

The Lateral Superior Olive: A Functional Role in Sound Source Localization

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Sound location in azimuth is signaled by differences in the times of arrival (interaural time difference, ITDs) and the amplitudes (interaural level differences, ILDs) of the stimuli at the ears. Psychophysical studies have shown that low- and high-frequency sounds are localized based on ITDs and ILDs, respectively, suggesting that dual mechanisms mediate localization. The anatomical and physiological bases for this “duplex theory” of localization are found in the medial (MSO) and lateral (LSO) superior olives, two of the most peripheral sites in the ascending auditory pathway receiving inputs from both ears. The MSO and LSO are believed to be responsible for the initial encoding of ITDs and ILDs, respectively. Here the author focuses on ILDs as a cue to location and the role of the LSO in encoding ILDs. Evidence from disparate fields of study supports the hypothesis that the LSO is the initial ILD processor in the mammalian auditory system. *NEUROSCIENTIST* 9(2):127–143, 2003. DOI: 10.1177/1073858403252228

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One of the main functions of the auditory system is to determine the spatial location of sound sources. The auditory system accomplishes this using different mechanisms from the other spatial senses of vision and touch. Visual and somatosensory receptors can encode the location of visual and tactile objects directly via the topographic organization of the rods and cones of the retina and the mechano-receptors of the skin. The auditory receptors cannot. Rather, the hair cells of the cochlea encode sound frequency owing to their position along the basilar membrane and the frequency-dependent mechanical properties of the basilar membrane itself. Therefore, sound location must be computed at more central levels in the auditory pathway based entirely on the neural representations of the spectral and temporal characteristics of the acoustic stimuli arriving at the two ears.

Whether predator or prey, mate or foe, the quick and accurate localization of sound is of utmost importance to most mammals. This was recognized early in the history of experimental psychology and physiology, and the problem of how sound is localized has been investigated seriously for more than 200 years (Boring, 1942). Historically, the primary experimental goal has been to determine the nature of the physical acoustical param-

eters of the sounds, or cues, arriving at the ears that are required for localization. There are three primary cues to location, each of which is created by interactions of the incident sound waves with the head and outer ears, or pinnae (Middlebrooks and Green 1991; Wightman and Kistler 1993): 1) the interaural differences in the time of arrival of the sound at the two ears (ITDs), 2) interaural differences in sound level at the ears (ILDs), and 3) monaural spectral cues.

The Duplex Theory of Sound Localization and the Superior Olivary Complex

Psychophysical investigations on the ability of human observers to locate sources of sound have been the key to understanding how the acoustical cues are used for the perception of location, particularly for sources in azimuth. Such experiments have revealed that the azimuthal position of both low- and high-frequency tones can be accurately determined by both humans and cats but that mid-frequency tones (1500–3000 Hz) cannot. A discontinuity in such a sensory function suggests that separate physiological mechanisms (see Gescheider 1985) mediate the localization capabilities for the high- and low-frequency regions, respectively. The poor performance for the mid-frequency tones presumably reflects the transition from using one cue and/or mechanism to another. Based on this evidence, a dual mechanism for localization, the so-called duplex theory, was proposed whereby low-frequency sounds are localized based on the ITD cues whereas higher frequency sounds are localized based on the ILD cue (Lord Rayleigh 1907; Stevens and Newman 1936; Mills 1958; Casseday and Neff 1973).

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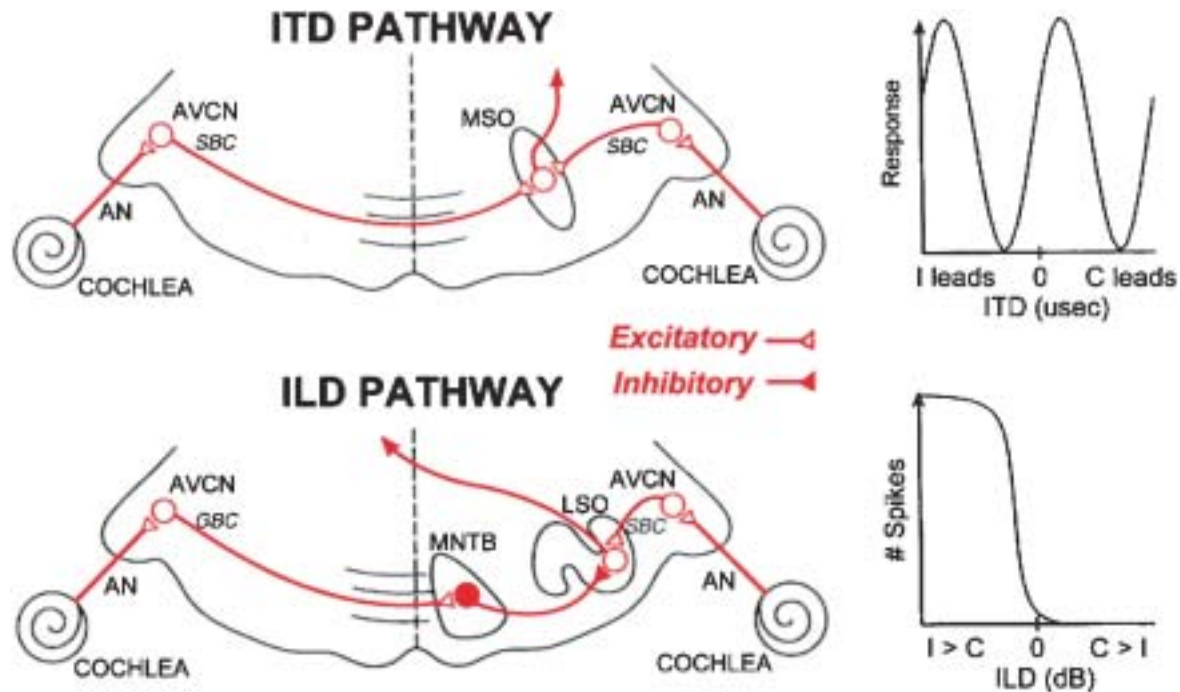


Fig. 1. Illustration of two frontal sections through the brainstem showing the two parallel ascending pathways through the nuclei of the superior olivary complex that are believed to be responsible for encoding the two binaural cues to sound localization, the interaural differences in time (ITD) and level (ILD). ITD pathway: Cells of the medial superior olive (MSO) receive bilateral excitatory input from the spherical bushy cells (SBCs) in the anteroventral cochlear nucleus (AVCN), which in turn receive their inputs directly from the auditory nerve (AN). These bilateral excitatory inputs confer on MSO cells sensitivity to the ITD cue to sound localization, as illustrated in the figure directly to the right. ILD pathway: Cells of the lateral superior olive (LSO) also receive bilateral inputs from both ears. The input from the ipsilateral SBCs is excitatory, but the input from the globular bushy cells (GBCs) of the contralateral AVCN is inhibitory due to the additional synapse in the ipsilateral medial nucleus of the trapezoid body (MNTB). The interplay of the ipsilateral excitation and contralateral inhibition confers on LSO cells sensitivity to the ILD cue to location as indicated by the figure to the right. Figure adapted by permission from Joris and others (1990).

Although the duplex theory has served as the principal model of localization for more than a century (Haftner 1984), the question of how the localization cues are separately encoded and ultimately integrated in the responses of auditory neurons remains unsolved. Motivated by the duplex theory, neuroscientists have been searching for its anatomical and physiological basis, and several candidate sites have been offered (reviewed in Rosenzweig 1961). Because early anatomical studies revealed that the first sites in the ascending auditory pathway to receive massive converging inputs from both ears were two of the primary nuclei comprising the superior olivary complex (SOC) (Fig. 1), the medial superior olive (MSO) and the lateral superior olive (LSO) have received the most attention as possible sites where the two binaural cues for location, ITDs and ILDs, are first extracted. Later, physiological studies reported neurons in the SOC that were separately sensitive to ITDs and ILDs. And more recently, lesion studies demonstrated that sectioning SOC inputs (Masterton and others 1967; Moore and others 1974) or lesioning the SOC (Kavanagh and Kelly 1992) dramatically decreases the ability of experimental animals to localize sounds in the horizontal plane, suggesting that the SOC nuclei are necessary for localization. Together, these lines of evidence

suggest that at this very early stage in the auditory pathway, the MSO and the LSO provide the anatomical and physiological bases for the duplex theory of sound localization. Because the evidence for the hypothesis that the MSO is the initial site for extracting ITDs has been presented in several recent reviews, we will not discuss the MSO further (Joris and others 1998; Yin 2002).

The goal of this review is to examine the hypothesis that ILDs are processed in the LSO. This hypothesis was initially based largely on two observations: the LSO is one of the earliest sites of convergence of inputs from the two ears, and its cells respond in a systematic way to ILDs (see the review by Boudreau and Tsuchitani 1970). Evidence from disparate fields provides strong support for the hypothesis that the LSO is the earliest site where a correlate of the ILDs present in free-field sounds is extracted and is, hence, the initial de facto ILD processor in the auditory pathway. In what follows, the ILD as an acoustical cue to location will first be assessed. Second, the characteristics of an “ideal” ILD processor will be compared with the anatomical and physiological evidence for and against the ILD pathway (Fig. 1) possessing these characteristics. Finally, comparative studies that have questioned the functional roles of the SOC nuclei through combined anatomical, physiological, and

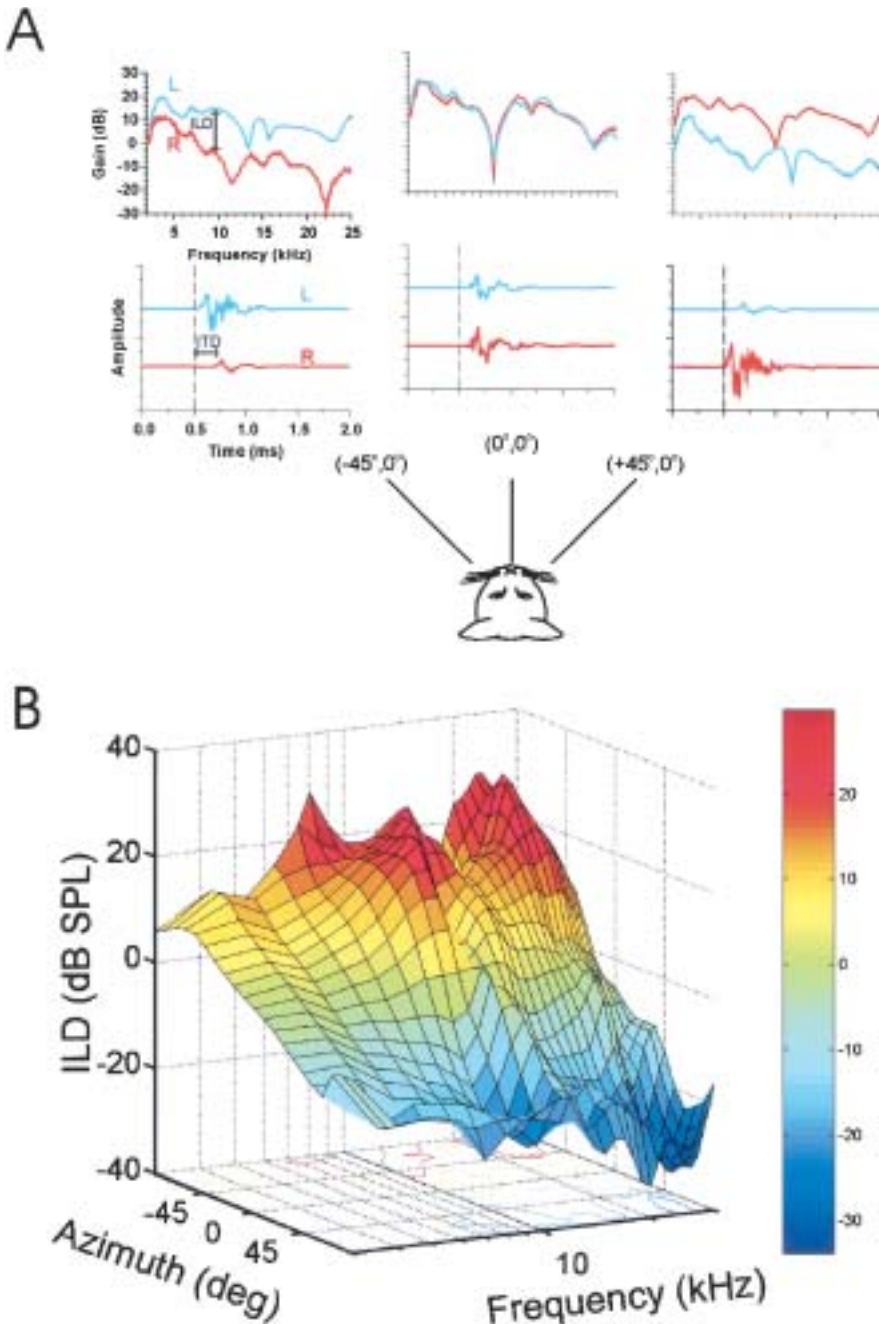


Fig. 2. The acoustical cues for the spatial localization of sounds available to an adult cat for three locations in azimuth along the horizontal plane. *A*, The two panels at each location show the head-related transfer functions (HRTFs, top) and associated time-domain impulse response (bottom) of the left (L) and right (R) ears resulting from the presentation of broadband clicks from a loudspeaker positioned at the labeled azimuths. The HRTFs are plotted in terms of the acoustical gain introduced by the presence of the head and pinnae relative to the sound level in response to the click delivered in the absence of the cat. The three primary cues to sound location are captured in the HRTFs and impulse responses. Interaural time differences (ITDs) are represented by the relative differences in the onset times of the impulse responses at each ear and interaural level differences (ILDs) by the relative differences in the gains of the HRTFs as a function of frequency. The monaural spectral cues are captured by the changes in the shapes of the spectra as a function of azimuth; note in particular the deep spectral notch that occurs at 11.5 kHz for a stimulus at the midline. *B*, The spatial and frequency dependence of ILDs. The ILDs were computed by taking the difference of the left and right ear HRTFs after filtering them through a bank of 1/6-octave Gaussian filters with different center frequencies. For illustrative purposes, sources were restricted to the horizontal plane and only in the frontal hemisphere for frequencies between 3 and 30 kHz. ILDs are a complicated function of azimuth and frequency for high-stimulus frequencies. The HRTFs in *A* and the ILDs shown in *B* were derived directly from the acoustical measurements of Musicant and others (1990).

psychophysical observations will be considered. Although most of what we know about the psychophysical basis of localization comes from human observers, most of the anatomical and physiological data comes from the domestic cat. Whenever possible, then, the cat will be used as a representative mammal.

The Acoustical Cues to Sound Source Location

Sound localization differs from other spatial senses because the cues for location are generated by the anatomy supporting the receptors of the ear, namely, the head

and pinnae, and not by the topography of the receptors themselves. To understand the neural mechanisms for localization, the acoustical basis for the cues must be considered. There are three primary acoustical cues to location: ITDs, ILDs, and spectral cues. Each is illustrated in Figure 2*A* for the cat. These three categories of cues are believed to be the same for all mammalian species, although their magnitudes and the frequency ranges over which they are relevant can differ considerably. Figure 2*A* shows the cues available from three different sound source azimuths along the horizontal plane. The top and bottom portions of the three panels show the so-called head-related transfer functions (HRTFs) and

associated time impulse responses, respectively. HRTFs are measured by recording with small microphones the acoustic responses near the tympanic membrane of each ear to a broadband probe stimulus from which the acoustic transfer function of the ear as a function of the location of the probe is determined. A left and right ear pair of HRTFs for any given location captures the frequency- and direction-dependent changes to the acoustic stimulus from that location due to interactions of the incident sound waves with the head, pinnae, and torso (Wightman and Kistler 1989; Musicant and others 1990; see Blauert 1997).

The two binaural cues, ITD and ILD, that mediate localization in azimuth are readily apparent in the impulse responses of the HRTFs (lower panels). The binaural cues result from the fact that owing to their position on the head, the ears not only occupy different actual locations in space but are also separated by an acoustically opaque object, the head. ITDs arise from the differences in path lengths that sound must travel to reach each ear at disparate locations. In the cat, ITDs increase monotonically with azimuth to 300 to 400 μ s for the most lateral azimuthal locations (Roth and others 1980). As expected, the range of ITDs is directly proportional to head diameter, so larger species exhibit larger ITDs (Masterton and Diamond 1967). The maximum ITD in humans is \sim 700 μ s (Wightman and Kistler 1993), whereas for smaller mammals, such as some species of bats and rodents with head diameters less than 1 cm, it can be as small as 40 μ s!

The ILD cue results from frequency-dependent modifications of the incident sound pressure waves made by the head and pinnae and is defined as the difference in sound pressure level of the signals arriving at the ears at one frequency. The ILDs result in part from an acoustic “shadowing” effect that occurs for sounds whose wavelengths are similar or smaller than the diameter of the head so that they are reflected. Relative to the sound level at the pinna ipsilateral to (or facing) the sound source, this shadow effectively attenuates the sound arriving at the contralateral (opposite side as the source) ear resulting in an ILD (Lord Rayleigh 1877). Acoustical measurements in adult cats show that amplification by the ipsilateral pinna due to the sound collection capabilities of the pinnae itself also contributes to ILDs (Wiener and others 1966; Phillips and others 1982; Calford and Pettigrew 1984; Irvine 1987). Although the effective amplification provided by the ipsilateral pinnae can approach 20 to 25 dB sound pressure level (SPL) at some frequencies (Phillips and others 1982; Musicant and others 1990), for most frequencies, decreases in the level at the far ear, and hence the acoustic shadow, account for much of the ILD (Irvine, 1987).

Detailed acoustical measurements in cats reveal that the magnitude of ILDs varies systematically with location (Wiener and others 1966; Moore and Irvine 1979; Phillips and others 1982; Calford and Pettigrew 1984; Irvine 1987; Martin and Webster 1989; Musicant and others 1990; Rice and others 1992). However, at any one location, ILDs also vary in a complicated way with fre-

quency. This can be seen graphically in the top panels of Figure 2A, in which the ILD is given by the difference in the gains at the two ears at each frequency. To illustrate these patterns of ILD, Figure 2B shows the ILD in narrow frequency bands as a function of azimuth and frequency. Two main points are apparent. First, for frequencies <10 kHz, the ILD-azimuth functions are nearly monotonic, and the rate of change of ILD with azimuth is moderate. Second, for frequencies higher than 10 kHz, the rate of change of ILD near the midline is great, and the ILD-azimuth functions are highly nonmonotonic and exhibit peaks and dips. The nonmonotonicity of the ILD-azimuth functions (a pattern also present in measurements of human ILDs) at higher frequencies creates problems for the use of this cue in any single frequency band to represent azimuthal location unambiguously (see Martin and Webster 1989; Middlebrooks and others 1989; Johnson and others 1990).

Last, monaural spectral cues also arise from differential reflection and diffraction of pressure waveforms from sounds originating from different directions by the head, torso, and pinna resulting in broadband spectral patterns that change with location (Shaw 1974). Prominent direction-dependent features in the spectra, such as the deep notches that occur at some locations as shown in Figure 2A, are thought to be critical both for the localization of sounds in elevation, where the binaural cues change little with variations in elevation, and for facilitating the distinction between sources in front of an observer from sources behind (human: Wightman and Kistler 1989; cats: Huang and May 1996). Principal cells of the dorsal cochlear nucleus encode these spectral cues (Young and Davis 2002).

The Lateral Superior Olive as an Interaural-Level Difference Processor

For ILDs to be useful for localization, there must be neural mechanisms along the auditory pathway to sense them. It is easy to imagine that at some point along the ascending pathway, the physiologically encoded sound level of the stimulus arriving at one ear is somehow subtracted from the encoded level at the other, yielding a neural correlate of the acoustical ILD cue. It has been suggested that such a correlate of ILD is encoded by the discharge rates of LSO neurons and that ILD sensitivity results because LSO neurons are inhibited by sounds to the contralateral ear and excited by sounds to the ipsilateral ear (Boudreau and Tsuchitani 1968), the inhibition being the neural equivalent of subtraction. Many neurons in higher auditory nuclei, including inferior colliculus (IC), medial geniculate body, and auditory cortical areas, are sensitive to changes in sound location, usually for sounds in the contralateral hemifield (Irvine 1986). These neurons probably derive their spatial sensitivity to contralateral space in large part from the LSO, which projects excitatory afferents to the contralateral dorsal nucleus of the lateral lemniscus and IC and inhibitory afferents to the ipsilateral IC (Glendenning and Masterton 1983; Glendenning and others 1992). Thus, it

Box 1: Properties and Characteristics of an Ideal Interaural Level Difference (ILD) Processor

We shall define the ILD as the relative difference in the sound pressure level of the acoustical stimuli arriving at the two ears computed in temporal register on a frequency-by-frequency and a time-by-time basis.

Listed below are seven properties that the lateral superior olive (LSO) circuit shown in Figure 1 should collectively possess:

1. LSO cells must receive inputs from both ears, one excitatory and one inhibitory.
2. Inputs to the LSO must collectively encode the spectrum of the acoustic stimuli at each ear.
3. Inputs to LSO cells from each ear must be matched in their frequency selectivity.
4. Inputs to LSO cells must accurately encode the temporal variations in the acoustical stimulus at each ear.
5. Inputs to the LSO from the two ears must arrive in temporal register.
6. Inputs to the LSO from each ear must be compared over short time intervals.
7. The responses of LSO cells should reflect the ILDs present in the stimulus.

is important to understand the mechanisms of ILD sensitivity at the LSO and the possible limitations it might place on the spatial selectivity exhibited by these higher-order neurons and ultimately sound localization performance.

For this review, we shall adopt a strategy different from that employed by previous reviews that have covered the LSO. Instead of simply reviewing the literature on ILD coding by LSO cells, we first list in Box 1 some of the characteristics or requirements that an ideal ILD processor might possess. This list is neither exhaustive nor complete. Then, we provide a concise review of the extent to which the anatomy and the physiological responses of the neurons comprising the actual ILD pathway through the LSO (Fig. 1) compare to the requirements set forth by an ideal ILD processing scheme. Those interested in a more general discussion of the SOC are referred to the recent reviews by Yin (2002) and Irvine (1992).

LSO Cells Must Receive Inputs from Both Ears, One Excitatory and One Inhibitory

For the responses of LSO neurons to exhibit a neural correlate of subtraction, and hence, ILD, the input from one ear must be inhibitory and the input from the other ear excitatory. Figure 1 summarizes the known major afferent inputs from the two ears to the LSO. It has been

shown unequivocally that LSO cells are innervated bilaterally from both ears. LSO cells receive excitatory inputs from the ipsilateral ear through the spherical bushy cells (SBCs) of the ipsilateral anteroventral cochlear nucleus (AVCN) (Stotler 1953; Warr 1966; Osen 1969; van Noort 1969; Shneiderman and Henkel 1985; Glendenning and others 1985; Cant and Casseday 1986; Smith and others 1993). They also receive inhibitory afferents from the contralateral ear via cells in the ipsilateral medial nucleus of the trapezoid body (MNTB) (Harrison and Warr 1962; van Noort 1969; Warr 1972; Elverland 1978; Tolbert and others 1982; Glendenning and others 1985; Spangler and others 1985; Friauf and Ostwald 1988; Bledsoe and others 1990; Smith and others 1991, 1998), which in turn receive their excitatory input from the globular bushy cells (GBCs) of the contralateral AVCN (Harrison and Warr 1962; Warr 1972; Tolbert and others 1982; Glendenning and others 1985; Smith and others 1991). The SBCs and GBCs receive a direct excitatory input from the auditory nerve (Young 1998).

Although the LSO has been thought to detect differences in the synaptic inputs they receive from each ear, this hypothesis was first inferred from the patterns of neural discharges elicited when presented with acoustic stimuli containing ILDs (e.g., Galambos and others 1959; Boudreau and Tsuchitani 1968; Caird and Klinke 1983; Sanes and Rubel 1988; Joris and Yin 1995; Park and others 1997; Tollin and Yin 2002a). This inference was based on the observations that ipsilateral sound-evoked discharge rates of LSO cells could be progressively reduced by raising the sound level of the stimuli presented to the contralateral ear. However, that discharge rate changes with ILD does not by itself directly implicate the LSO as the actual site of ILD computation. The actual computation could have occurred more peripherally, or sensitivity to ILD might arise coincidentally from other integrative functions.

Moore and Caspary (1983) showed that ILD sensitivity results directly from the nature of the synaptic inputs onto LSO cells. They revealed that the input from the ipsilateral MNTB is glycinergic and inhibitory. They noted that the inhibition evoked by presenting an acoustic stimulus to the contralateral ear could be blocked by the glycine receptor antagonist strychnine and could also be mimicked by directly applying glycine. Additional immunocytochemical studies have confirmed that the principal neurons of the MNTB are glycinergic (Glendenning and Baker 1988; Helfert and others 1989; Adams and Mugnaini 1990; Henkel and Brunso-Bechtold 1995). Consistent with the functional observations of ILD sensitivity inferred from extracellular responses, intracellular recordings in vivo from single LSO cells have demonstrated directly that acoustic stimulation of the ipsilateral and contralateral ears generates excitatory and inhibitory postsynaptic potentials (EPSPs and IPSPs), respectively (Finlayson and Caspary 1989). In subsequent in vitro recordings in LSO slices in which the input pathways to the LSO from each ear could be electrically stimulated, it was found that stimu-

lation of ipsilateral inputs generated glutamatergic EPSPs whereas stimulation of contralateral inputs generated glycinergic IPSPs, although there were exceptions (Caspary and Faingold 1989; Sanes 1990; Wu and Kelly 1991; Glendenning and others 1991; Wu and Kelly 1992). The responses of some LSO cells can be inhibited by ipsilateral acoustic stimulation by tones with frequencies away from the best frequency of the cell consistent with side-band inhibition (Brownell and others 1979; Caird and Klinke 1983). Studies in slices have demonstrated that some ipsilateral inhibition results from glycinergic inputs directly to LSO cells themselves, although the source of this input is not clear (Wu and Kelly 1991, 1994). Sideband inhibition could play a role in refining the frequency selectivity of the ipsilateral input.

Inputs to the LSO Must Collectively Encode the Spectrum of the Acoustic Stimuli at Each Ear

For the LSO to compute a correlate of the ILD across frequency, the afferent inputs to the LSO must encode the broadband spectral characteristics of the acoustic inputs to each ear. Collectively, the input arrays should span the range of frequencies for which the ILD cue is actually available, from 2 to more than 40 kHz for cats (this requirement is addressed in the next section). Because of the narrow frequency selectivity of auditory nerve fibers (ANFs) (Kiang and others 1965), the input spectrum of high-frequency stimuli at each ear must be represented via the pattern of discharge rates across the population of ANFs. Because of the topographic projections of ANFs to the cochlear nucleus (Rose and others 1959; Young 1998), the representation of the spectrum will be dispersed across the tonotopic array of CN neurons, including the bushy cells of the AVCN. The main question here is whether the population of ANFs can encode the spectra present at the two ears necessary for the accurate computation of ILDs. Moreover, is this information faithfully preserved by the responses of the bushy cells and the MNTB cells?

The ability of the ANF population to represent the input spectrum of HRTFs was reported by Rice and others (1995). They recorded the responses of a population of cat ANFs, spanning a range of best frequencies, to broadband noise stimuli that had been filtered by HRTFs measured from adult cats. They concluded that such a population could not adequately encode the most salient broadband spectral characteristics, such as the deep spectral notches, via their discharge rate. However, they used only a small set of the possible HRTF measurements, so it is difficult to know whether the ANF array could encode the more general spectral characteristics necessary for the computation of ILD independent of the notches. May and Huang (1997) reexamined this possibility with a computational model. Using the empirical response characteristics of the ANFs of Rice and others (1995), May and Huang (1997) simulated the responses of a larger population of ANFs and showed that, in general, there was indeed sufficient information carried in the discharge rates across a population of ANFs to

encode the ILD. One important piece of evidence for this was that the simulated responses could accurately predict the behavioral measurements of sound localization acuity by cats over a range of stimulus frequencies for which ILDs were the primary localization cues (Martin and Webster 1989). This is in agreement with the earlier findings by Poon and Brugge (1993) that single ANFs could encode the spatial location-dependent spectral features of cat HRTFs via their discharge rates.

What is known about the response properties of bushy cells and MNTB cells, which provide the actual inputs to the LSO? Although studies similar to those described above have not yet been performed, it is known that the SBCs (Rhode and Smith 1986; Spirou and others 1990; Smith and others 1993) as well as the principal cells of the MNTB (Guinan, Guinan, and Norris 1972; Tsuchitani 1997; Smith and others 1998; Tollin and Yin 2001) have physiological response characteristics that are nearly identical to their ANF or GBC inputs, respectively: narrow frequency tuning, “primary-like” or “primary-like with notch” responses to tone pips at CF; similar dynamic ranges, and so forth. Based on the close correspondence in physiological responses to sound, it is very likely that the ANF rate representation of the spectrum of the stimuli arriving at the two ears is accurately preserved through the SBCs and GBCs as well as the MNTB. Future experiments should investigate the spectral coding capabilities of the bushy cells and the principal cells of the MNTB.

Inputs to LSO Cells Must Be Matched in Their Frequency Selectivity

For ILD to be computed correctly, the inputs to individual LSO neurons must encode corresponding frequency points of the spectrum or, more correctly, the activity of corresponding points of the basilar membrane. All the available evidence supports this requirement. Like the cochlear nucleus, the S-shaped LSO of the cat exhibits a tonotopic organization with neurons responding preferentially to high frequencies located in the ventromedial limb, and neurons responding to lower frequencies represented in the dorsolateral limb. There is, however, a biased representation of the cochlea so that most of the cells of the LSO respond to high frequencies (Tsuchitani and Boudreau 1966; Guinan, Norris, and Guinan 1972; Tsuchitani 1977). A similar and parallel disproportionate representation of high frequencies exists in the MNTB (Guinan, Norris, and Guinan 1972), and there is some evidence that the frequency selectivity of GBCs is skewed toward high frequencies (Smith and others 1991). The parallel overrepresentation of high frequencies by the GBCs, MNTB, and LSO correlates well with the finding from acoustical measurements in cats that ILDs are prominent only for frequencies greater than approximately 2 to 3 kHz. (The MSO, thought to encode ITDs, has a disproportionate representation of lower frequencies; Guinan, Norris, and Guinan 1972).

Additional supporting evidence from anatomical studies shows that the LSO tonotopy determined from phys-

iological studies matches the topography of the afferent projections to the LSO from the ipsilateral CN tonotopy (Warr 1966; van Noort 1969) and from the ipsilateral MNTB (Elverland 1978; Glendenning and others 1985; Spangler and others 1985; Smith and others 1998). Physiological studies have measured contralateral inhibitory frequency tuning curves by determining the sound level at the contralateral ear that just inhibited a set percentage of the ipsilaterally evoked discharges and showed that the inhibitory frequency tuning curves were similar in shape and yielded nearly identical estimates of the characteristic frequency as the ipsilateral excitatory tuning curves (Boudreau and Tsuchitani 1968; Caird and Klinke 1983; Tsuchitani 1997). That is, the inhibition tends to occur at the lowest intensity of contralateral stimulation when the frequencies of the stimuli presented to the two ears are the same. However, there was a slight tendency for the bandwidths of the frequency tuning estimated from the inhibitory input to be wider than those of the ipsilateral excitatory tuning curves. It was also noted that the tuning curves of MNTB cells of similar best frequencies were narrower than the inhibitory tuning curves of LSO cells, suggesting that there is a convergence of inhibitory MNTB inputs with slightly different frequencies onto LSO cells (Boudreau and Tsuchitani 1968; Sanes and Rubel 1988; Tsuchitani 1997; Tollin and Yin 2001). There are also differences in the inhibitory and the excitatory thresholds at the best frequency, and it is thought that these differences contribute to the encoding of ILDs over different absolute ranges by different cells (Park and others 1997; Tsuchitani 1997).

Inputs to LSO Cells Must Accurately Encode the Temporal Variations in the Acoustical Stimulus at Each Ear

Sounds are characterized not only by their frequency spectra but also by the temporal variations of spectral patterns; that is, most sounds are modulated over time in both frequency and amplitude. Species-specific communications such as speech and animal vocalizations are prime examples as are natural sounds such as rustling leaves and snapping twigs. To determine the ILD present in these signals, the representations of the inputs to the two ears must reflect the temporal variations in the spectra. How do the components of the ILD pathway accomplish this?

The ascending pathway through the LSO contains anatomical and physiological specializations for accurate encoding of temporal information. Anatomical studies have indicated that both the ANF synapses onto the bushy cells of the CN (Brawer and Morest 1975; Cant and Morest 1979; Smith and Rhode 1987) and the intrinsic biophysical properties of the bushy cells themselves (Oertel 1999; Trussel 2002) appear to be specialized to permit the accurate preservation of temporal information. Indeed, physiological evidence suggests that the ability of bushy cells to encode the temporal variations in the fine structure of low-frequency stimuli may be enhanced over that of their ANF input (Joris and others

1994). At high frequencies where ILDs are useful, ANFs cannot encode temporal fine structure (Johnson 1980), but they can encode the amplitude (Joris and Yin 1992) and frequency modulations of the stimuli (Britt and Starr 1976) with high fidelity. Moreover, the representations of the amplitude and frequency modulations are accurately preserved in the responses at the CN bushy cells and MNTB principal cells (Moller 1974; Rhode and Smith 1986; Rhode and Greenberg 1994; Joris and Yin 1998). MNTB cells also have membrane properties that are similar to the bushy cells (Wu and Kelly 1991; Banks and Smith 1992) and are thus well suited to preserve temporal information (e.g., Joris and Yin 1998).

Inputs to LSO Cells from the Two Ears Must Arrive in Temporal Register

A critical and related requirement is that the inputs to the LSO must also be compared in temporal register. If the peripheral representations of brief sounds or of sounds having rapid amplitude and/or frequency modulations do not arrive in approximate register, then the computation of the ILD will be compromised. Because this timing-related point runs counter to many of the assumptions regarding ILD selectivity, we shall delve more deeply into it.

The ILD-timing problem is illustrated by Joris and Yin (1995) in Figure 3. The figure shows the hypothetical encoding of a sinusoidally amplitude-modulated (AM) tone by the neurons comprising the ILD pathway (see Fig. 1). In Figure 3A, three periods of the AM waveform are shown as arriving at the ears with zero time delay, or zero interaural phase difference in the envelopes. The figure reflects the fidelity by which the inputs to the LSO actually encode the temporal pattern of the AM stimulus; that is, the temporal fluctuations in the amplitude of the stimulus are conveyed in the timing of the discharge rates of the cells. For the LSO to compute the "correct" ILD present for this condition, which is 0 dB because the stimuli are of equal amplitude, the inputs from the ipsilateral SBC and the ipsilateral MNTB cell must affect the LSO cells synaptically at the same time. For this ideal scenario, Figure 3A shows that the LSO response is minimal when the ILD of the stimulus is 0 dB. However, if at any point along the pathway from the acoustic source of the stimuli to the synaptic inputs to the LSO there is an added delay, then the inputs will not arrive at the LSO in register, and, consequently, there will be a corresponding change in the relative levels of excitation and inhibition. The functional consequences of such a delay are illustrated in Figure 3B, in which the neural representation of the contralateral AM stimulus is shown as arriving at the LSO later than the ipsilateral representation. (In the figure, the delay is imposed on the acoustical stimuli themselves, but in principle the delay could also arise at any point in the circuitry prior to the LSO.) In this case, because the temporally precise excitatory and inhibitory representations of the AM waveforms from the ipsilateral and contralateral ears, respectively, are not being compared in register, there is

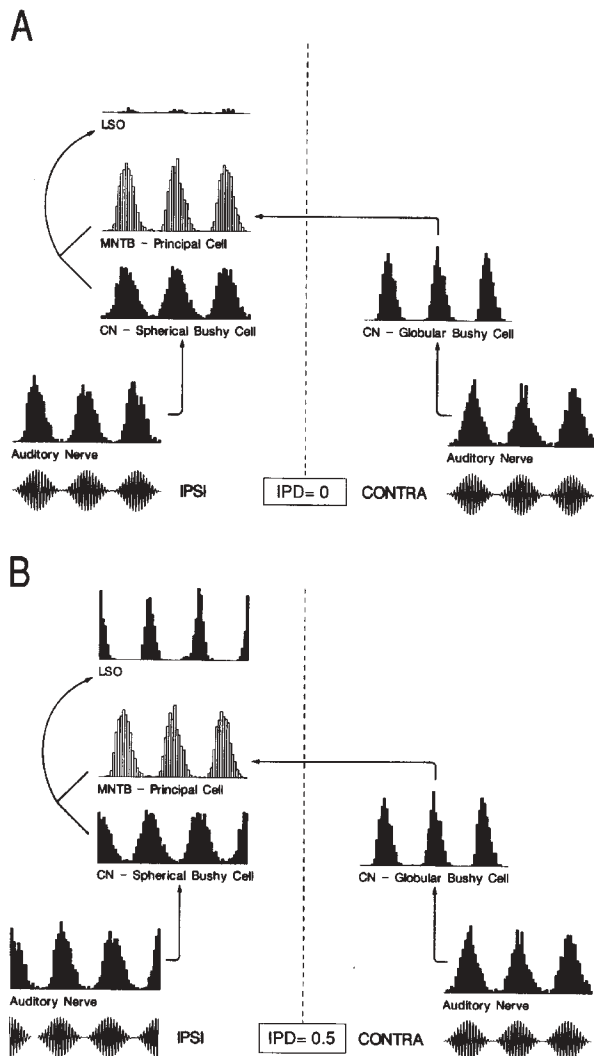


Fig. 3. Schematic illustration of the hypothetical effect of time-delayed contralateral inhibition on interaural level difference (ILD) coding at the lateral superior olive (LSO). *A*, Hypothetical responses of an LSO cell and its afferent inputs (see Fig. 1) plotted as poststimulus time histograms to an amplitude-modulated (AM) stimuli presented in phase to the two ears (e.g., no time delay) and with an ILD of 0 dB. In this example, the afferents are shown as accurately encoding the ongoing modulations in the amplitude (or envelopes) of the stimuli and the excitatory and inhibitory representations of the stimuli arriving at the LSO cell in temporal register. This results in a strong suppression of the discharge rate at the LSO. In this case, an ILD of 0 dB yields a small discharge rate. *B*, Hypothetical responses of an LSO cell and its afferents to an AM stimuli with an ILD of 0 dB but with a time delay (or, equivalently, an interaural phase difference [IPD] in the envelopes) imposed on the stimulus at the contralateral ear. This delay is preserved by the contralateral afferents to the LSO so that the excitation and inhibition do not arrive in temporal register but rather with a delay. Due to the rapid encoding of the amplitude modulations, there is an effective release from inhibition resulting in much larger discharge rate than that shown for the example in *A*. Although the ILDs of these two stimuli are identical, the discharge rate of the LSO cell is not the same due to the specifics of the arrival times from the two sides. Although the delay in this example is imposed on the acoustic stimuli themselves, a similar effect could occur by imposing a delay at any point along the contralateral pathway to the LSO as shown in Figure 1. MNTB = medial nucleus of the trapezoid body; CN = cochlear nucleus; IPSI = ipsilateral; CONTRA = contralateral. Figure reprinted with permission from Joris and Yin (1995). Copyright 1995 by the Society for Neuroscience.

a corresponding release from inhibition leading to the discharge of the LSO cell. Hence, the consequence of a delay is the possibility that the ILD being conveyed by the discharge rate of the LSO cell is different from that actually present in the stimulus.

There are at least three factors that could potentially delay the arrival of the contralateral input and work against the seemingly simple requirement of computing the ILD in temporal register: 1) anatomically, the path to the LSO is longer from the contralateral than the ipsilateral ear; 2) there is an additional synapse, in the MNTB, that the information from the contralateral ear must traverse; and 3) the stimulus may not arise equidistant from the two ears, generating an additional sound path length to the far ear, or ITD. But there are also at least three anatomical specializations along the contralateral pathway that work in concert to compensate for the delay brought about by the added path length and extra synapse in the contralateral ear input. First, the axonal diameters of the GBCs, which provide the input to the contralateral MNTB, are about three times larger than the axons from the SBCs that provide the excitatory

input from the ipsilateral CN and MNTB axons and are roughly twice the diameter of SBCs (see Joris and Yin 1998, p 264). Thus, conduction times through axons are relatively shorter in the contralateral than in the ipsilateral circuit. Second, although the MNTB has traditionally been thought of as a relay nucleus whose sole purpose is to invert the sign of the synaptic input to the LSO from the contralateral CN from excitatory to inhibitory, the GBC/MNTB synapse may have further functions. A massive synaptic terminal from the contralateral GBCs referred to as the calyx of Held (Held 1893) excites MNTB cells. Each MNTB principal neuron receives only a single calyx from a GBC, the claw-like calyx enveloping about half of the available surface of the soma, and large terminals that produce large synaptic currents (Banks and Smith 1992; Smith and others 1998). Moreover, the GBCs act on MNTB neurons that have short time constants and fast receptors. These properties together result in large, rapid EPSPs that excite MNTB cells with invariant synaptic delays (Trussell 2002). Collectively, these synaptic specializations allow the physiological response properties of MNTB to be

virtually identical to their GBC inputs not only in their representation of the stimulus spectrum but also in their representation of the time structure of the stimulus (Guinan, Guinan, and Norris 1972; Tsuchitani 1997; Smith and others 1998). Finally, there is anatomical evidence that the MNTB afferents to the LSO synapse right on or near the soma whereas the excitatory inputs synapse more on the distal dendrites (Cant 1984; Helfert and others 1992; Smith and others 1998). Collectively, these specializations ensure both rapid and precise transmission to LSO cells of the spectral and temporal characteristics of the stimulus arriving at the contralateral ear. Finally, in a series of physiological experiments using two independent methods, Joris and Yin (1998) showed that on average, the contralateral inhibitory input reaches the LSO within only about 200 μ s of the excitatory input from the ipsilateral ear, although individual cells showed some variability in the relative time of arrival of the inhibitory input.

The data reviewed above show that the components of the ILD pathway come very close to fully supporting the requirement that the inputs be compared in exact temporal register. The functional implication of the rapid transmission to the LSO of the contralateral inhibition is that for transient sounds or sounds with ongoing rapid amplitude or frequency modulations, the inhibition of the discharge rate of the LSO should be nearly maximal when these stimuli are presented to the two ears with no delay between their onsets. This is precisely what has been found in physiological experiments for which the delay between the onsets of transients or AM stimuli of equal level presented to the two ears were systematically varied (Caird and Klinke 1983; Joris and Yin 1995; Park and others 1996; Batra and others 1997; Irvine and others 2001). These data confirm earlier reports that the initial onset discharges by some LSO neurons to stimuli delivered with equal amplitude to the two ears and with zero onset delay could be inhibited (Boudreau and Tsuchitani 1968) and are also consistent with *in vitro* intracellular recordings of synaptic potentials that demonstrate that the relative time of arrival of evoked EPSPs and IPSPs can have a dramatic effect on the discharge probability of LSO neurons (Wu and Kelly 1991). As suggested by Joris and Yin (1998), the apparent sensitivity of LSO neurons to the ITDs of AM tones and transient stimuli probably reflects the very rapid encoding of ILDs in the temporal waveforms of the stimuli rather than ITD per se (Joris and Yin 1998). Hence, one likely explanation for the remarkable timing specializations observed along the contralateral pathway to the LSO is to minimize the relative delays and jitter in the synaptic delays incurred along the ILD pathway so that ILDs in the stimulus, particularly for brief, transient stimuli, are faithfully encoded.

Inputs to the LSO from Each Ear Must Be Compared over Short Time Intervals

Closely related to the points made above, for transient stimuli or stimuli with rapid amplitude or frequency

modulations (e.g., Fig. 3), the functional usefulness of the LSO afferents' accurate encoding of the temporal variations in the stimuli and the comparison of the inputs in nearly temporal register is reduced unless the inputs are compared over short time intervals. That is, the integration time of the comparison should be short so that ILDs are computed only over brief, temporally corresponding portions of the stimuli. Although *in vitro* intracellular studies have revealed that evoked IPSPs in LSO cells have relatively long durations (3.2–8.1 ms; Sanes 1990), physiologically they are functionally effective in suppressing ipsilaterally evoked discharges of LSO cells for only about ~1.0 to 2.0 ms (Sanes 1990; Wu and Kelly 1992; Joris and Yin 1995; Park and others 1996; Irvine and others 2001). Such a short integration time ensures that only those portions of the ongoing waveform whose neural representations arrive at the LSO in register will be compared.

The Responses of LSO Cells Should Reflect the ILD Present in the Stimulus

Physiological studies spanning 4 decades have consistently found that LSO cells are ILD sensitive, with the discharge rates of single neurons correlated with the ILDs in a narrow band of frequencies present in the acoustic waveforms, which are around the best frequency of the cell (Galambos and others 1959; Boudreau and Tsuchitani 1968; Guinan, Guinan, and Norris 1972; Caird and Klinke 1983; Sanes and Rubel 1988; Joris and Yin 1995; Park and others 1997; Irvine and others 2001; Tollin and Yin 2002a). Figure 4 shows the method by which ILD sensitivity has been typically studied. First, a pure tone stimulus at the best frequency (BF) of the cell is presented to the ipsilateral excitatory ear at a constant level resulting in a constant discharge rate. The effectiveness of the inhibition is then assessed by observing how the discharge rate decreases as a function of the sound level of a simultaneously presented tone to the contralateral ear (top abscissa, Figure 4E). Figure 4A–D shows the responses of this neuron to stimuli at four different ILDs displayed as dot rasters and associated post-stimulus time histograms. The data points marked A–D in panel E show the discharge rates evoked by these ILDs. With the ipsilateral level held constant, as the level of the contralateral tone was increased, the firing rate decreased. The bottom abscissa plots the ILD, which, by our definition, is the difference between the contralateral and ipsilateral stimulus levels. For ILDs that favor the contralateral ear, the discharge of this neuron became completely inhibited. The response rate fell even below the spontaneous firing rate of the cell (horizontal dashed line), as shown for an ILD of 15 dB in panel D. Note that this cell preferentially encodes stimuli with ILDs favoring the ipsilateral excitatory ear. Most cells in the LSO respond preferentially to this pattern of ipsilateral ILDs (Boudreau and Tsuchitani 1968; Caird and Klinke 1983; Sanes and Rubel 1988; Joris and Yin 1995; Park and others 1997; Tollin and Yin 2002a). Extrapolating from the ILDs actually available to cats (see Fig. 2), each LSO,

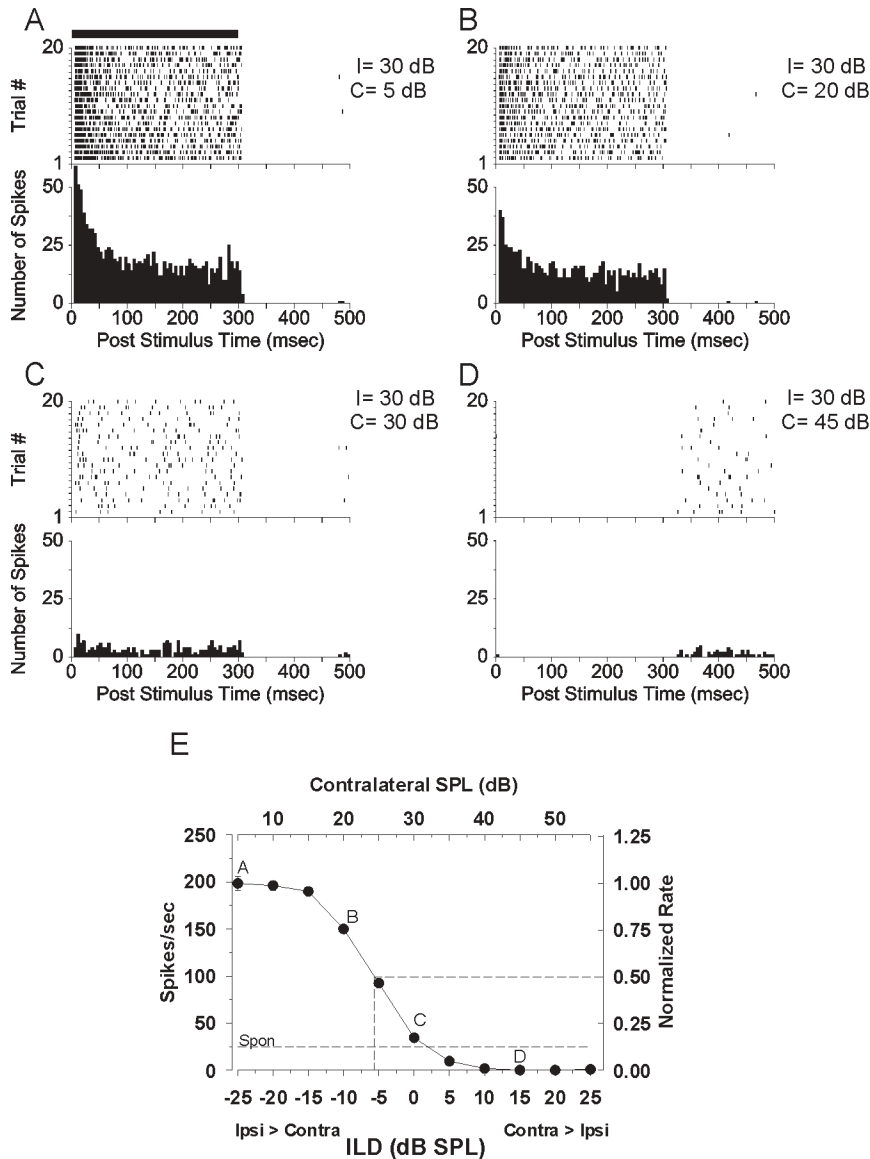


Fig. 4. Lateral superior olive (LSO) cells are sensitive to interaural level differences (ILDs). *A-D*, Extracellular responses of one LSO cell with a best frequency (BF) of 16 kHz displayed as dot rasters and associated poststimulus time histograms to 300-ms tone bursts at the BF of the cell presented 20 times for each ILD (indicated in the top right-hand corner). The level of the tone to the ipsilateral excitatory ear was fixed at 30 dB sound pressure level (~20 dB above threshold) whereas the level of the same BF tone presented to the contralateral inhibitory ear was increased. *E*, Responses of the LSO cell to variations in the ILD expressed as the mean discharge rate ± 1 SEM computed over the duration of the stimuli and across the 20 repetitions. The top abscissa indicates the level of the stimulus to the contralateral ear, whereas the bottom abscissa indicates the ILD, defined as the difference between the sound level at the contralateral ear and that at the ipsilateral ear. Hence, negative ILDs indicate greater sound levels at the excitatory ear. The dashed horizontal line indicates the spontaneous rate. Ipsi = Ipsilateral; contra = contralateral. Figure reprinted with permission from Tollin DJ, Yin TC. 2002a. The coding of spatial location by single units in the lateral superior olive of the cat. *J Neurosci* 22(4):1454–67. Copyright 2002 by the Society for Neuroscience.

then, would likely encode information primarily about ipsilateral sound sources because they would be inhibited for contralateral sources.

LSO cells have been shown to respond to ILDs over a range sufficient to encode the ILDs expected from acoustical measurements (see Fig. 2*B*). Different LSO cells display sensitivity over different absolute ranges of ILDs and can signal the ILD for different types of acoustical signals provided the stimuli fall within the frequency selectivity of the cell (Boudreau and Tsuchitani 1968; Caird and Klinke 1983; Sanes and Rubel 1988; Joris and Yin 1995; Park and others 1997; Batra and others 1997; Tollin and Yin 2002a). However, there are complications. Although LSO cells have been shown to encode changes in the ILD of simple deterministic stimuli (e.g., pure tones) via corresponding changes in their discharge rates, the rates generally are not consistent as global aspects of the signal are changed. For example, the discharge rate of many LSO

cells can change dramatically as the overall level of the stimuli is changed despite a constant ILD (Tsuchitani and Boudreau 1969). Also, as shown in Figure 3, large delays in the contralateral input to the LSO can change the discharge rate. Consequently, a given ILD does not always correspond to a fixed discharge rate. It is important to remember, however, that evidence of this sort need not suggest that across the population of cells the LSO is not computing a correlate of the ILD in the stimulus. More population studies need to be done for binaural stimulation at the level of the SOC in general and the LSO in particular. Second, although naturally occurring ILDs are created through joint increases in the sound level at the ipsilateral ear and attenuation at the contralateral ear (Irvine 1987), few studies have examined ILD sensitivity under this more natural condition.

There are at least two additional issues. First, until recently, no experiment has ever tested whether LSO cells actually can encode the ILDs present in broadband

stimuli that contain all the acoustical cues to location in their native combinations, such as would be the case for sounds presented in the free field. Second, LSO cells are sensitive to each of the cues to horizontal location when they are presented in isolation; that is, certain types of ITDs (Caird and Klinke 1983; Finlayson and Caspary 1991; Joris and Yin 1995; Park and others 1996; Batra and others 1997; Tollin and others 2000; Irvine and others 2001), overall sound level which is important for the spectral cues (Tsuchitani and Boudreau 1966; Tsuchitani 1997; Tollin and Yin 2002a), and, of course, ILDs. A recent series of studies has addressed both of these points by presenting broadband noise stimuli that contained all the acoustical cues to location in their natural combinations over earphones to anesthetized cats (Tollin and Yin 2002a, 2002b). The broadband noise was first filtered by a left- and right-ear HRTF from a desired location, taken from a larger set of HRTF measurements from many different locations made by Musicant and others (1990), and presented over earphones (see Wightman and Kistler 1989; Brugge and others 1994, for a description of the technique). Because the HRTFs contain the complete spatial- and frequency-dependent transformation a sound undergoes as it travels from source to eardrum (see Fig. 2A), the HRTF-filtered sounds presented to the two ears from the earphones were similar to those that would have arisen had the cat been stimulated by the sound stimuli delivered from that location in space. This is the basis of the so-called virtual space (VS) technique.

Figure 5 shows the response of the same LSO cell as in Figure 4 to 200-ms broadband noise bursts from five different virtual locations along the horizontal plane under two different conditions. Figure 5A shows the normal binaural condition for which all the acoustical cues to location were presented in their natural combinations at each of the five azimuthal locations. As expected from the response of this cell to ILDs of a pure tone stimulus at the BF of the cell in Figure 4, there was a vigorous response of the cell for sound sources in the ipsilateral field, a diminished response at the midline, and what appears to be inhibition for sources in the contralateral field. This pattern of responses is partly expected because for ipsilateral sources, the sound level to the excitatory ear, as seen through the frequency selectivity of the cell, exceeded the sound level at the inhibitory ear and vice versa for sources in the contralateral field.

That the spatial sensitivity of this cell was determined in part by the contralateral inhibition was confirmed in Figure 5B, which shows the response to the VS stimuli presented only to the ipsilateral excitatory ear by turning off the contralateral earphone. Under this condition, the actual effect of the contralateral inhibition on the spatial sensitivity is clear, as evidenced by the increased responsiveness for sounds at all locations, particularly at the midline and for contralateral locations where there is no longer evidence of inhibition. Figure 6A shows the spatial sensitivity of this cell plotted as the mean discharge rate for 21 different azimuths in the frontal hemisphere for the normal binaural ear and the monaural ipsilateral-

ear-only conditions. By comparing the discharge rates as a function of azimuth for the normal binaural condition to those evoked by the ipsilateral ear only, the effect of the contralateral inhibition is particularly evident. We refer to these as spatial receptive fields (SRFs) in azimuth.

Tollin and Yin (2002a) repeated the measurements of the spatial receptive fields for a population of LSO cells and showed that they are sensitive to variations in the azimuth of sounds consistent with their ipsi-excitatory and contra-inhibitory binaural interaction as assessed from the pure tone stimuli. All cells appeared to encode information about sound location for stimuli in the ipsilateral field as most were inhibited for sources contralateral to the midline. More important, strong correlations were documented between the shapes of the spatial receptive fields as a function of the BF of the cell being studied and the ILD cues actually present (see Fig. 2B) in a narrow band of frequencies around the BF of the cells. The cells maintained their sensitivity to azimuth over a wide range of overall sound levels under binaural but not monaural stimulation.

But what about the sensitivity to the other cues and what do they contribute to the SRFs? To more directly test this, the VS stimuli were digitally manipulated in such a way as to hold constant (or vary) with changes in stimulus azimuth each of the localization cues in turn while varying (or holding constant) the remaining cues (Tollin and Yin 2002b) in what might be described as a localization cue titration experiment. Panels B-D in Figure 6 show for the same cell as in Figures 4, 5, and 6A the SRFs that result from these manipulations. Figure 6B shows the effects of manipulating the ILD cues, Figure 6C shows the effects of manipulating the ITD cues, and Figure 6D shows the effects of manipulating the monaural spectral cues. In each of these three panels, the normal binaural SRF is shown for reference (filled circles), and the two additional plots show the effect on the SRF of manipulating one of the cues by holding it at a constant value for all azimuths while letting the remaining cues vary naturally (open squares) or allowing that cue to vary with azimuth while holding the remaining two cues constant (red squares). When a cue or cues were held constant, we set them to values consistent with the cues provided by a stimulus delivered from the midline. When the ILD cue was manipulated, it was done so by appropriately increasing or decreasing the amplitude of the stimuli presented to each ear until the desired ILD, as computed through a 1/3-octave Gaussian filter centered on the BF of the unit being studied, was obtained.

Through the selective manipulation of the acoustical cues to location, Tollin and Yin (2002b) were able to determine directly that the ILDs present in a small band of frequencies around the BF of each cell were the primary determinants of the VS fields that were measured under the normal binaural conditions for which all the cues varied naturally. An example is shown in Figure 6B. When the ILD cue varied naturally with azimuth but the ITD and the monaural spectral shape cues held constant (the Δ -ILD condition), the SRF was similar to that meas-

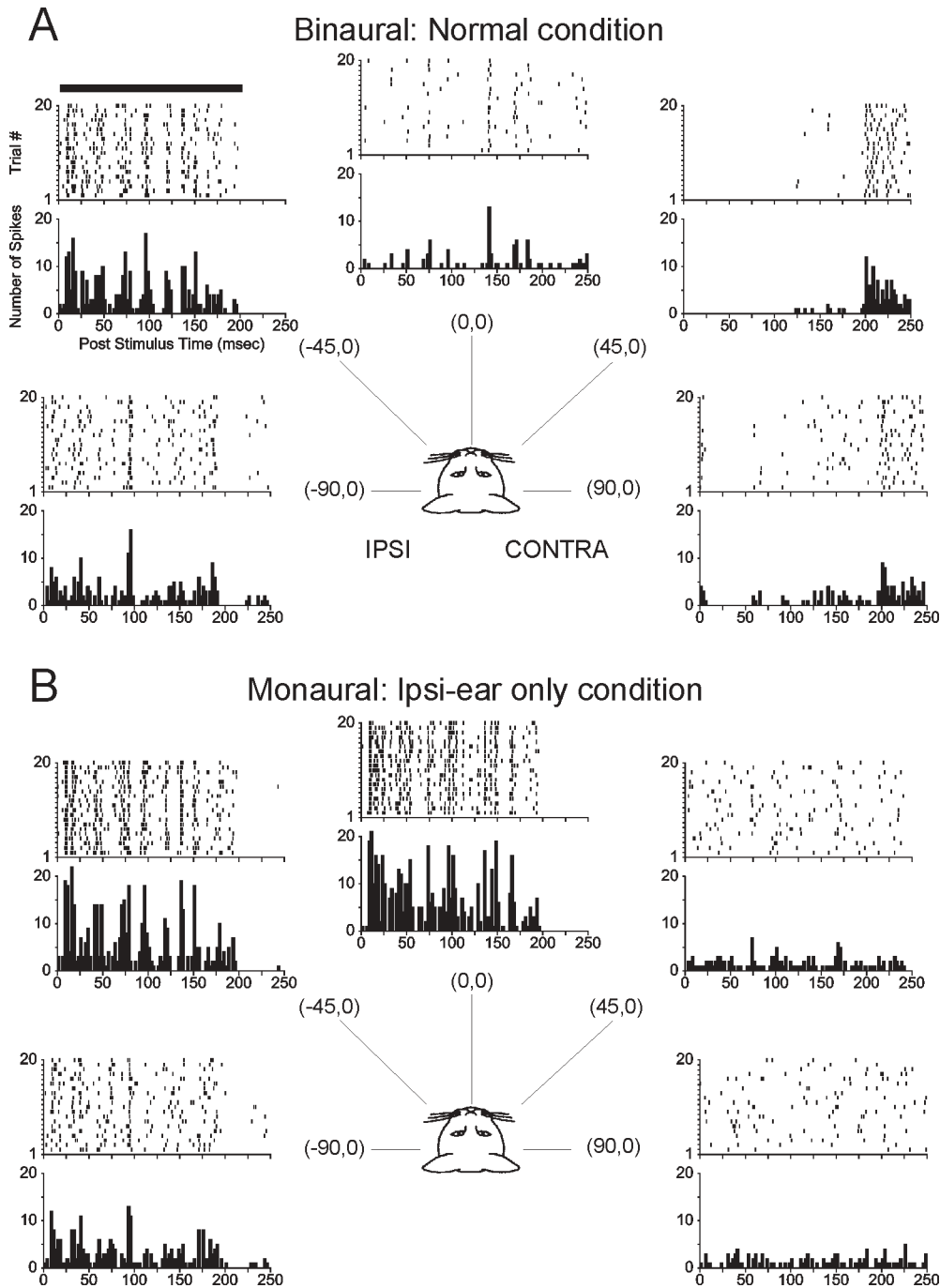


Fig. 5. Lateral superior olive (LSO) cells are sensitive to the spatial location of broadband sound sources. Extracellular responses of the same LSO cell seen in Figure 4 shown as dot rasters and associated poststimulus time histograms to variations in the virtual space azimuth of a 200-ms broadband noise stimuli. The location of the stimulus was manipulated by filtering the same noise with a left- and right-ear head-related transfer functions appropriate for each azimuthal position and presenting the stimuli over earphones. The stimuli were presented 20 times each at 21 different azimuths, 5 of which are shown here, under two conditions, binaural (A) and monaural (B). A, Responses for the normal binaural condition for which all the acoustical cues to location were presented to the two ears in their natural combination at each azimuth. Note the strong responses for ipsilateral azimuths and the apparent inhibition for contralateral azimuths. This is expected because ipsilateral sources result in higher sound levels at the excitatory ear relative to those at the contralateral ear, resulting in increased responses, whereas contralateral sources result in higher sound levels at the inhibitory ear than at the excitatory ear, resulting in decreased responses. B, Responses in the monaural ipsilateral-ear-only condition. Here, the stimulus was presented only to the excitatory ear as a function of azimuth; the contralateral earphone was simply shut off. The increased discharge rate at all azimuths reveals the effect of the contralateral inhibition observed in the example shown in A. ILD = interaural level difference. Figure reprinted with permission from Tollin DJ, Yin TC. 2002a. The coding of spatial location by single units in the lateral superior olive of the cat. I. Spatial receptive fields in azimuth. *J Neurosci* 22(4):1454–67.

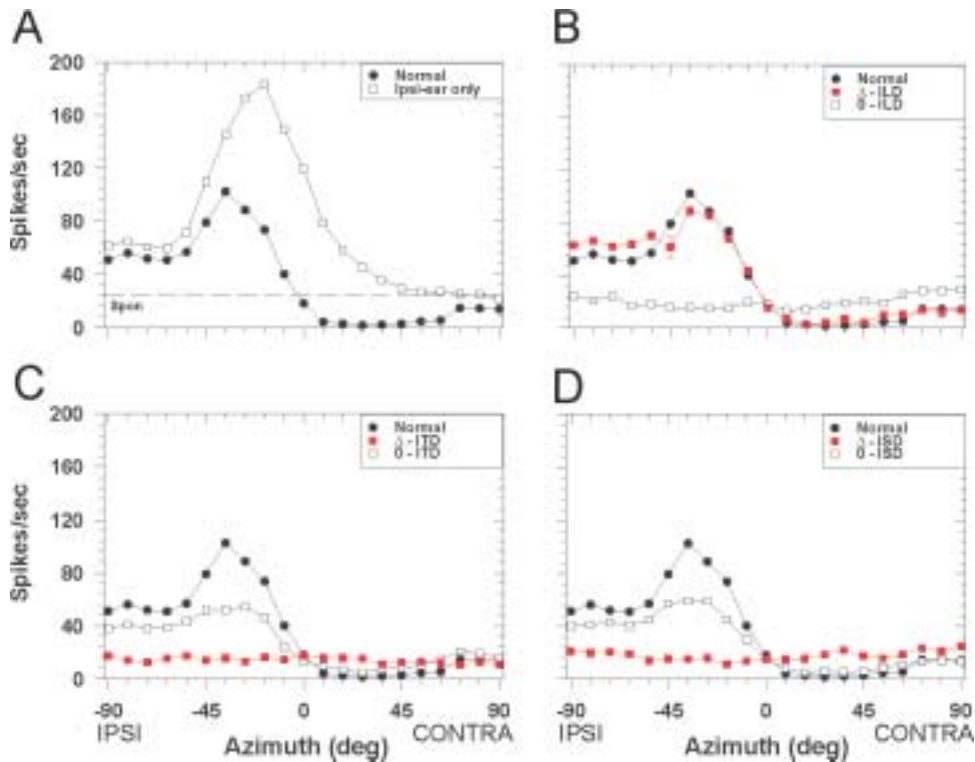


Fig. 6. Spatial receptive fields in azimuth of lateral superior olive (LSO) cells. *A*, The spatial receptive field (SRF) in azimuth of the same LSO cell shown in Figures 4 and 5 plotted as the mean discharge rate ± 1 SEM for both the normal binaural condition (filled circles) and the monaural ipsilateral-ear-only condition (open squares). The apparent inhibition for contralateral sound sources as shown in Figure 5 is readily apparent in the SRF. Presenting the stimulus to only the excitatory ipsilateral ear reveals the effect of the contralateral inhibition seen in the normal binaural condition. The dashed line indicates the spontaneous activity of this cell. *B-D*, Effects of manipulating the acoustical cues to location on the SRFs in azimuth. Each cue was either held constant while the remaining two cues were allowed to vary naturally with changes in the azimuth of the sound sources (open squares) or changed naturally with azimuth while the remaining cues were held at fixed values (red squares). Cues held constant took values consistent with those for the midline location; that is, zero interaural time difference (ITD) and interaural level difference (ILD) and monaural spectral shape cues identical for a stimulus at the midline. For comparison, the normal binaural SRF is shown in each panel (filled circles). *B*, Effects of manipulating the ILD cues. *C*, Effects of manipulating the ITD cues. *D*, Effects of manipulating the monaural spectral cues. Only when the ILD cues were allowed to change with azimuth (Δ -ILD in *B*, 0-ITD in *C*, and 0-ISD in *D*) was the response of the LSO cell similar to the response under the normal binaural condition in which all the cues varied with azimuth. As shown in *C* and *D*, there was little response modulation as either ITD (Δ -ITD) or the spectral cues (Δ -ISD) were varied in isolation with azimuth. IPSI = ipsilateral; CONTRA = contralateral.

ured when all three of these cues varied naturally with azimuth. Because the ITD and spectral cues were held fixed for all azimuths, the close correspondence between the SRF for the Δ -ILD condition and the normal SRF strongly implicate the ILD in the narrow band of frequencies around the BF of the stimuli as the primary determinant of the normal SRF for this cell. In contrast, when the ILD cue in the same narrow band was held constant at 0 dB for all azimuths but the ITD and spectral cues changed naturally (0-ILD condition), there was no modulation of the response with azimuth (Figure 6 *C*, *D*, red squares). Hence, ILDs and not ITDs or the monaural spectral shape determined the SRF for this LSO cell. Similar results were obtained across a population of LSO cells (Tollin and Yin 2002b). The finding that ITDs and the spectral cues contributed little to the spatial sensitivity is consistent with earlier reports of ILD dominance in LSO responses to complex sounds with limited combinations of physiologically plausible ITDs and ILDs (Caird and Klinke 1983; Joris and Yin 1995).

However, for stimuli of transient nature, ITDs can have a larger effect through the mechanisms described in Figure 3 (Caird and Klinke 1983; Park and others 1996; Irvine and others 2001).

Comparative Studies and the Functional Role of the LSO

The existence of marked differences across mammalian species in the relative sizes of the major nuclei comprising the SOC provides important clues as to the different functions of these nuclei (Harrison and Irving 1966; Irving and Harrison 1967; Harrison and Feldman 1970; Glendenning and Masterton 1998; Moore 2000). For example, in mice, hedgehogs, dolphins, and echolocating bats, the LSO and MNTB are extremely large and well developed whereas the MSO is small and sparse. But in primates, including humans, the LSO and MNTB tend to be small whereas the MSO is large. Yet for some mammals, such as cats, dogs, chinchillas, and guinea

pigs, all three main nuclei are well developed. One striking feature of these differences is the consistent parallel development of MNTB and LSO so that mammals with large LSOs typically also have large MNTBs. This finding supports the hypothesis that the LSO and the ipsilateral MNTB form a functional circuit. Interestingly, in a study of the relative sizes of 10 different auditory nuclei in 53 mammals, although all mammals possessed an LSO and MNTB, the MSO was the only nucleus that was found to be entirely absent in some mammals (Glendenning and Masterton 1998).

Why should there be such variation in the relative sizes of the MSO and LSO in different species if both nuclei contribute to encoding the cues to location? In short, because the types and magnitudes of the cues to location that are available to these species differ because of variations in the diameter of the head (see discussion of the localization cues). For example, the usefulness of the ITD cue is diminished in animals with small heads because the magnitude of the maximum ITD is small, yet in these same mammals, the ILDs for high frequencies can be large. Based on this relationship, it has been suggested that the critical need to use ILDs for localization, rather than for communication, has provided the main selective pressure for the evolution of high-frequency hearing in mammals (Masterton and others 1969). Indeed, there is a large and significant correlation between high-frequency hearing and interaural diameter so that mammals with smaller heads have higher frequency hearing limits than do those with larger heads (Masterton and Diamond 1967). And anatomically, the ratios of the sizes of the major nuclei of the SOC are also closely related to the frequency range of hearing in the species (Masterton and Diamond 1973) so that, in general, the higher the frequency the animals can detect, the larger and more developed the MNTB/LSO circuit, whereas the lower the frequencies that animals can detect, the larger and more well developed the MSO.

Based jointly on the comparative anatomical findings and the localization cues that are available to different species, Masterton and Diamond (1967) suggested that the MSO is involved in ITD coding and that the LSO is concerned with ILD coding. Paralleling the anatomical and physiological correlations, psychophysical data also support this hypothesis. For example, the hedgehog lacks an MSO and also cannot use ITDs in low-frequency stimuli to localize sounds, but it can use ILDs at high frequencies (Masterton and others 1975). Likewise, horses and cattle have diffuse and disorganized LSOs and also lack the ability to use ILDs to localize high-frequency sounds (Heffner RS and Heffner HE 1986). In general, species that cannot localize low-frequency sounds or that rely principally on high-frequency sound have well-developed LSO and MNTB and poorly developed MSO (Irving and Harrison 1967; Masterton and others 1969; Masterton and Diamond 1973; Masterton and others 1975; Heffner RS and Heffner HE 1986). Conversely, animals that cannot localize high-frequency sounds or that typically use low-frequency sounds for communication, like humans, tend to have a prominent MSO but a smaller LSO and

MNTB (Harrison and Feldman 1970; Moore 2000). Finally, in mammals that are sensitive to both low and high frequencies, such as the cat, both the MSO and the LSO/MNTB are prominent and are consequently able to locate accurately both low- and high-frequency stimuli.

There are exceptions to these trends. Several hoofed mammals including pigs, cattle, horses, and goats appear to possess an LSO and MNTB but seem unable to use ILDs to localize high-frequency tones (Heffner RS and Heffner HE 1986, 1989). And although humans have a predictably smaller LSO due to increased head diameter and good low-frequency hearing, the MNTB has been reported to be small (Richter and others 1983) to nonexistent (Moore 2000) despite the fact that humans are extraordinarily sensitive to ILDs over virtually their entire range of hearing (Mills 1960). Clearly, then, in addition to head diameter, and hence the differential availability of ITDs and ILDs, other factors must have provided selective evolutionary pressure for the divergent development of the SOC nuclei across mammals. In fact, head diameter itself accounts for only a small fraction of the variance of sound localization abilities in a large number of mammals tested (Heffner 1997). Interestingly, the one factor (among many tested) that accounts for the highest proportion of the variance is the width of the best field of vision (Heffner 1997), supporting earlier hypotheses that the primary function of the binaural auditory system is to direct the eyes to the source of the sound to permit further visual inspection (Pumphrey 1950; Harrison and Irving 1966). These exceptions aside, comparative studies also strongly implicate the LSO as necessary for ILD processing consistent with our review of the anatomical and physiological data above.

Summary

In summary, we restate here the duplex theory, which posits that the spatial localization of low-frequency sounds is based on the ITD cue whereas the localization of high-frequency sounds is based on ILD cues. It is at the earliest stages in the ascending auditory pathway that we find, in the nuclei of the SOC, the anatomical and physiological specializations necessary to form the neural bases for the duplex theory. The MSO is believed to encode ITD cues whereas the LSO, along with the inhibitory input from the MNTB, is believed to encode ILDs. We approached this review by first listing seven requirements that an ideal ILD processor might possess. In each case, we found strong experimental support for the notion that these requirements are generally implemented by the specializations in the anatomical structures and in the physiological response properties of the cells along the ILD pathway shown in Figure 1. Moreover, comparative studies of the SOC nuclei, the available localization cues, and the localization abilities in a large number of mammals have substantiated these findings. In summary, the literature reviewed here collectively supports the long-held hypothesis that the LSO is the initial ILD processor in the mammalian ascending

auditory pathway. Finally, it has been stated for the MSO, and its presumed role in encoding ITDs, that it is one of the few circuits in the mammalian CNS for which a strong and specific functional hypothesis has been formulated and for which the anatomical and physiological bases can be tested experimentally (Joris and others 1998; Brand and others 2002). We believe that the same should be said of the LSO.

References

- Adams JC, Mugnaini E. 1990. Immunocytochemical evidence for inhibitory and disinhibitory circuits in the superior olive. *Hear Res* 49(1-3):281-98.
- Banks MI, Smith PH. 1992. Intracellular recordings from neurobiotin-labeled cells in brain slices of the rat medial nucleus of the trapezoid body. *J Neurosci* 12(7):2819-37.
- Batra R, Kuwada S, Fitzpatrick DC. 1997. Sensitivity to interaural temporal disparities of low- and high-frequency neurons in the superior olivary complex. I. Heterogeneity of responses. *J Neurophysiol* 78(3):1222-36.
- Blauert J. 1997. *Spatial hearing: the psychophysics of human sound localization—revised edition*. Cambridge (MA): MIT Press.
- Bledsoe SC Jr, Snead CR, Helfert RH, Prasad V, Wenthold RJ, Altschuler RA. 1990. Immunocytochemical and lesion studies support the hypothesis that the projection from the medial nucleus of the trapezoid body to the lateral superior olive is glycinergic. *Brain Res* 517(1-2):189-94.
- Boring EG. 1942. *Sensation and perception in the history of experimental psychology*. New York: Appleton-Century-Crofts.
- Boudreau JC, Tsuchitani C. 1968. Binaural interaction in the cat superior olive S segment. *J Neurophysiol* 31:442-54.
- Boudreau JC, Tsuchitani C. 1970. Cat superior olive s-segment cell discharge to tonal stimulation. In: Neff WD, editor. *Contributions to sensory physiology*. New York: Academic. p 143-213.
- Brand A, Behrend O, Marquardt T, McAlpine D, Grothe B. 2002. Precise inhibition is essential for microsecond interaural time difference coding. *Nature* 417(6888):543-7.
- Brawer JR, Morest DK. 1975. Relations between auditory nerve endings and cell types in the cat's anteroventral cochlear nucleus seen with the Golgi method and Normarski optics. *J Comp Neurol* 160:491-506.
- Britt R, Starr A. 1976. Synaptic events and discharge patterns of cochlear nucleus cells. II. Frequency-modulated tones. *J Neurophysiol* 39(1):179-94.
- Brownell WE, Manis PB, Ritz LA. 1979. Ipsilateral inhibitory responses in the cat lateral superior olive. *Brain Res* 177(1):189-93.
- Brugge JF, Reale RA, Hind JE, Chan JC, Musicant AD, Poon PW. 1994. Simulation of free-field sound sources and its application to studies of cortical mechanisms of sound localization in the cat. *Hear Res* 73(1):67-84.
- Caird D, Klinke R. 1983. Processing of binaural stimuli by cat superior olivary complex neurons. *Exp Brain Res* 52:385-99.
- Calford MB, Pettigrew JD. 1984. Frequency dependence of directional amplification at the cat's pinna. *Hear Res* 14(1):13-9.
- Cant NB. 1984. The fine structure of the lateral superior olivary nucleus of the cat. *J Comp Neurol* 227(1):63-77.
- Cant NB, Casseday JH. 1986. Projections from the anteroventral cochlear nucleus to the lateral and medial superior olivary nuclei. *J Comp Neurol* 247(4):457-76.
- Cant NB, Morest DK. 1979. Organization of the neurons in the anterior division of the anteroventral cochlear nucleus of the cat. Light-microscopic observations. *Neuroscience* 4(12):1909-23.
- Caspary DM, Faingold CL. 1989. Non-N-methyl-D-aspartate receptors may mediate ipsilateral excitation at lateral superior olivary synapses. *Brain Res* 503(1):83-90.
- Casseday JH, Neff WD. 1973. Localization of pure tones. *J Acoust Soc Am* 54:365-72.
- Elverland HH. 1978. Ascending and intrinsic projections of the superior olivary complex in the cat. *Exp Brain Res* 32(1):117-34.
- Finlayson PG, Caspary DM. 1989. Synaptic potentials of chinchilla lateral superior olivary neurons. *Hear Res* 38(3):221-8.
- Finlayson PG, Caspary DM. 1991. Low-frequency neurons in the lateral superior olive exhibit phase-sensitive binaural inhibition. *J Neurophysiol* 65(3):598-605.
- Friauf E, Ostwald J. 1988. Divergent projections of physiologically characterized rat ventral cochlear nucleus neurons as shown by intra-axonal injection of horseradish peroxidase. *Exp Brain Res* 73(2):263-84.
- Galambos R, Schwartzkopf J, Rupert A. 1959. Microelectrode study of superior olivary nuclei. *Am J Physiol* 197:527-36.
- Gescheider GA. 1985. *Psychophysics: Method, theory, and application*. 2nd ed. Hillsdale (NJ): Lawrence Erlbaum Associates.
- Glendenning KK, Baker BN. 1988. Neuroanatomical distribution of receptors for three potential inhibitory neurotransmitters in the brainstem auditory nuclei of the cat. *J Comp Neurol* 275(2): 288-308.
- Glendenning KK, Baker BN, Hutson KA, Masterton RB. 1992. Acoustic chiasm V: inhibition and excitation in the ipsilateral and contralateral projections of LSO. *J Comp Neurol* 319(1):100-22.
- Glendenning KK, Hutson KA, Nudo RJ, Masterton RB. 1985. Acoustic chiasm II: anatomical basis of binaurality in lateral superior olive of cat. *J Comp Neurol* 232:261-85.
- Glendenning KK, Masterton RB. 1983. Acoustic chiasm: efferent projections of the lateral superior olive. *J Neurosci* 3(8):1521-37.
- Glendenning KK, Masterton RB. 1998. Comparative morphometry of mammalian central auditory systems: variation in nuclei and form of the ascending system. *Brain Behav Evol* 51(2):59-89.
- Glendenning KK, Masterton RB, Baker BN, Wenthold RJ. 1991. Acoustic chiasm. III: nature, distribution, and sources of afferents to the lateral superior olive in the cat. *J Comp Neurol* 310(3):377-400.
- Guinan JJ Jr, Guinan SS, Norris BE. 1972. Single auditory units in the superior olivary complex. I: responses to sounds and classifications based on physiological properties. *Int J Neurosci* 4:101-20.
- Guinan JJ Jr, Norris BE, Guinan SS. 1972. Single auditory units in the superior olivary complex. II: location of unit categories and tonotopic organization. *Int J Neurosci* 4:147-66.
- Hafer ER. 1984. Spatial hearing and the duplex theory: how viable is the model? In: Edelman GM, Gall WE, Cowan WM, editors. *Dynamic aspects of neocortical function*. New York: John Wiley and Sons. p 425-48.
- Harrison JM, Feldman ML. 1970. Anatomical aspects of the cochlear nucleus and superior olivary complex. In: Neff WD, editor. *Contributions to sensory physiology*. Vol. 4. New York: Academic. p 95-142.
- Harrison JM, Irving R. 1966. Visual and nonvisual auditory systems in mammals. Anatomical evidence indicates two kinds of auditory pathways and suggests two kinds of hearing in mammals. *Science* 154(750):738-43.
- Harrison JM, Warr WB. 1962. A study of the cochlear nuclei and ascending auditory pathways of the medulla. *J Comp Neurol* 119:341-80.
- Heffner RS. 1997. Comparative study of sound localization and its anatomical correlates in mammals. *Acta Otolaryngol Suppl* 532:46-53.
- Heffner RS, Heffner HE. 1986. Localization of tones by horses: use of binaural cues and the role of the superior olivary complex. *Behav Neurosci* 100(1):93-103.
- Heffner RS, Heffner HE. 1989. Sound localization, use of binaural cues and the superior olivary complex in pigs. *Brain Behav Evol* 33(4):248-58.
- Held H. 1893. Die centrale Gehorleitung. *Arch Anat Physiol Abt* 201-48.
- Helfert RH, Bonneau JM, Wenthold RJ, Altschuler RA. 1989. GABA and glycine immunoreactivity in the guinea pig superior olivary complex [published erratum appears in *Brain Res* 1990 Feb 12;509(1):180]. *Brain Res* 501(2):269-86.
- Helfert RH, Juiz JM, Bledsoe SC Jr, Bonneau JM, Wenthold RJ, Altschuler RA. 1992. Patterns of glutamate, glycine, and GABA immunolabeling in four synaptic terminal classes in the lateral superior olive of the guinea pig. *J Comp Neurol* 323(3):305-25.
- Henkel CK, Brunso-Bechtold JK. 1995. Development of glycinergic cells and puncta in nuclei of the superior olivary complex of the postnatal ferret. *J Comp Neurol* 354(3):470-80.
- Huang AY, May BJ. 1996. Sound orientation behavior in cats. II. Mid-frequency spectral cues for sound localization. *J Acoust Soc Am* 100(2 Pt 1):1070-80.

- Irvine DRF. 1986. The auditory brainstem: processing of spectral and spatial information. Berlin: Springer-Verlag.
- Irvine DR. 1987. Interaural intensity differences in the cat: changes in sound pressure level at the two ears associated with azimuthal displacements in the frontal horizontal plane. *Hear Res* 26(3):267–86.
- Irvine DRF. 1992. Physiology of the auditory brainstem. In: Popper AN, Fay RR, editors. *The mammalian auditory pathway: neurophysiology*. New York: Springer-Verlag. p 153–231.
- Irvine DR, Park VN, McCormick L. 2001. Mechanisms underlying the sensitivity of neurons in the lateral superior olive to interaural intensity differences. *J Neurophysiol* 86(6):2647–66.
- Irving R, Harrison JM. 1967. The superior olivary complex and audition: a comparative study. *J Comp Neurol* 130(1):77–86.
- Johnson DH. 1980. The relationship between spike rate and synchrony in responses of auditory-nerve fibers to single tones. *J Acoust Soc Am* 68:1115–22.
- Johnson DH, Dabak A, Tsuchitani C. 1990. Function-based modeling of binaural processing: interaural level. *Hear Res* 49(1-3):301–19.
- Joris PX, Carney LH, Smith PH, Yin TCT. 1994. Enhancement of neural synchronization in the anteroventral cochlear nucleus. I. Responses to tones at the characteristic frequency. *J Neurophysiol* 71(3):1022–36.
- Joris PX, Smith PH, Yin TC. 1998. Coincidence detection in the auditory system: 50 years after Jeffress. *Neuron* 21(6):1235–8.
- Joris PX, Yin TC. 1992. Responses to amplitude-modulated tones in the auditory nerve of the cat. *J Acoust Soc Am* 91(1):215–32.
- Joris PX, Yin TC. 1995. Envelope coding in the lateral superior olive. I. Sensitivity to interaural time differences. *J Neurophysiol* 73(3):1043–62.
- Joris PX, Yin TCT. 1998. Envelope coding in the lateral superior olive. III. Comparison with afferent pathways. *J Neurophysiol* 79(1):253–69.
- Joris PX, Yin TC, Smith PH. 1990. Mechanisms of azimuthal sound localization in the central nervous system of the cat. *J Dutch Acoust Soc* 104:23–35.
- Kavanagh GL, Kelly JB. 1992. Midline and lateral field sound localization in the ferret (*Mustela putorius*): contribution of the superior olivary complex. *J Neurophysiol* 67(6):1643–58.
- Kiang NYS, Watanabe T, Thomas EC, Clark LF. 1965. *Discharge patterns of single fibers in the cat's auditory nerve*. Cambridge (MA): MIT Press.
- Lord Rayleigh. 1877. Acoustical observations. *Phil Mag* 3(6th Ser.):456–64.
- Lord Rayleigh. 1907. On our perception of sound direction. *Philos Mag* 13(6th Ser.):214–32.
- Martin RL, Webster WR. 1989. Interaural sound pressure level differences associated with sound-source locations in the frontal hemifield of the domestic cat. *Hear Res* 38(3):289–302.
- Masterton B, Diamond IT. 1967. Medial superior olive and sound localization. *Science* 155(770):1696–7.
- Masterton B, Diamond IT. 1973. Hearing: central neural mechanisms. In: Carterett EC, Friedman MP, editors. *Handbook of perception: biology of perceptual systems*. Vol. 3. New York: Academic. p 408–48.
- Masterton B, Heffner H, Ravizza R. 1969. The evolution of human hearing. *J Acoust Soc Am* 45(4):966–85.
- Masterton B, Jane JA, Diamond IT. 1967. Role of brainstem auditory structures in sound localization. I. Trapezoid body, superior olive, and lateral lemniscus. *J Neurophysiol* 30(2):341–59.
- Masterton B, Thompson GC, Bechtold JK, RoBards MJ. 1975. Neuroanatomical basis of binaural phase-difference analysis for sound localization: a comparative study. *J Comp Physiol Psychol* 89(5):379–86.
- May BJ, Huang AY. 1997. Spectral cues for sound localization in cats: a model for discharge rate representations in the auditory nerve. *J Acoust Soc Am* 101(5 Pt 1):2705–19.
- Middlebrooks JC, Green DM. 1991. Sound localization by human listeners. *Annu Rev Psychol* 42:135–59.
- Middlebrooks JC, Makous JC, Green DM. 1989. Directional sensitivity of sound-pressure levels in the human ear canal. *J Acoust Soc Am* 86(1):89–108.
- Mills AW. 1958. On the minimum audible angle. *J Acoust Soc Am* 30:237–46.
- Mills AW. 1960. Lateralization of high frequency tones. *J Acoust Soc Am* 32:132–4.
- Moller AR. 1974. Responses of units in the cochlear nucleus to sinusoidally amplitude-modulated tones. *Exp Neurol* 45(1):105–17.
- Moore CN, Casseday JH, Neff WD. 1974. Sound localization: the role of the commissural pathways of the auditory system of the cat. *Brain Res* 82:13–26.
- Moore DR, Irvine DR. 1979. A developmental study of the sound pressure transformation by the head of the cat. *Acta Otolaryngol* 87(5-6):434–40.
- Moore JK. 2000. Organization of the human superior olivary complex. *Microsc Res Tech* 51(4):403–12.
- Moore MJ, Caspary DM. 1983. Strychnine blocks binaural inhibition in lateral superior olivary neurons. *J Neurosci* 3(1):237–42.
- Musicant AD, Chan JC, Hind JE. 1990. Direction-dependent spectral properties of cat external ear: new data and cross-species comparisons. *J Acoust Soc Am* 87(2):757–81.
- Oertel D. 1999. The role of timing in the brain stem auditory nuclei of vertebrates. *Annu Rev Physiol* 61:497–519.
- Osen KK. 1969. The intrinsic organization of the cochlear nuclei in the cat. *Acta Otolaryngol* 67:352–9.
- Park TJ, Grothe B, Pollak GD, Schuller G, Koch U. 1996. Neural delays shape selectivity to interaural intensity differences in the lateral superior olive. *J Neuroscience* 16(20):6554–66.
- Park TJ, Monsivais P, Pollak GD. 1997. Processing of interaural intensity differences in the LSO: role of interaural threshold differences. *J Neurophysiol* 77(6):2863–78.
- Phillips DP, Calford MB, Pettigrew JD, Aitkin LM, Semple MN. 1982. Directionality of sound pressure transformation at the cat's pinna. *Hear Res* 8(1):13–28.
- Poon PW, Brugge JF. 1993. Virtual-space receptive fields of single auditory nerve fibers. *J Neurophysiol* 70(2):667–76.
- Pumphrey RJ. 1950. Hearing. Symposium of the Society for Experimental Biology 4:1–18.
- Rhode WS, Greenberg S. 1994. Encoding of amplitude modulation in the cochlear nucleus of the cat. *J Neurophysiol* 71(5):1797–825.
- Rhode WS, Smith PH. 1986. Encoding timing and intensity in the ventral cochlear nucleus of the cat. *J Neurophysiol* 56(2):261–86.
- Rice JJ, May BJ, Spirou GA, Young ED. 1992. Pinna-based spectral cues for sound localization in cat. *Hear Res* 58(2):132–52.
- Rice JJ, Young ED, Spirou GA. 1995. Auditory-nerve encoding of pinna-based spectral cues: rate representation of high-frequency stimuli. *J Acoust Soc Am* 97(3):1764–76.
- Richter EA, Norris BE, Fullerton BC, Levine RA, Kiang NYS. 1983. Is there a medial nucleus of the trapezoid body in humans? *Am J Anat* 68:157–66.
- Rose JE, Galambos R, Hughes JR. 1959. Microelectrode studies of the cochlear nuclei of the cat. *Bull Johns Hopkins Hosp* 104:211–51.
- Rosenzweig MR. 1961. Development of research on the physiological mechanisms of auditory localization. *Psychol Bull* 58:376–89.
- Roth GL, Kochhar RK, Hind JE. 1980. Interaural time differences: implications regarding the neurophysiology of sound localization. *J Acoust Soc Am* 68(6):1643–51.
- Sanes DH. 1990. An in vitro analysis of sound localization mechanisms in the gerbil lateral superior olive. *J Neuroscience* 10(11):3494–506.
- Sanes DH, Rubel EW. 1988. The ontogeny of inhibition and excitation in the gerbil lateral superior olive. *J Neurosci* 8(2):682–700.
- Shaw EA. 1974. Transformation of sound pressure level from the free field to the eardrum in the horizontal plane. *J Acoust Soc Am* 56(6):1848–61.
- Shneiderman A, Henkel CK. 1985. Evidence of collateral axonal projections to the superior olivary complex. *Hearing Res* 19(3):199–205.
- Smith PH, Joris PX, Carney LH, Yin TC. 1991. Projections of physiologically characterized globular bushy cell axons from the cochlear nucleus of the cat. *J Comp Neurol* 304(3):387–407.
- Smith PH, Joris PX, Yin TCT. 1993. Projections of physiologically characterized spherical bushy cell axons from the cochlear nucleus of the cat: evidence for delay lines to the medial superior olive. *J Comp Neurol* 331(2):245–60.

- Smith PH, Joris PX, Yin TC. 1998. Anatomy and physiology of principal cells of the medial nucleus of the trapezoid body (MNTB) of the cat. *J Neurophysiol* 79(6):3127–42.
- Smith PH, Rhode WS. 1987. Characterization of HRP-labeled globular bushy cells in the cat anteroventral cochlear nucleus. *J Comp Neurol* 266(3):360–75.
- Spangler KM, Warr WB, Henkel CK. 1985. The projections of principal cells of the medial nucleus of the trapezoid body in the cat. *J Comp Neurol* 238(3):249–62.
- Spirou GA, Brownell WE, Zidanic M. 1990. Recordings from cat trapezoid body and HRP labeling of globular bushy cell axons. *J Neurophysiol* 63(5):1169–90.
- Stevens S, Newman E. 1936. The localization of actual sources of sound. *Amer J Psychol* 48:297–306.
- Stotler WA. 1953. An experimental study of the cells and connections of the superior olivary complex of the cat. *J Comp Neurol* 98:401–32.
- Tollbert LP, Morest DK, Yurgelun-Todd DA. 1982. The neuronal architecture of the anteroventral cochlear nucleus of the cat in the region of the cochlear nerve root: horseradish peroxidase labelling of identified cell types. *Neuroscience* 7(12):3031–52.
- Tollin DJ, Joris PX, Yin TCT. 2000. Coding of interaural phase differences in low-frequency cells in the lateral superior olive of the cat. *Assoc Res Otolaryngol* 23:113.
- Tollin DJ, Yin TCT. 2001. Comparison of the response properties of the principal cells of the lateral superior olive and the medial nucleus of the trapezoid body. *Assoc Res Otolaryngol* 24:57.
- Tollin DJ, Yin TC. 2002a. The coding of spatial location by single units in the lateral superior olive of the cat. I. Spatial receptive fields in azimuth. *J Neurosci* 22(4):1454–67.
- Tollin DJ, Yin TC. 2002b. The coding of spatial location by single units in the lateral superior olive of the cat. II. The determinants of spatial receptive fields in azimuth. *J Neurosci* 22(4):1468–79.
- Trussell LO. 2002. Cellular mechanisms for information coding in auditory brainstem nuclei. In: Oertel D, Popper AN, Fay RR, editors. *Integrative functions in the mammalian auditory pathway*. New York: Springer-Verlag. p 72–98.
- Tsuchitani C. 1977. Functional organization of lateral cell groups of cat superior olivary complex. *J Neurophysiol* 40(2):296–318.
- Tsuchitani C. 1997. Input from the medial nucleus of trapezoid body to an interaural level detector. *Hearing Res* 105(1-2):211–24.
- Tsuchitani C, Boudreau JC. 1966. Single unit analysis of cat superior olive S segment with tonal stimuli. *J Neurophysiol* 29(4):684–97.
- Tsuchitani C, Boudreau JC. 1969. Stimulus level of dichotically presented tones and cat superior olive S-segment cell dcharge. *J Acoust Soc Am* 46(4):979–88.
- van Noort JV. 1969. The structure and connections of the inferior colliculus. An investigation of the lower auditory system. Assen (the Netherlands): Van Gorcum.
- Warr WB. 1966. Fiber degeneration following lesions in the anterior ventral cochlear nucleus of the cat. *Exp Neurol* 14:453–74.
- Warr WB. 1972. Fiber degeneration following lesions in the multipolar and globular cell areas in the ventral cochlear nucleus of the cat. *Brain Res* 40(2):247–70.
- Wiener FM, Pfeiffer RR, Backus ASN. 1966. On the sound pressure transformation by the head and auditory meatus of the cat. *Acta Otolaryngol* 61:255–69.
- Wightman FL, Kistler DJ. 1989. Headphone simulation of free-field listening. I: stimulus synthesis. *J Acoust Soc Am* 85(2):858–67.
- Wightman FL, Kistler DJ. 1993. Sound localization. In: Yost WA, Popper AN, Fay RR, editors. *Human psychophysics*. New York: Springer-Verlag. p 155–92.
- Wu SH, Kelly JB. 1991. Physiological properties of neurons in the mouse superior olive: membrane characteristics and postsynaptic responses studied in vitro. *J Neurophysiol* 65(2):230–46.
- Wu SH, Kelly JB. 1992. Synaptic pharmacology of the superior olivary complex studied in mouse brain slice. *J Neuroscience* 12(8):3084–97.
- Wu SH, Kelly JB. 1994. Physiological evidence for ipsilateral inhibition in the lateral superior olive: synaptic responses in mouse brain slice. *Hearing Res* 73(1):57–64.
- Yin T. 2002. Neural mechanisms of encoding binaural localization cues in the auditory brainstem. In: Oertel D, Popper AN, Fay RR, editors. *Integrative functions in the mammalian auditory pathway*. New York: Springer-Verlag. p 99–159.
- Young ED. 1998. Cochlear nucleus. In: Shepard GM, editor. *The synaptic organization of the brain*. 4th ed. New York: Oxford University Press. p 121–58.
- Young ED, Davis KA. 2002. Circuitry and function of the dorsal cochlear nucleus. In: Oertel D, Popper AN, Fay RR, editors. *Integrative functions in the mammalian auditory pathway*. New York: Springer-Verlag. p 160–206.

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