

Interaural Time Sensitivity in Medial Superior Olive of Cat

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SUMMARY AND CONCLUSIONS

1. We studied the sensitivity of cells in the medial superior olive (MSO) of the anesthetized cat to variations in interaural phase differences (IPDs) of low-frequency tones and in interaural time differences (ITDs) of tones and broad-band noise signals. Our sample consisted of 39 cells histologically localized to the MSO.

2. All but one of the cells had characteristic frequencies <3 kHz, and 79% were sensitive to ITDs and IPDs. More than one-half (56%) of the cells responded to monaural stimulation of either ear, and both the binaural and monaural responses were highly phase locked. All of the cells that were sensitive to IPDs and monaurally driven by either ear responded in accord with that predicted by the coincidence model of Jeffress, as judged by comparisons of the phases at which the monaural and binaural responses occurred. The optimal IPDs were tightly clustered between 0.0 and 0.2 cycles. Most cells exhibited facilitation of the response at favorable ITDs and inhibition at unfavorable ITDs compared with the monaural responses.

3. Cells in the MSO exhibited characteristic delay, as judged by a linear relationship between the mean interaural phase and stimulating frequency. Characteristic phases were clustered near 0 indicating that most cells responded maximally when the two input tones were in phase. With the use of the binaural beat stimulus we found no differential selectivity for either the direction or speed of interaural phase changes.

4. The cells were also sensitive to ITDs of broad-band noise signals. The ITD curve in response to broad-band noise was similar to that predicted by the composite curve, which was calculated by linearly summing the tonal responses over the frequencies in the response area of the cell. Most (93%) of the peaks of the composite curves were between 0 and $+400 \mu\text{s}$, corresponding to locations in the contralateral sound field. Moreover, computer cross correlations of the monaural spike trains were similar to the ITD curve generated binaurally for both correlated and uncorrelated noise signals to the two ears. Thus our data suggest that the cells in the MSO behave much like cross-correlators.

5. By combining data from different animals and locating each cell on a standard MSO, we found evidence for a spatial map of ITDs across the anterior-posterior (A-P) axis of the MSO. Low ITDs, near $0 \mu\text{s}$, were located near the anterior pole, and more positive ITDs, corresponding to delays of the ipsilateral stimulus, were mapped at more posterior locations.

6. Some general response characteristics, such as spontaneous activity, shape of the poststimulus time histogram, tuning curves, response areas, and rate-level curves, were also examined. Generally, the response characteristics in response to ipsilateral and contralateral stimulation were similar. The phase-locking ability of cells in the MSO, as measured by the synchronization coefficient, was consistently elevated over that seen in the auditory nerve.

7. We compared the monaural and binaural response properties of cells in the MSO with that in the central nucleus of the inferior colliculus (ICC). Although many similarities were seen,

there were also differences that presumably reflected additional processing at the level of the ICC.

INTRODUCTION

The superior olivary complex (SOC) occupies a pivotal position in the auditory system. It represents the second synaptic relay for most ascending fibers and the first point at which there is significant binaural interaction. In mammals two parallel circuits, which appear to be primarily responsible for encoding the two binaural cues, interaural time and level differences, that make up the traditional duplex theory of sound localization, emerge from the SOC. It appears that interaural time differences (ITDs), which for tonal stimuli are relevant primarily at low frequencies, are primarily encoded in the medial superior olive (MSO), whereas interaural level differences (ILDs), which are maximal at high frequencies, are encoded in the lateral superior olive (LSO) (see reviews by Boudreau and Tsuchitani 1970; Goldberg 1975; Irvine 1986; Yin and Kuwada 1984). Behavioral experiments also support the importance of the MSO and LSO for sound localization of low- and high-frequency sounds, respectively (Masterton et al. 1975). The duplex theory has also been the base for many psychoacoustical and modeling studies of binaural interaction (see review by Blauert 1983). Based on these simplified concepts the LSO and MSO would seem to be the critical places to study binaural interactions. However, there have been surprisingly few comprehensive studies of the binaural response properties of cells in either of these important nuclei. Further investigations of the SOC are clearly needed to understand the neural mechanisms established at the first level of binaural interaction.

The shortage of reliable and systematic studies is particularly true for the MSO. This is due in large measure to the well-known technical difficulties of obtaining single-unit recordings from the MSO (Guinan et al. 1972b). These difficulties arise in part because of the thinness of the nucleus and in part because of the large field potentials that are present in this area, presumably as a consequence of the convergence of many fibers carrying synchronized, phase-locked activity. Reports of difficulties in recording from the MSO also extend to nonmammalian species (e.g., owls; Moiseff and Konishi 1983). Thus even extensive surveys of the SOC have not been able to record from many cells in the MSO; for example, in Guinan et al.'s (1972b) survey of 432 cells in the SOC, only 11 were located in the MSO. As a result our understanding of the properties of the MSO derives chiefly from scattered reports in different species of animals.

In addition to the scarcity of MSO studies, there are even fewer data from the MSO of the cat, whose central auditory system has been the most thoroughly studied of any animal. The classic studies of Goldberg and Brown (1969) and Moushegian and his colleagues (Crow et al. 1978; Moushegian et al. 1964, 1967, 1975; Rupert et al. 1966) were done in the dog and kangaroo rat, respectively. Only the general mapping studies of the SOC by Guinan et al. (1972a,b) and Caird and Klinke (1983) were done in the cat.

Therefore conclusions about the physiological response properties of cells in the MSO, particularly in the cat, must be tempered with the recognition that they are based on small samples. Like most other auditory nuclei, there appears to be an orderly mapping of frequencies onto the MSO; in the cat low frequencies are represented dorsally and high frequencies ventrally (Guinan et al. 1972b). There appears to be an overrepresentation of low frequencies, which is consonant with the ideas that the MSO is important for coding ITDs and further that ITDs are primarily useful for low-frequency stimuli (Guinan et al. 1972b). Most cells in the MSO are binaural, responsive to stimulation of either ear, and sensitive to changes in ITD of tones and clicks (Goldberg and Brown 1969; Moushegian et al. 1975). Comparisons of the timing of monaural and binaural responses with ITDs of tones at characteristic frequency (CF) show that cells in the MSO act like the coincidence detectors first proposed by Jeffress (1948) (Crow et al. 1978; Goldberg and Brown 1969). Generally speaking, the monaural responses of cells in the MSO are similar to those seen in the auditory nerve: threshold tuning curves are V-shaped, rate-level functions are monotonic and saturating, and poststimulus time histograms are primary-like (PL) in shape (Goldberg 1975). The presence of a small number of cells with inhibitory sidebands or nonmonotonic rate-level functions has also been reported (Goldberg and Brown 1969; Moushegian et al. 1964). However, virtually nothing is known about the ITD sensitivity at frequencies other than CF and for stimuli other than tones and clicks. Furthermore, the more general description of coincidence as a cross-correlation has not been tested in the MSO nor are there any data on the possibility of a spatial map of ITDs across the MSO as described in the barn owl (Carr and Konishi, unpublished observations; Sullivan and Konishi 1986).

The inputs to the MSO of cats originate from the large spherical cells in the anterior part of the anteroventral cochlear nucleus (AVCN) of both sides (Cant and Casseday 1986; Osen 1969; Warr 1966, 1982). The large spherical cells in the AVCN receive input from the auditory nerve by way of the large, axosomatic synapses known as the endbulbs of Held (Brawer and Morest 1975; Ramon y Cajal 1909; Cant and Morest 1979; Fekete et al. 1984; Held 1893; Lorente de No 1981) and respond in a PL fashion (Bourk 1976; Pfeiffer 1966). The PL designation indicates the similarity of the response to that of auditory nerve fibers and suggests that the temporal information carried on the auditory nerve fibers is faithfully relayed to the spherical/bushy cells. For pure tones the timing information is carried in the form of phase-locked responses for frequencies below ~ 4 kHz. Thus cells in the MSO receive inputs carrying temporal information about the fine struc-

ture of the acoustic stimulus, which enables them to achieve sensitivity to ITDs.

Anatomically, the MSO consists of a narrow sheet of cells extending ~ 3.5 mm in the rostral-caudal dimension and angled from dorsomedial to ventrolateral. The principal cells of the MSO are fusiform in shape with two or three primary dendrites, which are oriented orthogonal to the plane of the nucleus. The dendritic trees are also elongated to a considerable degree in the rostral-caudal dimension, so that in three-dimensional views they have a distinct planar shape (Scheibel and Scheibel 1974). The axons from the contralateral and ipsilateral AVCN provide synaptic inputs that are segregated onto the medial and lateral dendrites, respectively, of the cells in the MSO (Stotler 1953; Warr 1966). Each cell receives input from the contralateral ear situated primarily on the medially directed dendrites and from the ipsilateral ear on the laterally directed dendrites. In this way the cells seem ideally suited to compare the inputs arriving from the two ears.

The coincidence model only emphasizes the excitatory inputs to the MSO, yet there is ample anatomic evidence for inhibitory inputs. Electron microscopic studies of the MSO have revealed several different classes of terminal endings (Clark 1969; Lindsey 1975; Schwartz 1972, 1980, 1984). The majority of endings contain large spherical vesicles, make multiple asymmetric synaptic contacts that densely cover a large proportion of the soma and dendrites, degenerate after destruction of the cochlear nucleus, and are consequently associated with the spherical/bushy cell input from the AVCN (Kiss and Majorossy 1983; Lindsey 1975; Schwartz 1984). There are other terminals, which contain smaller vesicles of various shapes and do not degenerate after lesions of the cochlear nucleus. Terminals with flat vesicles are found on the somas and proximal dendrites, whereas terminals with spherical vesicles are widely distributed over the cell and are the only ones found on the distal dendrites (Clark 1969; Lindsey 1975; Perkins 1973; Schwartz 1984). The origin of the terminals with nonspherical vesicles is not known and is pertinent to the issue of the nature and origin of a possible inhibitory input to the MSO.

The aims of the present work were to study systematically several important issues regarding the interaural time sensitivity of cells in the MSO of the cat: to test the Jeffress (1948) coincidence model in more detail for tones and for more complex noise stimuli, to examine the differences between responses seen at the level of the MSO with those reported in the central nucleus of the inferior colliculus (ICC), and to look for evidence of characteristic delay (Rose et al. 1966; Yin and Kuwada 1983b), inhibitory inputs to the MSO and a spatial map of ITDs. In agreement with earlier reports we have also had difficulty in recording from many cells in the MSO. Nonetheless, we feel that our relatively small sample provides important information on binaural processing. Preliminary accounts of these results have been presented earlier (Chan and Yin 1984; Yin and Chan 1988).

METHODS

Detailed accounts of our experimental procedures have been given earlier (Yin et al. 1986). Briefly, cats with no sign of middle

ear infection were initially anesthetized with an intrathoracic injection of pentobarbital sodium (35 mg/kg), and a subcutaneous injection of atropine methyl nitrate (0.2 mg/kg) was given to minimize mucous secretions. Supplemental doses of anesthetic were administered as needed through a venous cannula to maintain an areflexic state. A tracheal cannula was inserted. Rectal temperature was maintained near 37°C with a heating pad. Both external ears were removed and both external auditory meati were cut transversely to allow insertion of tight-fitting hollow metal earpieces, through which the acoustic stimuli were delivered. The earpieces were aimed toward the malleus and sealed into the ear canals with Audilin ear impression compound. A small hole was drilled into the wall of each bulla and a polyethylene tube of 0.86 mm ID and ~60 cm length was inserted into the hole and sealed with glue to maintain the middle ear cavity at atmospheric pressure.

Access to the SOC was afforded by a ventral approach. The basioccipital bone was exposed by removing or deflecting aside the overlying trachea, esophagus, and muscles. A bone flap was removed to expose the ventrolateral brain stem at a point between the bulla and the pyramid. We directed microelectrodes into the SOC either vertically or aimed laterally at a 10–20° angle near the exit of the abducens nerve. Warmed agar was dripped over the microelectrode after it was in position.

The animal was placed in a double-walled, sound-insulated and electrically shielded room (IAC). Acoustic stimuli were generated by the digital stimulus system developed by Rhode (1976) and delivered by a pair of Telex 140 speakers coupled to the earpieces with Tygon tubing. A hollow tube, which could be coupled to a 1.27-cm Bruel and Kjaer microphone for calibration of the acoustic stimulus, was inserted into each earpiece until the tip was ~2 mm from the eardrum. For each experiment the sound-delivery system to each ear was calibrated for intensity and phase of tones between 60 and 40,000 Hz in 20-Hz steps. Calibrations were stored in the computer (Harris/6) and used to set the attenuator values during delivery of sinusoidal tones. In this way the sound pressure level (SPL) of the signal at the eardrum relative to 20 μ Pa was specified for all tonal stimuli.

Extracellularly recorded action potentials from single MSO cells were amplified, filtered (300–3000 Hz), and displayed on oscilloscopes and audiomonitors. A Trent Wells hydraulic stepping motor microdrive was used to control the movement of the microelectrode. Single spikes were isolated with a level discriminator, and the standard pulses were sent to a unit event timer interfaced to the computer so that the time of occurrence of each spike with respect to the onset of the stimulus was saved in the data file. This enabled us to generate histograms of many different varieties (e.g., period, interval, or poststimulus time histograms). The search stimulus was a binaural beat (see below) or monaural tone burst, whose frequency, laterality, SPL, and timing characteristics could be varied. After isolating a single cell, we determined its best frequency (BF), which was the frequency evoking the most vigorous response at a given SPL. In some cells we also used an automated threshold tracking program to determine the CF, which was the frequency of the tone with the lowest threshold. The degree of response to monaural stimulation of each ear was used to classify the cell as EE, Ee, E0, etc., according to the convention that E and 0 referred to excitation and no response, respectively; capital letters represented considerably stronger responses than small letters; and the response to monaural stimulation of the contralateral ear was expressed by the first letter whereas the ipsilateral response was given by the second.

Because we were interested in the interaural time sensitivity of cells in the MSO, many of our stimuli were tones or noise with ITDs interposed. In all cases, the entire waveform was delayed, and positive ITDs were designated by convention as delays of the ipsilateral stimulus with respect to the site of recording. For tones

we also studied sensitivity to interaural phase differences (IPDs) with the use of the binaural beat stimulus, which was generated by delivering tones to the two ears that differed by a small beat frequency (f_b) of 1 Hz. Period histograms synchronized to the period of f_b were used to express the interaural phase sensitivity of the cell at a particular frequency and SPL.

Pseudo-Gaussian noise stimuli were generated digitally. The standard noise sequence was 1 s in duration and presented at a rate of 8,000 samples/s. It had a nominally flat spectrum (± 6 dB) as measured at the eardrum over 60–4,000 Hz. This and other noise files were stored on computer disk and loaded into general waveform buffers (one for each ear) in the digital stimulus system when needed (see Yin et al. 1986 for details). For all stimuli the duration, repetition rate, and onset delay of the stimulus to each ear were under computer control and could be specified to a precision of 1 μ s, and a trapezoidal gating envelope with a rise-fall time of 3.9 ms was used. The stimulus level could be varied in 1-dB steps.

In one high-frequency cell we used sinusoidal amplitude modulated (AM) waveforms to study ITD sensitivity. We used carrier frequencies f_c set to the CF of the neuron, modulation frequencies f_m between 50–1,000 Hz, and 100% depth of modulation. In response to AM stimuli the monaural responses of this high-frequency cell were phase locked to f_m not to f_c , and under binaural conditions it was sensitive to ITDs of the envelope but not the carrier signal.

Because of difficulties in recording from cells in the MSO, we tried several different types of electrodes and paid special attention to localizing the recording site. We used parylene-coated tungsten microelectrodes (Microprobe) and low-impedance (5–20 M Ω at 1 kHz) glass micropipettes filled with a saturated dye solution (Fast Green) in 3 M KCl. Because of the large field potentials, which tended to obscure extracellularly recorded spikes in the vicinity of the MSO, we tried a pair of the tungsten electrodes glued together and recorded differentially between them. Single-ended recordings were used to determine from which of the two electrodes the spike was recorded. Although the differential recording helped to reduce the field potentials, there was little improvement in the ability to record single units from the MSO. We found a somewhat higher percentage of successful penetrations with the micropipettes. After each penetration we made several electrolytic lesions or dye marks near cells of interest.

Histology

At the conclusion of each experiment the animal was given a lethal dose of pentobarbital sodium and perfused intracardially with 0.9% saline followed by 10% Formalin. The brain stem was then cut by standard techniques into frozen frontal sections (50 μ m) and stained with thionin. The locations of all recording sites were transferred onto a standard SOC by normalizing each brain stem along its rostrocaudal axis for the length of the MSO. The lesions from tungsten microelectrodes were almost always visible, but the dye marks and lesions from micropipettes were less consistent. For five cells in which the lesions were not visible, the gliosis from the electrode tract was used to ensure that the penetration traversed the MSO, and the depth of the recording was inferred from the characteristic change with depth in the slow potentials evoked from either ear as the electrode passed through the middle of the MSO (Guinan et al. 1972b). Figure 1 shows micrographs of six such sections that show penetrations with successful recordings from the MSO. It is possible that some of these recordings were made from axons of cells in the MSO rather than from cell bodies or that the small number of recordings from monaural cells (18%, see below) were made from fibers of the trapezoid body that course through or terminate in the MSO.

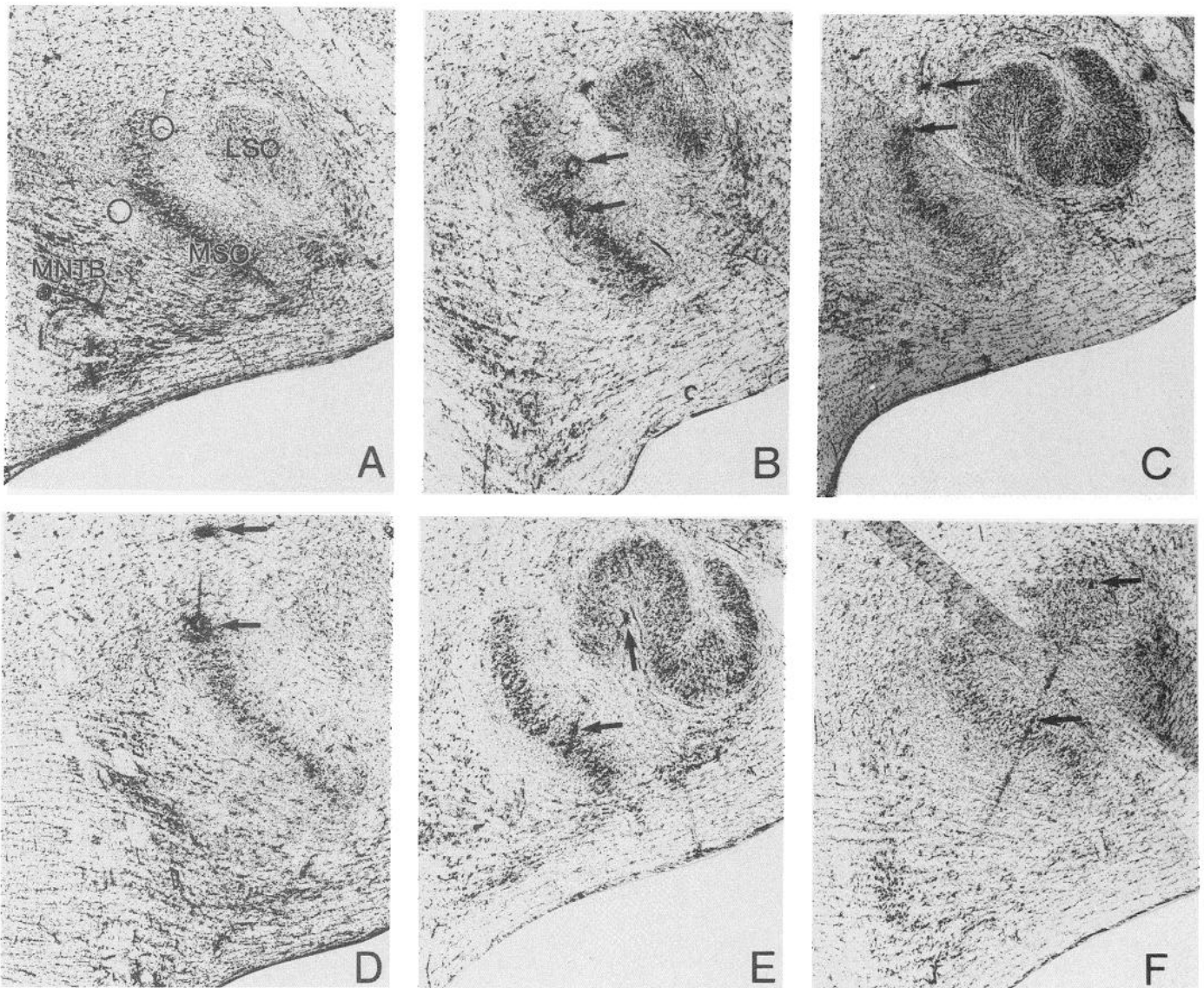


FIG. 1. Histological sections through the SOC of 6 cats showing electrode penetrations made through the MSO. In each penetration 2 lesions were made, and except for panel *A*, the gliosis from these lesions are marked by arrows. In panel *A* the cat was perfused immediately after lesions (o) were made, and there was insufficient time for gliosis to occur, but the lesions are marked by small holes in the tissue. *A*: cat 82157, penetration 2. Cell with BF of 200 Hz was recorded at the site of the dorsal lesion. *B*: cat 84017, penetration 5. One cell was recorded at the site of the dorsal arrow with a BF of 300 Hz. The lesion visible at the edge of the LSO was made in another penetration. *C*: cat 83226, penetration 3. Four cells were found just ventral to the ventral lesion; their BFs ranged from 300 to 900 Hz. *D*: cat 83034, penetration 1. Four cells were recorded in this penetration ranging in BFs from 800 Hz most ventrally to 400 Hz most dorsally; all of them were ventral to the ventral lesion. *E*: cat 84005, penetration 1. Cell with BF of 900 Hz was found at the site of the ventral lesion. Another cell with a BF of 14 kHz that had the characteristics of LSO cells, i.e., excited by stimulation of the ipsilateral ear and inhibited by contralateral ear, was found at the site of the dorsal lesion. *F*: cat 84015, penetration 1. Three cells with BFs ranging from 900 to 1,300 Hz were found near the ventral lesion, and another LSO-like cell with BF of 24 kHz was found at the dorsal lesion.

RESULTS

These data were obtained from 39 cells, of which 34 were histologically confirmed to be in the MSO and its immediate vicinity, and five were recorded in penetrations where the lesions were not found. In 19 cats we made 85 penetrations into the SOC, of which 75 traversed the MSO. In only 29% (22/75) of these penetrations were we successful in recording from at least one cell in the MSO. In a number of penetrations we recorded from several individual cells

clustered in a small area (Fig. 1*C*, *D*, and *F*) so that over one-half (54%, 21/39) of the cells were recorded from only six penetrations.

Responses to interaural time delays of tones: evidence for coincidence and inhibition

Because we were interested in studying sensitivity to ITDs, we aimed our electrodes at the low-frequency region of the MSO. Most of our sample did indeed have low CFs;

with one exception the CFs were <3 kHz and 85% (33/39) were <1 kHz. Most (59%, 23/39) of our cells exhibited a robust sensitivity to interaural phase of pure tones, and another eight of them were weakly phase sensitive. Only 18% (7/39) of the cells showed no sensitivity to ITDs; they responded like monaural cells. The remaining cell had a high CF (15 kHz), was driven with an onset response to stimulation of either ear, and was sensitive to IPDs of the envelope of amplitude modulated tones. We will discuss its responses separately (see Fig. 14).

Most of our analysis was restricted to low-frequency cells that were sensitive to IPDs. Figure 2 shows responses of two such cells to changes in the ITDs at their BF. In each case we chose ITDs so that samples were obtained for each 0.1 cycle. For both cells the discharge rate varied cyclically as a function of ITD at the frequency of the stimulus, as described earlier for the MSO (Goldberg and Brown 1969) and for cells that are sensitive to ITDs in other areas (see review by Yin and Chan 1988). However, unlike other areas, most cells in the MSO responded to monaural stimulation of either ear and, for frequencies below ~ 2 kHz, did so in a highly phase-locked manner (Fig. 2, right).

The monaural period histograms indicate the relative timing of inputs to the MSO from each ear. We computed the mean phase angle ϕ and vector strength, or synchroni-

zation coefficient r , of the period histograms using the vector averaging method of Goldberg and Brown (1969). The mean phase angle of the monaural ipsilateral response ϕ_i indicated the most probable phase angle at which the ipsilateral input arrived at the MSO. Similarly, ϕ_c represented the mean phase angle for the contralateral input. The value of r measures the degree of phase-locking and varies from 0 (no preferred phase) to 1.0 (all spikes in 1 bin of the cycle histogram). If the responses were in accord with the Jeffress (1948) coincidence model, then the maximum binaural response should occur when the two monaural phases were made equal by the introduction of the appropriate ITD so that the inputs from both sides arrived at the MSO simultaneously. For the responses shown in Fig. 2A, this predicted that coincidence should occur when the ipsilateral stimulus was delayed by 0.15 cycles (i.e., $\phi_c - \phi_i = 1.02 - 0.87$), or 150 μ s for the 1,000-Hz stimulus tone. The central peak of the delay curve (Fig. 2A, left) occurred at +100 μ s, corresponding to a phase of 0.10 cycles; and the mean interaural phase ϕ_d of the delay curve averaged over four cycles (Kuwada and Yin 1983) was equal to 0.09, both of which were close to the 0.15 predicted from the monaural responses and the coincidence model. For the response shown in Fig. 2B, the predicted phase was -0.03 cycles ($\phi_c - \phi_i = 0.82 - 0.85$) whereas $\phi_d = +0.03$ cycles. Thus for both cells the predic-

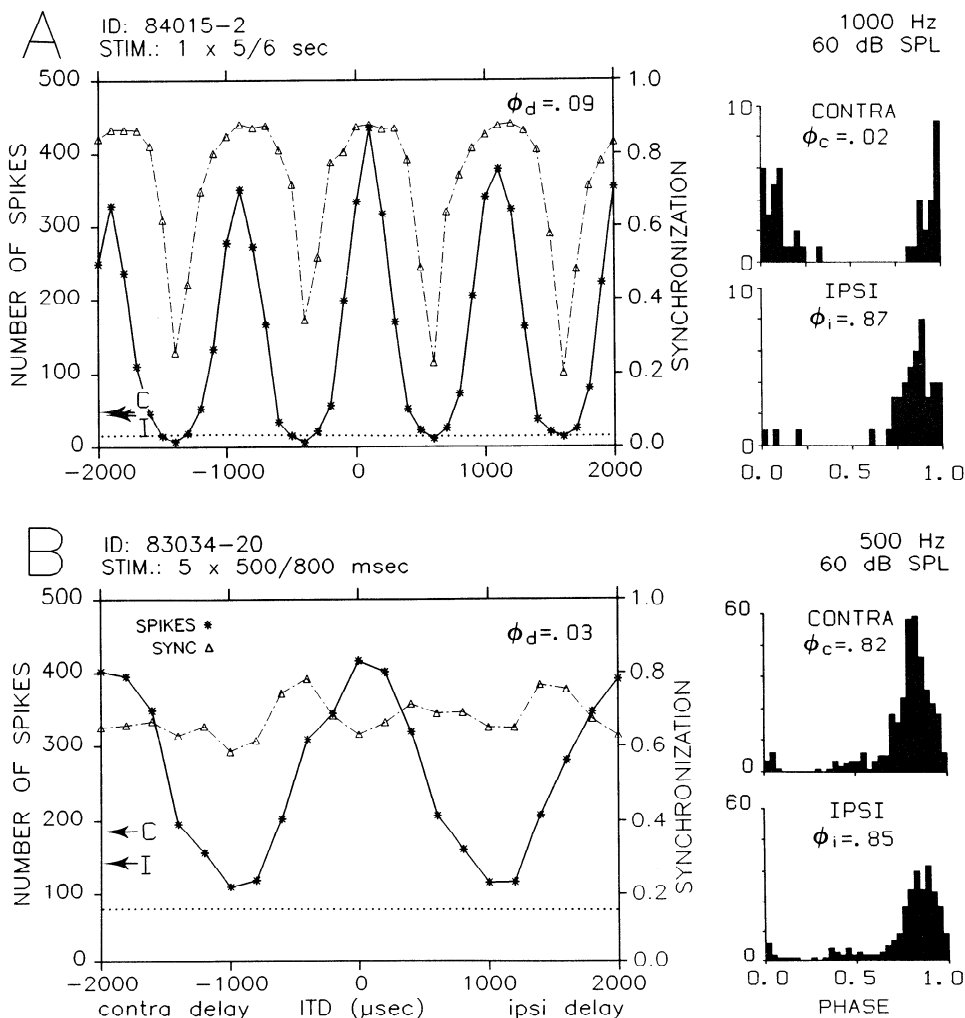


FIG. 2. Interaural time delay curves for discharge rate and synchronization (left) and monaural period histograms (right) for 2 cells in the MSO. For the ITD curve, the mean interaural phase ϕ_d , calculated by averaging all cycles of the periodic ITD curve, is also given. Ordinate to the left is for spike discharge and that to the right for synchronization coefficient, both of which were computed over the duration of the stimulus. Arrows marked C and I represent discharge rates obtained for monaural stimulation of contralateral and ipsilateral ears, respectively, and the mean spontaneous rate is shown by the dotted line. By convention, positive ITDs denote delays of the ipsilateral stimulus. Mean phase of monaural period histograms for stimulation of the contralateral ϕ_c and ipsilateral ϕ_i ear are shown above histograms. In this and in all subsequent figures, the cell identification number, stimulus frequency, SPL, and stimulation time are shown above each panel. Penetrations containing the cells in panel A and B are shown in Figs. 1F and 1D, respectively.

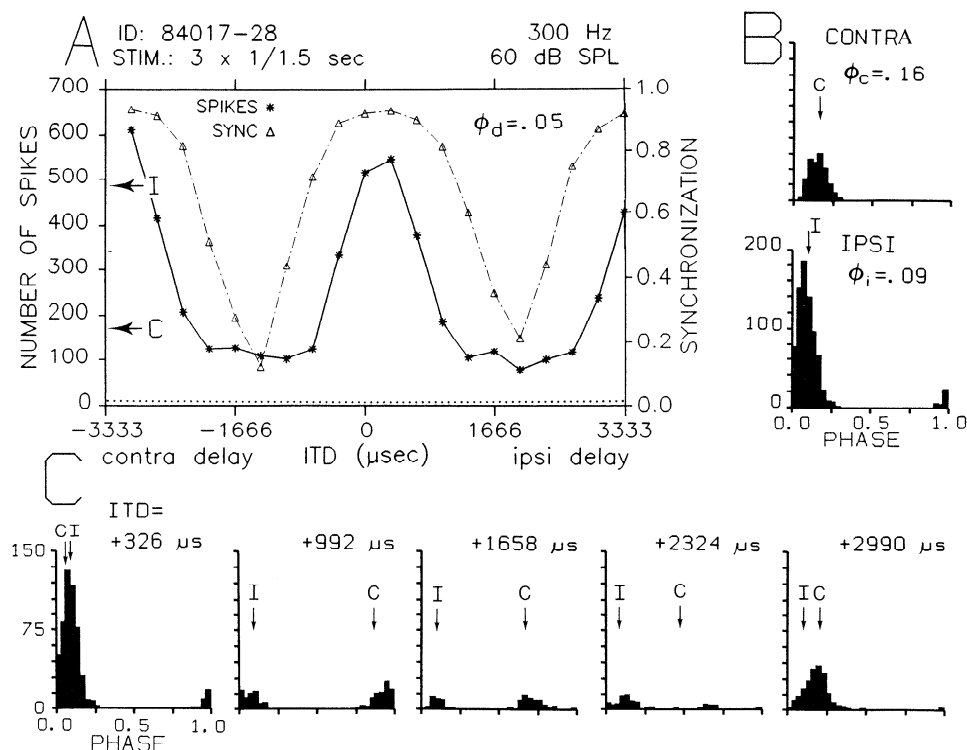


FIG. 3. ITD curves (A), monaural (B), and binaural period histograms (C) for a cell in the MSO. Histograms in C were derived from 5 of the ITDs. A: same conventions as in Fig. 2, except that vertical arrows marked C and I in B denote ϕ_c and ϕ_i , respectively, and in C they indicate the expected time of arrival of these inputs as judged from ϕ_c and ϕ_i in B. This cell was recorded in the penetration of Fig. 1B.

tion was within 0.06 cycles of that observed from binaural stimulation.

Additional evidence for the coincidence model was found by examining the times of occurrence of the binaurally evoked spikes relative to the expected monaural responses. In both Figs. 3 and 4, panels A and B show the interaural delay curve and monaural period histograms in the same format as for Fig. 2. The phase angle $\phi_c - \phi_i$, which

was predicted from coincidence of monaural inputs, was nearly equal to that (ϕ_d) obtained from binaural stimulation. In Fig. 3, $\phi_c - \phi_i = 0.16 - 0.09 = 0.07$ cycles compared to $\phi_d = 0.05$ cycles; in Fig. 4, $\phi_c - \phi_i = 0.52 - 0.39 = 0.13$ cycles compared to $\phi_d = 0.15$ cycles. In addition, panel C of Figs. 3 and 4 shows five period histograms obtained under binaural stimulation conditions at the different ITDs indicated. As expected, the maximal response was obtained

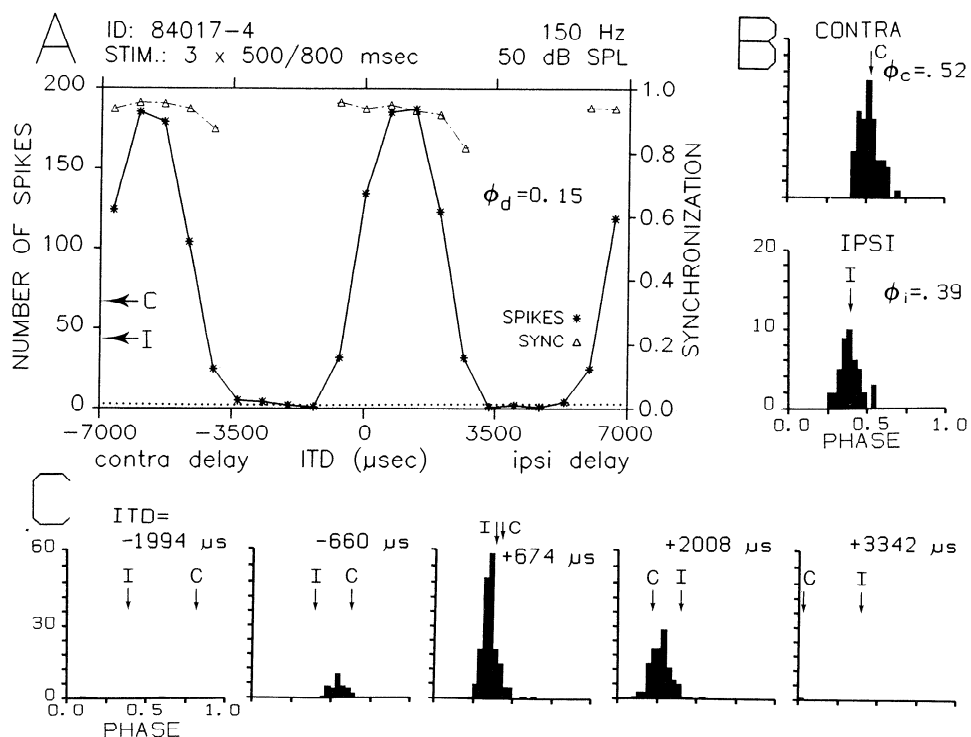


FIG. 4. ITD curves (A), monaural (B), and binaural period histograms (C) for a cell in the MSO. Same conventions as in Fig. 3.

when the inputs from the two ears were nearly coincident (Fig. 3C, +326 μ s; Fig. 4C, +674 μ s). In addition, at the unfavorable delay (+1,658 μ s) of Fig. 3C the period histogram had two peaks, which corresponded in time to the expected inputs from the two ears. However, for most of the cells in our sample, the binaural period histograms were like those in Fig. 4C, where the response at unfavorable ITDs was not bimodal.

The behavior of synchronization of the binaural responses with changes in ITD varied from one cell to the next, as shown in Figs. 2–4. In nearly all cases maximum synchrony occurred at or near the peak of the ITD curve. For most cells the binaural synchrony dropped at unfavorable ITDs (Figs. 2A and 3), whereas in others the synchrony did not vary substantially with ITD (Fig. 2B).

As indicated earlier, there is both anatomic and physiological evidence for inhibitory inputs to MSO cells, though this is not a feature of most models of ITD sensitivity. Because most of the cells had low spontaneous activity, we could usually not detect inhibitory inputs except by com-

paring monaural with binaural responses. The horizontal arrows labeled C and I to the *left* of the ITD curves in Figs. 2–4 mark the response amplitudes obtained from monaural stimulation at the same SPL of the contralateral and ipsilateral ears, respectively. For most cells (65%, 13/20) in our sample, the minimum of the binaural ITD curve fell well below the monaural levels of either ear (as in Figs. 2–4), and in a few cases the minimum binaural response was below the spontaneous level (as in Fig. 2A) or the predominant effect of varying ITDs was suppression below the monaural levels (Fig. 3). Likewise, for most cells (60%, 12/20) the maximum of the binaural response was considerably higher than the sum of the monaural responses (Figs. 2A and 4). These comparisons of the monaural and binaural response rates indicate that for most cells in the MSO there seemed to be inhibition at unfavorable delays and facilitation at favorable delays.

The presence of inhibition at unfavorable ITDs when compared with the monaural levels was suggested more clearly by the experiment shown in Fig. 5 in which we varied the ipsilateral SPL while holding the contralateral SPL constant at four different ITDs. The cell did not respond when stimulated monaurally with an ipsilateral tone at 20 dB (see Fig. 16B), and when the ipsilateral level was 20 dB SPL (Fig. 5, *bottom row*), the response in terms of number of spikes evoked and their timing was essentially equivalent to a monaural contralateral response (Fig. 4B). When the ITD was at an unfavorable delay of $-2,000 \mu$ s (Fig. 5A), raising the ipsilateral level initially caused a suppression so that virtually no spikes were elicited at 40, 50, or 60 dB SPL. This corresponded with the lack of response at $-2,000 \mu$ s, which was obtained with 50 dB SPL at both ears (Fig. 4A). Evidently the ipsilateral input, though excitatory by itself (Fig. 4B), had an inhibitory influence whose effect must also be phase locked. If the experiment had been done by holding the stimulus to the ipsilateral ear constant while varying the contralateral level, presumably we would have seen similar results because the ipsilateral monaural response also exceeded the response at unfavorable ITDs. This suggests that there was both excitatory and inhibitory input from both sides. When the inputs were brought into near coincidence by setting the ITD to +500 μ s (Fig. 5D), raising the ipsilateral level to 50 dB resulted in a facilitation of the response, corresponding to the peak in the ITD curve of Fig. 4A around 700 μ s.

Raising the ipsilateral level above 60 dB caused an unexpected result (Fig. 5). At an ITD of $-2,000 \mu$ s where the ipsilateral input at 50 dB was inhibitory, raising the ipsilateral level to 80 and 90 dB SPL evoked a brisk response that was considerably greater than the monaural contralateral response. Moreover, the phase at which this response occurred was different from that corresponding to either ear stimulus by itself at 50 dB. Likewise, at an ITD of +500 μ s where the ipsilateral input was facilitatory at 50 dB, raising the ipsilateral level to 90 dB SPL caused a decline in the driven response and the appearance of a bimodal period histogram. Thus when the ipsilateral stimulus was at 90 dB, the optimal ITD was near $-1,000 \mu$ s rather than at 500 μ s.

This unexpected shift in the ITD curve at high ipsilateral levels is explicable if we assume that increasing the ipsilateral intensity caused a phase delay on the order of 0.3

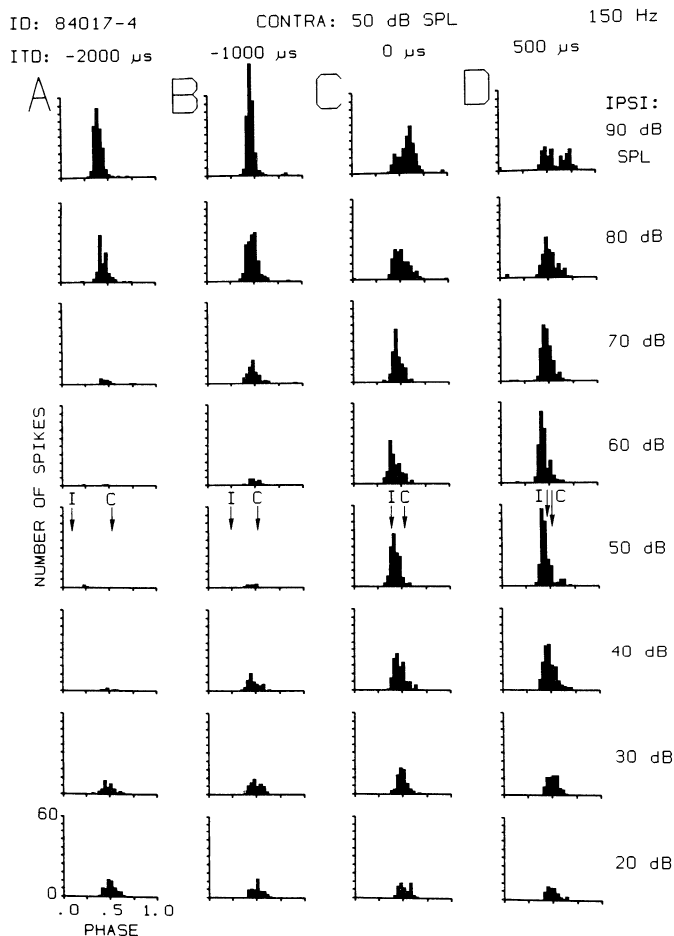


FIG. 5. Binaural period histograms obtained at 4 different ITDs (columns) and 8 different ILDs (rows) for the same cell as in Fig. 4. ILD was varied by holding the SPL to the contralateral ear at 50 dB SPL while varying the SPL to the ipsilateral ear from 20 to 90 dB. Expected arrival times of monaural inputs for 50 dB SPL to both ears are marked along that row. Note that the IPSI 20 dB response was essentially the same as a monaural contralateral response. At unfavorable delays ($-2,000 \mu$ s) increasing the level to the ipsilateral ear caused a suppression of the response until >70 dB SPL. Period histograms were synchronized to the contralateral stimulus.

cycles at 90 dB with respect to the phase at 50 dB. The monaural ipsilateral response showed just such a phase shift: at 50 dB the mean phase was 0.39 and at 80 dB it was 0.69, a shift of 0.01 cycles/dB. A complicating factor for this cell was that the monaural ipsilateral response was also highly nonmonotonic at 150 Hz, so that the number of spikes evoked at 80 dB was only 23% of that evoked at 50 dB. There was virtually no monaural response at 90 dB, though the *top* row of Fig. 5 shows that the 90 dB ipsilateral stimulus had a facilitative binaural effect.

The shift in response phase as a function of SPL could be a reflection of similar shifts that occur at the level of the auditory nerve. When auditory nerve fibers are stimulated at frequencies above or below CF, the phase of the response varies as a function of level (Anderson et al. 1971). Thus if the CFs of the inputs to the cell from the ipsilateral side in Fig. 5 were greater than the stimulating frequency of 150 Hz, the phases of its response would be expected to have increasing lag with increasing level, which would explain the shift in best ITD seen in Fig. 5. This cell exhibited a

nonzero characteristic phase of 0.21, suggesting a slight mismatch in frequencies from the two sides (Yin and Kuwada 1983b). Such shifts in the ITD curve with the introduction of ILDs were unusual, as three other cells in which we tested the sensitivity of interaural phase at different ILDs showed much smaller phase shifts, on average 0.0016 cycles/dB. However, we did not systematically study the effects of ILDs in many cells.

Responses to binaural beats

The cyclic nature of the ITD curves shown in Figs. 2–4 is compelling evidence that these cells are sensitive to the IPD that results from delaying one of the tones. Further evidence of this sensitivity to IPDs was seen in the responses of these cells to a binaural beat stimulus, which was generated when the frequency of the tone to one ear was slightly different from that delivered to the other ear. Yin and Kuwada (1983a) showed in the ICC that the responses to ITDs are similar to responses to IPDs set up by a binaural beat and that binaural beats are a much more efficient way to study IPD sensitivity.

The period histograms in Fig. 6, *A* and *B*, show the responses of a cell in the MSO to monaural stimulation of the contralateral and ipsilateral ear, respectively, and the mean phase angles ϕ_c and ϕ_i of the monaural responses are shown above each histogram. The period histograms in Fig. 6*C* were obtained in response to binaural beats by synchronizing, or binning, the period histogram to the beat frequency f_b of 1 Hz. Because the interaural phase shifted linearly during the course of the binaural beat at the frequency of f_b , the abscissa in Fig. 6*C* represented the IPD. When the frequency to the ipsilateral ear was lower, as in Fig. 6, the first one-half cycle of interaural phase corresponded to delays of the ipsilateral stimulus and the last one-half to delays of the contralateral. The coincidence model predicted that the maximal response should occur when the ipsilateral tone was delayed by $\phi_c - \phi_i$; thus this difference should be equal to the mean phase of the binaural beat response ϕ_b . In all cases of Fig. 6 the differences between ϕ_b and $\phi_c - \phi_i$ were less than 0.06 cycles, except at 800 Hz where the responses were weak.

Because the cell whose responses were shown in Fig. 6 phase locked to monaural stimulation of either ear, this monaurally evoked phase locking was also evident in the binaural responses. By rebinning the same spike trains that generated the histograms in Fig. 6*C* but synchronized on the frequencies f_c delivered to the contralateral ear (400, 500, 600, 700, and 800 Hz), the resulting histograms were also phase locked (Fig. 6*D*), and the mean phase angles ϕ_{bc} were in good agreement with ϕ_c obtained from monaural stimulation (Fig. 6*A*) of the contralateral ear. Figure 6*E* shows analogous data for the ipsilateral stimulus, and again ϕ_{bi} was close to ϕ_i (Fig. 6*B*). For all cells, comparisons of ϕ_c with ϕ_{bc} (Fig. 7*A*) and of ϕ_i with ϕ_{bi} (Fig. 7*B*) had linear regression lines with high correlation coefficients and near unity slopes, indicating good correspondence between the estimates of the mean phase angle from monaural responses and those obtained during binaural stimulation.

The results in Figs. 6 and 7 show that the responses to the binaural beat were phase locked to f_b as well as to both f_c

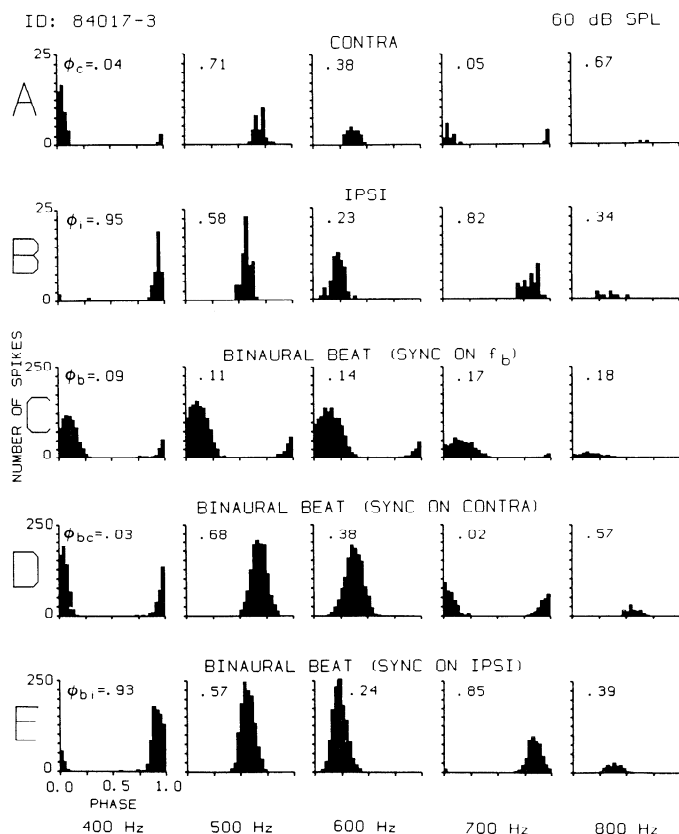


FIG. 6. Period histograms of a cell in the MSO in response to monaural stimulation and to binaural beats. For the binaural beat stimulus (*C*, *D*, and *E*), the frequency of the tone to the ipsilateral ear was 1 Hz less than that to the contralateral ear. For example, in the case of 400 Hz the contralateral frequency was 400 Hz and the ipsilateral 399 Hz. Period histograms show the following: *A*, responses to stimulation of the contralateral ear; *B*, of the ipsilateral ear; *C*, to binaural beat stimuli when synchronized to f_b ; *D*, binaural responses synchronized to the contralateral, and *E* to the ipsilateral stimulus. Period histograms shown in *C*, *D*, and *E* were all derived from the same responses but synchronized on different frequencies. Frequency of the contralateral stimulus is shown at the bottom of each row. Mean phase angle of each histogram is given as an inset. ϕ_b refers to phase angles derived from responses to binaural beat stimuli synchronized on f_b .

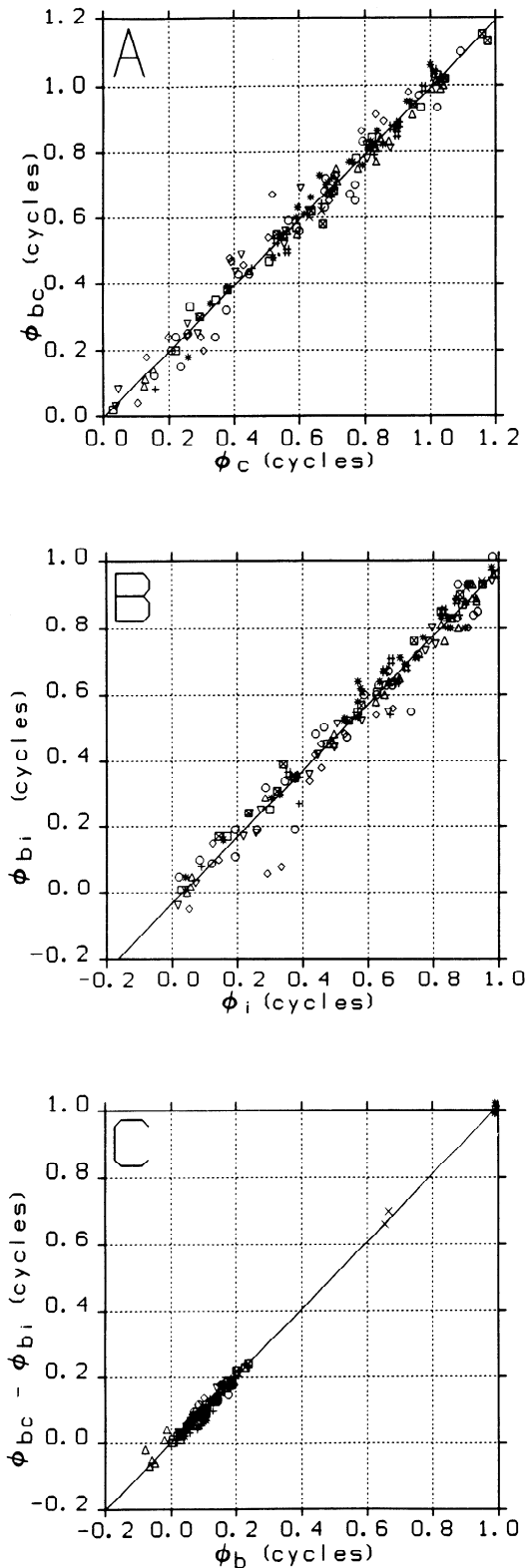


FIG. 7. Comparisons of the mean phase angles calculated in response to binaural beats. *A* and *B* compare the monaural phases ϕ_c and ϕ_i with the phases found when synchronizing the binaural beat response to the contralateral (ϕ_{bc}) or ipsilateral (ϕ_{bi}) stimulus, respectively. *C*: comparison of the interaural phase obtained from the binaural beat (ϕ_b) with that predicted from the difference between ϕ_{bc} and ϕ_{bi} . Regression lines for each case is given by the solid line. Correlation coefficients and slopes for the curve in *A*, *B*, and *C* were 0.989 and 0.996; 0.985 and 1.008; and 0.995 and 1.011, respectively. Data represent 143 runs measured in 12 cells.

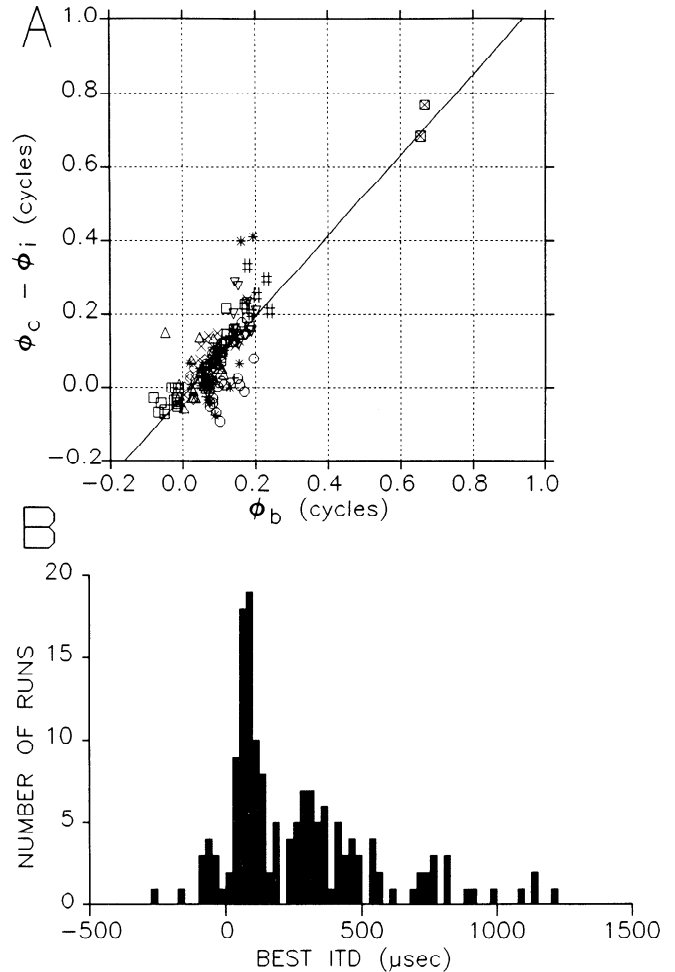


FIG. 8. *A*: comparisons of the mean interaural phase (ϕ_b) with the difference between monaural contralateral and ipsilateral phases ($\phi_c - \phi_i$) as predicted from the coincidence model. These data are from both ITD and binaural beat responses. Regression line has a correlation coefficient of 0.83 and a slope of 1.09. $n = 179$ from 14 cells. *B*: histogram of the best ITD calculated by multiplying ϕ_b by the period of the stimulus. Three points had best ITDs greater than +1500 μs and were not plotted. Mean ITD of 161 points plotted was 263 μs .

and f_i . Because $f_b = f_c - f_i$, the phases of the three frequencies (f_c , f_i , and f_b) were not independent. A cell that phase locked to f_b and to f_c was of necessity also phase locked to f_i . Furthermore, the phase angle ϕ_b , at which the locking to the binaural beat must occur, was $\phi_{bc} - \phi_{bi}$ (Fig. 7C).

As we have seen in Figs. 2–6, the coincidence model provided a good prediction of the optimal phase from the monaural responses as compared with the binaural responses. Data from all of the cells in our sample are shown in Fig. 8A. For the 14 cells that responded to monaural stimulation of both ears in a phase-locked fashion, we compared the interaural phase for which there was optimal binaural interaction and the predicted phase based on the monaural responses at the same frequency and SPL. So, for example, in the responses shown in Figs. 2, 3, 4, and 6 we compared ϕ_b (or ϕ_d) with $\phi_c - \phi_i$. For each cell we usually had data at several different frequencies and SPLs. Only those period histograms that were clearly phase locked, as determined by the Rayleigh test (Ruggero and Rich 1983) at the $P < 0.005$ significance level, were included in this

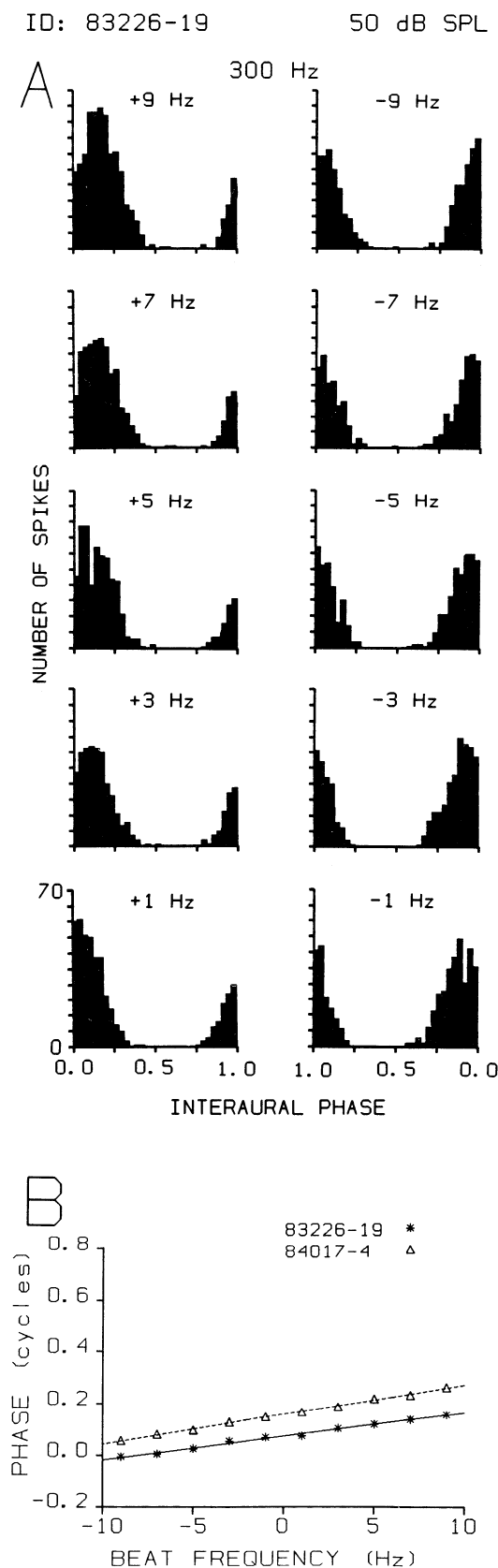


FIG. 9. *A*: responses of a cell in the MSO to changes in the beat frequency f_b . Value of f_b is given as an insert. Positive f_b 's represent beat frequencies in which the tone to the contralateral ear is higher. This cell was recorded in the penetration of Fig. 1C. *B*: plots of the mean phase of the binaural response when synchronized to f_b as a function of f_b for 2 cells.

plot. The linear regression line relating these two variables had a slope of 1.09 and a correlation coefficient of 0.83 ($n = 179$). The values of ϕ_d and ϕ_b were not evenly distributed across the range of possible phases but were clustered between 0.0 and 0.2: 87% (156/179) had ϕ_b between 0.0 and 0.2 cycles and 89% represented delays of the ipsilateral ear ($0.0 < \phi_b < 0.5$). If the peak responses were expressed in terms of ITD rather than interaural phase, then 66% (109/164) of the peaks fell in the range of 0 to +400 μ s ITD (Fig. 8B), 74% (122/164) were within the physiological range of ± 400 μ s and 92% (151/164) were positive.

RESPONSES TO VARIATIONS IN BEAT FREQUENCY f_b . The results in Figs. 6 and 7 show the responses of cells in the MSO to binaural beat stimuli with a beat frequency of 1 Hz. Variations in the sign and magnitude of f_b provide dynamic changes in interaural phase (Fig. 9A) and mimic the phase changes seen with moving stimuli in terms of direction and velocity of movement along the azimuth, respectively (Yin and Kuwada 1983a). In our small sample of MSO cells tested with variable f_b ($n = 9$), none exhibited significant selectivity to either direction or speed of interaural phase change. There was a linear relationship between the interaural phase and f_b (Fig. 9B). The magnitudes of the slope of the regression lines relating ϕ_b and f_b were dependent on the BF of the cell; they ranged from 6.4 ms for a BF of 800 Hz to 16.9 ms for a BF of 100 Hz. In the ICC the slopes of the regression lines relating ϕ_b and f_b varied from 7.8 ms for a BF of 1,000 Hz to >50 ms at low BFs with a mean near 12 ms (Yin and Kuwada 1983a).

Characteristic delay in the MSO

Previous studies of the MSO have only investigated responses of cells at one frequency, near their BF. By the use of the binaural beat stimuli we could easily study IPD sensitivity at many different frequencies and SPLs within each cell's response area. These data were used to examine the occurrence of characteristic delay (CD), which is defined as the ITD at which the cell responds at the same relative amplitude over different stimulus frequencies (Rose et al. 1966). The presence of CD was detected by a linear relationship between stimulus frequency and interaural phase (Yin and Kuwada 1983b). The phase intercept of the phase-frequency plot is the characteristic phase (CP) of the cell, which specifies the interaural phase at which the CD occurs.

Figure 10 shows responses of a cell to stimulation at eight different frequencies within its response area. The data were collected as period histograms of binaural beat responses (as in Fig. 6C) and plotted in Fig. 10A on a common ITD axis (Yin et al. 1986). The plot of interaural phase and frequency was approximately linear (Fig. 10C) with a CD of 33 μ s and a CP of 0.063. The CP near 0.0 indicated that the CD occurred near the peak response of the cell, i.e., the maximal discharge occurred near the ITD corresponding to the CD (Yin and Kuwada 1983b). The composite curve, which was obtained by averaging responses to ITDs of tones spanning the response area of the cell (Fig. 10B), represents the response predicted for a wide-band stimulus, assuming that all of the individual

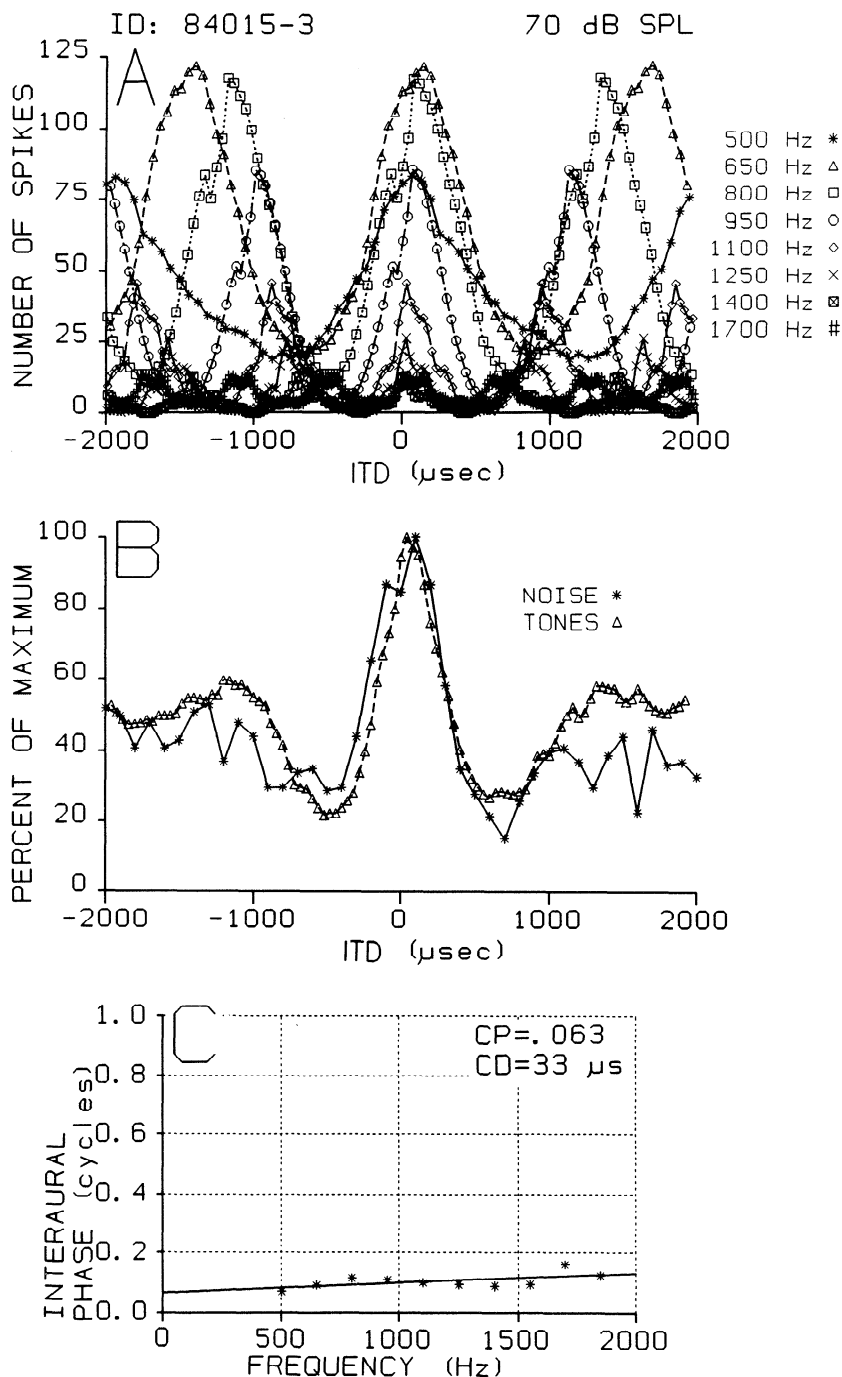


FIG. 10. Binaural responses of a cell to changes in the frequency of stimulation. *A*: superimposed ITD curves at 8 different frequencies that cover the response area of the cell. *B*: ITD curves that are measured from responses to noise (*) or derived from responses to ITDs of tones by computation of the composite curve (Δ), which is the sum of the curves in *A*. *C*: interaural phase-frequency plot for the data in *A*. Slope and y -intercept of the regression line represent the characteristic delay (CD) and characteristic phase (CP) of the cell, respectively (Yin and Kuwada 1983b). This cell was recorded in the penetration of Fig. 1*F*.

frequency components are summated linearly (Yin et al. 1986).

The distribution of CPs for all of our sample was tightly clustered near 0, as 95% (40/42) were between -0.20 and $+0.20$ (see Fig. 18*C*, below). The distributions of the CD and the peaks of the composite curves were similar, such that most composite curve peaks (93%, 39/42) were within the physiological range between 0 and $+400 \mu\text{s}$, corresponding to stimuli in the contralateral sound field. In 12 cells we measured the CD, CP, and peaks of the composite curves at more than one SPL. In general the values of CD were much more sensitive to variations in the overall SPL to the two ears than were the locations of the peaks of the

composite curves. The mean change in CD/dB SPL was $13.1 \mu\text{s/dB}$, which was nearly 3 times larger than the mean change in composite curve peak/dB SPL ($4.9 \mu\text{s/dB}$).

Responses to ITDs of noise: evidence for cross-correlation

In response to ITDs or IPDs of pure tones, the responses in the MSO appear to satisfy the coincidence model. However, tones are artificially pure stimuli, and they evoke unusual responses in the auditory nerve in that at low frequencies all fibers are synchronized to the same frequency. We wanted to test the coincidence model in more depth with a spectrally complex stimulus and therefore examined responses to ITDs of broad-band noise stimuli. All of the

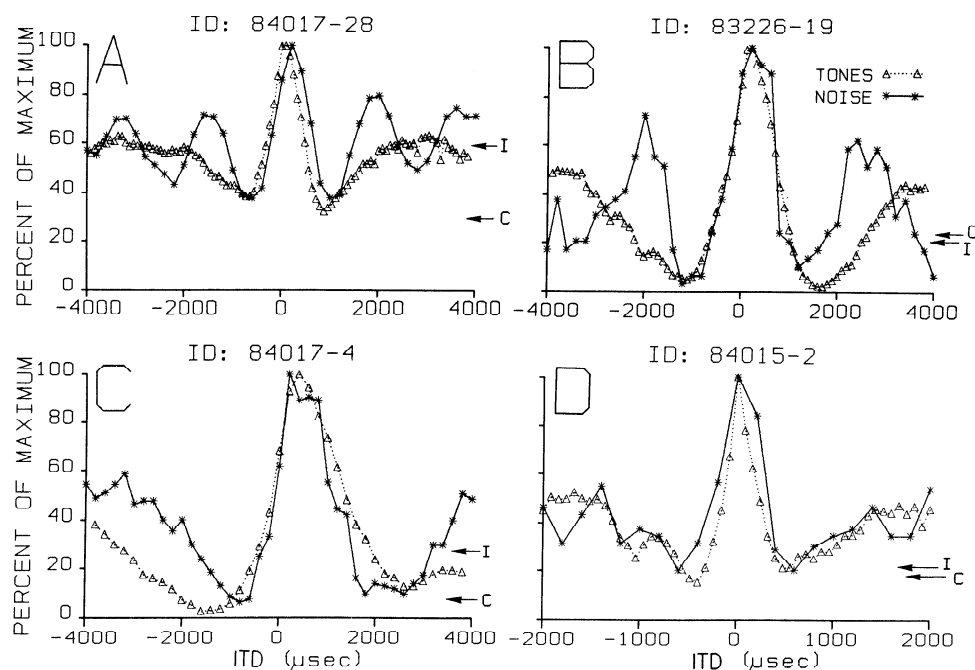


FIG. 11. Comparisons of the noise-delay curves (*) and tonal-composite curves (Δ) for 4 cells in the MSO. In each case the response to monaural stimulation of contralateral and ipsilateral ears with the same noises are marked by arrows C and I. BFs and figure showing the penetration are as follows: A, 300 Hz, Fig. 1B; B, 300 Hz, Fig. 1C; C, 150 Hz, penetration not shown; D, 1,000 Hz, Fig. 1F.

cells in the MSO that were sensitive to IPDs of tones were also sensitive to ITDs of broad-band noise. To a first approximation the shape of the ITD curve to a broad-band noise stimulus could be predicted by the composite curve. The results shown in Fig. 10B, along with those presented in Fig. 11 for four more cells, confirm for the MSO that there was good agreement between the curves obtained with ITDs of noise and those predicted from linear summation of the tonal responses. The predictions were particularly good near the central peak of the ITD curves, i.e., within the physiological range of $\pm 400 \mu\text{s}$, and systematic deviations of the tone and noise ITD curves were evident at larger delays. The most common discrepancy was that the noise delay curves were more cyclic than predicted from the tone responses, as first noted in the ICC (Yin et al. 1986).

The sensitivity to ITDs of broad-band noise stimuli was usually studied with identical noises delivered to the two ears. When two independently generated, and thus uncorrelated, noise signals, A and B, were used as stimuli, one to each ear, the cells' responses were no longer modulated by changes in ITD (Fig. 12A, UNCORRELATED), as they were when identical noise signals were delivered (Fig. 12A, CORRELATED). In the ICC we had interpreted these responses to ITDs of noise as evidence that the binaural interaction seen in the ICC resembled a process of cross-correlation by the binaural cells (Yin et al. 1987). However, because cells in the ICC generally do not respond to monaural stimulation of both ears, cells in the MSO provide valuable conditions for a more stringent test of the model of binaural interaction by comparing computer cross correlation of the inputs from both ears with the binaural responses.

The monaural responses evoked by stimulation of the ipsilateral and contralateral ears with the same noise were cross correlated on the computer. An output spike was generated whenever the impulses on the two input spike trains occurred within a rectangular window of $200 \mu\text{s}$. By time shifting either the ipsilateral or contralateral mon-

aural response, we generated a hypothetical ITD curve (Fig. 12A, CORREL. SPIKES) that was compared with the actual binaural response obtained by varying ITDs of the same broad-band noise (Fig. 12A, CORRELATED). The general forms of the two ITD curves were similar in the locations of the central and secondary peaks, though there were differences in the relative amplitudes between peaks and troughs of the two curves. The monaural responses were well phase locked to tonal stimuli and exhibited a periodicity in response to noise, as demonstrated by a prominent peak in the reverse correlation (deBoer and deJongh 1978; Carney and Yin 1988) at its approximate CF of 500 Hz (not shown). The cyclic behavior of the cross correlation of the monaural spike trains, however, was not simply due to this periodicity in the responses of the inputs to noise, because the cross correlation of the monaural responses obtained from stimulating the contralateral ear by noise A and the ipsilateral ear by noise B was also insensitive to ITDs (Fig. 12A, UNCORREL. SPIKES), similar to the cell's binaural response to this same combination of noises (Fig. 12A, UNCORRELATED).

One of the prominent features of the responses of cells in the MSO to broad-band noise was a marked temporal patterning. These patterns showed the propensity for spikes to occur or to be suppressed at particular times during the noise stimulus for either monaural or binaural stimulation (Fig. 12C). Note the long ($\sim 25\text{-ms}$) period in which spikes were suppressed during both binaural and monaural stimulation immediately after 750 ms, as well as the synchronous well-timed responses, which showed up as vertical columns of dots. The low degree of jitter in the timing between different trials is more clearly evident in the *bottom* set of dot rasters of Fig. 12C showing responses during the last 200 ms of five ipsilateral stimulus presentations. Similar patterns were also seen in responses of cells in the ICC (Carney and Yin 1989).

The width of the ITD curves provides a measure of the degree of temporal tuning (TT) of the cell to variations in

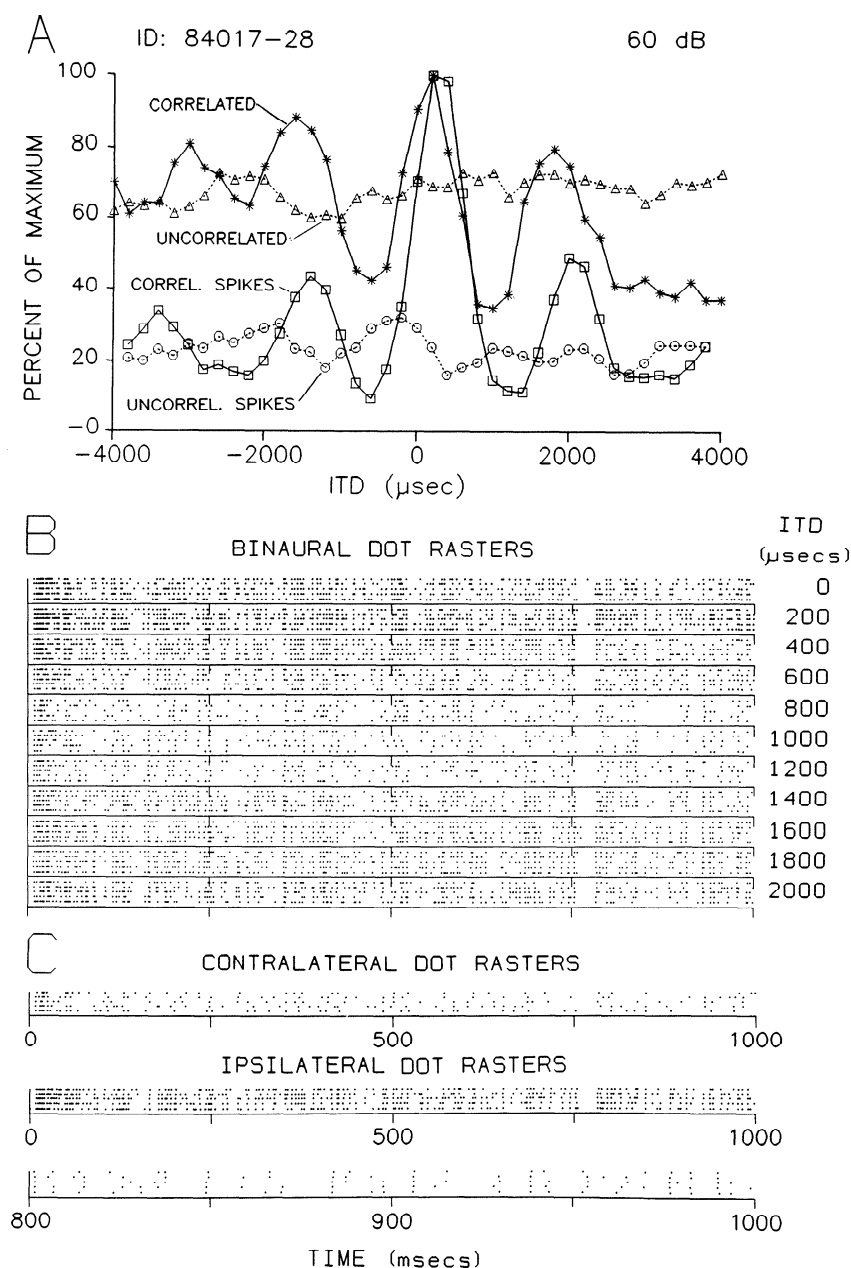


FIG. 12. Test of the cross-correlation model of binaural interaction. This is the same cell as shown in Fig. 11A. *A*: comparisons of binaural responses to identical noises to 2 ears (*, CORRELATED) with the computer cross-correlation of monaural spikes trains in response to these same noises to 2 ears (□, CORREL. SPIKES). Also shown are binaural responses to different noises to 2 ears (Δ, UNCORRELATED) and the computer cross-correlation of monaural spike trains in response to these 2 uncorrelated noises (○, UNCORREL. SPIKES). Computer cross-correlation was done with a 200-μs rectangular window. Curves are normalized pairwise, both neural responses to the maximum value of the correlated binaural response and both computer generated cross-correlations to the maximum value of correlated spikes. *B*: dot rasters of responses in *A* to identical noises to 2 ears. *C*: dot rasters of monaural responses to contralateral and ipsilateral ear stimulation with identical noises. All dot rasters show responses during the entire 1-s duration of the stimulus except for the *bottom* set in which the ipsilateral response over the last 200 ms of the stimulus is shown.

ITD (Yin et al. 1986). If these cells are useful for sound localization, then TT would be translated to spatial tuning for sound sources at different azimuthal positions. The psychoacoustical observation that the perceived extent of a free field signal is inversely related to its frequency content can be related to the TT of binaural cells (Chan et al. 1987). We measured the width of the central peak of the noise-delay curves at the point midway between the central peak and trough and plotted its reciprocal against the median frequency of the synchronized rate curve. The median frequency is a measure of the binaural BF of the cell when both discharge rate and synchrony to interaural phase are considered (Yin et al. 1986). For the six cells in the MSO that were studied with noise delays, there was a linear relationship between $1/TT$ and BF with an intercept of 0.38 and a slope of 0.0017. In the ICC the intercept and slope were both larger, 0.58 and 0.0020, respectively, indicating that cells in the MSO had somewhat wider noise-delay

curves, and hence poorer TT, than cells in the ICC when matched for frequency.

Topography of ITDs

Even within our small sample of cells, there was considerable variability in the ITD at which cells were maximally activated, as was evident from responses to both tones and noises. One of our major interests was to examine the possibility that different ITDs were mapped spatially in the MSO. Because the tonotopic map of frequencies runs from dorsal to ventral and because the nucleus is very thin in the medial-lateral dimension, the most obvious place to look for a map of ITDs is along the anterior-posterior (A-P) dimension. Therefore we endeavored to sample the MSO along the A-P axis in each animal. Unfortunately, we were rarely able to record from cells in more than one penetration so that we could not gather any topographical data

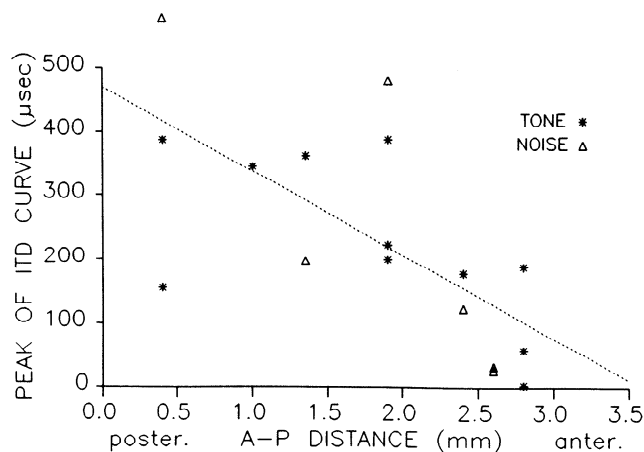


FIG. 13. Spatial map of ITDs in the MSO. Peaks of ITD curves in response to tones and noise are plotted against the A-P position of the cell on a standard nucleus. Tonal responses were derived from peaks of composite curves. Figure plots responses obtained at 60 dB SPL for tones and for cells whose BF < 500 Hz.

from any one animal. To study topography, then, we had to combine data from many animals. We reconstructed each of our electrode penetrations onto a standard nucleus by normalizing the length of the MSO in the A-P axis.

We examined the relationship between each cell's A-P position and the values of CD, CP, and locations of the peaks of the composite and noise-delay curves. When we restricted the sample to cells within a small range of BFs at a single SPL, there was a clear relationship between location and the peaks of the composite and noise-delay curves. In Fig. 13, cells with BFs between 100 and 500 Hz at 60 dB SPL were chosen, because they represented the largest proportion of our sample. Cells in the anterior MSO tended to have the peaks in their ITD curves, whether measured by noise or by tones, at low values, and cells in increasingly posterior positions responded maximally at more positive values of ITD. The regression line fitted to these points had

a slope of $-131 \mu\text{s}/\text{mm}$ with a correlation coefficient of 0.674 ($P < 0.01$) (Fig. 13). Note, however, that at any given A-P position, cells with a large range of ITDs could be represented, and conversely the same ITD was represented over a large range of A-P positions. The relationship between CD and spatial location was similar but less clear than for the composite peaks, and there was no apparent topography for CP.

Responses to ITDs of AM signals

Thus far all of the ITD sensitivity presented in this study was due to interactions between phase-locked inputs to tone or noise signals. Because phase locking to pure tones of auditory nerve fibers is limited to frequencies less than ~ 4 kHz (Johnson 1980), interaural phase sensitivity is also limited to these low frequencies (Kuwada and Yin 1983). However, high-frequency auditory nerve fibers will phase lock to a low-frequency envelope of AM waveforms (Joris and Yin 1988; Møller 1976), and high-frequency binaural cells in the ICC are sensitive to IPDs of the envelope of AM signals (Yin et al. 1984). Therefore we also studied the responses in the MSO to ITDs of AM tones. Only one cell was studied in detail. Its responses are of interest despite our small sample because there were many similarities in the ITD sensitivity of this cell to AM stimuli with that exhibited by the low-frequency cells to ITDs of pure-tone stimulation.

The cell, which had a CF of 15 kHz, was driven by monaural stimulation of either ear and that response was phase locked to the modulation frequency (f_m). Figure 14A shows the responses to ITDs of AM tones at four different f_m s. At all f_m the response maximum was between -200 and $0 \mu\text{s}$. The cell's responses to monaural AM stimulation of either ear were phase locked to f_m as shown for the case of 400 Hz in Fig. 14B. The period histograms in Fig. 14C were derived from binaural stimulation at five different values of ITD with f_m of 400 Hz. Like the results presented

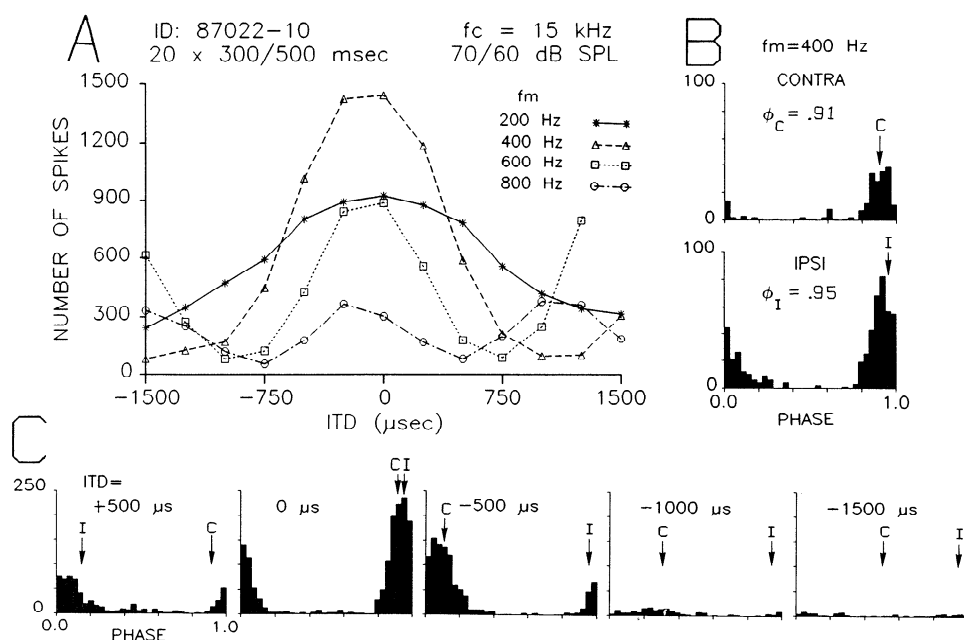


FIG. 14. ITD curves at 4 different f_m (A), monaural (B), and binaural (C) period histograms of a high-frequency cell to AM stimuli at a modulation depth of 100%. Same conventions as in Fig. 3 except that period histograms were synchronized to f_m .

in Figs. 2–4 for sensitivity to low-frequency pure tones, this cell also responded in a manner consistent with the coincidence model: the maximal response under binaural conditions was obtained when the expected inputs from the two sides arrived simultaneously. For the example shown at an f_m of 400 Hz, the phase angle $\phi_c - \phi_i = -0.04$ cycles whereas $\phi_d = -0.03$ cycles. At the other three f_m at which we calculated AM ITD curves (200, 600, and 800 Hz), the values of $\phi_c - \phi_i$ were -0.01 , -0.03 , and -0.09 cycles, respectively, whereas the values of ϕ_d were -0.003 , -0.05 , and -0.12 cycles, respectively. Thus interaural phase predicted from coincidence and the monaural responses ($\phi_c - \phi_i$) differed from that found under binaural stimulation by at most 0.03 cycles. Furthermore, the plot of mean interaural phase versus f_m (not shown) showed that the cell had a CD of $-206 \mu\text{s}$ with a CP of 0.06 cycles. These results suggest that the coincidence model also applies to binaural interaction of high-frequency cells in response to ITDs of complex signals.

This cell displayed a prominent band-pass characteristic for both ipsilateral and contralateral AM stimuli, and the best response (in terms of both discharge rate and synchrony to f_m) occurred at $f_m = 300$ Hz. By contrast, the discharge rate of auditory nerve fibers does not vary with f_m , and their synchronization to the AM signal has a low-pass modulation transfer function (Joris and Yin 1988). PL cells in the AVCN have low-pass modulation transfer functions similar to that seen in the auditory nerve (Frisina et al. 1990).

General response characteristics

Although the emphasis of our study was on the sensitivity of cells in the MSO to ITDs, we also collected data on other response characteristics. Given the paucity of experimental data on responses in the MSO, it seems useful to present these results as well. In general, the monaural re-

sponse characteristics seen in the MSO were similar to those reported for the PL neurons of the AVCN, which project directly to the MSO, and for the auditory nerve fibers, which drive the AVCN. However, there were some striking differences for certain response parameters, though the small sample size may reflect uneven sampling of the MSO. The binaural responses were also similar to those previously seen in the ICC, though there were some marked differences, which presumably reflect processing in the ICC.

MONAURAL RESPONSES. The threshold tuning curves of cells in the MSO were generally V-shaped and similar to those seen in the auditory nerve. The Q_{10} s of tuning curves in our sample were on the low end compared with a larger sample of auditory nerve fibers of matching CFs (Joris, unpublished observations). Thus MSO cells are slightly more broadly tuned, suggesting convergence from cells with similar but not identical CFs.

Most of the cells in our sample from the MSO had CFs < 1 kHz and were phase locked to low-frequency tonal stimulation. Most (34/39, 87%) of the responses to a tone at CF delivered to the most effective ear were sustained, usually with an initial period of adaptation, so that they resembled PL responses. Only 3/39 (8%) of the cells had purely onset responses to a tone at CF. Two cells had no response to stimulation of either ear under monaural conditions, but both of these cells responded robustly to binaural stimulation and were sensitive to interaural phase. The spontaneous activity of these cells in the barbiturate anesthetized condition was generally low (< 1 spike/s) or 0 (29/39, 74%); only 8% (3/39) were highly spontaneous (> 20 spikes/s); and the remaining 18% (7/39) had medium spontaneous rates.

The response areas of cells in the MSO, when plotted as isolevel responses, usually exhibited a shift in the BF toward lower frequencies at higher SPLs (Fig. 15). Figure 15,

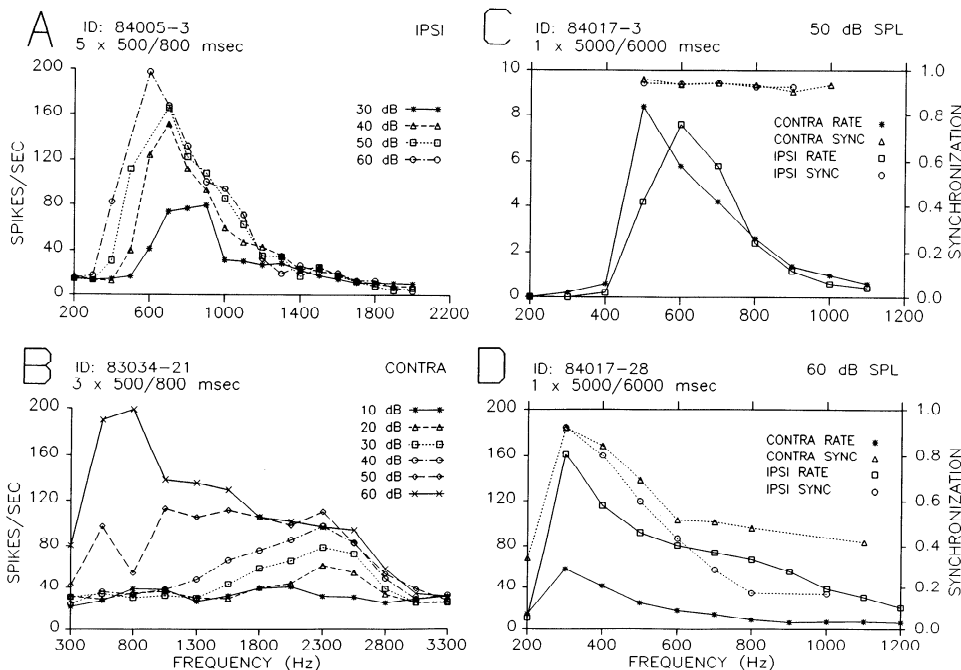


FIG. 15. *A* and *B*: monaural iso-intensity response areas for 2 cells. Cell in *A* had a relatively small shift in BF from 900 to 600 Hz as the level was raised, whereas that in *B* showed a large shift from 2,300 to 800 Hz. *C* and *D*: monaural rate (—) and synchronization (---) plots for 2 ears for 2 cells. *C* had a low response rate and high r over the entire response area whereas *D* showed much higher response rates and a bias in both rate and r toward lower frequencies. Note the similarity of both rate and synchrony responses for 2 ears. r was plotted only if $P < 0.01$.

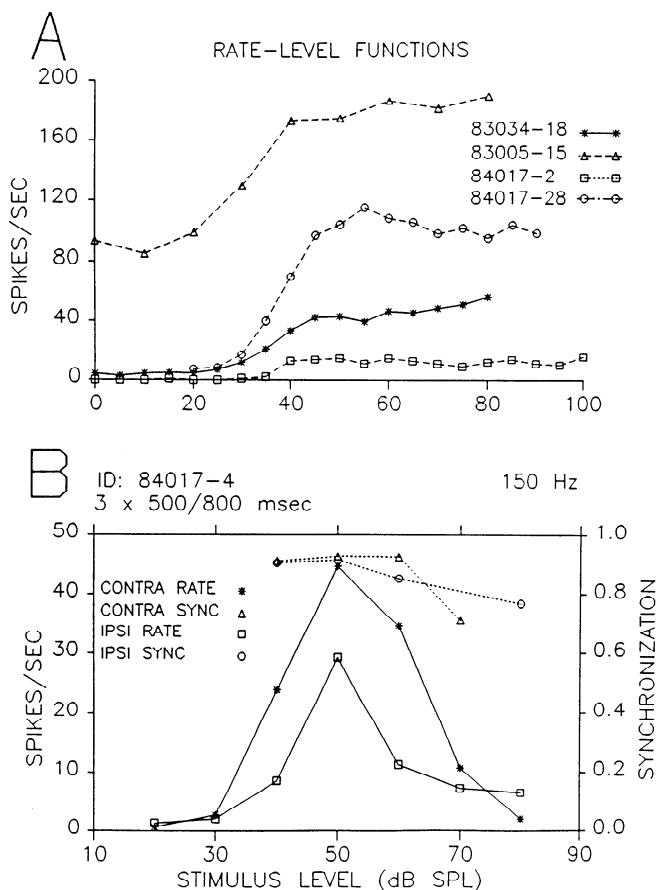


FIG. 16. *A*: rate-level functions for 4 cells. Responses are all derived from tones at CF except for 84017-28, which shows rate-level curve responses to broad-band noise. All responses were sustained, and the ordinate represents spike rate except for the case of 84017-2, which responded only at onset; its ordinate represents spikes/20 stimuli. *B*: nonmonotonic rate-level functions for a cell in response to stimulation of either ear. Variation of synchrony with level is also shown by dotted lines. ITD sensitivity of this cell is shown in Figs. 4 and 5.

A and *B*, shows examples of a small and large shift in BF, respectively. Usually, responses at lower frequencies had higher synchronization coefficients than at BF or higher frequencies (Fig. 15*D*).

Most cells had rate-level functions that were monotonic and saturating. Figure 15*E* shows four examples, one with a high spontaneous level and high saturation rate (83005-15), another with low spontaneous and low saturation rate (83034-18), another (84017-2) that had only an onset response, and another (84017-28) in response to noise. There was considerable variability in the maximal driven rate of the MSO cells; many reached 200 spikes/s (Fig. 15) whereas for others the maximal rate was <50 spikes/s (Figs. 15*C* and 16*A*). The dynamic range of most cells was 20–30 dB, though a few cells had nonmonotonic rate-level functions (Fig. 16*B*).

Normally, MSO cells showed a very high degree of synchronization to low-frequency tones, as can be seen from the monaural and binaural period histograms given in Figs. 2, 3, 4, and 6 and by the high values of synchronization plotted in Figs. 15 and 16. It is interesting to compare the synchronization found in the MSO with those recorded on the auditory nerve for it may give an indication of the

transformation of phase-locked information from the auditory periphery into the MSO. Figure 17 shows a comparison of the maximal synchronization found in the MSO with that reported by Johnson (1980) in auditory nerve fibers. Most of the cells in the MSO could exhibit a higher degree of synchronization to low-frequency tones (<1 kHz) than auditory nerve fibers. The high synchronization at frequencies <1 kHz is similar to that seen in a subset of cells in the cochlear nucleus and trapezoid body fibers, some of which project to the MSO (Rhode and Smith 1986; Yin et al. 1988).

In general, if the cell responded to monaural stimulation of both ears, as was the case for 56% (22/39) of the cells, the response characteristics of the two ears were similar. For example, the BFs of the responses to stimulation of either ear were similar: they differed by <0.2 octaves for 72% (13/18) and by 50 Hz or less for 77% of the cells. In addition other response features of the cells were also similar for stimulation of either ear: most (77%, 17/22) had sustained (15) or onset (2) responses to stimulation of either ear; Fig. 15, *C* and *D*, shows cells with similar isolevel rate responses; and Fig. 16*B* shows a cell with similar nonmonotonic rate-level functions for the two sides. In all three of these cases, the degree of synchrony to the tones was also comparable on the two sides. We attempted to examine the relative monaural latencies in our data, but unfortunately we usually used only a few repetitions of long duration stimuli, which precluded accurate estimates of response latencies.

Comparisons with the ICC

The results presented above indicate that many features of interaural phase sensitivity of cells in the MSO were similar to those previously described in the ICC. The responses to ITDs and IPDs with the binaural beat stimulus, the incidence of inhibitory inputs and characteristic delay,

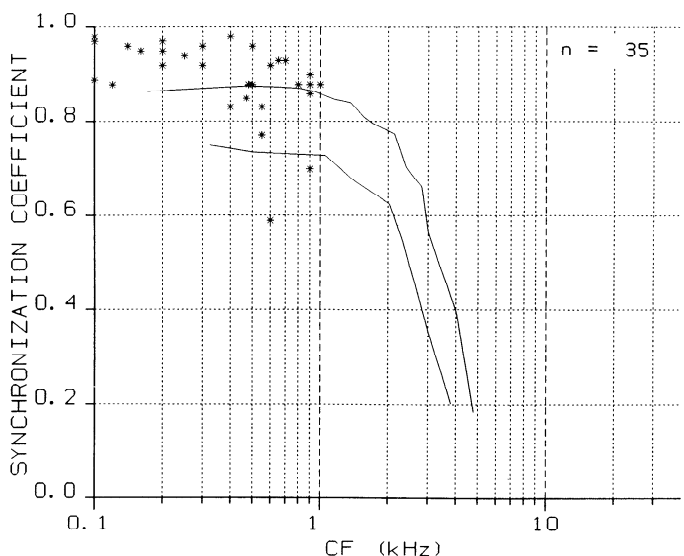


FIG. 17. Maximal synchronization coefficient obtained under monaural stimulation conditions as a function of the CF of the cell. Solid lines mark the range of the maximal synchronization coefficients recorded on the auditory nerve by Johnson (1980).

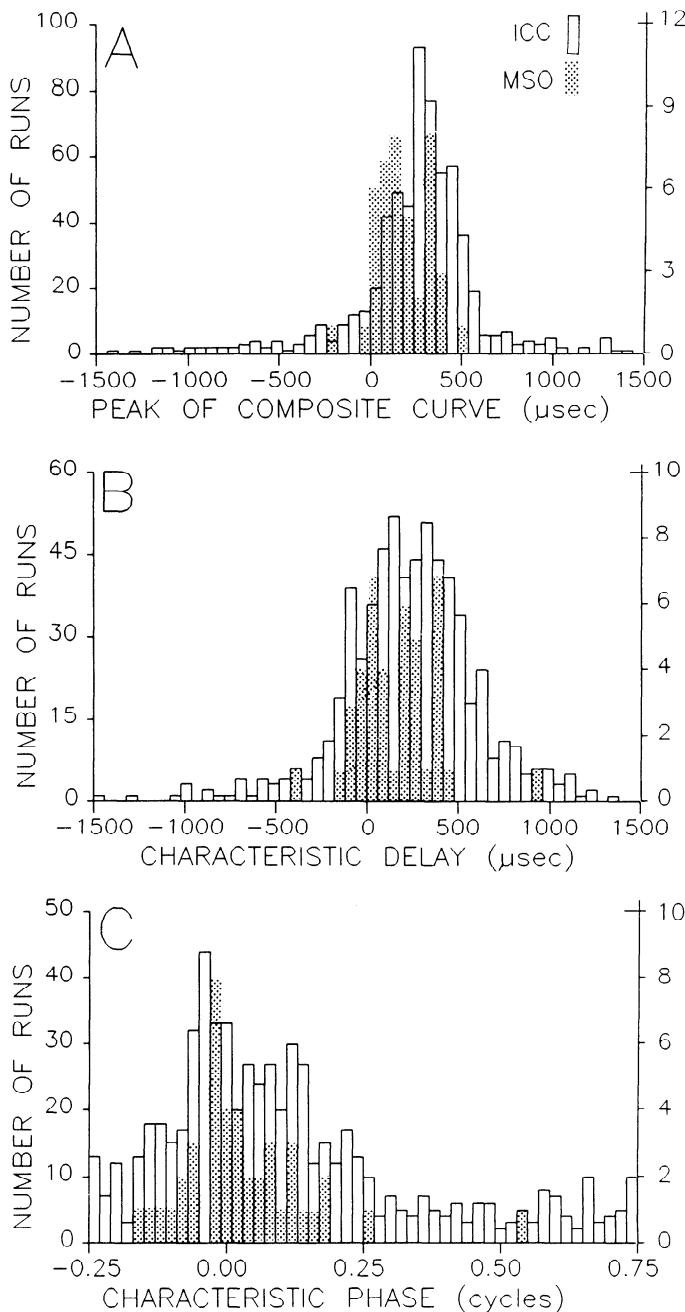


FIG. 18. Comparisons of responses in the MSO (cross-hatched) and ICC (open). Histograms compare distributions of peaks of composite curves (A), CD (B), and CP (C). Ordinate at the left of each histogram applies to results from the ICC and that at the right to the MSO. Only cells with CF < 1.0 kHz were included in the ICC data from the mapping study of Yin et al. (1983) to match the frequency range of MSO cells.

and the sensitivity to ITDs of tones and noise were all reminiscent of properties seen in the ICC. There were, however, some notable differences between the distributions of CD, CP, and the peak of the composite curve for the ICC and MSO (Fig. 18). In the MSO the distribution of CPs were tightly clustered near 0, as 95% (40/42) were between -0.20 and $+0.20$. The distributions of the CD and the peaks of the composite curves were similar, such that most composite curve peaks (93%, 39/42) were within the physiological range between 0 and $+400 \mu\text{s}$, corresponding

to stimuli in the contralateral sound field. The sensitivity of CD, CP, and composite-curve peaks to variations in SPL in the MSO was similar to that seen in the ICC where the trends were the same though the absolute values were smaller by $\sim 60\%$; in the ICC for CD the mean was $4.9 \mu\text{s}/\text{dB}$ whereas for the composite-curve peak it was $2.0 \mu\text{s}/\text{dB}$ (Yin and Kuwada 1983b). These differences between the ICC and MSO may reflect the proportionately larger low-frequency sample of MSO cells. In the MSO the mean change in CP was 0.0047 cycles/dB.

The major difference between the MSO and ICC was that the distribution of CPs, CDs, and composite peaks in the ICC was broader than in the MSO (Fig. 18). The differences in these distributions reflect the same phenomena: whereas most cells in both the ICC and MSO tended to respond when the inputs were in phase, or nearly so, there was a substantial population of cells in the ICC that responded when the stimuli from the two ears were not in phase. There was only one such cell in our sample from the MSO. All but one MSO cell had the peak of the composite curve located within the physiological range of $\pm 400 \mu\text{s}$. In fact 93% (39/42) of the runs in 22 cells had their peaks located between 0 and $+400 \mu\text{s}$. In the ICC only 69% (538/779) had peaks of the composite curves between $\pm 400 \mu\text{s}$ and 60% (465/779) between 0 and $+400 \mu\text{s}$.

The distribution of best interaural phases in the MSO (Fig. 8A) was not evenly distributed across all possible phases but was clustered tightly between 0 and 0.2, reflecting the same bias for CPs to be clustered around 0.0. In the ICC interaural phases are more evenly distributed between 0.0 and 1.0. This difference in the distribution of best interaural phases and CPs between the ICC and MSO may reflect inherent differences in the binaural interaction at the two levels and may indicate additional processing at the level of the ICC. On the other hand we cannot be confident that this difference is not simply an artifact of inadequate sampling in the MSO. This could include missing cells with the same CFs but that responded at other ϕ_{b} s, or missing more cells with higher CFs. Because our sample of MSO cells was biased to those with low CFs, when their best phases were translated into best ITDs, the entire range of positive physiological ITDs was covered (Figs. 8B and 18A). Thus a sample that included more cells with higher

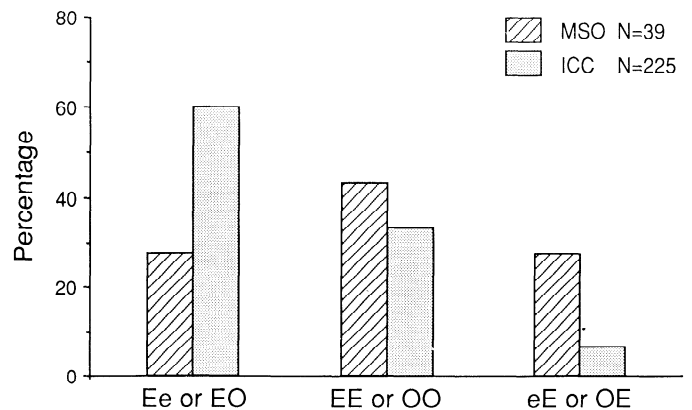


FIG. 19. Comparison of the different cell classes in the MSO and ICC based on monaural responses. See METHODS for classification convention.

frequencies (in the range between 1 and 3 kHz) might show a more uniform distribution of ϕ_{bs} .

BINAURAL RESPONSES. It is customary in binaural studies to classify cells according to their responses to monaural stimulation and by the nature of their binaural interaction, for example, by the EE and EI classes of Goldberg and Brown (1968) or by more complicated schemes (see Irvine 1986). As indicated earlier, most cells that are sensitive to ITDs exhibit both binaural facilitation and inhibition, depending on the ITD, so it is not possible to classify these cells on the basis of the binaural interaction. Nonetheless, it is useful to categorize the cells according to their monaural responses for comparisons with responses at other levels of the nervous system. With the convention described in METHODS, 38% (15/39) of our sample of cells were EE, 10% (4/39) were Ee, 10% (4/39) were eE, 18% (7/39) were E0, 18% (7/39) were 0E, and 5% (2/39) were 00 (Fig. 19). No cells showed inhibition of the spontaneous rate as a result of monaural stimulation of either side, but only 8% of the cells had the high spontaneous rates necessary to show such inhibition. Overall, cells in the MSO received a more balanced input from both ears, whereas in the ICC there was a bias toward cells responding more vigorously to stimulation of the contralateral ear (Fig. 19).

DISCUSSION

The prevailing view of the neural mechanisms underlying interaural time sensitivity is embodied in a model first proposed by Jeffress (1948). Jeffress' model has two important components: "coincidence detection" by the binaural cells in the central auditory system and neural delay lines established by differences in the conduction time from the two ears to different parts of the nucleus. The result of coincidence and a systematic distribution of neural delay lines is the formation of a spatial map of ITD detectors across one axis of the MSO.

These results provide evidence for two important features of Jeffress' model for binaural interaction. First, we have shown that cells in the MSO respond in accordance with a coincidence mechanism. With the use of broadband noise signals, we have also shown that cross correlation provides a more general description of the response mechanism. Second, we have found the first evidence for a spatial map of ITDs in the mammalian MSO. Our data suggest a map of ITDs across the A-P axis of the MSO with low ITDs, near 0 μ s, at the anterior pole and increasing ITDs at more posterior positions. Furthermore, our results confirm that many of the basic observations made on binaural interaction in the ICC of the cat (Kuwada and Yin 1983; Yin and Kuwada 1983a,b; Yin et al. 1986, 1987) are also applicable to the MSO, which reaffirms the suggestion that many of the binaural phenomena seen in the ICC are reflections of binaural processing originating in the MSO.

Coincidence and cross correlation

For all of the low-frequency cells that responded to monaural stimulation of both ears, the responses to ITDs of tones corresponded with those predicted by the coincidence model (Figs. 2–4, 8). These results corroborate previous studies of the MSO in the dog (Goldberg and Brown 1969) and kangaroo rat (Crow et al. 1978), which only

examined coincidence at the cell's BF; we showed that coincidence also extends to other frequencies within the cell's response area (Fig. 6). Furthermore, the results shown in Fig. 14 indicate that this model can also be extended to sensitivity to ITDs of the envelope of high-frequency AM signals, as in the ICC of anesthetized cats (Yin et al. 1984) and awake rabbits (Batra et al. 1989). The advantage of studying coincidence of the envelope of high-frequency AM stimuli in the MSO lies in the ability to study monaural responses of both ears.

Although the coincidence model can be tested with tonal stimulation, it is a special case of the more general cross-correlation model (Licklider 1951, 1959). In addition to being applicable to any arbitrary stimulus, the cross-correlation model is also important on theoretical grounds, because nearly all modern theories of binaural interaction developed from psychophysical studies rely on a cross correlator as the comparator element for signals arriving at the two ears (Blauert 1983; Colburn 1977; Jeffress et al. 1956; Lindemann 1986; Osman 1971; Sayers 1964; Sayers and Cherry 1957; Webster 1951). Our results with ITDs of noise show that the cross-correlation model can also be applied to the MSO (Figs. 11 and 12) as first demonstrated in the ICC (Yin et al. 1987). However, the results shown in Fig. 12 do not provide the best test of the cross-correlation model. It would be preferable to compare the response of the binaural cell with cross correlation of the input synaptic potentials from either side. This test awaits intracellular recordings from the MSO.

Spatial map of ITDs

We found evidence for a spatial map of ITDs along the A-P axis of the MSO. These data are the first indication of such a systematic map of ITDs in the mammalian auditory system. However, some precaution should be noted. In particular, given the wide variation in anatomic features and the difficulty in equating sections from different animals, it is problematic to draw conclusions based on averaging a relatively small number of cells across animals, as was necessary to generate the data in Fig. 13. A more definitive demonstration of such a map will require more data from a single animal. Nonetheless, we believe that there is a clear indication of topography in the mapping of ITDs in the MSO in the form of the peaks of the composite curves. There was a weaker relationship between CD and spatial location. The CD is more level dependent than is the location of the peaks of the composite and noise-delay curves (Yin and Kuwada 1983b, Yin et al. 1987) and therefore is less likely to be the relevant parameter spatially mapped across the MSO.

If the spatial map of ITDs is generated by a systematic distribution of neural delay lines, as proposed by Jeffress (1948) and as appears in nucleus laminaris of the chick (Young and Rubel 1983) and barn owl (Carr and Konishi, unpublished observations), the map in Fig. 13 provides constraints on the projection patterns of the afferent axons to the MSO from the AVCN. To have ITDs near 0 represented rostrally and large positive delays caudally (representing large delays of the ipsilateral stimulus), the delay line must provide contralateral input relatively earlier to the anterior than to the posterior MSO, or, equivalently,

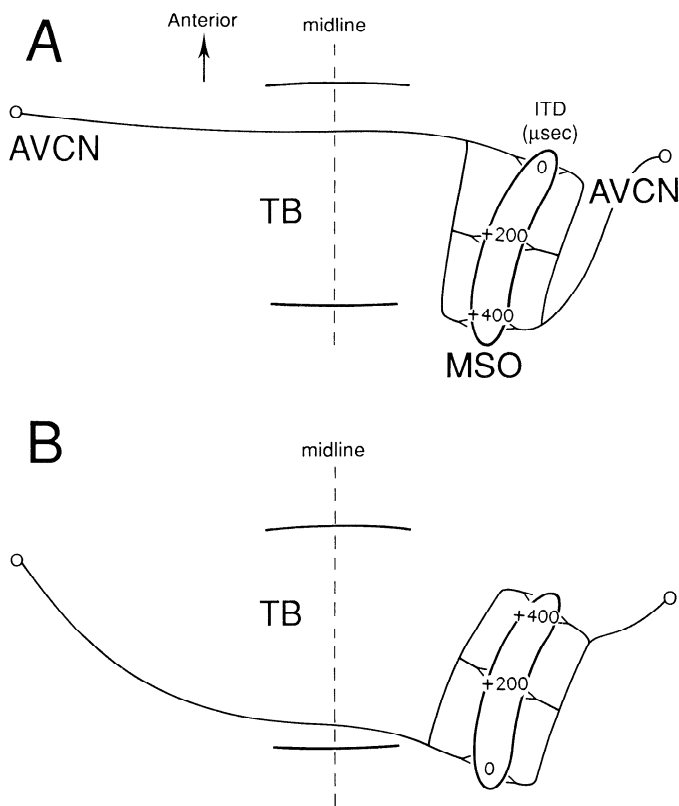


FIG. 20. Hypothetical drawings in a horizontal view of the course of afferent axons from the AVCN to the MSO in which the map of ITDs is set up by neural delay lines. In *A* the map has relatively low ITDs near the anterior pole whereas in *B* low ITDs are near the posterior pole of the nucleus. Delay lines are drawn for both ipsilateral and contralateral afferents, though delay lines on only one side are required.

ipsilateral input relatively earlier to the posterior than to the anterior MSO. This could be done by the contralateral axons crossing the midline rostrally and then coursing caudally, or by the ipsilateral axons starting caudally and projecting rostrally, or by both (Fig. 20*A*). The topography of the map prohibits the other two combinations of projection patterns, which would generate a map of ITDs in the opposite direction (Fig. 20*B*). Thus, for example, if the sound source is directly opposite the left ear, the stimulus will reach the left ear $\sim 400 \mu\text{s}$ earlier than the right ear. The afferents to the right MSO from the left side will arrive at the rostral pole of the nucleus before reaching the caudal pole in the scheme diagrammed in Fig. 20*A*. Thus cells at the caudal pole will receive a delayed contralateral input, which will compensate for the acoustic interaural lead of the contralateral side and will be maximally activated. The conduction velocity of the fibers should be close to the inverse of the slope of the regression line of the data in Fig. 13 corrected for the three-dimensional length of the nucleus, or $\sim 8.8 \text{ m/s}$.

Two pieces of anatomic evidence support the scheme shown in Fig. 20*A*. First, medium-sized axons, which originate from spherical cells of the anterior AVCN and have PL responses, preferentially cross the midline in the anterior portion of the trapezoid body (Brownell 1975; Warr 1966, 1982). Second, intraaxonal injections of single fibers in the trapezoid body show evidence for a delay line in the projection of PL fibers from the contralateral, but not the

ipsilateral, side that is in accord with the scheme shown in Fig. 20*A* (Joris et al. 1990).

Several theories have proposed that cochlear travel time could be used instead of neural conduction delay lines to generate varying auto- or cross-correlation computations (Loeb et al. 1983; Shamma et al. 1989). Both of these theories hypothesize that variable time delays are created by convergence of inputs with different BFs in the MSO. However, the similarity of BFs of the inputs from the two sides in the MSO does not support these theories. Moreover, our anatomic data on projections to the MSO also suggest that cochlear delays are not necessary.

The relative changes in optimal ITD across the rostral-caudal extent of the MSO could be established by the pattern of afferents shown in Fig. 20*A*, but how are the absolute values of ITDs set up? In other words how is it that ITDs near $0 \mu\text{s}$ are encoded at the rostral pole of the nucleus? To compensate for the longer distance from the contralateral side, there may be anatomic differences in the parameters governing conduction velocity (e.g., axon diameter, internodal length) in the axons projecting to the two sides, which could be tuned up during development. Further detailed studies of the innervation of the MSO seem warranted to provide clues to these interesting questions.

The timing of monaural latencies should also help in understanding the map of ITDs. Unfortunately, we used too few repetitions to estimate response latencies. Moushegian et al. (1964, 1967) and Rupert et al. (1966) showed that the input from the contralateral ear often arrived earlier in the MSO than that from the ipsilateral ear, often in the form of inhibition. They suggested that the conduction velocity from the contralateral side was greater or that the ipsilateral input was delayed by additional synapses. Similar observations have also been made at the level of the ICC (Carney and Yin 1989).

The spatial map of ITDs is reminiscent of the map of ITDs suggested in nucleus laminaris of the barn owl (Carr and Konishi, unpublished observations; Sullivan and Konishi 1986). In that system, however, the map of ITDs does not run along the A-P axis but instead appears to be across the thin dimension of the nucleus, which is much thicker in the owl than in the cat. Because the spatial map is established by the arrangement of delay lines in the afferents to the MSO or nucleus laminaris, the differences in the axes of the spatial maps in the cat and owl imply that there must be corresponding differences in the projection path of the afferents to MSO. Carr and Konishi (unpublished observations) recorded from ipsilateral and contralateral afferents to nucleus laminaris in the barn owl and found evidence for a delay line along the thin axis. Similar experiments in another bird, the chick, indicate an organization like that of the cat rather than of the owl (Young and Rubel 1983), though this may be due to the fact that nucleus laminaris in the chick consists of only a monolayer of cells. These differences between the cat, chick, and owl may also reflect the relative frequencies at which ITDs can be used. The upper frequency limit of phase locking is much higher in the owl (6–8 kHz) (Sullivan and Konishi 1984) than in the cat (3–4 kHz) (Johnson 1980); therefore the owl can use conduction delay lines that are correspondingly shorter.

The presence of a map of ITDs in the MSO has impor-

tant functional implications. The anatomic data on the projection of the MSO to the ipsilateral ICC suggests that this map is not retained in the cat, at least not in a simple point-to-point fashion, because a small region of the MSO seems to project to a large area of an isofrequency contour in the ICC (Henkel and Spangler 1983), though the projection in the barn owl from nucleus laminaris to the ICC appears to be more point-to-point (Takahashi and Konishi 1988). However, physiological mapping of an isofrequency contour in the ICC suggest that ITDs are systematically mapped along the contour (Aitkin et al. 1985; Yin et al. 1983).

Inhibitory inputs to the MSO

A shortcoming of the Jeffress model as well as the strict cross-correlation model of binaural interaction is that it assumes only excitatory inputs. We believe that there is substantial evidence for inhibitory processing in the MSO, though this has received little attention from anatomists or physiologists. This belief stems from several pieces of evidence. First is the well-known physiological result that the minimum in the ITD curve, whether for tones (Figs. 2–5) or for noise (Fig. 11), usually falls below the monaural response to stimulation of either ear and in a few cases below the spontaneous level (Fig. 2A). This result can be seen in the delay curves of Figs. 2–4 and is graphically illustrated in Fig. 5, where the effects of varying the level to one ear was explored. Similar results have also been commonly reported in the MSO (Goldberg and Brown 1969), ICC (Geisler et al. 1969; Kuwada and Yin 1983; Rose et al. 1966; Yin and Kuwada 1983a) and dorsal nuclei of the lateral lemniscus (Brugge et al. 1970). Second, studies using ITDs of clicks in the MSO have demonstrated an inhibitory component to the response, usually after a short excitatory component (Galambos et al. 1959; Moushegian et al. 1964, 1967; Rupert et al. 1966, Watanabe et al. 1968). Similar inhibitory components are seen in responses to clicks in the ICC (Carney and Yin 1989). Third, examination of the responses to ITDs of noise stimuli have indicated the possible role of inhibitory processes in producing strict temporal patterns of responses to the noise stimuli (Fig. 12, see below). Fourth, anatomic studies have shown that collaterals of axons from cells in the medial nucleus of the trapezoid body (MNTB), which provide the inhibition from the contralateral side to the LSO, also terminate in the MSO (Smith et al. 1989; Spangler et al. 1985). Finally, ultrastructural studies have shown the presence of synaptic terminals with flat or pleomorphic vesicles and symmetric contacts (Clark 1969; Lindsey 1975; Schwartz 1984), which have been assumed to represent inhibitory synapses.

Although the evidence cited above strongly implicate a role for inhibition in binaural interactions, they are only indirect. An alternative and plausible view is that the monaural responses represent coincidence of phase-locked inputs from the driven side with spontaneous activity from the unstimulated side (Colburn et al. 1990). At an unfavorable ITD the response falls below the monaural level because the previously unstimulated side now contributes spikes, but they are out of phase with the other side. In the

absence of intracellular recordings from the MSO, it is not possible to distinguish between these alternative models.

More indirect evidence is available from other physiological responses. In the model proposed by Colburn et al. (1990) the spontaneous activity on the unstimulated side must be random, which when correlated with the noise-evoked responses from the stimulated side will cause the MSO cell to discharge. If this were the case, then we would not expect to see long periods (~ 25 ms in Fig. 12, A and C) with no spikes, because noise-evoked responses at the level of the auditory nerve at comparable CFs do not contain such long pauses in activity (Carney and Yin, unpublished observations). Furthermore, we would also not expect to see spikes consistently evoked on repeated trials at a given time in the stimulus, as seen in the dot rasters of Fig. 12C. To achieve the consistent firing at preferred times of every trial with the Colburn et al. (1990) scheme, the rate of spontaneous discharge would have to be very high. The degree of jitter of the vertical rows of dots on Fig. 12C specifies the afferent spontaneous discharge rate required for this model; for the data shown in Fig. 12 the variation in time of occurrence of spikes for some of these rows is on the order of $100 \mu\text{s}$, which would require a spontaneous rate of ~ 10 kHz. This seems excessive and would also make the long periods of silence unlikely. Moreover, such a high rate of spontaneous activity on the monaural inputs would be expected to produce a high spontaneous rate in the MSO cell, which is not consonant with the low spontaneous rates we measured in the cell shown in Fig. 12 and in 74% of our sample. Thus we favor a model with at least some inhibition.

The inhibition could, like the excitation, also be phase locked but, more likely, it is simply long lasting and sculpted by phase-locked excitation. Our results suggest that at least for some cells there was both inhibitory and excitatory input from both sides, because the response at unfavorable delays dropped below the monaural level for both sides. The primary function of the inhibition may be to provide increased temporal acuity by enhancing the peaks of the ITD curves. The increased synchrony to monaural stimulation (Fig. 17) may also arise from inhibitory inputs.

The sources of possible inhibitory inputs to the MSO are not known. Some candidate structures, based on anatomic evidence, are the MNTB and the lateral nucleus of the trapezoid body (LNTB). There is good evidence that the MNTB cells are inhibitory onto cells in the LSO (Boudreau and Tsuchitani 1968; Moore and Caspary 1983), and intra-axonal labeling of single low-frequency MNTB axons have shown that at least in some cases there is a collateral innervation of the MSO (Smith et al. 1989). Cells in the LNTB are one of the few cell groups consistently retrogradely labeled after small horseradish peroxidase (HRP) injections confined to the MSO (Cant, unpublished observations), and both MNTB and LNTB cells are darkly immunostained by antibodies to glycine, a putative inhibitory neurotransmitter (Saint Marie et al. 1989; Wenthold et al. 1987). Such a scheme has a logical appeal: inputs from the MNTB would provide inhibition from the contralateral side whereas inputs from the LNTB would provide inhibition from the ipsilateral side, and both of these inputs

would be derived from projections of globular bushy cells (Smith et al. 1990). However, the low-frequency cells in the MNTB seem to exhibit strong phase locking to CF tones (Smith et al. 1990).

Comparisons with other studies

Although our results confirmed previous studies of coincidence detection in the MSO, some aspects of our results were at odds with other studies. A surprising feature was the strong bias for cells to respond near the time at which the signals from the two ears were in phase. In contrast, the most thoroughly documented MSO cell in the literature is *unit 67-82-5* of Goldberg and Brown (1969) in the dog, whose responses are shown in five different figures in their classic paper and represent the backbone of the evidence for coincidence in the MSO. Unlike almost all cells in our study, it responded maximally when the ipsilateral stimulus was delayed by 0.29 cycles. Figures 7C and 8 show that only one cell had values of ϕ_b between 0.25 and 0.90, and none were between 0.25 and 0.60. Such a difference in the best interaural phase could be due to differences in the path length from the ear phones to the two ears or to an inversion in the electrical connections to one phone. There is no indication in the paper if such phase differences were observed in the acoustic calibrations in their experiments. Of the other seven cells that Goldberg and Brown (1969) studied, three responded at interaural phases that were >0.2 cycles away from 0 and the remaining four responded maximally when the inputs were in phase or nearly so.

The only other MSO study where comparable results can be ascertained is that by Crow et al. (1978) in the kangaroo rat. They plotted the most favorable ITD against stimulus frequency for 28 cells, and their distribution of maximal ITDs is less biased toward the range of interaural phases between 0 and 0.2 than ours. However, an earlier report by Moushegian et al. (1975) also in kangaroo rats found 5/7 cells with maximal interaural phases between 0 and 0.2. Of course the distributions found in all studies, including the present one, could well be biased because the sample sizes are both meager and nonuniform.

ITDs measured near the eardrum of cats in response to free-field stimuli from the midline to one side vary from 0 to 400 μ s (Roth et al. 1980). The distribution of best ITDs in our sample as determined from the peaks of the composite curves (Fig. 18A) nearly coincides with this range. The near absence of cells with peaks at negative ITDs suggests that each MSO is coding exclusively the contralateral sound field. This is consistent with a number of behavioral studies in which unilateral transection of the lateral lemniscus resulted in a deficit of head orientation or localization of responses only to signals presented in the sound field contralateral to the side of the lesion (Chan 1983; Jenkins and Masterton 1982; Thompson and Masterton 1978).

Our distribution of cells in the MSO of the cat is very different from that reported in Goldberg and Brown's (1969) classic studies in the dog in some other aspects. Out of 22 cells presumed to be in the MSO in their study, 73% were relatively high-frequency (>1.5 kHz) cells that were

not sensitive to IPDs but were binaural, either EE or EI. We found only one such cell in the MSO. Of course this may be due to our infrequent sampling of the high-frequency portions of the nucleus; the response properties of our low-frequency cells are similar in most respects to theirs. However, there may also be a species difference that reflects the anatomic disparity between the MSO of the beagle and cat, or some of Goldberg and Brown's (1969) cells may have been outside of the MSO because they did not make lesions to confirm the exact location of each cell.

Our results are also at variance with the report by Langford (1984) in the MSO of the chinchilla in two important ways. First, all 30 of the cells that were sensitive to interaural phase in his study were ones that could not be driven by monaural stimulation of either ear. We found only two such cells in a sample of 39. Second, none of the peaks of the ITD curves in his study occurred at ITDs in which the contralateral ear leads (positive ITDs in our convention). In contrast 95% of our sample had their maximal response at positive ITDs. Other than species difference we can offer no explanation for the differences between our results and Langford's, nor can we explain why Hall (1965) found almost all cells in the cat's MSO were excited by monaural stimulation of the contralateral ear, unresponsive to the ipsilateral ear, but inhibited by the ipsilateral stimulus under binaural stimulation with clicks. No cells in our sample responded in this way to BF tones.

Comparisons with the ICC

Comparisons of our results from the MSO with the more extensive and complete studies of ITD sensitivity in the ICC show many similarities, such as the incidence of interaurally phase-sensitive cells, apparent inhibition and facilitation during binaural stimulation, responses to the binaural beat stimuli, occurrence of characteristic delay, sensitivity to ITDs of AM signals at high frequency, the responses to ITDs of noise stimuli, and the similarity between composite and noise-delay curves. These similarities suggest that many of these response characteristics are set up at the level of the MSO and relayed to the ICC. In addition, the monaural response characteristics, such as the BF, shape of rate-level functions, and degree of synchronization, were generally well-matched for the inputs from the two sides.

There are, however, certain distinct differences between the MSO and ICC, which suggest the need for additional processing at the level of the ICC. Perhaps the most striking difference in our data is the more balanced input from the two ears in the MSO as compared with the contralateral bias in the ICC (Fig. 19). Because most cells in the MSO project ipsilaterally to the ICC (Adams 1979; Aitkin and Schuck 1985; Brunso-Bechtold et al. 1981; Henkel and Spangler 1983), there must be either inhibitory input originating from the ipsilateral side or additional contralateral excitation projecting to the ICC. In addition intracellular and pharmacologic studies in the ICC have also demonstrated the importance of inhibitory processes in binaural interactions. For example, prominent inhibitory postsynaptic potentials (IPSPs) are seen in intracellular recordings in response to acoustic stimulation of either ear or to elec-

trical stimulation of the commissural pathway (Kuwada et al. 1980; Nelson and Erulkar 1963; Smith 1986); and iontophoretic application of picrotoxin, a γ -aminobutyric acid (GABA) antagonist, produces disinhibition of responses (Watanabe and Simada 1971). The source of any ipsilateral inhibition to the ICC is not known.

The other major difference between the ICC and the MSO was the increased bias of MSO cells to respond when the input stimuli were in phase. This was reflected in the differences in the distributions of CD, CP, and composite peaks (Fig. 18) as well as in the distribution of ϕ_b (Fig. 8). It is difficult to see how the small number of ICC cells with CPs that are not near 0 could be generated from our sample of MSO cells. An obvious possibility is that we may have missed a population of cells in the MSO or that there are additional interactions at the level of the ICC that do not involve the MSO, for example, from low-frequency inputs from the nuclei of the lateral lemniscus or LSO to ICC (Aitkin and Schuck 1985).

Transformations at the level of the MSO

Although the response of most cells in the MSO reflects the input that they receive from spherical/bushy cells with their PL responses from the AVCN, there were some distinct transformations evident in the features of the responses at the level of the MSO. A consistent finding of the majority of cells was the high synchronization to monaural tone stimulation (Fig. 17). It is commonly believed that the ability of PL cells in the AVCN to phase lock is not significantly different from that of their auditory nerve fiber inputs (Bourk 1976; Irvine 1986; Palmer et al. 1986). However, in recordings from trapezoid body fibers Yin et al. (1988) found a large number of fibers with low CF that had maximum synchronization coefficients for tones at CF that were >0.90 , which is higher than ever seen in the auditory nerve. By injecting these fibers intra-axonally and following the axonal termination pattern in the SOC, some of them were found to possess features characteristic of globular/bushy cells (i.e., a calyceal ending in the MNTB) (Smith et al. 1990) whereas others were like spherical/bushy cells (i.e., projections to the ipsilateral LSO and bilaterally to the MSO). Therefore the high synchronization that we have seen in the MSO may be a reflection of processing in the AVCN in addition to that at the level of the MSO. Such an increase in synchronization to tones may be produced by the convergence both at the level of the AVCN and MSO, coincidence on the postsynaptic cell (Yin et al. 1988) or the presence of inhibitory inputs.

Other transformations were only evident in a minority of cells, as reported by others (Goldberg and Brown 1969; Moushegian et al. 1964). For example, we found a small number of cells with nonmonotonic rate-level functions (Fig. 16B) and a small number of onset cells. Both of these response features are commonly identified with inhibitory processes.

A still puzzling question is why it is so difficult to record from the MSO. As noted earlier, this appears to be a common trait of the MSO and its homologous nuclei in other species. We cannot add anything definitive to the resolution of this problem except to make some anecdotal obser-

vations and speculations. Although the thinness of the nucleus and the presence of the large field potential make extracellular recording difficult, we believe that these factors do not provide the whole explanation. The reversal of the field potential at the center of the MSO provides an accurate clue as to the position of the microelectrode tip, so one can easily know when to look for MSO responses. We speculate that perhaps the spike-generating mechanism in the MSO cells is further out on the axon than in normal cells and that the action potential is largely diminished after propagating back to the soma. This would mean that recordings from the MSO are made from the axons, which is not incompatible with our observations. Obviously further investigations are necessary to solve this dilemma.

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