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Monaural Spectral Processing Differs between the Lateral Superior Olive and the Inferior Colliculus: Physiological Evidence for an Acoustic Chiasm

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Abstract

Evidence suggests that the lateral superior olive (LSO) initiates an excitatory pathway specialized to process interaural level differences (ILDs), the primary cues used by mammals to localize high-frequency sounds in the horizontal plane. Type I units in the central nucleus of the inferior colliculus (ICC) of decerebrate cats exhibit monaural and binaural response properties qualitatively similar to those of LSO units, and are thus supposed to be the midbrain component of the ILD pathway. Studies have shown, however, that the responses of ICC cells do not often reflect simply the output of any single source of excitatory inputs. The goal of this study was to compare directly the monaural, spectral response properties of LSO and type I units measured in unanesthetized decerebrate cats. Compared to LSO units, type I units have narrower V-shaped excitatory tuning curves, higher spontaneous rates, lower maximum stimulus-evoked firing rates and more nonmonotonic rate-level curves for tones and noise. In addition, low frequency type I units have lower thresholds to tones than corresponding LSO units. Taken together, these results suggest that the excitatory ILD pathway from LSO to ICC is mostly a high-frequency channel, and that additional inputs transform LSO influences in the ICC.

Keywords

hearing; frequency tuning; interaural level differences; functional pathways

INTRODUCTION

Interaural level differences (ILDs) are the primary cues that animals use to localize high-frequency sounds in the horizontal plane (Erulkar, 1972; Mills, 1972). An excitatory pathway specialized to process these cues is initiated by the lateral superior olive (LSO), where coded sound intensities at the two ears are compared to each other on a frequency-by-frequency basis (Boudreau and Tsuchitani, 1968; Brownell et al., 1979; Caird and Klinke, 1983; Guinan et al., 1972a,b; Tollin and Yin, 2002a,b). The frequency-specific ILD sensitivity of an LSO cell is derived largely from the pattern of its afferent inputs. LSO cells receive excitatory inputs from spherical bushy cells in the ipsilateral cochlear nucleus (CN) and inhibitory inputs from

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globular bushy cells in the contralateral CN via a synapse in the medial nucleus of the trapezoid body (for review, Schwartz, 1992). Thus, LSO cells show tuned excitatory responses to stimulation of one ear, and inhibitory responses to stimulation of the other ear. In response to changing ILDs, the firing rates of LSO cells decrease as ILDs shift to favoring the inhibitory ear. Information from the LSO is conveyed bilaterally to the central nucleus of the inferior colliculus (ICC). The contralateral projection to the ICC originates predominantly from LSO cells sensitive to high frequencies and is mostly excitatory in nature, whereas the ipsilateral projection is mainly from low-frequency LSO cells and largely inhibitory (Brunso-Bechtold et al., 1981; Glendenning et al., 1992).

Single units in the ICC of unanesthetized decerebrate cats can be grouped into three major response types based on the patterns of excitation and inhibition observed in contralateral pure-tone frequency response maps (Ramachandran et al., 1999). The response maps of type I units show a narrow I-shaped area of excitation at frequencies around best frequency (BF), with flanking regions of inhibition. Type V units produce frequency response maps that exhibit a broad V-shaped excitatory area with no signs of inhibition, and type O units have maps that are dominated by inhibition except for an O-shaped island of excitation at low stimulus levels. Units that produce type I and type O maps have BFs that span the cat's range of audible frequencies, whereas type V units typically have low BFs. When tested with dichotic stimuli, type I units show binaural excitatory/inhibitory interactions, type V units show facilitation and type O units show only weak binaural interactions (Davis et al., 1999). Based on the close resemblance of their monaural and binaural response properties with those of LSO units, it has been conjectured that type I units, at all BFs, receive their dominant excitatory inputs from the LSO and thus represent the midbrain component of the ILD pathway.

Several lines of evidence suggest, however, that the response properties of ICC type I units are not likely to reflect simply the output of the LSO. First, *in vivo* recordings show that most ICC neurons receive synaptic inputs from inhibitory as well as excitatory sources (Covey et al., 1996; Kuwada et al., 1997). Second, pharmacological studies reveal that inhibitory inputs shape the frequency tuning and ILD sensitivity of many ICC units (e.g. Burger and Pollak, 2001; Faingold et al., 1993; Klug et al., 1995; LeBeau et al., 2001; Li and Kelly, 1992a,b; Vater et al., 1992; Yang et al., 1992). In particular, blockade of these inputs can result in ICC response maps showing broader excitatory tuning curves, and some ICC units losing altogether their sensitivity to ILD. Finally, studies in Mexican free-tailed bats have shown that ILD processing differs quantitatively in the LSO and ICC (Park, 1998; Park et al., 2004).

The goal of the present set of studies was to compare directly the monaural and binaural response properties of units in the LSO and the ICC of unanesthetized decerebrate cats; here, we report on differences in their monaural spectral response characteristics. Standard extracellular recording techniques were used to obtain single-unit data from the LSO. Comparable data from ICC type I units were available (Ramachandran et al., 1999) but were collected anew to reduce any methodological differences. The main result of this study is that the response properties of LSO and ICC type I units are qualitatively similar, but quantitatively different in many respects. Most notably, ICC type I units have lower thresholds to tones at low BFs and narrower tuning curves at all frequencies than corresponding LSO units. The former result suggests that, contrary to expectations, the LSO is not a suitable source of dominant excitatory inputs for most low-BF type I units. Thus, the excitatory ILD pathway from LSO to contralateral ICC is primarily a high-frequency channel, consistent with prior anatomical and pharmacological observations. The latter result indicates that hierarchical transformations (in the form of additional excitatory and inhibitory inputs) sharpen the high-level frequency selectivity of type I units thereby enhancing the analysis of complex sounds.

METHODS

Experiments were performed on 23 adult male cats (3–4 kg) (10 LSO; 13 ICC) with clean external ears and clear tympanic membranes. All procedures were approved by the University Committee on Animal Resources at the University of Rochester.

Surgical Procedures

Cats were anesthetized with intramuscular (im) injections of ketamine (40 mg/kg im) and xylazine (0.5 mg/kg im), and given atropine (0.05 mg/kg im) to minimize respiratory secretions and dexamethasone (2 mg/kg im) to reduce cerebral edema. Thereafter, body temperature was maintained at $39 \pm 0.5^\circ\text{C}$ using a regulated heating blanket, and respiration and heart rates were monitored. The cephalic vein was cannulated to allow intravenous (iv) infusions of fluids, and a tracheotomy was performed to facilitate quiet breathing. Supplemental doses of ketamine (20 mg/kg im) and xylazine (0.25 mg/kg im) were administered as needed (e.g. a heart rate over 180 beats/min) to maintain areflexia until the decerebration procedure was complete.

A midline incision was made over the skull and the temporalis muscles reflected to visualize the top of the skull and the ear canals. A craniotomy was performed over the left parietal cortex, and cats were made decerebrate by aspirating under visual control the brainstem between the superior colliculus and the thalamus. No further anesthesia was given.

Both ear canals were transected near the tympanic membrane to accept hollow ear bars for delivering closed-field acoustic stimuli. The animal's head was then fixed in the recording position, 30° and 0° nose-down with respect to stereotaxic horizontal coordinates for the LSO and the ICC, respectively, using a headpiece and two ear bars. The left LSO was accessed by removing the skull along the midline at the nuchal ridge, and aspirating the cerebellum overlying and bordering the floor of the fourth ventricle. The left IC was exposed by performing a craniotomy just rostral to the bony tentorium, aspirating the underlying cortical tissue and removing a small semicircular section of the tentorium. Surgery was usually confined to a single target nucleus within an experiment to minimize trauma to the nervous system.

Cats were euthanized at the end of each experiment with an overdose of sodium pentobarbital (100 mg/kg iv). Four cats used in LSO experiments were perfused intracardially with 0.9% saline followed by fixative (3% paraformaldehyde and 0.1% glutaraldehyde in 0.1M phosphate buffer; pH 7.4) and two sucrose solutions (10 and 30%). The brains of these cats were removed from the skull and immersed in a 30% sucrose solution until they sank. Frontal sections (40 μm thick) of frozen brain were cut on a sliding microtome and stained with cresyl violet. The location of electrode tracks and recording sites within the LSO were verified from patterns of gliosis and electrolytic lesions. Images of sections were acquired using a MicroFire digital camera mounted on an Olympus AX70 microscope and Image-Pro software.

Data collection and analysis

Experiments were conducted inside a double-walled sound-attenuating chamber (IAC). Acoustic stimuli were delivered bilaterally via electrostatic speakers (TDT or STAX) that were coupled to hollow ear bars. The frequency response of each closed system was calibrated at the start of an experiment by inserting a probe tube microphone into the ear bar near the tympanic membrane. Responses of the TDT systems decreased monotonically from 110 dB SPL at 800 Hz to 90 dB SPL at 48 kHz; responses of the STAX systems were flat at 100 dB SPL (± 5 dB) at frequencies from 40 Hz to 25 kHz and decreased by 20dB/oct for frequencies above 25 kHz. Interaural crosstalk was at least 30 dB (and typically > 50 dB) down at all frequencies in the ear opposite to the sound source (Davis, 2005; Gibson, 1982), which is well below the maximum ILD used during binaural testing (used here to aid unit identification).

All test stimuli, including tones and broadband noise, were digitally created with TDT System 3 hardware. Frequency response maps were constructed from responses to tone bursts that were 50 ms in duration and presented at a rate of 4 bursts/s; rate-level (and rate-ILD) curves were generated from responses to stimuli that were 200 ms long presented at a rate of 1 burst/s. All stimuli were gated on and off with 10 ms rise/fall times. Analog signals were created by playing the waveforms through a 16-bit D/A converter at a sampling rate of 100 kHz. Tones were attenuated relative to the acoustic ceiling at each frequency to achieve a desired input sound pressure level in dB SPL. Noise stimuli were flat at the tympanic membrane (i.e., corrected for non-flat calibration curves) and attenuated relative to the maximum spectrum level achievable without any attenuation (~45 dB SL).

Single-unit activity was recorded with platinum-iridium microelectrodes (with resistances between 1–4 M Ω). Individual electrodes were advanced using a motor-controlled multi-electrode positioning system (EPS; Alpha-Omega). The electrode signal was amplified (2,000–5,000 $\times$) and filtered from 0.3 to 6 kHz (MCP; Alpha-Omega). Template matching software (MSD; Alpha-Omega) was used to discriminate action potentials from background activity. Templates for all units had error histograms with a single well-defined peak indicating good isolation of one waveform; signal-to-noise ratios were greater than two-to-one and often greater than ten-to-one. Spike times relative to stimulus onset were stored for on- and off-line analyses.

Recording electrodes were advanced dorsoventrally through the LSO or the ICC, while 50-ms search tones were presented to the excitatory ear. Electrodes to enter the LSO were placed on the surface of the brainstem 3–4 mm lateral to the midline and about 1–2 mm caudal of the cerebellar peduncle. In practice, the rostral-caudal position of the electrode was set relative to the caudal extent of the medial nucleus of the trapezoid body. That is, electrodes immediately adjacent to the midline were moved progressively more caudal until the background activity at depth (5–6 mm) no longer responded strongly to contralateral monaural stimulation (Guinan et al., 1972a,b); the “initial” recording electrode was then moved 1 mm rostral (and 3–4 mm lateral) from this location and advanced into the brainstem to access the LSO. Units were identified as being within the LSO based upon depth (~5–6 mm) and their monaural and binaural response properties (Finlayson and Caspary, 1991; Guinan et al., 1972a,b; Tollin and Yin, 2005; Tsuchitani, 1977); in some cases, units were verified to be in the LSO via tract tracing techniques.

Electrodes to enter the ICC were placed on the surface of the IC, where electrodes passed through either the external or dorsal nucleus of the inferior colliculus before entering the ICC. A reversal in the trend of BFs (from high-to-low to low-to-high) marked the transition between subdivisions (Aitkin et al., 1975; Merzenich and Reid, 1974). ICC units with sustained discharge rates were classified as type V, I, or O according to their responses to monaural and binaural stimuli (Davis et al., 1999; Ramachandran et al., 1999).

When a single unit was isolated in either the LSO or the ICC, its BF and threshold were determined using audiovisual feedback and the following characterization protocol was initiated. Detailed monaural frequency response maps were created from responses to tone bursts presented to the excitatory ear over a 60 dB range in intensities (2 dB steps) and a three-octave range in frequencies centered on the unit's BF (0.1 octave steps). The stimuli were presented in ascending intensity at BF, and then at frequencies alternately above and below BF. Rate-level functions were obtained for BF tones and broadband noise presented to the excitatory ear by sweeping the level of the stimulus over a 100-dB range. To evaluate the binaural sensitivity of units, BF tones were presented to both ears but a 40-dB range of ILDs was created by varying the level of the tone in the inhibitory ear relative to a fixed-level tone in the excitatory ear. The intensity of the tone in the excitatory ear was fixed at 10 dB re

threshold. In some LSO experiments, electrolytic lesions ($\sim 10 \mu\text{A}$; 30 s) were made at the end of unit-rich electrode tracks to mark the location of recording sites.

Sound-driven activity was analyzed in terms of average discharge rates over the final 80% of the stimulus-on interval to reflect steady-state responses; no onset units were recorded in the current study. Spontaneous rates were computed over the last 50% of the stimulus-off interval. Excitatory (inhibitory) responses were defined as those for which the stimulus-evoked rate was at least two standard deviations above (below) the spontaneous discharge rate. For display purposes, data were smoothed with a three-point triangularly weighted moving-average filter.

RESULTS

Results are based on recordings from 87 single units in the LSO and 100 type I units in the ICC (Table 1). Units were localized to the ICC based on two physiological criteria: the reversal in the sequence of unit BFs from high-to-low to low-to-high observed 1–2 mm below the surface of the IC, which indicated entry into the ICC (Aitkin et al., 1975; Merzenich and Reid, 1974), and similarity of monaural and binaural response characteristics to published ICC data (Davis et al., 1999; Ramachandran et al., 1999). Units were localized to the LSO based on histological reconstruction of electrode tracks (4/10 experiments; 31 units) or stereotaxic coordinates and physiological criteria. In particular, histological verification of recording sites was performed in the first three experiments (and again in the last experiment), during which time a standardized dorsoventral approach to the LSO was developed (see Methods). Thereafter, units were localized to the LSO based on stereotaxic location with respect to the caudal pole of the medial nucleus of the trapezoid body, recording depth (~ 5 – 6 mm) and similarity of monaural response properties to histologically-localized units. Consistent with prior reports (Finlayson and Caspary, 1991; Guinan et al., 1972a,b; Tollin and Yin, 2005; Tollin et al., 2008; Tsuchitani, 1977, 1982), most LSO units in decerebrate cat show chopper-type monaural temporal discharge patterns and all show binaural excitatory-inhibitory interactions; details on these response characteristics will be described in future reports.

The photomicrograph in Figure 1 shows the single reconstructed path (vertical line) of two recording passes through the LSO; that is, the electrode was advanced through the LSO, retracted until background acoustic driving ceased and then advanced again along nominally the same path. The numerical labels to the left and right of the line indicate the BFs of the units isolated along the first and second passes of the electrode, respectively, and the circle just above the facial nerve (7N) encloses one of the three electrolytic lesions made after the second pass down this track. The electrode for this track was placed on the dorsal surface of the brainstem just caudal to the cerebellar peduncle and about 3.5 mm lateral to the midline. As the electrode advanced, it passed through a number of non-auditory regions, including several vestibular nuclei where units with regular discharge patterns were encountered. Upon reaching the superior olivary complex (SOC), the electrode passed through the dorsolateral periolivary nucleus (DLPO), and then the lateral and central limbs of the LSO. Note that the BFs of isolated units increased with depth as the electrode advanced dorsoventrally through the lateral limb of the LSO but decreased as the electrode passed through the central limb. These BF progressions are consistent with the known tonotopic organization of the nucleus (Tsuchitani and Boudreau, 1966); dorso-ventral penetrations through the medial limb (not shown) produced rising BFs. After exiting the LSO, the electrode passed through the ventral nucleus of the trapezoid body (not shown). In other penetrations, the electrode passed through either the lateral nucleus of the trapezoid body (LNTB) or medial superior olive (MSO) before exiting the SOC. Electrode tracks were found throughout the LSO, and recorded unit BFs encompassed nearly the entire cat's range of audible frequencies, which suggests that the full extent of the LSO was sampled.

Monaural frequency response maps

The frequency selectivity of LSO and ICC units was mapped in the frequency-intensity domain by recording single-unit responses to tone bursts across a range of frequencies and sound pressure levels presented to the excitatory ear. As illustrated in Figs. 2A–C, the ipsilateral frequency response maps of LSO units exhibited a wide range of patterns of excitation and inhibition. In these plots, stimulus-driven rates (vertical bars) are plotted at the frequency and level coordinates of the tones that elicited the responses, where the length of a bar is proportional to the maximum spike rate evoked in that unit by stimulation of the ipsilateral ear. The frequency response map of the unit in Fig. 2A exhibits a broadly tuned V-shaped excitatory area that widens considerably about the unit's BF (arrow at top) with increasing sound levels. No inhibition is detectable because the unit lacked spontaneous activity. By contrast, the response map in Fig. 2B shows a much narrower I-shaped excitatory area that maintains its sharp tuning at higher levels. The excitatory bandwidth of the unit in Fig. 2C is intermediate between the first two units. Unlike the other units, however, this unit had a high level of spontaneous activity relative to the LSO population, thus sideband inhibition is visible. The contralateral response maps of ICC type I units recorded here (e.g., Fig. 2D) generally showed an I-shaped excitatory area that was flanked on both sides by inhibition, consistent with the receptive field organization reported by Ramachandran et al. (1999).

Figure 3A shows the BFs and thresholds for monaural stimulation of the excitatory ear for all the LSO (circles) and ICC type I units (vertical lines) in our sample, together with data from 81 non-LSO SOC units (x's) collected in the same experiments as the LSO data and the best threshold curve of auditory nerve fibers (ANFs; solid line) in the cat (Calhoun et al., 1997; Miller et al., 1997). For all the units, threshold was identified as the lowest stimulus level at a given frequency that evoked a response two standard deviations above or below the average spontaneous rate of the unit, and BF was identified as the frequency with the lowest threshold. Note first that the BFs of the LSO and ICC units were distributed roughly uniformly between 0.5–45 kHz, and that for both unit types the distribution of thresholds showed a tendency to decrease as BF increased. This overall threshold pattern likely reflects, in part, the fact that low frequency units in both nuclei had lower spontaneous rates on average than did high frequency units (see Fig. 6A), and threshold was inversely correlated with spontaneous rate (not shown).

The unit types, however, showed differences in their relative sensitivity to tones as a function of frequency (Table 1; second row). In particular, LSO units showed higher thresholds to tones than ICC units at low BFs (shaded region), whereas the unit types showed comparable thresholds at higher frequencies. The cut-off frequency between the low- and high-BF zones is somewhat arbitrary; here, we defined the cut-off to be 3 kHz, where the running medians of the thresholds for the two populations converged. The elevated thresholds of low-BF LSO units are not an artifact due to collection of data in cats with low-frequency hearing loss. That is, note that the thresholds of low-BF LSO units are also higher than the thresholds of low-BF non-LSO SOC units (x's) collected in the same cats, which are comparable to those of ICC units. The mismatch in LSO and ICC unit thresholds at low frequencies suggests that low-BF LSO units cannot provide the dominant excitatory drive to most low-BF ICC type I units.

Further support for this interpretation is provided by the histograms in Fig. 3B, which plot the distribution of unit thresholds in each nucleus relative to the ANF best threshold curve at the same BF. Negative (positive) values in these histograms indicate units with lower (higher) thresholds than their auditory nerve counterparts. The counts for low-BF units are shaded gray, whereas counts for high-BF units are shaded white. Note that the thresholds of low-BF LSO units were significantly higher than those of low-BF type I units (median threshold difference = 15 dB; Mann Whitney U test; $P < 0.001$, $z = 3.64$). In contrast, the thresholds of high-BF LSO and ICC units were comparable ($P > 0.18$, $z = 1.32$), with the thresholds of most type I units

clustering near the median value of the LSO population. These data, coupled with prior anatomical and pharmacological results (Brunso-Bechtold et al., 1981; Glendenning et al., 1992), indicate that the excitatory LSO to ICC pathway is predominantly a high-frequency channel. Consequently, low- and high-BF data are distinguished in the following plots, and statistical comparisons are discussed only between the high-BF populations.

The sharpness of frequency tuning was quantified using Q_n values at +10 and +40 dB (defined as BF divided by the bandwidth of excitation 'n' dB above threshold). At 10 dB above threshold (Fig. 4A), Q_{10} values for units in each nucleus increase with BF. Many of the data points fall within the range exhibited by ANFs (solid lines; Calhoun et al., 1997; Miller et al., 1997) suggesting that the low-level tuning of LSO and ICC units is determined by peripheral processes. At 40 dB above threshold (Fig. 4B), the tuning of LSO units continues to match overall the tuning properties of ANFs (Lieberman, 1978), although some high-BF LSO units show comparatively sharper tuning (symbols above the upper solid line). In contrast, many ICC type I units show much sharper tuning than ANFs suggesting that the high-level tuning of type I units is sculpted by central inhibitory mechanisms. To compare more directly the high-level tuning properties of LSO and ICC unit types, the Q_{40} values of individual units were normalized by the maximum Q_{40} value of ANFs at that BF (thick line in Fig. 4B). Figure 4C plots the distribution of normalized Q_{40} values for both unit types at low (gray-shaded counts) and high BFs, where values greater than 1 indicate units with tuning sharper than that of the best-tuned ANFs. Note that there is substantial overlap of the distributions, but that the tails of the ICC distributions extend substantially above the value of 1. For high-BF units, the median value for the LSO population (white-filled bars) is 0.79, whereas for ICC units it is 1.14 (Table 1; fourth row); this difference is significant (Mann Whitney U test; $P < 0.001$, $z = -4.40$) and suggests that the prototypical ICC type I unit is 45% sharper than an LSO unit (i.e., the bandwidth of an ICC unit is roughly 2/3rds that of an LSO unit).

Responses to BF tones

The on-BF responses of LSO and ICC type I units were characterized by obtaining rate-level curves for BF tone bursts presented to the excitatory ear. Figure 5A shows representative data from the three LSO units (labeled a–c) whose corresponding frequency response maps are shown in Fig. 2. The responses of units c and a are essentially monotonic: that is, the firing rate climbs to a maximum and then either increases slightly or saturates at higher stimulus levels. By contrast, the rate-level function of unit b is slightly nonmonotonic; as the stimulus level increases, the unit exhibits a rate increase followed by a rate decrease. The rate-level functions of most type I units recorded here (Fig. 5A; curve labeled ICC; offset to the right by 10 dB for clarity) exhibited some degree of non-monotonicity (Ramachandran et al., 1999).

To compare the shapes of rate-level functions of LSO and ICC units, a straight-line (least squares) fit was applied to the portion of the curve between the maximum (the first sharp change in slope) and the end of the data (e.g., the dashed lines on the rate-level curves in Fig. 5A). This estimate of slope was then normalized by the maximum rate (Young and Voigt, 1982), and multiplied by 100 to obtain % rate change per dB. Figure 5B shows the distributions of normalized slopes for each unit type; undefined values are for curves that failed to reach a maximum. The typical saturating monotonicity of LSO units is indicated by the clustering of values around 0 ($\pm 1\%$ /dB). The majority of ICC type I units also displayed monotonic properties, although a substantial number of units had nonmonotonic slopes (values $\leq -1\%$ /dB). Overall, the rate-level functions of high-BF type I units were significantly more nonmonotonic than those of LSO units (Mann Whitney U test; $P < 0.001$, $z = 4.18$).

Rate-level functions like those in Fig. 5A also can be used to define basic trends in spontaneous and maximum driven rates for LSO and ICC units; these data are summarized in Table 1 separately for low- and high-BF units. As shown in Fig. 6A, most LSO units exhibited

spontaneous firing rates below 5 spikes/s; in fact, the median spontaneous rates of both low- and high-BF populations were less than 1 spikes/s. By contrast, the majority of ICC type I units had spontaneous rates greater than 5 spikes/s. With regards to maximum BF-tone driven rates (Fig. 6B), most LSO units had maximal firing rates above 100 spikes/s, whereas almost one-half of all ICC units had maximum driven rates below 100 spikes/s. The differences in spontaneous and maximum driven rates for high-BF LSO and ICC units were highly significant (Mann Whitney U test; $P \ll 0.01$, $z = -6.13$, and $P < 0.01$, $z = 2.89$, respectively).

Responses to broadband noise

The spectral integration properties of LSO and ICC units were assessed by obtaining rate-level responses to broadband noise bursts. Figure 7A shows representative data from the three LSO units (labeled a–c) whose corresponding frequency response maps are shown in Fig. 2, and from one ICC unit. As for BF tones, the LSO unit responses are generally monotonic and saturating (e.g., curves c and b); in some cases (e.g., unit a), units did not achieve a maximum rate within the limits of the acoustic system. The noise rate-level curves for most type I units were also monotonic (Ramachandran et al., 1999).

The monotonicity of each unit's noise and BF tone-driven responses is compared in Fig. 7B, which plots the normalized slope of the noise rate-level function against the value obtained with BF tones. Each symbol represents an individual unit and the diagonal line represents equal slopes for both stimuli. Units with undefined noise or tone slopes are plotted beyond the axes. Note that the majority of the data points for LSO and ICC units are clustered about the origin indicating that the responses to noise and tones in both nuclei are monotonic and saturating. For high-BF units, there is no relationship between the slopes of noise and tone responses in the LSO, whereas a unit's noise response is usually more monotonic than its tone response in the ICC (the data points lie above the equality line; Wilcoxon signed rank test; $P < 0.01$, $z = -2.99$).

Each unit's threshold for noise is plotted against its threshold for tones in Fig. 7C. To allow a direct comparison with tone thresholds, noise thresholds are specified in terms of the total noise power in the bandwidth of the unit 10 dB above threshold. In general, the data points are distributed along the equity line, suggesting that tone threshold provides a good estimate of noise threshold. As for BF tones, low-BF LSO units (gray circles) were less sensitive to noise than low-BF ICC units (gray lines), whereas the sensitivities to noise of high-BF LSO and ICC units were comparable (black symbols).

Figure 7D plots each unit's maximum discharge rate to noise against its maximum tone-driven rate. For low-BF units in the LSO and the ICC, the data are too few to draw conclusions. With regard to high-BF units, the unit types in both nuclei showed significantly lower discharge rates to noise than to tones (the data points lie below the equity line; Wilcoxon signed rank test; $P \ll 0.01$, $z = -4.12$ and -3.60 , respectively). The reduced responsiveness of ICC type I units to noise is likely due to noise-evoked activation of the extensive inhibitory sidebands of these units (Ramachandran et al., 1999); a similar explanation may apply in the LSO since inhibitory sidebands are visible in units with sufficient spontaneous activity (e.g., Fig 2C).

DISCUSSION

The two major findings of this study are that low-BF LSO units have higher thresholds to tones than those of low-BF type I units, and that the monaural response properties of high-BF LSO and ICC type I units are quantitatively different. These results suggest that the excitatory projection from the LSO to the ICC is primarily a high-frequency pathway, and that local circuit connections transform high-frequency LSO influences within the ICC. In the following discussion we consider each finding separately.

Functional pathways from the LSO to the ICC

Physiological (Tollin and Yin, 2002b; Tollin, 2003) and behavioral evidence (Kavanagh and Kelly, 1992) suggests that the LSO performs the initial extraction of ILDs, which are the primary acoustic cues used by mammals for the horizontal localization of high-frequency sounds (Erulkar, 1972; Irvine, 1992; Mills, 1972). The idea that the excitatory ILD processing pathway from LSO to ICC is principally a high-frequency channel is consistent with the combined results of numerous prior anatomical, pharmacological and physiological studies. As shown in Fig. 1, the LSO appears S-shaped in frontal sections. Units are organized tonotopically along this axis, with low BF units represented in the lateral limb and high BFs in the medial limb (Guinan et al., 1972a; Guinan et al., 1972b; Tsuchitani and Boudreau, 1966). The LSO is known to project bilaterally to the ICC; however, the projection is asymmetrical. That is, most cells in the medial limb of the LSO project to the contralateral ICC, while most cells in the lateral limb project to the ipsilateral ICC (Glendenning and Masterton, 1983). This anatomical segregation of projections is accompanied by a corresponding segregation of neurotransmitters: most of the ascending contra-lateral projection is glutamatergic and/or aspartergic, whereas most of the ipsilateral projection is glycinergic (Glendenning et al., 1992; Saint Marie et al., 1989; 1990). Taken together, these results suggest that the contralateral projection from LSO to ICC is mainly excitatory and high-frequency, whereas the ipsilateral projection is inhibitory and low-frequency.

Although the anatomical and pharmacological data suggest straightforward physiological correlates, the differences in LSO efferent projection patterns and pharmacology grade rather smoothly across the limbs of the LSO (Glendenning et al., 1992). The threshold difference pattern observed in the present study between LSO and ICC units provides the physiological basis for claiming that the excitatory ILD pathway from the LSO to the ICC is mainly a high-frequency channel. In particular, the median threshold for low-BF LSO units was approximately 15 dB above that for low-BF ICC type I units, whereas the median thresholds for high-BF LSO and ICC units were nearly identical (Table 1; Fig. 3). These data thus suggest that the LSO is not a suitable source of dominant excitatory inputs to most low-frequency ICC type I units, but is a suitable source at high frequencies.

Two lines of evidence provide independent physiological support for the existence of a functional acoustic chiasm between the LSO and ICC. First, the threshold difference pattern observed here is also seen in barbiturate-anesthetized cat, the only other preparation in which population data from both the LSO (Tsuchitani and Boudreau, 1967) and ICC (excitatory-inhibitory units; Ehret and Merzenich, 1988) are available, albeit collected from different laboratories with different stimulus parameters. These data are represented in Fig. 8A by dots and squares, respectively, together with the best threshold curves of our LSO (solid line) and type I units (dotted line). Second, LSO units also showed substantially higher thresholds to tones than the most sensitive non-LSO SOC units at low, but not high, frequencies (Fig. 3A). This pattern has been seen in three prior studies, all in anesthetized cats, although in each case the number of low-BF units was low. For example, Fig. 8B shows the thresholds for monaural stimulation of the excitatory ear for the LSO (dots) and MNTB units (diamonds) in the sample of Tsuchitani (1997), together with the best threshold curves of our LSO (solid line) and SOC units (dashed line). Note that Tsuchitani's minimum LSO unit thresholds are elevated compared to those of MNTB units by 10–20 dB at frequencies below 3 kHz, but not at higher frequencies. This pattern of threshold differences (though not necessarily actual threshold values, see Tollin and Yin, 2005) is repeated in the two other studies with data from both LSO and MNTB units (Guinan et al., 1972a,b, class 6 vs. class 4 units; Tollin and Yin, 2005, data obtained via personal communication), suggesting that low frequency LSO unit tone thresholds are usually elevated with respect to those observed in other auditory structures.

The foregoing discussion of the physiological evidence for a functional acoustic chiasm between the LSO and the ICC is *not* all-or-none. That is, the threshold difference pattern observed at the population level neither precludes the possibility that some (high threshold) low-frequency type I units receive their dominant excitatory inputs from the LSO, nor requires that all high-frequency type I units receive their dominant inputs from the LSO. With regards to the former point, the disparity in thresholds may be larger or smaller in certain binaural conditions. For example, some low-BF ICC type I units show binaural facilitation for diotic stimuli (Davis, 1999), whereas LSO units do not exhibit such properties (e.g. Tollin and Yin, 2005); this would widen the threshold disparity. On the other hand, some low-BF LSO units show facilitation when binaural stimuli are out-of-phase (Finlayson and Caspary, 1991), potentially closing the threshold gap. However, this property has been attributed to a post-inhibitory rebound effect, which ICC units also exhibit (Spitzer and Semple, 1998). Consistent with the latter point, pharmacological studies have revealed that some ICC units lose altogether their sensitivity to ILDs in the presence of locally applied inhibitory blockers (e.g. Klug et al., 1995; Vater et al., 1992; Yang et al., 1992), or during reversible inactivation of nuclei that project to the ICC (Burger and Pollak, 2001; Faingold et al., 1993; Kelly and Li, 1997; Li and Kelly, 1992a,b). Clearly, the ILD sensitivity of such neurons is not inherited from the LSO, but rather is created *de novo* from a suitable convergence of inputs in the ICC (e.g., excitatory inputs from the contralateral CN and inhibitory inputs from the contralateral dorsal nucleus of the lateral lemniscus (DNLL); Burger and Pollak, 2001).

The functional role of the low frequency inhibitory projection from the LSO to the ipsilateral ICC is less clear. Anterograde tract-tracing experiments have shown that the projection from the ipsilateral LSO converges with that from the ipsilateral MSO (Loftus et al., 2004). It is known that MSO units and low-frequency ICC neurons play an important role in the encoding of stimulus location based on interaural time differences (ITDs; Batra et al., 1997; Kuwada et al., 1987; Palmer et al., 1990; Yin and Kuwada, 1983a,b), and that ITD tuning curves are sharper in the ICC than in the MSO (Fitzpatrick et al., 1997; Spitzer and Semple, 1998). Evidence is equivocal for a role of GABAergic inhibition in sharpening ITD curves in the ICC (D'Angelo et al., 2005; Ingham and McAlpine, 2005); perhaps glycinergic inhibition from the low-frequency LSO plays this role. Consistent with this possibility, low-BF LSO units have been shown to exhibit ITD sensitivity in rabbits and rodents (Batra et al., 1997; Finlayson and Caspary, 1991). In addition, ipsilateral LSO projections likely converge with efferents from the contralateral CN (Malmierca et al., 2005). Such a convergence would create low-frequency ICC units with the monaural (Shofner and Young, 1985) and *de novo* binaural properties of type I units. Glycinergic inhibition (Klug et al., 1995) and input from the ipsilateral LSO are known to shape the binaural response properties of some ICC units (Kelly and Li, 1997; Li and Kelly, 1992a); however, ILDs are most salient at high frequencies (Erulkar, 1972; Mills, 1972), thus the role of such binaural ICC neurons in audition is unclear.

Transformation of spectral sensitivity along the excitatory ILD processing pathway

The observation that spectral sensitivity is shaped to some degree within the ICC is consistent with data from numerous pharmacological studies (Fuzessery and Hall, 1996; LeBeau et al., 2001; Palombi and Caspary, 1996; Vater et al., 1992; Yang et al., 1992). These studies combined extracellular recording techniques with iontophoresis of inhibitory neurotransmitter antagonists to show that both GABAergic and glycinergic inputs shape the tuning characteristics of ICC neurons (Davis et al., 1999; Fuzessery and Hall, 1996; LeBeau et al., 2001; Palombi and Caspary, 1996; Vater et al., 1992; Yang et al., 1992). In particular, blocking these inputs with their respective antagonists, bicuculline and strychnine, can result in ICC response maps showing broader excitatory tuning and/or a loss of sideband inhibition.

The differences in spectral processing between primarily high-BF LSO and ICC type I units can be interpreted in terms of the simple connectionist model shown in Fig. 9. In this model, ICC type I units receive excitatory inputs from the contralateral LSO, inhibitory inputs (INH) and additional excitatory inputs (EXC). The projection from the LSO is supported by the most evidence. First, anatomical and pharmacological studies have shown that the contralateral projection from the LSO to the ICC is predominantly excitatory (Glendenning et al., 1992; Saint Marie et al., 1989; 1990). Second, LSO and ICC type I units qualitatively share a number of monaural response properties, including the general shapes of their excitatory tuning curves (Fig. 2) and BF-tone rate-level functions (Fig. 5), and relative responsiveness to narrowband versus wideband stimuli (Fig. 7). Finally, LSO and type I units share a similar sensitivity to ILDs (Boudreau and Tsuchitani, 1968; Caird and Klinke, 1983; Davis, 1999; Greene et al., 2008; Guinan et al., 1972a,b; Tollin et al., 2008).

Quantitative differences in the stimulus-driven responses of LSO and ICC type I units suggest the need to add an inhibitory (INH) input to the type I unit (Fig. 9). In particular, in comparison to LSO units, ICC type I units show more level tolerant excitatory tuning curves (Fig. 4), more nonmonotonic BF-tone rate-level curves (Fig. 5) and lower maximum BF-tone and noise-driven rates (Figs. 6 and 7). Consistent with this interpretation, type I units show broader excitatory tuning curves and higher BF-tone driven rates during application of inhibitory blockers (Davis, 1999, 2005). For example, Davis found that the Q_{40} values of type I units decreased by an average of 33% in the presence of bicuculline and 8% in strychnine, which combined could explain the median difference in Q_{40} values for high-BF LSO and ICC units (45%; Fig. 4). The changes in firing rate were observed at frequencies and levels throughout a unit's receptive field, suggesting that the inhibition arises from sources whose inhibitory fields are aligned with and are broader than their ICC targets (Palombi and Caspary, 1996). Pharmacological studies suggest that the ipsilateral DNLL and VNLL are excellent candidates to provide the GABAergic and glycinergic inhibition, respectively, to type I units (e.g., Saint Marie et al., 1997), and both nuclei contain well-tuned units (Batra et al., 1997; Davis et al., 2007).

Differences in the spontaneous rates of high-BF LSO and type I units (0.2 vs. 11.2 spikes/s; Fig. 6) suggest that it is necessary to add an excitatory source (EXC) to the prototypic type I unit (Fig. 9). Dorsal cochlear nucleus (DCN) principal cells are one potential candidate for this input. DCN principal cells exhibit high spontaneous discharge rates in the decerebrate cat (e.g., Young and Brownell, 1976), and it is known that the projections from the contralateral DCN and LSO overlap substantially within the ICC (Oliver et al., 1997). Consistent with this hypothesis, Davis (2002) found that type I units show lower spontaneous rates after the output of the DCN is blocked by application of lidocaine. DCN principal cells are excited by low-level BF tones, but inhibited by most high-level tones. Thus, the excitatory areas in the response maps of type I units would reflect primarily those of its overriding LSO inputs, whereas the inhibitory sidebands of type I units might reflect a more substantial contribution from its DCN inputs. Stellate cells in the CN are a second suitable source of EXC inputs to type I units (Adams, 1979; Cant, 1982; Osen, 1972). These cells have spontaneous activity and response maps that show V-shaped excitatory areas flanked by inhibitory sidebands that could overlap well that of an LSO unit (Shofner and Young, 1985).

From a signal processing perspective, the extra-olivary inputs to type I units may serve several purposes. First, the enhanced sharpness of type I unit tuning curves ensures that sounds are processed in narrow frequency channels, perhaps establishing critical bands for the perception and recognition of complex sounds (Ehret and Merzenich, 1988). Such a refined analysis of ILDs may also have important implications for the processing of competing free-field sounds (each having some distinct spectral content) that reach the listener with different directional signatures. Second, the reduced responsiveness of type I units may be a form of gain control

or attentional filter, which allows neurons to adjust the dynamic portion of their input-output function to the range of inputs (e.g., Ingham and McAlpine, 2005). Finally, the additional inputs may effect the processing of ILDs. For example, LSO and ICC units differ in the level tolerance of sensitivity to ILDs and latency mismatches of the binaural inputs to ICC units appear to play a substantial role in establishing this difference (Park et al., 2004; Tsai et al., 2010). In particular, Park and colleagues (2004) suggested that ICC units receive, in addition to LSO inputs, additional excitatory inputs driven by the excitatory ear and inhibitory inputs driven by the inhibitory ear. Perhaps the EXC input above serves the role of the contralaterally excited source. The exact roles of the extra-olivary inputs to type I units await the results of future studies.

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ABBREVIATIONS

7N	seventh cranial nerve
ANF	auditory nerve fiber
BF	best frequency
CN	cochlear nucleus
DLPO	dorsolateral periolivary nucleus
DNLL	dorsal nucleus of the lateral lemniscus
EXC	excitatory inputs
GABA	γ -amino butyric acid
IC	inferior colliculus
ICC	central nucleus of the inferior colliculus
ILD	interaural level difference
im	intramuscular
INH	inhibitory inputs
ITD	interaural time difference
iv	intravenous
LNTB	lateral nucleus of the trapezoid body
LSO	lateral superior olive
MNTB	medial nucleus of the trapezoid body
MSO	medial superior olive
Q	quality factor
SOC	superior olivary complex
VNLL	ventral nucleus of the lateral lemniscus

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FIG. 1.

Frontal section of the left lateral superior olive (LSO). The vertical line indicates the path of the electrode through the facial nerve (7N) and into the LSO; two recording passes were made down this track. The circle encloses the second of three lesions made along this penetration to aid path reconstruction; the other lesions are out of this plane of section. Tick marks show the locations of LSO units isolated within the track; the numerical labels on the left and right of the line indicate the best frequency (BF; kHz) of the units isolated in the first and second electrode passes, respectively. D, dorsal; M, medial; MSO, medial superior olive; LNTB, lateral nucleus of the trapezoid body.

FIG. 2.

Monaural frequency response maps for LSO and ICC units. A–C: Range of patterns of excitation and inhibition observed in ipsilateral response maps of LSO units (A, 03/19/08 4.02; B, 03/13/07 1.08; and C, 10/23/07 4.10). D: Contralateral response map for a representative ICC type I unit (08/08/06 2.04). Plots show stimulus-evoked discharge rates (vertical bars) as a function of tone frequency and level. Bar length is proportional to the maximum rate elicited in that unit. The maximum rates (in spike/s) are as follows: A, 300; B, 235; C, 350; and D: 500.

FIG. 3.

BFs and thresholds for monaural, excitatory stimulation for all LSO and ICC type I units. **A:** scatterplot of BF-tone thresholds as a function of BF; for comparison, data from non-LSO superior olivary complex (SOC) units are shown. The gray-shaded area encloses units designated as low-BF units (BFs < 3 kHz). The solid line shows the best threshold curve for auditory nerve fibers (ANFs) in cat (Calhoun et al., 1997; Miller et al., 1997). **B:** distribution of thresholds within unit types. Data are plotted in decibels relative to the best threshold of ANFs with similar BFs. The gray-filled counts in the histograms indicate low-BF units within the populations. Gray and black symbols above the histograms indicate median values for low- and high-BF units, respectively, within each population.

FIG. 4.

Excitatory bandwidths for all LSO and ICC type I units. A: scatterplot of single-unit Q_{10} values (BF divided by the excitatory bandwidth 10 dB above threshold) as a function of BF. For comparison, lines show the range of Q_{10} values for ANFs (Calhoun et al., 1997; Miller et al., 1997). B: Q_{40} values (same definition as above but excitatory bandwidths are measured 40 dB above threshold). ANF data are taken from Liberman (1978). C: distribution of Q_{40} values within unit types. Data are normalized by the maximum Q_{40} values of ANFs with similar BFs; values greater than 1 indicate units with sharper tuning than that of ANFs. Gray-filled counts indicate low-BF units within the populations. Gray (black) symbols above the histograms indicate median values for low-BF (high-BF) units within each population.

FIG. 5.

Shapes of BF-tone rate-level functions in LSO and ICC. A: functions for the three LSO units whose response maps are shown in Fig. 2 (correspondingly labeled 2a–c) and one representative ICC type I unit (04/12/06 1.02; offset +10 dB for visual clarity). The dashed lines identify the data used in the calculation of the normalized slopes for these units. B: distribution of normalized slope values for all LSO and ICC type I units. Gray-filled counts indicate low-BF units within the unit types. Gray (black) symbols above the plots indicate median values for low-BF (high-BF) units within each population.

FIG. 6. Spontaneous and maximum BF-tone driven rates of all LSO and ICC type I units. A: distribution of spontaneous rates for low-BF (gray-filled counts) and high-BF units within unit types. B: distribution of maximum driven rates within unit types. Gray (black) symbols above each plot indicate median values for low-BF (high-BF) units within a population.

FIG. 7.

Comparison of broadband noise and BF-tone response properties for LSO and ICC type I units. A: rate-level curves to bursts of broadband noise for the three LSO units whose response maps are shown in Fig. 2 (labeled 2a–c) and for a representative ICC type I unit (10/09/08 2.05). The dashed lines identify the data used in the calculation of the normalized slopes for these units. B: scatter plot comparing each unit's normalized slope for noise versus BF-tone stimulation. Symbols represent individual units. The line indicates equal slopes. C: comparison of noise versus BF-tone thresholds for all units. Noise thresholds are specified in terms of the total noise power in the bandwidth of each unit 10 dB above threshold. The line indicates equal thresholds to both stimuli. D: comparisons of each unit's maximum driven rate for noise versus tone stimulation. Line indicates equal driven rates to the two stimuli.

FIG. 8.

Comparison of BF-tone thresholds of SOC and ICC units in decerebrate and anesthetized cats. A. Comparison of LSO and excitatory-inhibitory ICC unit thresholds. Symbols show tone thresholds as a function of BF for units in the LSO (Tsuchitani and Boudreau, 1967) and the ICC (Ehret and Merzenich, 1988) in anesthetized cat. The solid and dotted lines show the best threshold curve for LSO and ICC type I units, respectively, in the current study of decerebrate cat. B. Comparison of LSO and non-LSO unit thresholds. Symbols show tone thresholds as a function of BF for units in the LSO and the medial nucleus of the lateral lemniscus (MNTB) in anesthetized cat (Tsuchitani, 1997). The solid and dashed lines show the best threshold curve for LSO and non-LSO SOC units, respectively, in the current study of decerebrate cat.

FIG. 9. Model of the LSO-to-ICC type I pathway. Each LSO and ICC is divided roughly into two parts: a low-frequency limb (BFs < 3 kHz) shaded gray, and a high-frequency limb. Circles in the LSO and ICC represent principal cells with low or high BFs. Filled (empty) symbols are excitatory (inhibitory) connections. INH, inhibitory inputs; EXC, excitatory inputs.

Table 1

Monaural response properties of LSO and ICC type I units

	LSO units		ICC type I units	
	Low-BF	High-BF	Low-BF	High-BF
Number of units	20	67	22	78
BF-tone threshold re ANF (dB)	39.8 <i>aba</i>	16.0 <i>aβ</i>	25.5 <i>bc</i>	13.8 <i>c</i>
Noise threshold re ANF (dB)	29.1 <i>da</i>	8.4 <i>dβ</i>	21.1 <i>e</i>	13.1 <i>e</i>
Q ₁₀ re narrowest ANF	0.38 <i>fg</i>	0.58 <i>f</i>	0.70 <i>g</i>	0.63
Q ₄₀ re narrowest ANF	0.75 <i>h</i>	0.79 <i>i</i>	1.25 <i>h</i>	1.14 <i>i</i>
Spontaneous rate (spikes/s)	0.05 <i>j</i>	0.21 <i>k</i>	5.63 <i>j</i>	11.2 <i>k</i>
Max rate for BF tones (spikes/s)	121	144 <i>lγ</i>	108	113 <i>lδ</i>
Max rate for noise (spikes/s)	64	102 <i>mγ</i>	72	63 <i>mδ</i>
Norm slope for tones (%/dB)	0.091	-0.002 <i>n</i>	-0.22	-0.79 <i>ne</i>
Norm slope for noise (%/dB)	0.14	-0.040	0.096	-0.31 <i>ε</i>

Table entries are median values. ANF, auditory nerve fiber. Noise thresholds were computed over a bandwidth 10 dB above the best frequency (BF)-tone threshold for each unit. Statistical tests within a row, designated,

a-n are nonparametric Mann Whitney U tests; tests within a column,

α-ε are Wilcoxon signed-rank tests; all P values < 0.01.