S I O N**

The current study has confirmed that responses of LSO neurons are not invariant with respect to changes in overall stimulus level and, consequently, their sensitivity, or acuity, to small changes in ILD was impaired when the overall stimulus level was randomly roved. Thus the psychophysical invariance to overall level for ILD acuity does not have its origin in the responses of single neurons in the LSO. Two potential explanations can account for the deleterious consequence of overall level changes: a smaller rate versus ILD slope and/or a larger rate-ILD function could not account for the substantial decrease in ILD sensitivity observed.

The alternative explanation is that variance of the discharge rate is substantially increased under the roved level condition. *Equation 4* indicates that the variance of the across-level mean discharge rate is the mean of the individual variances with the addition of a correction term involving the individual discharge rates themselves. This correction term is always nonnegative and is zero when individual discharge rates are identical and greater than zero with increasing variability of the rates. At any pedestal ILD, roving overall stimulus level increases the variability of the discharge rates because it changes the peak and/or the half-maximal point of the rate-ILD function. We conclude that roving stimulus level increases the ambiguity in the stimuli as reflected in a greater variance of the response rates, which in turn leads to poorer ILD discrimination thresholds. Put another way, from the point of view of an ideal observer (Green and Swets 1988), when the overall sound level is varied, there is some additional uncertainty as to what stimulus variable caused the change in discharge rate. Did the rate change because the ILD was changed for a fixed overall sound level at the two ears? Or for a fixed ILD did the overall stimulus level to the two ears change? Or did both stimulus parameters change? The increase in rate variance in the roving-level condition (*Eq. 4*') captures this uncertainty.

**Comparisons to other studies of ILD coding under variable stimulus levels**

**DIRECTION OF THE SHIFT OF THE RATE-ILD FUNCTION.** Irvine and Gago (1990) and Semple and Kitzes (1987) reported that in the IC the most common change in the rate-ILD functions with changes in overall sound level was a progressive shift of the function in the direction of ILDs producing greater sound intensities at the ipsilateral (inhibitory) ear (re: the IC). With the exception of one neuron (1/17), this direction of shift of rate-ILD functions with increasing overall level is exactly the opposite what we have observed in the LSO. Here we observed in 16/17 neurons that the ILD functions shift systematically toward the ipsilateral (excitatory) ear. In this regard, our results are in better agreement with Wenstrup et al. (1988) where 68% of their rate-ILD functions in the IC were found to shift toward the contralateral (excitatory) ear with overall level, in the same direction as observed here. Park et al. (2004) found that a smaller proportion of IC neurons were affected by overall level, only 18% of neurons shifting toward the contralateral (excitatory) ear with the bulk of the neurons showing either no shift at all (~60%) or mixed shifts (~20%). Our results in the LSO also support the observations by Park et al. (2004) where 73% (22/30) of their LSO neurons exhibited shifts toward the ipsilateral ear with increasing level.

As pointed out by Irvine and Gago (1990), one important methodological difference between the Wenstrup et al. (1988) study and those of Semple and Kitzes (1987) and Irvine and Gago (1990) was that the former used overall stimulus levels that were within ~30 dB or less of threshold, whereas the latter studies employed stimulus levels over a much higher range above threshold. A plausible explanation for the different directions of shift in rate-ILD functions with higher or lower overall sound levels was provided by Irvine and Gago (1990; pg 588). Paraphrasing from Irvine and Gago (1990) and applying this to the LSO neurons studied here, consider a neuron the ILD sensitivity of which was measured at three fixed ipsilateral (excitatory) levels of 10, 20, and 30 dB above the ipsilateral ear only threshold. For these three stimulus levels, as the ILD is varied by changing the overall sound level to the contralateral (inhibitory) ear, the inhibitory stimulus becomes suprathreshold at all ILDs (by our convention, ILDs that are greater at the ipsilateral, excitatory ear are labeled positive) that are <10, 20, and 30 dB SPL, respectively. The ILD at which the contralateral stimulus can first exert an effect on the discharge rate of the neuron thus shifts progressively to the left toward ILDs favoring the ipsilateral ear (see Fig. 1 for example). Thus the half-maximal ILDs would also shift progressively to the left. Put another way, the relative discharge rate measured as a function of overall sound level for a given
pedestal ILD (e.g., 0 dB in Fig. 1A) would decrease with increasing sound level as if the relative strength of the inhibition systematically exceeded that of the excitation. Evidence for this latter scenario was first observed by Tsuchitani and Boudreau (1969), where they demonstrated that LSO cells presented with a fixed ILD of 0 dB generally decreased their discharge rate with increases in overall stimulus level to the two ears. The leftward shift of the ILD functions observed here in LSO neurons is also consistent with the leftward shift in each of 6 neurons reported by Tollin and Yin (2002).

The explanation by Irvine and Gago (1990) describes both our results here and those of Tollin and Yin (2002) and Park et al. (2004) in the LSO and Wenstrup et al. (1988) in the IC. For neurons examined with overall levels substantially above threshold, the inhibitory inputs would always be expected to be above threshold. The shift to the right (e.g., toward negative ILDs in our convention which correspond to ILDs favoring the inhibitory ear), indicates that with increases in overall sound level the relative strength of the inhibitory input is systematically lower than that of the excitatory input. Our result for the one neuron that shifted to the right is in agreement with this explanation; for this particular neuron (not shown), overall sound levels ranging from 75 to 85 dB SPL were used, which were well above the threshold of 30 dB SPL. All other neurons were examined within a range of ~5–40 dB SPL of threshold and all of these neurons exhibited shifts to the left. Similar stimulus ranges re: threshold were used in the studies of Wenstrup et al. (1988), Tollin and Yin (2002), and Park et al. (2004). This is clearly an area where more investigation is required.

Invariance of ILD coding with overall level changes between the LSO and IC

In the most comprehensive study to date, Park et al. (2004) compared the effect of overall stimulus level on the encoding of ILDs by neurons in the LSO and the IC under similar stimulus conditions. While most (73%) neurons in the LSO showed shifts in ILD sensitivity with increasing level (see preceding text), only 18% of neurons in the IC showed similar shifts. Nearly 80% of the IC neurons showed no shifts at all, or mixed shifts. Thus significantly more neurons in the IC had rate-ILD functions that were stable with increases in overall sound level. These results suggest that there was a hierarchical transformation in ILD coding from the LSO to the IC that increased the coding invariance (Park et al. 2004).

In a study of 40 high-CF IC neurons that exhibited monotonic sensitivity to ILDs of the general form illustrated in this paper for LSO neurons, Irvine and Gago (1990) reported that 40% (16/40) of those neurons exhibited level-invariant sensitivity to ILD as expressed by a shift metric that was <0.4. Park et al. (2004) reported that 54% (60/111) of IC neurons exhibited level invariance. Wenstrup et al. (1988) reported that 62% of their IC neurons had shift metrics <0.5. In contrast, LSO neurons showed less level invariance sensitivity to ILD. Park et al. (2004) reported that only 10% of their LSO neurons fit the level invariance criteria. Our results here confirm their observations in that in 17 high-CF LSO neurons, we observed only ~24% that had shift metrics <0.4, thus the ILD coding of ~75% of the LSO neurons were substantially affected by overall stimulus level. Park et al. (2004) reported that across their 30 LSO neurons, the half-maximal ILDs shifted with overall sound level by an average of 0.79 dB/dB change in overall level. Here, we found in 17 neurons an average shift of 0.61.

There is qualitative agreement across the studies that have examined the level invariance of ILD coding that the neurons in the IC are much more invariant to level changes than neurons in the LSO. Granted even in the IC most neurons on average are still affected by changes in overall sound level but much less so than in the LSO. Taken together what these data do appear to support is a hypothesis that some form of level invariance for ILD coding begins to emerge in some cells at the level of the IC and that some aspect of the neural circuitry from the LSO to the IC must provide the explanation. Thus the proportion of neurons in the IC that are level tolerant is greater than that in the LSO (Park et al. 2004). Several additional studies have reported level-invariant ILD coding in IC neurons (Aitkin et al. 1984; Grothe et al. 1996), although the goals of those studies were not to investigate level invariance directly. In the spirit of the “lower envelope hypothesis,” (Parker and Newsome 1998) where only those neurons with the best acuity or sensitivity are posited to contribute to perception, it may be that the responses of the most level-tolerant IC neurons produce the level-tolerant psychophysical output. A population coding model of ILD coding by Park et al. (2004) based on the empirical neural responses demonstrated that the ensemble of IC neurons were more invariant to level changes than the ensemble of LSO neurons.

One potential limitation of all of the ILD-coding studies cited in the preceding text is that the neurons were studied only with pure tone stimuli at each neuron’s CF. Such studies do not consider how non-CF neurons contribute to the encoding of ILDs (see Tsuchitani and Boudreau 1969). Moreover, our roving-level simulation procedure assumes that there was no short-term adaptation or plasticity in the responses of LSO neurons to changing ILDs and/or overall stimulus levels given the long intertrial intervals of 500 ms used here (Park et al. 2008). In support of this assumption, Finlayson and Adam (1997) showed that there was no short-term adaptation in LSO responses provided that interstimulus intervals exceeded 100 ms. Therefore our simulations were expected to capture the real behavior of the neurons without the confound of short-term adaptation. However, ILD coding has been recently shown to be dynamic due to retrograde signaling based on postsynaptic activity (Magnusson et al. 2008). The implications of this for ILD coding are not fully understood. The analysis technique used here assumed that the distributions of response rates recorded during fixed-intensity blocks would be the same as those measured in an actual experiment where the intensities of the stimuli to the two ears were randomly changed (roved). As such, our analysis technique may not preclude longer-term forms of adaptation, such as those that have been recently reported in the inferior colliculus (Dean et al. 2005) and auditory nerve (Wen et al. 2009).

Implications for the neural encoding of ILDs

Prior experiments in our laboratory showed that in cats the range of pedestal ILDs corresponding to the best ILD discrimination thresholds encoded by the population of LSO cells spans a wide range from ~18 to +22 dB, which is approxi-
imately the same range of ILDs spanned by the half-maximal ILD (Tollin et al. 2008). Maximal acoustical ILDs also spans approximately ±25 dB for frequencies <32 kHz in the cat (Tollin and Koka 2009). If each LSO nucleus possesses the capacity to encode stimulus locations in both hemi-fields, what teleological purpose might be served by having bilateral LSOS? We suggest that the differential connections from bilateral LSO to the DNLL and IC allow for disambiguation of small ILD signals from larger fluctuations in stimulus level encountered in the natural environment. Our model generates a testable prediction: lesion of unilateral LSO nucleus would be expected to cause adverse consequences for robust encoding of ILDs in the contralateral hemi-field (Litovsky et al. 2002). The basis for this prediction is that both LSO nuclei provide crucial input to the subtraction model; thus destruction of unilateral LSO impacts ILD processing at both IC. There is some evidence in support of this hypothesis from the experiments of Kavanagh and Kelly (1992), who measured sound localization performance in animals after lesion of the LSO unilaterally and found localization impairment in both left and right lateral fields.

Comparisons to other computational models of stimulus invariance in the auditory and other sensory systems

To investigate how level invariance might emerge in the circuitry from the LSO to the IC, we proposed a model that was motivated by some of the known connections between the LSO and the IC. The model demonstrates that invariance in ILD sensitivity can emerge in this circuitry. Our model is comparable to the opponent-process model of Stecker et al. (2005) in which they postulated that sound-source locations are represented by differences in the activity of two broadly tuned channels in the auditory cortex formed by contra- and ipsilateral sound source preferring neurons. Similarly, the interaural time difference coding strategy hypothesized by McAlpine and colleagues (Brand et al. 2002; Harper and McAlpine 2004; McAlpine et al. 2001) follows a similar rubric. All of these models of the encoding of the cues to source location can be traced back to early models and explanations by von Békésy (1930) and van Bergeijk (1962) that described coding via the suppression field. The suppression field is generally more broadly tuned to the stimulus than the stimulation field, and one way to construct it is to pool over the simulation field responses of many neurons that have a wide range of tuning characteristics (Carandini et al. 1997; Heeger 1992). In effect, a neural response is “judged” relative to that of its peers, hence the term normalization. A key idea is that the suppression field encompasses the responses of a large population and therefore reflects the common stimulus features in the input. Normalizing by this quantity leaves the component of the response that is invariant with respect to the “common bias.”

Our subtraction model of ILD coding analogously removes the common bias. Notably, however, the mathematical operation is a subtraction rather than a division as in the normalization model (although we note here that division can be converted to subtraction if the logarithm of the quotient is computed). What is the relationship between these two models? In constructing the subtraction model, the pairing of the model LSO and its anti-neuron follows a precise rule: the rate-ILD function of the anti-neuron is mirror symmetric with respect to an axis of pedestal ILD, which is the offset used to calculate $T_{\text{offset}}$. Taking the difference between the two rate-ILD functions then introduces a steepest slope at that very point (see Fig. 5). In short, the subtraction model as implemented here relies on the precise pairing of the model LSO neuron and its counterpart. In contrast, the suppression field of the normalization model is pooled over a large number of nonspecific responses. The normalization model requires no specific pairing rules at the cost of additional wiring. In practice, this latter strategy may be implemented in the auditory system. For example, LSO neurons (and/or DNLL) with differing sensitivity to pedestal ILD (e.g., the ILD corresponding to half-maximum discharge rate) may interact in the subtraction model ensuring a population of neurons at the level of the IC or higher that produce level-invariant ILD sensitivity over a wide range of pedestal ILDs. Moreover, there are known short-term adaptation effects in ILD coding by LSO neurons that may also play a role in normalization (Finlayson and Adam 1997; Park et al. 2008). Which computational strategy is adopted by these higher-order neurons and deeper insights into the relationship between the subtraction and division normalization models in regards to auditory processing are subjects for additional study.

APPENDIX

We will now derive Eq. 1. For simplicity, we will first show details assuming roving between two fixed stimulus intensities, then state the generalized case of $N$. 

J Neurophysiol • VOL 103 • FEBRUARY 2010 • www.jn.org
Given two random variables $X_1$ and $X_2$ with means $E[X_1], E[X_2]$ and variance $\text{Var}[X_1], \text{Var}[X_2]$ respectively, construct a new variable $Y$ which is randomly assigned with probability $p$ to $X_1$, and with probability $(1 - p)$ to $X_2$.

It follows that $E[Y] = p E[X_1] + (1 - p) E[X_2]$. \hfill (A1)

By definition, $\text{Var}[Y] = E[Y^2] - (E[Y])^2$. Furthermore, \hfill (A2)

$$E[Y^2] = p E[X_1^2] + (1 - p) E[X_2^2] = p (\text{Var}[X_1] + (E[X_1])^2) + (1 - p) (\text{Var}[X_2^2] + (E[X_2])^2).$$

Combining Eqs. A1 and A3, after collecting terms, we have

$$\text{Var}[Y] = p \text{Var}[X_1] + (1 - p) \text{Var}[X_2] + (E[X_1])^2 (1 - p)$$

Extrapolating from Eq. A4, it can be shown that for $N$ variables $X_1, X_2, \ldots, X_N$, each selected with probability $p_1, p_2, \ldots, p_N$

$$\text{Var}[Y] = \sum p_i \text{Var}[X_i] + \sum (E[X_i])^2 (1 - p_i) - \sum E[X_i] E[X_j] p_i p_j \hfill (A5)$$

where the first two terms are summed over $i = 1$ to $N$, and the last term summed over all combination of $i$ and $j$ where $i \neq j$.

Assume all $p_i$ are equal to $1/N$, Eq. A5 becomes

$$\text{Var}[Y] = 1/N \sum \text{Var}[X_i] + (N - 1)/N^2 \sum (E[X_i])^2 - 1/N^2 \sum E[X_i] E[X_j].$$

which, after collecting terms gives

$$\text{Var}[Y] = 1/N \sum \text{Var}[X_i] + 1/N \sum (E[X_i])^2 - 1/N^2 \sum (E[X_i])^2.$$


