Mechanisms Underlying the Sensitivity of Neurons in the Lateral Superior Olive to Interaural Intensity Differences

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Irvine, D.R.F., V. N. Park, and L. McCormick. Mechanisms underlying the sensitivity of neurons in the lateral superior olive to interaural intensity differences. J Neurophysiol 86: 2647–2666, 2001. The initial processing of interaural intensity differences (IIDs), the major cue to the azimuthal location of high-frequency sounds in mammals, is carried out by neurons in the lateral superior olivary nucleus (LSO) that receive excitatory input from the ipsilateral ear and inhibitory input from the contralateral ear (IE neurons). The “latency” hypothesis asserts that it is the effects of intensity differences on the latency, and hence the relative timing, of the synaptic inputs to these neurons that is the basis of their sensitivity to IIDs, while other models assign the major role to changes in the relative amplitude of the inputs. To test the latency hypothesis and to determine the contributions of changes in the relative timing and amplitude of synaptic inputs to the IID sensitivity of LSO neurons, a method was developed of generating sets of stimuli that produced either the same changes in the relative timing of inputs without any change in their amplitude (equivalent interaural time difference stimuli) or the same differences in amplitude without any difference in timing (delay-cancelled IID stimuli) as a given range of IIDs. Data were obtained from a sample of IE neurons in the LSO of anesthetized rats using these stimulus paradigms and click and tone-burst stimuli. For click stimuli, the IID sensitivity of a small proportion of neurons was explained entirely by sensitivity to differences in input timing, but the sensitivity of most neurons reflected either sensitivity to the relative amplitude of inputs or to the joint operation of both factors. In neurons whose sensitivity was tested at a number of different absolute sound pressure levels (SPLs), the relative contributions of the two factors tended to differ at different SPLs. The IID sensitivity of onset responses to tone stimuli could be classified into the same three categories but was explained for a larger proportion of neurons by sensitivity to differences in input timing. The IID sensitivity of the late response component of neurons with sustained responses to tones in all cases reflected sensitivity to the relative amplitude of the inputs. The results confirm the contribution of changes in latency produced by intensity changes to the IID sensitivity of the onset responses of many IE neurons in LSO but require rejection of the strong form of the latency hypothesis, which asserts that this factor alone accounts for such sensitivity.

INTRODUCTION

Differences in the sound pressure level (SPL) at the two ears, commonly termed interaural intensity differences (IIDs), are, for mammals, the major cue to the azimuthal location of high-frequency sounds. The initial processing of this cue is carried out by neurons in the lateral division of the superior olivary complex (LSO) that receive inhibitory (I) input from the contralateral ear and excitatory (E) input from the ipsilateral ear (IE neurons). Although the responses to IIDs of these LSO neurons, and of neurons receiving contralateral excitatory and ipsilateral inhibitory (EI) input at this and other levels of the auditory pathway, have been described in numerous studies (see e.g., Boudreau and Tsuchitani 1970; Clarey et al. 1992; Irvine 1992 for reviews), the mechanisms underlying this sensitivity remain uncertain.

In vivo intracellular studies of IE neurons in the LSO of the chinchilla (Finlayson and Caspary 1989) have revealed contralaterally evoked inhibitory and ipsilaterally evoked excitatory postsynaptic potentials (IPSPs and EPSPs) of similar time course in response to short tone bursts. In studies of LSO neurons in slice preparations, it has been shown that variation in the intensity of electrical stimulation of fiber bundles afferent to the LSO affects both the amplitude and the latency of EPSPs and IPSPs and that the response of the neurons is influenced by both the timing and the amplitude of these synaptic inputs (Sanes 1990; Wu and Kelly 1992). Because changes in the intensity of the acoustic stimulus at a given ear result in changes in both the latency and the magnitude (the number of active neurons and the spike rate in individual neurons) of the response evoked in the auditory nerve (AN) and at higher levels, IIDs would be expected to result in changes in both the relative timing and the relative amplitude (because of spatial and temporal summation) of the excitatory and inhibitory inputs to a given LSO neuron. These changes are illustrated schematically in Fig. 1, top (labeled “IID”). The inhibitory and excitatory inputs to the neuron at zero IID are shown here as being of identical amplitude and duration, and, as occurring at exactly the same time, a situation which would rarely, if ever, be the case in reality. This assumption has been made for clarity in the presentation of the analysis of input variations and of the procedures based on this analysis, but neither the analysis nor the procedures depend on its being the case. For reasons that will be made clear in the following text, IIDs have been produced here by holding the intensity at the inhibitory contralateral ear constant and varying the intensity at the excitatory ipsilateral ear rather than by other more conventional methods (Irvine 1987).

When the intensity at the ipsilateral ear is greater (negative IIDs by the convention adopted here), the excitatory input is of
larger amplitude and occurs earlier in time. Conversely, at positive IIDs, the excitatory input is smaller and occurs later in time. Although IIDs almost certainly involve changes in both the relative timing and amplitude of synaptic inputs, the contributions of these changes to the IID sensitivity exhibited by IE neurons in LSO (or by IE and EI neurons in other structures) in vivo remains uncertain. A dominant role of the amplitudes of excitatory and inhibitory inputs was implicitly assumed by Goldberg and Brown (1969) in their discussion of the IID sensitivity of EI neurons in the medial superior olivary complex (MSO), and subsequent models of the IID sensitivity of LSO neurons (Colburn and Moss 1981; Johnson et al. 1990) and of the coding of IIDs by populations of SOC neurons (Reed and Blum 1990) have been cast in terms of the effects of intensity on input spike rates (see Colburn 1996 for review).

In contrast, the “latency” hypothesis, originally proposed by Jeffress (1948), contends that sensitivity to the differences in the timing of inputs that are produced by the effects of intensity on latency is the fundamental mechanism underlying IID sensitivity. Jeffress’s (1948) original statement of this hypothesis was made almost in passing, and the scope of the hypothesis has varied in different formulations of it. It will be convenient to distinguish between “strong” and “weak” forms of the hypothesis. The strong form of the hypothesis states that IID sensitivity depends solely on sensitivity to differences in the timing of inputs, i.e., that IIDs are converted into “neural time differences” (e.g., Deatherage and Hirsh 1959). The weak form of the hypothesis asserts merely that such neural time differences contribute to IID sensitivity.

As discussed by Irvine et al. (1995), the fact that IE neurons in LSO (and EI neurons at higher centers) are often sensitive to interaural time differences (ITDs) that exceed those occurring naturally but are of comparable magnitude to the changes in latency produced by intensity changes, has provided indirect support for the latency hypothesis (e.g., Caird and Klinke 1983; Park et al. 1996; Pollak 1988; Yin et al. 1985). Yin et al. (1985) provided support for the strong form of the latency hypothesis by demonstrating that the sensitivity to IIDs of EI neurons in the deep layers of the superior colliculus in the cat could be accounted for by a qualitative model in terms of the effects of intensity on latency and of a coincidence detection mechanism. Recently, Park and his colleagues (Park 1998; Park et al. 1996, 1997) have presented evidence on the effects of ITDs on the IID sensitivity of neurons in the LSO and inferior colliculus (IC) of the Mexican free-tailed bat. The data obtained in these studies were compatible with a model in which IIDs produced changes in both the timing and the amplitude of synaptic inputs, and the timing changes helped to shape IID sensitivity functions (i.e., they provided support for the weak form of the hypothesis).

Despite this support for the contribution of both factors, the extent to which the actual differences in the timing and amplitude of inputs associated with a particular range of IIDs contribute to sensitivity to those IIDs has not been determined. One way of evaluating empirically the relative importance of the two factors would be to compare, at each of a range of IIDs, the effects of the combined changes in amplitude and timing with the effects of the identical changes in each parameter in isolation. A means of doing this in principle is illustrated schematically in Fig. 1. In the middle section of this figure, differences in the relative timing of the two inputs that correspond to those in the IID condition have been produced, without any change in the amplitude of the inputs, by introducing interaural time differences (ITDs). This has been called the “equivalent ITD” condition because each ITD tested is “equivalent” to a particular IID in the sense that it produces

FIG. 1. Schematic illustration of stimulus paradigms used to investigate contributions of changes in amplitude and timing of inputs to interaural intensity difference (IID) sensitivity of lateral superior olivary (LSO) neurons. Details in text.
exactly the same changes in the relative timing of inputs to the LSO neuron without any variation in the amplitude of the inputs.

A procedure for examining the effects of the amplitude of the inputs in isolation is illustrated in Fig. 1, bottom. Here the original IIDs have been introduced in conjunction with ITDs that are equal in magnitude but opposite in direction to the equivalent ITDs. In this condition, the differences in the amplitude of the inputs are the same as in the standard IID condition, but the changes in the relative timing of inputs produced by the IIDs are cancelled. This condition has therefore been termed the “delay-cancelled IID” condition. It should be clear that the use of these two paradigms to examine the effects of changes in the relative timing and amplitude of inputs does not depend on the assumption that the differences are zero at zero IID (i.e., Fig. 1 could be redrawn with any combination of amplitude and timing differences in the IID condition appropriately matched in the other 2 conditions).

Application of these procedures depends on being able to determine the equivalent ITDs (ITD_e), i.e., the range of ITDs that is equivalent to, in the sense that it produces the same changes in the relative timing of inputs as, a given range of IIDs. Irvine et al. (1995) developed a procedure for determining ITD_e in a study of the IID sensitivity of neurons in the inferior colliculus (IC) of the rat. This procedure (see METHODS) depends on the assumption that the neuron from which recordings are made either is the initial site of convergence of excitatory and inhibitory inputs from the two ears or directly reflects the properties of a neuron that is the original site of convergence, an assumption that cannot be satisfied for most neurons in IC (see Irvine et al. 1995 for discussion). Available anatomical evidence supports this assumption for LSO neurons, however, and the aim of this study was to use the procedure developed by Irvine et al. to estimate ITD_e, and the stimulus paradigms illustrated in Fig. 1 to determine the contribution of changes in the amplitude and timing of inputs to the IID sensitivity of IE neurons in the LSO.

Data will be presented for responses to IIDs in both click and tone-burst stimuli. Heil and his colleagues (Biermann and Heil 2000; Heil 1997a,b, 1998; Heil and Irvine 1997) have presented compelling evidence that the latency and amplitude of tone onset responses, although commonly plotted as a function of the steady-state SPL (i.e., intensity) of the stimulus, are in fact determined not by this parameter but by dynamic features of the stimulus onset. In accordance with this view, Heil (1998) demonstrated that the sensitivity of neurons in IC of the rat to IIDs in tonal stimuli is more correctly considered as sensitivity to interaural differences in these dynamic features of the stimulus onset. In the experiments to be reported here, the rise time of tonal stimuli was constant in the two ears, and the dynamic properties of stimulus onset therefore covaried with steady state SPL. It is therefore convenient to characterize the stimuli in conventional steady-state terms (i.e., in terms of intensity and IIDs). A preliminary account of some of the click data has appeared (Irvine et al. 1998).

**Methods**

**Animal preparation**

Experiments were carried out on adult male Long-Evans rats (weight range: 226–460 g). Most surgical and stimulation procedures were as reported previously (Irvine et al. 1995) and will be described only briefly except for procedures specific to these experiments. Each animal was anesthetized with pentobarbital sodium (40 mg/kg ip) and given an injection of atropine sulfate (60 μg im) to reduce mucous secretions. Anesthesia was maintained during surgery and recording by additional intraperitoneal doses of pentobarbital sodium supplemented by injections of xylazine hydrochloride (1 mg im). Heart rate and rectal temperature were monitored continuously, and the latter was maintained at 38° by means of a thermostatically controlled heating pad.

The rat’s head was supported by a steel bar, the flattened end of which formed an attachment plate that was fixed to the skull with small screws and dental acrylic. The pinnae were removed, leaving metal stubs through which the tympani could be examined, and into which sound delivery speculae were fitted. The caudal surface of the skull was cleared to expose the foramen magnum, and the latter was enlarged laterally and dorsally. Part of the cerebellum was then aspirated to expose the dorsal surface of the brain stem.

**Stimulation and recording procedures**

The animal was located in a sound-attenuated, electrically shielded recording chamber. Tone- and noise-burst (50-ms duration; 2-ms linear rise-fall times) and click (100-μs rectangular pulses) waveforms were synthesized digitally (Tucker Davis Technologies) and transduced by Stax (SRS MK3) speakers in specially constructed couplers (Sokolich 1981), which terminated in speculae that fitted snugly into the meatal stubs. Calibration procedures have been described previously (Irvine et al. 1995).

Auditory brain stem evoked responses (ABERs) were recorded by means of a stainless-steel hook electrode placed over the ventral edge of the foramen magnum. Only those animals for which the click thresholds for the two ears were in the normal range and within 6 dB of each other were used for LSO recordings. For single-unit recording, the animal’s head was tilted nose down at 20° from the horizontal, and glass-insulated tungsten microelectrodes (impedance at 1 kHz of 2.8–5.0 MΩ) or, in a few cases, KCl-filled micropipettes (impedance of 3–10 MΩ), were advanced into the brain stem at a caudal-to-rostral angle of 54° to the horizontal by means of a stepper-motor microdrive. To facilitate locating the LSO, an initial series of penetrations was made along a rostrocaudal axis 1 mm lateral to the midline to locate and define the rostral and caudal limits of the medial nucleus of the trapezoid body (MNTB), which was usually readily identified by the exclusively contralaterally driven activity and, in many cases, the presence of prepotentials in the action potential waveforms. Electrode penetrations directed to LSO were then made at a site ~1 mm lateral to the midpoint of the rostrocaudal extent of MNTB, if neuronal activity characteristic of LSO in response to noise burst stimuli with a large IID favoring the ipsilateral ear was not encountered in this initial penetration, subsequent penetrations were made at locations in a 100-μm matrix around this site. After the first successful penetration, subsequent penetrations were made after smaller (~20 μm) movements in directions based on the characteristic frequency (CF; frequency at which threshold was lowest) of the neurons isolated in the previous penetration. Extracellularly recorded neural activity was conventionally amplified and displayed. The action potentials of well-isolated neurons were passed through a Schmitt trigger, the output pulses from which were sent to the computer and timed with 10-μs precision. Response histograms, and spike count and latency measurements, were generated on-line, and stimulus and response event times were stored for off-line analysis.

For each neuron, responsiveness to clicks and pure tones was established, and the CF was determined using audio-visual criteria. For some cells that remained well isolated after the data described in the following section were obtained, a detailed quantitative frequency response area was also obtained by a procedure described elsewhere (Irvine et al. 1995). For some neurons responsive to tones, it was not
possible to obtain data on click IID sensitivity: some neurons with high CF were unresponsive to clicks or had such high click thresholds that their dynamic range was insufficient to allow collection of the required IID-sensitivity data (see following text), while for some neurons that were responsive to clicks, the amplitude of the click evoked potentials (EPs) (which had a time course very similar to that of the single-neuron action potentials) was such that unequivocal isolation of the single neuron response could not be achieved.

Data-collection procedures and generation of IID and ITD sensitivity functions

For each neuron for which click responses permitted data collection, these data were obtained first, and the following detailed account of procedures describes that for click stimulation. Procedures for collection of tone data were identical except for some minor differences reported below. The first quantitative data obtained were detailed rate- and latency-intensity functions for monaural stimulation of the ipsilateral (excitatory) ear at SPLs ranging from below threshold to 95 or 100 dB in 5-dB steps. At each level, a peristimulus response histogram based on 100 stimulus presentations (rate: 3 Hz) was generated. On each presentation, the number of spikes occurring within a time window (from 2–3 to 10–15 ms post stimulus; selected to capture the response spikes at all SPLs tested) was counted, and the latency of the first spike occurring within the window was measured with 10-μs accuracy. The on-line analysis program returned values for the mean and SE of the spike count and latency measures. Rate- and latency-intensity functions obtained in this way for a representative neuron are shown in Fig. 2, A ("ipsilateral alone" function) and B, respectively. As illustrated by this neuron (Fig. 2, A and B), the security of discharge and the precision of timing of many LSO neurons were such that SEs at suprathreshold levels were too small to be plotted.

An IID sensitivity function was then obtained by holding the contralateral SPL constant and varying the ipsilateral SPL (i.e., by the method illustrated schematically in Fig. 1). The constant contralateral SPL (which will be termed the base intensity) was usually selected to be near the middle of the ipsilateral dynamic range (although the inhibition in some IE neurons was such that an SPL at 1 extreme of the dynamic range had to be used), and the ipsilateral intensity was varied in 5-dB steps to generate an IID range over which the neuron’s response was modulated from maximum to minimum. At each IID level, 100 stimuli were presented, and the mean number of spikes and first-spike latency in the count window were obtained. Thus, the function in Fig. 2A was generated by holding the contralateral intensity constant at 75 dB and varying ipsilateral intensity from 50 to 100 dB to generate an IID range from +25 to −25 dB. Over this range, the response varied from zero (total inhibition; at IIDs from +10 to +25 dB) to maximum (0.8–0.9 spikes per stimulus and little or no inhibition of the ipsilateral monaural response; at −20 dB).

The rationale for using this unconventional procedure for generating IIDs relates to the methods employed to derive the estimates of the ITD50 that are required for measurement of ITDc and delay-cancelling IID (IIDc) sensitivity functions. In the absence of spontaneous activity, extracellular recording provides no information about the latency of the inhibitory contralateral input to a given IE neuron in LSO. However, the fact that the contralateral intensity is held constant means that the latency (and thus the timing) of the inhibitory input to the neuron does not change as IID is varied. In contrast, the changes in SPL of the ipsilateral stimulus will result in changes in the timing of the excitatory input, and these changes will be reflected in the latency-intensity function for monaural stimulation of that ear. In Fig. 2B, the intensity axis for the latency function has been aligned with the ipsilateral intensity axis for the IID function in Fig. 2A so that the effects of the changes in intensity used to generate the IIDs can be readily appreciated. As the ipsilateral SPL is reduced from 75 to 60 dB to generate the +15-dB IID, the ipsilateral latency increases by 211 μs. Given the constant contralateral latency, this change in the relative timing of inputs is equivalent to that produced by delaying the ipsilateral stimulus by that amount. That is, the ITD that is “equivalent” to the +15-dB IID, in the sense that it produces the same change in the relative timing of inputs, is +211 μs (given the convention that...
ipsilateral delays are positive). Conversely, the decrease in latency as the ipsilateral stimulus is increased from 75 to 90 dB to generate the −15-dB IID is 86 μs. This change in relative timing is equivalent to that produced by having the ipsilateral stimulus lead the contralateral stimulus by that amount, and the equivalent ITD is therefore 86 μs. It must be emphasized that the equivalent changes here are changes in the relative timing of inputs; there is no assumption that any particular neural time difference is associated with either zero IID or zero ITD.

These and the other ITDe values associated with the range of specific IIDs tested in the case of this cell are shown in Fig. 2B: bottom abscissa. For each neuron, the ITDs equivalent to the particular range of IIDs tested were calculated on-line by the computer, and an ITD sensitivity function incorporating these values was obtained with the SPL in each ear at the base intensity used for the IID sensitivity function. In most cases, responses were also measured at a range of additional ITDs to define the full range of ITD sensitivity. Thus for the ITD sensitivity function presented in Fig. 3B, the densely spaced ITD measures from +562 to −91 μs represent the calculated ITDe values, while the additional values were added to define the limits of sensitivity. Following collection of the ITDe data, the IIDac data (in which each of the original IIDs was presented together with the ITD that was equal in amplitude but opposite in sign to its equivalent ITD; see Fig. 1) were collected. At each ITD and IIDac level, 100 stimuli were presented and the normal response measures were obtained.

If the neuron remained well isolated after the collection of a full data set for click stimulation at the base intensity, additional data were obtained. In some cases, the additional data comprised click data at one or more other base intensities to provide information on the contributions of timing and amplitude differences to IID sensitivity at different points in the neuron’s dynamic range. In other cases, additional data were obtained using tonal stimuli at the neuron’s CF to allow comparison of click and tone responses. As noted in the preceding text, only tone data could be obtained for some neurons. For neurons with simple onset responses to tone-burst stimuli, the data collection procedures were identical to those described for clicks except that a slightly longer onset response window was needed in some cases. The derivation of ITDe values for tone responses is illustrated in Fig. 8, A and B. For neurons with sustained responses to tone bursts, latency and spike-count measurements were based on an onset window as for neurons with onset responses, but spike counts were also obtained for a late-response count window and for the total response (i.e., onset plus late response counts). Although it is a priori unlikely that the IID sensitivity at late (or steady-state) response components is determined by differences in onset latencies, it was considered desirable to establish this empirically. A small number of neurons remained well isolated for long enough (>3 h) for both click and tone data to be obtained at multiple base intensities.

In some of the early experiments, click latency-intensity functions were obtained for monaural contralateral neurons isolated in the preliminary MNTB penetrations, using the procedures described in the preceding text for LSO recording. As noted in DISCUSSION, these observations bear on the timing of the inhibitory input to LSO neurons.

Data analysis

Data for each neuron were analyzed individually, as the relative contributions of ITDe and IIDac were found to differ between neurons. Multiple regression analysis was first used to determine the extent to which the form of the IID sensitivity function was predicted by ITDe and IIDac sensitivity. Simple linear regression analysis for the regression of IID sensitivity on ITDe sensitivity yielded values for \( r^2 \) (the square of the Pearson correlation coefficient), \( b_{\text{ITDe}} \) (the regression coefficient), and \( b_c \) (the constant value in the linear regression equation). To test whether \( r^2 \) was significantly different from zero, an F test with degrees of freedom (df; 1, \( n - 2 \)) was conducted. If \( r^2 \) was not significant, no further analysis of the regression of IID on ITDe was conducted. A significant \( r^2 \) value indicates only that the IID values can be predicted from the ITDe values, and \( r^2 \) would be high if, for example, the curves were approximately parallel. If the latency hypothesis was correct, IID sensitivity would be accounted for totally by ITDe sensitivity, and the linear regression model \( \text{IID} = b_{\text{ITDe}} \text{ITDe} + b_c \) would have a regression coefficient (\( b_{\text{ITDe}} \)) of 1.0 and a constant (\( b_c \)) of zero. For those cells for which \( r^2 \) for ITDe was significant, the hypothesis of identity of the IID and ITDe sensitivity functions was tested using t-tests (df = \( n - 2 \)) of the hypotheses: \( b_{\text{ITDe}} = 1.0 \) and \( b_c = 0 \) (at \( \alpha = 0.05 \)).

Analysis of the linear regression of IID sensitivity on IIDac was carried out using the same methods. In cases where \( r^2 \) for the linear
regression of IID on IID_{dc} was significant, the t-tests were used to examine the hypotheses relating to the identity of the two sensitivity functions (viz. b_{IIDdc} = 1.0 and b_{C} = 0).

In those cases where \( r^2 \) was significant in both simple linear regression analyses, multiple linear regression analysis of IID on ITD_{e} and IID_{dc} was used to determine the proportion of the variance in IID sensitivity accounted for by each of the two factors. Comparison of \( R^2 \) (the square of the multiple correlation coefficient) with the \( r^2 \) values from the simple regression analyses revealed the added amount of variation in the IID sensitivity function accounted for by including both variables in the equation compared with including only one of the variables.

**Histology**

Successful electrode penetrations in each experiment were marked by electrolytic lesions at the (or one of the) recording sites and at one or more other known depths. In most experiments, a large number of closely spaced penetrations were made in the process of locating LSO neurons, and track damage made the location of lesions difficult or impossible. To partially obviate this problem, a fluorescent dye (Di) was used in some of the later experiments to mark successful electrode penetrations following the methods described by Di Carlo et al. (1996). After a successful penetration and making the lesions described in the preceding text, the electrode was withdrawn, and its tip was passed through a small wire loop containing a drop of Di solution while maintaining the coordinates and orientation of the penetration. After allowing a few minutes for the dye coating to dry, the electrode was lowered back into the brain to the depth of the recording site and then withdrawn.

On completion of recording, the rat was killed with an overdose of anesthetic and decapitated, and the head was stored in 10% formal saline for \( \sim 6 \) days. A block containing the brain stem was then removed and stored in fixative for a further 6 days after which 50-\( \mu \)m sections were cut in the sagittal plane on a freezing microtome. All sections in the early experiments, and alternate sections in the dye experiments, were stained for Nissl. These sections were viewed on a profile projector, and recording sites were identified on the basis of recorded depth measurements and locations of lesions. In those cases in which electrode penetrations

**FIG. 4.** A–C: functions for unit 95-68-2 [characteristic frequency (CF) = 6.0 kHz] for click stimuli at 70 dB base intensity. Conventions as in Fig. 3; see text for details.

**FIG. 5.** A–C: functions for unit 95-45-9 (CF = 19.3 kHz) for click stimuli at 60 dB base intensity. Conventions as in Fig. 3; see text for details.
were marked with DiI, alternate sections were processed according to the methods described by Di Carlo et al. (1996) and were viewed in a fluorescence microscope.

RESULTS

General characteristics of the sample

As detailed in METHODS, the need for a high degree of precision in the measurement of the latency-intensity function required that data could only be obtained from well isolated neurons, and the experimental aims required that isolation be maintained for long enough for a full set of functions (latency-intensity, IID, ITD<sub>e</sub> and IID<sub>dc</sub>) to be obtained at least one base SPL. Data were obtained for a total of 37 IE neurons isolated in or close to the borders of LSO. Click data were obtained at one or more base SPLs for 24 neurons, for 14 of which data were also obtained with tone-burst stimuli. Data for tone-burst stimuli only, at one or more base SPLs, were obtained for 13 neurons.

In those cases in which lesions could be located, they were within or close to the borders of LSO, and all DiI-marked penetrations were observed to enter LSO. These observations, together with the IE characteristics and similar short latencies of the neurons [click minimum latencies ranged from 3.29 to 4.15 ms (mean ± SD, 3.68 ± 0.23 ms) and tone minimum latencies for neurons with CF >5 kHz from 2.81 to 5.15 ms (3.88 ± 0.57)] indicate that all neurons were located either within LSO or close to its borders.

FIG. 6. A–E: combined IID, ITD<sub>e</sub> and IID<sub>dc</sub> functions for unit 96-25-1 (CF = 3.1 kHz) for click stimuli at different base intensities (indicated in the top left corner of each panel). Conventions as in Fig. 3C.
Responses to click stimuli

The nature of the data obtained for an individual neuron at a particular SPL is illustrated in Fig. 3 for the unit that was used to demonstrate the derivation of ITD_e values in Fig. 2. Figure 3A presents the IID-sensitivity function at 75 dB and the ipsilateral monaural intensity function (as previously shown in Fig. 2A). In Fig. 3B, the neuron’s response to ITDs over the range ±1.0 ms (incorporating the ITD_e range from +582 to −91 μs) is shown, and it is apparent that the neuron’s response was inhibited over a range from approximately +1.0 to −0.5 ms, with total response suppression over the range of contralateral leads from −100 to 600 μs. This U-shaped function is typical of those obtained with clicks (see also Figs. 4B and 5B). As argued by others (e.g., Joris and Yin 1995), such functions reflect the fact that the response is determined by the summation of the contralaterally evoked IPSP and the ipsilaterally evoked EPSP. At larger ITDs, the IPSP either leads (at positive ITDs exceeding 1.0 ms in this case) or lags (at negative ITDs exceeding −0.5 ms) the EPSP by an interval such that it has no effect on the probability of the threshold for spike initiation being attained, while at intermediate ITDs, the summation of the IPSP and EPSP is such as to reduce the probability of discharge. As elaborated in DISCUSSION, the shape and location of the U-shaped portion of the function provide information on the duration of the effective inhibitory input to the neuron and on its timing relative to the excitatory input.

In Fig. 3C, the IID, ITD_e, and IID_dc functions are plotted on corresponding axes. Note that the stimulus conditions for the zero IID, ITD_e, and IID_dc points are identical so that the three measures at this point provide an index of response stability over the time taken to obtain the three functions. Inspection of Fig. 3C indicates that there is a close correspondence between the IID and ITD_e functions, whereas the IID_dc function shows little or no response modulation. At this base intensity, it would therefore appear that the IID sensitivity of this neuron is explicable entirely in terms of sensitivity to the differences in the timing of inputs produced by the IIDs, with differences in the amplitude of inputs making little or no contribution. This was confirmed by the regression analyses. Analysis of the linear regression of IID on ITD_e yielded \( r^2 = 0.981 \) (P < 0.001) and the equation \( \text{IID} = 0.988 \times \text{ITD}_e - 0.003 \). Neither the regression coefficient nor the constant were significantly different from the hypothesized values of 1.0 and 0, respectively, indicating identity of the IID and ITD_e functions. Although analysis of the regression of IID on IID_dc yielded a significant \( r^2 \) value of 0.443 (P < 0.05), multiple regression analysis yielded an \( R^2 \) value of 0.981, indicating that the inclusion of IID_dc into the multiple regression equation resulted in no increase in the proportion of variation in the IID function accounted for by ITD_e alone.

This pattern of effects was relatively uncommon, however, and in the majority of neurons, IID sensitivity appeared to be attributable either to differences in the amplitude of inputs alone or to the combination of differences in both the timing and the amplitude of inputs. Figure 4 presents data for a neuron for which there is a close correspondence between the IID and IID_dc functions, while the ITD_e function shows a very different (almost mirror-reversed) pattern of response modulation. This neuron’s IID sensitivity therefore appears to be dominated by the effects of the amplitude of the inputs, which are sufficiently powerful to overwhelm an effect of IID-produced differences in the timing of inputs that alone would have produced a different (almost mirror symmetric) function. In this case, linear regression analysis yielded a significant \( r^2 \) value for IID_dc \( (r^2 = 0.956; P < 0.001) \) but not for ITD_e \( (r^2 = 0.142; P > 0.05) \), and the values of the regression coefficient and constant in the linear regression equation (IID = 0.954 IID_dc − 0.12) did not differ from 1.0 and 0, respectively, indicating identity of the functions.

In contrast, both the ITD_e and IID_dc functions for the neuron for which data are presented in Fig. 5 are similar in shape to, but nevertheless differ substantially from, the IID function. This pattern of results suggests that both factors must contribute to the neuron’s IID sensitivity. Although this conclusion is supported by the results of the regression analyses, this case also illustrates some limitations of this analysis. Simple linear regression analyses yielded significant \( r^2 \) values of 0.894 and 0.800 for ITD_e and IID_dc respectively. The regression coefficient (1.078) and constant (0.102) for IID_dc did not differ significantly from 1.0 and 0, respectively, whereas for ITD_e the regression coefficient (1.781) was significantly different from 1.0 but the constant (0.033) did not differ significantly from 0. Although this analysis indicates that IID is perfectly predicted by IID_dc, the multiple regression analysis yielded an \( R^2 \) value of 0.92, indicating that the inclusion of ITD_e in the multiple regression equation accounted for an additional 12% of the variation in the IID sensitivity function, supporting the conclusion that both factors contribute in this case.

The discrepancy between the results of these two analyses suggests that the test on the linear regression equation might not have sufficient power to detect meaningful differences in those cases where IID and either ITD_e or IID_dc values are identical at a number of points (viz., those producing total inhibition). A further consideration complicating interpretation of those cases where both factors appear to contribute is that the stimulus paradigms used to generate the data do not allow

<table>
<thead>
<tr>
<th>ITD_e</th>
<th>IID_dc</th>
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<tr>
<td>Only</td>
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<td>3 (3)</td>
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<td>7 (13)</td>
<td>8 (9)</td>
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<tr>
<td>ITD_e and IID_dc</td>
<td>Unclassified</td>
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<td>5 (6)</td>
<td>2 (2)</td>
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Entries are the number of neurons for which interaural intensity difference (IID) sensitivity at one or more base intensities was classified as being determined by equivalent interaural time difference (ITD_e), delay-cancelled IID (IID_dc), or by both factors. The criteria for classification are described in the text. Note that the total number of neurons in the table exceeds the number of neurons for which click data were obtained, because a given neuron for which data were obtained at more than one base intensity could contribute to more than one category. Values in parentheses are the number of neuron-base intensity combinations in each category.
the nature of the interactions between the two factors to be analyzed. ITD, and IID, cannot be introduced in isolation, but each must be varied in the presence of some value of the other variable. In this paradigm, ITD is varied in the presence of a fixed amplitude difference, and IID, in the presence of a fixed time difference (in each case that associated with 0 IID), and the effects of particular combinations of the two variables therefore cannot be determined from the data. Thus in Fig. 5, the ITD, and IID, values associated with IIDs in the range −20 to −35 dB each appear to produce more inhibition individually than they do together (i.e., in the IID function). This result reflects the fact that each is varied in conjunction with a specific value of the other (that associated with 0 IID) that produces total inhibition.

The illustrative data presented in Figs. 3–5 suggest that LSO neurons might be classifiable into three groups in which IID sensitivity is explicable in terms of amplitude differences alone, time differences alone, or the combined operation of the two factors. However, these data were obtained at a single base intensity for each neuron, and an alternative possibility is that for a given neuron the relative contributions of the two factors varies as a function of base intensity. Click data were obtained at two or more base intensities for five neurons in an attempt to obtain data bearing on this issue. The combined functions for the most de-

FIG. 7. Tone response data for a neuron (95-44-8) with a simple onset (O) response pattern (CF = 6.9 kHz; base intensity of 55 dB). A: IID and monaural ipsilateral intensity function. B: latency function and derivation of ITD functions. C: ITD function. D: combined IID, ITD, and IID functions. Conventions as in Figs. 2 and 3. Regression analyses yielded a significant \( r^2 \) value (0.993; \( P < 0.001 \)) for regression of IID on ITD, and a nonsignificant \( r^2 \) value (0.003; \( P > 0.05 \)) for regression on IID, \( r^2 \). The regression coefficient of 1.09 for the linear regression equation for ITD was significantly different from 1.0; the constant was not significantly different from 0.
tailed case, tested at five base intensities, are presented in Fig. 6. At 70 and 80 dB (Fig. 6, C and D), there is a perfect or near-perfect correspondence between the IID and IID\(_{dc}\) functions, indicating that at these base intensities IID sensitivity is wholly or largely accounted for by amplitude differences. At other base intensities, most notably 50 dB (Fig. 6A), however, the correspondence between IID and IID\(_{dc}\) functions is less close, and it appears that although amplitude differences dominate, both factors contribute to IID sensitivity. In this case, regression analyses indicated that IID sensitivity could be accounted for solely in terms of IID\(_{dc}\) sensitivity at each SPL tested. At each level, \(r^2\) was significant only for IID\(_{dc}\), and the regression coefficient and constant for the linear regression of IID on IID\(_{dc}\) were not significantly different from 1.0 and 0, respectively. Again, it seems likely that this test did not have the power to detect what appear to be meaningful differences between the two functions over the −5 to −25 dB IID range.

**Fig. 8.** Tone response data for 2 neurons with pure onset (O1) responses, A–C: data for unit 97-6-3 (CF = 3.8 kHz; base intensity, 75 dB); D–F: data for unit 96-44-3 (CF = 9.5 kHz; base intensity, 55 dB). Conventions as in Fig. 3. Regression analyses for unit 97-6-3 yielded a significant \(r^2\) value for IID\(_{dc}\) (0.961; \(P\), 0.001) but not for ITD\(_e\), and the regression coefficient (1.014) and constant (−0.026) in the regression equation for IID\(_{dc}\) did not differ from 1.0 and 0, respectively. Regression analysis for unit 96-44-3 yielded a significant \(r^2\) value (0.993; \(P\), 0.001) for ITD\(_e\); the regression coefficient of 1.873 was significantly different from 1.0 (\(P < 0.001\)) and the constant (0.002) was not significantly different from 0. Regression analysis could not be completed for the regression of IID on IID\(_{dc}\) because all IID\(_{dc}\) values were 0.
range at 50-dB base intensity. The other four units for which data were obtained at multiple base intensities showed similar effects: in two there was a close correspondence between IID and IIDdc functions at each of four levels tested; in the other two, both factors appeared to contribute at each of the levels (2 in 1 case, 4 in the other) tested. Unfortunately data were not obtained at multiple levels for any of the small number of neurons (see following text) for which the results at a single level indicated close correspondence between IID and ITD functions.

Data for all neurons for which click data were obtained at

**FIG. 9.** IID, ITD, and IIDdc functions for onset, late, and total (i.e., onset + late) response components for 3 neurons with sustained responses to tones. Conventions as in Fig. 3C. In each case, the count window used to define the response component is specified in the top left corner. A–C: data for unit 95-45-4 (CF = 38.0 kHz; base intensity, 50 dB; transient chopper response pattern). Regression analyses for the onset component yielded a significant $r^2$ value for ITD (0.992), and a regression coefficient (1.023) and constant (0.003) that were not significantly different from 1.0 and 0, respectively. Although the $r^2$ value for IIDdc (0.443) was significant, the $R^2$ value indicated that inclusion of IIDdc in the multiple regression equation accounted for <1% additional variation in the IID function. For the late component, $r^2$ was significant only for IIDdc (0.961), and the regression coefficient (0.572) was significantly different from 1.0. Inspection of the functions indicates that both variables contributed to IID sensitivity. For the total response, $r^2$ was significant for both variables (0.961 for ITD and 0.815 for IIDdc), although the regression coefficient and constant for the regression of IID on IIDdc did not differ significantly from 1.0 and 0, respectively, the fact that inclusion of ITD in the multiple regression equation accounted for an additional 18% of the variation in the IID function indicates that both variables contributed. D–F: data for unit 95-44-7 (CF = 11.5 kHz; base intensity, 60 dB; transient chopper response pattern). For each component regression analyses yielded a significant $r^2$ value only for IIDdc (0.937, 0.963, and 0.972 for onset, late, and total responses, respectively), and small but statistically significant departures of the regression coefficient from 1.0 and/or the constant from 0 indicated that IID sensitivity should be classified as predominantly attributable to IIDdc in each case. G and H: data for unit 95-61-3 (CF = 5.3 kHz; base intensity, 50 dB; on-late response pattern). Regression analyses of the onset response data yielded a significant $r^2$ value (0.977) only for ITD, but the fact that the regression coefficient was significantly different from 1.0 and inspection of the functions indicated that both variables contributed to IID sensitivity. For the late component, $r^2$ (0.837) was significant only for IIDdc, the regression coefficient and constant did not differ from 1.0 and 0, respectively, and IID sensitivity was therefore classified as attributable to IIDdc alone. For the total response, $r^2$ was significant for both variables (0.955 for ITD and 0.612 for IIDdc), and the regression coefficients in the linear regression equations for both variables were significantly different from 1.0, indicating that both contributed to IID sensitivity.
one or more base intensities are summarized in Table 1. A neuron’s IID sensitivity at a given base intensity was classified as reflecting sensitivity only to ITDe or IIDdc if all of the following criteria were satisfied: the \( r^2 \) value for that variable was significant, the regression coefficient and constant in the linear regression equation for that variable were not significantly different from 1.0 and 0, respectively, and either the \( r^2 \) value for the other variable was not significant or the \( R^2 \) value indicated that the inclusion of the other variable in the multiple regression equation did not add >10% to the amount of variation in IID sensitivity accounted for. For a number of neurons, IID sensitivity at a particular base intensity was classified as reflecting sensitivity predominantly to IIDdc because the criteria outlined in the preceding text were nearly but not completely satisfied (e.g., the coefficient or constant in the regression equation differed from 1.0 or 0, respectively, by a small but statistically significant amount). A neuron’s sensitivity at a given base intensity was classified as reflecting sensitivity to both ITDe and IIDdc if \( r^2 \) was significant for both variables and the \( R^2 \) value indicated that inclusion of the second variable in the multiple regression equation increased the amount of variation in IID explained by >10%, and/or if inspection of the data indicated (as was the case for the unit shown in Fig. 5) that the responses to variations in one variable were influenced by the fact that they were presented at a value of the other variable that resulted in total inhibition. The responses of two neurons could not be classified because of incomplete data in one case and the fact that the IID sensitivity function showed total response suppression at all intensities (such that regression analyses were impossible) in the other.

Table 1 indicates that IID sensitivity could be accounted for entirely by ITDe sensitivity for only a small number of neurons, whereas it was accounted for entirely or predominantly by IIDdc sensitivity for a much larger number of neurons at one or more base intensities. The numbers in brackets in Table 1 indicate the total number of observations in each category (viz., units \( \times \) number of base intensities examined), and the difference is even more marked here, reflecting the fact that data were obtained at multiple base intensities only for some of the neurons for which IIDdc was the dominant variable. With respect to those cases for which IID sensitivity was classified as being predominantly attributable to IIDdc or to the operation of both factors, it should be noted that the distinction between these two categories is arbitrary, and at least some of the units in either category might reasonably have been included in the other. Despite these qualifications, it is clear that, under the conditions of these experiments, the relative amplitude of inputs (as reflected in IIDdc sensitivity) makes a greater contribution to the click IID sensitivity of the majority of LSO neurons than does the relative timing of inputs (as reflected in ITDe sensitivity).

Of the neurons whose click IID sensitivity was classified as attributable only or predominantly to IIDdc sensitivity, only two were insensitive to ITDs (i.e., their response was not modulated by changes in ITD) over the range examined. The remainder, like the vast majority of neurons, were extremely sensitive to ITDs over the relevant range, with U-shaped functions of the type illustrated in Figs. 3B, 4B, and 5B. These figures also illustrate the fact that the major factor that determines the way in which sensitivity to timing differences contributes to click IID sensitivity is the precise location of the ITD values along the neuron’s ITD function at the relevant base intensity. For example, although the shapes of the ITD functions and the ranges of the ITD values are similar for units 95-72-1 (Fig. 3B) and 95-68-2 (Fig. 4B), those ranges lie on different parts of the function in the two cases.

### Responses to tone stimuli

Tone responses were obtained for 27 neurons, which exhibited diverse response patterns to 50-ms tone bursts. Sixteen neurons had onset response patterns with no evidence of sustained drive throughout the stimulus. For one of these neurons, the onset response histogram exhibited multiple regular peaks, and it could therefore be described as an onset chopper (OC), whereas for the others, the response comprised one or two spikes with no suggestion of regularity (O). Rhode and Greenberg (1992). Of the 11 neurons with sustained response patterns, 5 were classified as transient choppers (C\(_T\)), 4 had a strong onset response with a low level of sustained discharge (O\(_L\)), and 2 were approximately primary-like. For those with a clearly defined onset response component, the onset count window was set to capture the spikes in this component, but in those cases in which there was no clear division between onset and late components, the break between the two count windows was set at a standard value which was necessarily somewhat arbitrary.

Derivation of ITDe values for the tone responses of a representative neuron (with an O\(_T\) response pattern) are illustrated in Fig. 7, A and B, and illustrate an important difference between click and tone responses. Comparison of the latency function for this neuron and the click function in Fig. 2B reveals that tone latency, and consequently the range of ITDe values, varies over a wider range for the tone than for the click responses. This difference reflects both the greater dynamic range of the tone response and the contribution of the tone rise time to the variation of latency with SPL. Although these functions were obtained from different neurons, the difference illustrated by them is representative of that across the sample: the mean ± SE range of click ITDe values (879 ± 89.2 μs) was much smaller than that for tones (2,542.7 ± 258.1 μs).

The tone ITD function for this neuron (Fig. 7C) is sigmoidal,
FIG. 10. Tone response data at multiple base intensities for 2 units with onset response patterns. Conventions as for Fig. 3C.

A–C: data for unit 95-45-5 (CF = 30.0 kHz; O₁ response pattern). Regression analyses of the 45 dB data (Fig. 10A) yielded significant $r^2$ values for both variables (0.984 for ITDₑ and 0.953 for IIDₜₜ), and regression coefficients for both (1.37 and 4.72, respectively) that were significantly different from 1.0. This pattern of results and inspection of the functions indicates that both variables contributed to IID sensitivity. At both 55 and 60 dB, analyses yielded a significant $r^2$ value only for ITDₑ, but in each case inspection of the functions indicates that both variables influenced IID sensitivity. 

D–F: data for unit 95-68-2 (CF = 6.0 kHz; O₁ response pattern). At 30 dB (Fig. 10D), $r^2$ was significant for both variables (0.706 for ITDₑ and 0.751 for IIDₜₜ), the regression coefficients, although large (2.63 and 1.83, respectively) were not significantly different from 1.0, and the constants (0.105 and 0.187, respectively) were not significantly different from 0. This pattern of results, and inspection of the functions, indicates that sensitivity to IIDs is determined by both variables. At 40 dB, $r^2$ was also significant for both variables (0.99 for ITDₑ and 0.657 for IIDₜₜ). The regression coefficients for ITDₑ (1.214) and IIDₜₜ (9.028) were both significantly different from 1.0, and both constants (0.038 and 0.048, respectively) were not significantly different from 0. Multiple regression analysis yielded an $R^2$ value of 0.993, indicating that the inclusion of IIDₜₜ in the multiple regression equation accounted for only an additional 0.3% of the variation in the IID function. This result, together with the minor departure of the ITDₑ regression coefficient from 1.0, suggests that IID sensitivity at this base intensity should be classified as predominantly determined by ITDₑ sensitivity, although it is clearly borderline with respect to the “determined by both” category. At 50 dB, $r^2$ was significant only for ITDₑ (0.876), the regression coefficient (1.902) was significantly different from 1.0 and the constant (0.027) was not significantly different from 0. This pattern of results and inspection of the functions indicates that IID sensitivity was determined by both factors.
As were those of the majority of neurons (see also Fig. 8E). The sigmoidal shape presumably reflects the fact that the contralateral stimulus evokes a long-duration IPSP. Over a wide range of contralateral stimulus leads, the summation of this IPSP with the EPSP that produces the onset response to ipsilateral monaural stimulation prevents the spike threshold from being attained. Determination of the duration of effective inhibition for tones would have required testing at positive ITDs up to and exceeding the 50-ms tone duration.

Comparison of the three functions in Fig. 7D indicates that this neuron’s IID sensitivity at this base intensity was accounted for almost entirely in terms of ITD_e sensitivity. This was confirmed by the regression analyses (see details in Fig. 7 legend) which indicated that sensitivity in this case was attributable predominantly to ITD_e sensitivity according to the criteria elaborated in the preceding text.

As was the case with click stimuli, the IID sensitivity at a particular base intensity of other neurons with onset responses to tones could be accounted for in terms of ITD_e sensitivity alone (e.g., Fig. 8, A–C; see details of regression analysis in Fig. 8 legend) or in terms of the joint operation of both factors (e.g., Fig. 8, D–F; see also Fig. 10). Although analysis of the regression of IID on ITD_e could not be completed for the unit for which data are presented in Fig. 8, D–F (see details in legend), inspection of Fig. 8F indicates that it satisfies the criterion for joint determination by both variables set out in the preceding text.

A similar pattern of determination of IID sensitivity by either one or both factors was observed for both the onset and late components of neurons with sustained response patterns. In Fig. 9, data for the onset, late, and total response windows at a single base intensity are presented for three neurons (and...
The IIDs of the onset components of these three neurons (at the particular base intensities for which data are presented) are accounted for by ITD alone in the case of the unit in Fig. 9A (unit 95-45-4), predominantly by IIDdc in the case of the unit in Fig. 9D (unit 95-44-7), and by the joint operation of the two factors in the case of the unit in Fig. 9G (unit 95-61-3). For unit 95-44-7, the IID sensitivity of both the onset and late components of the response (Fig. 9, D and E, respectively), and thus that of the total response (Fig. 9F), is determined by IIDdc alone. For unit 95-45-4, however, while the IID sensitivity of the onset response is determined by ITD alone (Fig. 9A), that of the late response (Fig. 9B), and consequently that of the total response (Fig. 9C), is determined by the joint operation of the two factors. For unit 95-61-3, the sensitivity of the onset and total response components is determined by the joint operation of ITD and IIDdc (Fig. 9, G and J), but the sensitivity of the weak late component is determined by IIDdc alone (Fig. 9H).

Overall, the sensitivity of late response components was most commonly determined by IIDdc sensitivity (see Table 2), and consistency between onset and late components was consequently most frequently seen in cases such that in Fig. 9, D–F, in which the sensitivity of both components was determined primarily by this factor.

Tone response data were obtained at multiple base intensities for seven neurons, four with onset and three with sustained responses. For all four of the onset-response neurons, IID sensitivity was determined by the joint operation of the two factors at all or most base intensities but with different contributions of the factors (e.g., Fig. 10). For two of the neurons with sustained responses, the IID sensitivity of both onset and late components was determined by IIDdc sensitivity at all or most base intensities. For the unit for which data are presented in Fig. 11, however, the basis of the sensitivity of the onset component varied dramatically but systematically with changes in base intensity. Thus sensitivity of the onset component was determined predominantly by IIDdc sensitivity at 35 dB (Fig. 11A), by both factors at 45 dB (Fig. 11D), and solely by ITD at 55 dB and 65 dB (Fig. 11, G and J; see details of regression analyses in Fig. 11 legend). In contrast, the sensitivity of the late component was determined predominantly by IIDdc at 35, 45, and 55 dB (Fig. 11, B, E, and H). At 65 dB, the near-total response suppression in all three functions made it impossible to establish the relative importance of the two factors. The total responses plotted in Fig. 11, C, F, I, and L, have not been analyzed statistically, but it is apparent that the functions reflect the relative magnitude of onset and late components and the pattern of determination of each.

Data for all neurons for which tone data were obtained at one or more base intensities are summarized separately for onset and sustained components in Table 2. Allocation to particular categories was based on the criteria developed above for click responses. With respect to the onset response component, the striking feature of Table 2 is that the proportion of neurons exhibiting IID sensitivity determined solely or predominantly by ITD at one or more base intensities (15/35 or 43%) is larger than that for which it was determined solely or predominantly by IIDdc (9/35 or 26%). When the former figure is combined with the proportion of neurons for which IID sensitivity at one or more base intensities was determined by both factors (10/35 or 29%), sensitivity to ITD contributed to the IID sensitivity of the tone onset responses of 72% of neurons. These figures are in marked contrast to the data for click responses presented in Table 1, where the IID sensitivity of only 3 of 25 (12%) of neurons was determined solely or predominantly by ITD sensitivity, and this factor contributed to the IID sensitivity of only 8 of 25 (32%) neurons. Also in contrast to the click data for those that for seven of the nine neurons whose IID sensitivity was attributable only or predominantly to IIDdc the lack of contribution of ITD sensitivity reflected the fact that the neuron was insensitive to changes in ITD over the range tested. This is illustrated in Fig. 8B, where the IFD function shows substantial inhibition but little modulation of response over the ITD range examined (see also Fig. 9B).

The data for tone onset responses are also in marked contrast to those for late responses. The sensitivity of the late response was not determined solely or predominantly by ITD sensitivity in any case, and for almost all of the small sample of neurons for whom late responses could be classified, sensitivity was attributable solely or predominantly to IIDdc. This result confirms the expectation that the IID sensitivity of late re-

![Fig. 11](http://jn.physiology.org/doi/10.1152/jn.00871.2001)
Response components is unlikely to be influenced by IID-produced variations in the latencies of the EPSPs and IPSPs evoked by stimulus onsets. The large proportion of cases for which late responses could not be classified included three cases of the type shown in Fig. 11K, one case in which the late response was insensitive to IIDs, and one neuron for which IID_{dc} data were not obtained at one base intensity.

**Comparison of click and tone responses**

Data on sensitivity to IIDs in both click and tonal stimuli were obtained for 13 neurons, in some cases at multiple base intensities for one or both stimuli. As indicated by the data for the whole sample in Tables 1 and 2, comparison of click and tone onset response data at the same or similar base intensities for individual neurons revealed a bias to determination of tone onset responses by ITD_{e} and of click responses by IID_{dc}. Thus for six neurons for which tone onset sensitivity was classified as determined predominantly or only by ITD_{e}, the click sensitivity of two was assigned to the same category (e.g., Fig. 12, E and F), two were classified as determined by both variables (e.g., Fig. 12, A and B), and two as determined by IID_{dc} only. Similarly, of the four neurons whose tone onset sensitivity was classified as being determined by both factors, the click sensitivity of two was assigned to the same category and that of the other two to the IID_{dc}-only category (e.g., Fig. 12, C and D). For two neurons, both tone onset and click sensitivity were determined predominantly or only by IID_{dc}, and for unit 96-25-I, for which data were obtained at multiple base intensities for each stimulus, click sensitivity was produced predominantly or only by IID_{dc} sensitivity at each level (Fig. 6), whereas tone onset sensitivity showed the complex transition...
between combinations of the two factors that was described in the previous section (Fig. 11, A, D, G, and J).

**DISCUSSION**

The major results obtained in these experiments relate to the mechanisms underlying the IID sensitivity of rat LSO neurons in response to clicks and to the onsets of tonal stimuli. The data indicate that for a proportion of these neurons IID sensitivity at some base intensities can be accounted for solely or predominantly in terms of their sensitivity to ITD es. Granted the assumptions on which the techniques employed in the study were based (which are examined in detail in the following text), this result indicates that in these cases IID sensitivity is dependent solely or predominantly on sensitivity to the changes in the relative timing of synaptic inputs that are produced by IIDs as a consequence of the effects of intensity on latency. For other neurons, IID sensitivity at some base intensities could be accounted for either solely or predominantly in terms of sensitivity to IID dc s, indicative of IID sensitivity based solely or predominantly on sensitivity to differences in the amplitude of synaptic inputs. Of these two patterns of determination of IID sensitivity, sensitivity based on the relative timing of the inputs was more common in responses to tone onsets, whereas sensitivity based on the relative amplitude of the inputs was more common in click responses. In other cases, IID sensitivity appeared to be accounted for by the combined effect of ITD es and IID dc s, indicative of IID sensitivity based on sensitivity to both the timing and the amplitude of synaptic inputs. For the small number of neurons for which the IID sensitivity of late (or steady state) components of responses to tonal stimuli were analyzed, sensitivity was, as expected, determined solely or predominantly by the amplitude of the inputs.

The existence of cases in which changes in the timing of inputs either determines or contributes to IID sensitivity provides support for what was referred to in INTRODUCTION as the weak form of the latency hypothesis, whereas the existence of cases for which changes in the amplitude of inputs determines or contributes to IID sensitivity indicates that the strong form of the latency hypothesis must be rejected. These conclusions depend, however, on the soundness of the assumptions on which the procedures used to assign sensitivity to one or the other factor were based. In the following sections, these assumptions and any qualifications on the conclusions will be considered, the data will be compared with those of previous studies, and their implications for models of IID coding will be examined.

**Methodological considerations**

The methods used to test the latency hypothesis in these experiments involve a number of assumptions. A basic assumption is that the neurons in the LSO that are designated IE in fact receive purely excitatory input from the ipsilateral ear and purely inhibitory input from the contralateral ear. A related assumption is that the convergence of these inputs occurs at the LSO neuron itself, i.e., that the activity evoked in the neurons providing input from a given ear is not itself affected by stimulation of the other ear. A third assumption, which is critical to the calculation of ITD es, is that changes in the timing of the excitatory input to an LSO neuron can be inferred from changes in the timing of the neuron’s response to that input.

With respect to the first assumption, there seem to be no reports in the literature of other than inhibitory responses of LSO neurons either to contralateral stimulation in vivo or to electrical stimulation of the trapezoid body (TB) on the midline in slice preparations. However, there is evidence that under certain conditions, the input from the ipsilateral ear is not purely excitatory. Brownell et al. (1979) reported that the excitatory ipsilateral tuning curves of IE neurons in LSO of decerebrate cats had inhibitory sidebands and that in two neurons tested before and after an anesthetic dose of pentobarbital sodium, both spontaneous activity and the inhibitory sidebands were abolished by barbiturate anesthesia. Caird and Klinke (1983) also described ipsilateral inhibitory sidebands in...
cat LSO neurons and claimed that such inhibition could be seen under barbiturate anesthesia provided the neuron inhibited spontaneous activity. In mouse brain stem slices, Wu and Kelly (1994) reported that IPSPs as well as EPSPs were evoked in LSO neurons by stimulation of the TB lateral to the LSO, and in one case in which pentobarbital sodium was added to the bathing medium, the IPSPs but not the EPSPs were eliminated. Together these observations suggest that there is ipsilateral inhibitory input to LSO neurons at frequencies other than CF and that this input is eliminated by barbiturate anesthesia that is deep enough to abolish spontaneous activity. The barbiturate anesthesia employed in the present study was of this depth, and it therefore appears that the data are unlikely to be compromised by the presence of inhibitory ipsilateral responses. However, generalization of the results from the anesthetized to the unanesthetized preparation is qualified by the presence of ipsilateral inhibitory input in the latter.

With respect to the assumption that binaural interaction takes place at the LSO neuron itself, the input to an LSO neuron from a given ear could potentially be influenced by stimulation of the other ear via either the efferent fibers of the olivocochlear bundle or direct projections between the cochlear nuclei on the two sides (e.g., Cant and Gaston 1982). Latency considerations make it improbable that click or tone onset latencies make it improbable that click or tone onset latencies takes place at the LSO neuron itself, the input to an LSO neuron might contribute to the observed responses.

The third assumption, on which the calculation of ITD_{50} is based, is that changes in the timing of the ipsilateral excitatory input to an LSO neuron can be inferred from changes in the timing of the action potential output evoked by that input. As noted previously (Irvine et al. 1995), although there are a number of ways in which this assumption could be violated, a pragmatic justification of it is provided by evidence from studies of coincidence-detection mechanisms in neurons in the MSO nucleus and IC that are excited by stimulation of either ear and are sensitive to interaural phase differences (e.g., Crow et al. 1978; Goldberg and Brown 1969; Kuwada et al. 1984; Yin and Chan 1990). The coincidence detection mechanism also involves coincidence of inputs, but in each of these studies, the only timing information available concerned the timing of a given neuron’s responses to its ipsilateral and contralateral inputs. The near-perfect correlations found for such neurons between best delay and the difference between the phase locking points for monaural stimulation of the two ears is prima facie evidence that the timing of inputs can reasonably be estimated from the timing of outputs.

In summary, it would appear that the major qualification of the conclusions stated earlier is the generalization of results to the unanesthetized animal given the possibility of ipsilateral inhibitory input to at least some LSO neurons in the latter preparation. This is a common qualification but by no means a trivial one given the general aim of understanding auditory processing mechanisms in awake behaving animals. Conclusions concerning the late components of tone responses are also qualified to some extent by uncertainty concerning the extent to which binaural interactions at sites other than the LSO neuron might contribute to the observed responses.

Comparison with previous studies of LSO neurons

The sigmoidal IID sensitivity functions of IE neurons in rat LSO were similar to those described for such neurons in LSO of a number of other species (e.g., cat: Caird and Klinke 1983; Tsuchitani and Boudreau 1969; bat: Grothe and Park 1995; Harnischfeger et al. 1985; Park et al. 1996, 1997; gerbil: Sanes and Rubel 1988). The only previous recordings of IID sensitivity in rat LSO appear to be those of Finlayson and Caspary (1993); although they did not present IID functions, their derived measures indicate that the functions were sigmoidal in form. Comparison of IID and monaural functions in the present study indicated that for all neurons IID sensitivity was produced solely by contralateral inhibition, with no evidence of the mixed facilitatory/inhibitory binaural interactions that contribute to IID sensitivity at higher levels (see Irvine 1992 for review). This observation supports the view that contralateral input to IE neurons in rat LSO is purely inhibitory.

A surprising feature of the results is that a substantial proportion (8 of 37) of IE neurons sensitive to IIDs in tones and/or clicks had relatively low CFs, in the range 2.2–3.5 kHz (e.g., Figs. 6 and 12). A similar observation was made in Irvine et al.’s (1995) study of rat IC, where it was noted that the size of the rat’s head and pinnae are such that IIDs in this frequency range would be expected to be extremely small (Harrison and Downey 1970) and that it is therefore unlikely that the major function of these neurons is to process IIDs. It is likely that the major function of low-frequency IE neurons is the processing of transient ITDs and that IID sensitivity is simply a consequence of the fact that the same binaural interactions underlie both forms of sensitivity. It is of interest that Sanes and Rubel (1988) reported a surprisingly high proportion of low-CF IE neurons in LSO of the gerbil.

There appears to have been no previous description of the ITD sensitivity of rat LSO neurons. The U-shaped click and sigmoidal tone ITD sensitivity functions exhibited by these neurons were of the same form as those described for IE neurons in the LSO of the cat (Caird and Klinke 1983; Joris and Yin 1995) but differed in one respect from those reported by Park et al. (1996) for LSO neurons in Mexican free-tailed bats, Park et al. (1996) used 2-ms tone pulses, transient stimuli that would be expected to generate ITD functions similar to those obtained here with clicks. However, their ITD functions at zero IID were V-shaped (with a single ITD of maximum or total suppression) in contrast to the U-shaped functions (with maximum or total suppression over an ITD range of some hundreds of microseconds) obtained for the majority of neurons tested with clicks in the present study (and in the cat studies). This difference does not seem to be attributable to the resolution with which ITD data were obtained and could reflect either a species difference or a difference between click and short tone-pulse stimuli.

A striking feature of most click ITD functions is the narrowness of the regions of response suppression (e.g., Figs. 3B, 4B, and 5B). As pointed out by Joris and Yin (1995), the U-shaped portion of the ITD function reflects the time course of the effective inhibitory event, i.e., the time course over which the IPSP is effective in reducing the ability of the EPSP produced by ipsilateral stimulation (at the particular base intensity) to evoke an action potential. The duration of effective inhibition in rat LSO neurons varied from ~0.8 to 2.0 ms, in
good agreement with Joris and Yin’s (1995) data in the cat and with the time period over which an electrically evoked IPSP in slice preparations effectively suppresses a spike evoked by ipsilateral electrical stimulation (Sanes 1990; Wu and Kelly 1992).

Joris and Yin (1995) also noted that approximate symmetry of the U-shaped click ITD function about zero ITD (as in Fig. 4B) suggests that the ipsilateral EPSP and contralateral IPSP are of similar duration and approximately equal latency. Such symmetry was seen in the click ITD functions of slightly less than half of the neurons in this study. In a similar proportion of neurons, the duration of effective inhibition was similar, but the ITD function was shifted toward positive ITDs (e.g., as in Figs. 3B and 5B), suggesting that the inhibitory latency was longer than the excitatory latency and that a contralateral lead was necessary to bring the two inputs to the neuron into coincidence. In a small number of neurons (not illustrated), the duration of effective inhibition was also similar, but the function was shifted toward negative ITDs, suggesting shorter inhibitory than excitatory latency in these cases. The proportions of neurons in these three groups are similar to those reported by Joris and Yin (1998; their Fig. 11B) for estimates of the ipsilateral and contralateral latencies of cat LSO neurons derived by a quite different method. The specializations for rapid transmission of the pathway from the contralateral cochlear nucleus over which the inhibitory input is derived are well established (see Irvine 1992 for review; Joris and Yin 1998 for recent data). The mean minimum click latency of the monaural contralateral units recorded in penetrations into MNTB in some of the early experiments was 2.18 ± 0.48 (SD) ms. Prepotentials were not clearly discernible in some cases, and some of these recordings could have been from fibers; but these latencies nevertheless indicate that the inhibitory input could reach LSO neurons with latency equal to or shorter than that of the excitatory input (minimum click latency = 3.68 ± 0.23 ms).

A surprising feature of the tone responses of rat LSO neurons was the relatively high proportion of neurons with various forms of onset response, in contrast to the predominance of chopper responses in the cat (see Irvine 1986 for review). Finlayson and Caspary (1993) also reported that the responses of LSO neurons in rats to 50-ms tones could be classified into O₁, O₂, and O₃ categories, but unfortunately gave no indication on the proportion of neurons assigned to each group. One factor contributing to this species difference in response patterns is a difference in the sources of inhibitory input to LSO: Friauf and Ostwald (1988) described projections from “on” neurons (presumably stellate cells) in the posteroventral cochlear nucleus to ipsilateral LSO in rats which have not been described in cats. A second factor is that in rodents the cells of origin of the lateral olivocochlear (LOC) system are dispersed throughout the LSO, whereas in cats they are concentrated in the dorsal hilus (see Irvine 1986 for review). Adams et al. (1999) have reported that two classes of neurons in slices of rat LSO could be identified on the basis of their responses to intracellular injection of 200-ms duration DC pulses. Neurons identified as principal neurons on morphological grounds exhibited chopper responses, while those identified as LOC neurons exhibited delayed repetitive firing, and a short-latency onset spike at higher current levels. The delay of the repetitive discharge in LOC neurons was typically >100 ms (≤180 ms), and the repetitive discharge component would therefore not be expected to occur in response to 50-ms acoustic stimuli, so LOC neurons would be expected to exhibit only onset responses to such stimuli.

**Relationship to other evidence bearing on the latency hypothesis**

The occurrence of psychophysical (e.g., Deatherage and Hirsh 1959) and physiological (e.g., Pollak 1988; Yin et al. 1985) time-intensity trading has often been invoked in support of the latency hypothesis because a compelling explanation of these phenomena is that the two disparities are converted into a “common neural code” (Hafer et al. 1990). However, an “intensity-to-time” conversion is not a necessary condition of either psychophysical time-intensity trading or physiological trading at the level of the IC and above. Such trading could also occur if ITDs and IIDs were processed in separate binaural pathways that converged on the same target, where weights were assigned to the different disparities. This does not happen, however, in the case of the LSO, where the evidence presented in the preceding text indicates that the binaural characteristics of at least the onset responses of IE neurons reflect convergence at these neurons. The fact that these neurons are sensitive to both IIDs and ITDs and exhibit time-intensity trading (cat: Caird and Klinke 1983; bat: Grothe and Park 1995; Harnischfeger et al. 1985; Park et al. 1996) provides strong support for the contribution to IID sensitivity of intensity-induced changes in the timing of inputs. All of these studies demonstrating physiological time-intensity trading in the LSO therefore concur with the present study in supporting what has been called the weak form of the latency hypothesis.

The present study is the first to provide a test of the strong form of the latency hypothesis by determining whether the actual changes in the relative timing of inputs to a given neuron that are associated with a particular range of IIDs account totally for the neuron’s sensitivity to those IIDs. Although this proved to be the case for some neurons at some base intensities, it was not generally the case, requiring rejection of the strong form of the latency hypothesis. In terms of the notion that time-intensity trading reflects the conversion of IIDs and ITDs to a “common neural code,” it would seem that at the level of the LSO, the common code should be thought of in terms of the final integrated synaptic response of the neuron, which is influenced by both the amplitude and the timing of its synaptic inputs. The latter, in turn, is determined by both the physical ITD and the effect of intensity on latency.

**Implications for models of binaural processing**

In demonstrating that both the amplitude and the timing of inputs to LSO neurons contribute to their IID sensitivity in vivo, these results have implications for models of binaural processing. As noted previously, current models of the processing of IIDs in sustained stimuli by neurons in LSO and at higher levels have been cast solely in terms of either temporal differences (e.g., Yin et al. 1985) or amplitude/rate differences (e.g., Colburn and Moss 1981; Johnson et al. 1990; Reed and Blum 1990). They have also considered the response as a whole rather than considering onset and late response components separately. The data presented here indicate that physi-
ologically realistic models of onset response sensitivity to IIDs will have to incorporate both factors, whereas models of late response components can be cast in terms of amplitude/rate differences alone.

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