Processing of Interaural Temporal Disparities in the Medial Division of the Ventral Nucleus of the Lateral Lemniscus

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INTRODUCTION

Localization of the source of a sound, particularly a tone, relies more on its earlier portion than on its later portion (e.g., Hartmann 1983; Rakker and Hartmann 1986; Zurek 1993). Tones with a slow onset are difficult to localize (Hartmann 1983; Hartmann and Rakker 1989; Yost et al. 1997), especially in an environment containing reflective surfaces. For noise, the situation is different. Even when reflective surfaces are present, noise with a slow onset is readily localized. Apparently listeners treat noise as a sequence of transients.

Recently, we discovered a region of the pons in which many neurons respond only at the onset of a tone and are sensitive to an important cue for sound location, the interaural temporal disparity (ITD) (Batra and Fitzpatrick 1997). This region forms the medial division of the ventral nucleus of the lateral lemniscus (VNLL) (Fig. 1). The VNLL is a major source of input to the inferior colliculus. In the rabbit, the medial division of the VNLL (VNLLm) (Fig. 1, m), consists of neurons embedded in the fiber tract medial to the cell-dense lateral division (Fig. 1, l). Neurons of the VNLLm are sensitive to the interaural phase difference near the onset of the sound rather than the difference in the time the sound is turned on. The responses of its neurons to noise, however, have not been examined. These neurons may be sensitive to the transients in noise, resulting in a sustained response in contrast to the transient response to tones.

It is not known if the VNLLm is a primary site of binaural interaction or if it inherits ITD sensitivity from the superior olivary complex (SOC). Many earlier studies of the VNLL did not distinguish a separate medial division. The VNLL as a whole receives input from the same nuclei that convey phase-locked input to the SOC: the anteroventral cochlear nucleus (Beckius et al. 1999; Covey and Casseday 1986; Friauf and Oswald 1988; Glendenning et al. 1981; Huffman and Covey 1995; Schofield and Cant 1997; Smith et al. 1993; Vater and Feng 1990; Warr 1966; Zoook and Casseday 1985) and the medial nucleus of the trapezoid body (Casseday et al. 1988; Glendenning et al. 1981; Huffman and Covey 1995; Smith et al. 1998; Sommer et al. 1993; Spangler et al. 1985). These inputs transmit information chiefly from the contralateral ear, but some inputs carrying ipsilateral information are present as well. On the other hand, the medial and lateral superior olives (MSO and LSO) also project to the VNLL, especially the medial region (Glendenning et al. 1981; Henkel and Spangler 1983). Thus the VNLLm potentially receives the substrates for generating sensitivity to ITDs and inputs that carry information about ITDs.

There were, therefore, two reasons for this study: to determine whether neurons in the VNLLm respond differently to tones and noise and to investigate how they obtain their sensitivity to ITDs.

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M E T H O D S

This paper is based on data from six adult Dutch-belted rabbits (~2 kg) with clean ears. Data from five of these animals have been used in two previous papers (Batra and Fitzpatrick 1997, 1999), but the analyses described here have not been reported before except in abstract form.

Surgery and recording

For surgery, the rabbits were anesthetized with a mixture of ketamine and xylazine (35 and 5 mg/kg im). Aseptic techniques were used. During the initial procedure, a restraint bar was implanted. Skin and fascia on the dorsal surface of the cranium were retracted to expose the bone. Fine screws were inserted to the left of midline, and ~5 cm of square brass stock was cemented to the screws. The bone overlying the VNLL was left exposed. While the rabbit was still restrained, clips were applied to the ears and nylon straps, and the restraint bar was clamped to immobilize the head. The rabbit was inserted into a body stocking and placed in a small padded couch inside the booth. It was further restrained with nylon straps, and the restraint bar was clamped to immobilize the head. The dura was desensitized with xylocaine (2%). A hypodermic needle was then driven through the dura. Inside the hypodermic was a microelectrode that could be moved independently with a Burleigh microdrive. The bone overlying the VNLL was left exposed. While the rabbit was still acclimating to the sound was delivered. The rabbit spent 1–2 wk acclimating to the running configuration. In the frozen configuration, the repetition interval was 200 ms. The spectrum of the noise was not corrected for the characteristics of the speakers. The acoustic calibrations indicated that the intensity level of the noise varied more or less monotonically with frequency, and, in different animals, increased or decreased over this range by ≤10 dB. Neurons in different animals had similar responses to noise, indicating that variations in spectrum probably did not influence our results. The pressure level of the noise was determined by integrating the calibration curve over the spectrum of the noise.

Noise bursts were digitally generated (35- to 70-kHz digitization rate, random phase) and were usually low-pass, with a cutoff frequency of 2–5 kHz. Occasionally other cutoff frequencies or band-pass noise was used. The duration of the noise bursts was similar to that of the tone bursts (4-ms rise and fall times, 75 ms long, repeated every 200 ms). The spectrum of the noise was not corrected for the characteristics of the speakers. The acoustic calibrations indicated that <2 kHz, the intensity level of the sound varied more or less monotonically with frequency, and, in different animals, increased or decreased over this range by ≤10 dB. Neurons in different animals had similar responses to noise, indicating that variations in spectrum probably did not influence our results. The pressure level of the noise was determined by integrating the calibration curve over the spectrum of the noise.

Noise could be delivered in either a “frozen” or “running” configuration. In the frozen configuration, all repetitions of the burst represented identical tokens of noise. In the running configuration, the repetitions were not identical. Each repetition was a 75-ms segment extracted from a single long token of noise that had a duration of 1–1.6 s. The segments were extracted sequentially from the long token and could overlap, but the start of each segment was typically delayed ~15 ms relative to the start of the preceding segment. A particular interval of noise occurred in only approximately five repetitions of the running noise.

The binaural-beat stimulus consisted of tones to the two ears that differed in frequency, resulting in a continuously varying interaural phase difference at the difference, or beat, frequency. Initial testing was performed with binaural-beat stimuli that had a 3-Hz beat frequency and a duration of 1.1 s repeated every 1.3 s. Measurements of characteristic delay and phase were made with binaural-beat stimuli that had a 1-Hz beat frequency and a duration of 5.1 s repeated every 5.3 s.

Localization of recording sites

The procedures for fixation, histological processing, and localizing the recording sites have been described previously (Batra and Fitz-
neurons to tone bursts was restricted to the stimulation. A weighted least-squares procedure was used to be accounted for partial cycles of cycles. The calculation of mean interaural phases was performed using the method of Yin and Kuwada (1983a), as modified by Kuwada et al. (1987) to account for partial cycles of stimulation. A weighted least-squares procedure was used to fit a straight line to phase plots of mean interaural phase versus frequency. The phases were weighted to reduce the contribution of weak responses to the fit. Synchronization coefficients (SCs) (vector strengths) were calculated as described by Goldberg and Brown (1969) and modified by Kuwada et al. (1987).

COMPOSITE DELAY CURVES. Composite delay curves were calculated in one of two ways. For comparison with measurements in other nuclei (Fig. 4), responses to tones as a function of ITD were first averaged to represent the response over one cycle of interaural delay. If responses were measured using binaural-beat stimuli, this average delay curve had 10 bins. The average delay curves were used to calculate the response of the neuron at 400 points over ±4 ms of ITD at a particular frequency. Responses at different frequencies were then averaged together to obtain the composite delay curve. The composite peak delay was obtained by a parabolic fit to the top 30% of the composite delay curve. This procedure is similar to what has been done previously (Batra et al. 1997a; Kuwada et al. 1987; Yin and Kuwada 1983b). For comparison of the response to tones with that to noise (Fig. 5), a slightly different procedure was used. As the noise was delivered uncalibrated, the responses to tones were first “uncorrected” using the phase calibration tables employed to deliver the tones. The rest of the calculation was the same, except that the composite delay curve was calculated over only ±2 ms using 200 points, and 50% of the peak was fit to obtain the composite peak delay.

RESULTS

The results are based on the responses of 55 neurons localized in and around the VNLLm that were sensitive to ITDs. In our dorsal approach, these neurons were almost invariably the first to be encountered in a penetration and were often accompanied by a weak neurophonic that was absent deeper in the penetration. In every case that the locations of such neurons were marked, they were found to lie in the VNLLm or in its anterior continuation (Fig. 1, •, n = 8) (Batra and Fitzpatrick 1999). Based on the similarity in location and responses, we deduce that all the neurons most likely lay within the VNLLm. Best frequencies (obtained using tone bursts at a constant intensity level, usually 60 or 70 dB SPL) were obtained for 53 neurons and ranged from 200 Hz to 5.6 kHz; two-thirds of the neurons had best frequencies between 800 and 1,200 Hz with the remainder equally distributed on either side of this range.

As stated in our earlier paper (Batra and Fitzpatrick 1997), most ITD-sensitive neurons in the VNLL had onset responses to contralateral and binaural tone bursts but did not respond to monaural ipsilateral stimulation. This was also true in the present, larger sample. When low-frequency tones were used, ~80% had onset responses (38/49) to contralateral stimulation, with about half the remainder being unresponsive (6/49) and the rest showing other than an onset response (5/49). Similarly, ~90% of the neurons had onset responses to binaural stimulation (43/48). Monaural ipsilateral stimulation, on the other hand, evoked a response from only 25% of the sample (10/39). Most of these neurons had onset responses (7/10). Neurons typically displayed the same response pattern at all frequencies. In the present sample, as before, only one-third of the neurons followed the continuous changes in ITD produced by binaural-beat stimuli (15/47).

Sensitivity to ITDs in tones

Neurons sensitive to ITDs fall into two broad categories: peak-type and trough-type (Batra et al. 1993, 1997a; Fitzpatrick et al. 2000; McAlpine et al. 2001). Peak-type neurons discharge maximally at a particular ITD irrespective of the frequency, whereas trough-type neurons discharge minimally at a particular ITD. In the VNLL, most neurons were of the peak-type (Fig. 2, A and B). This was true both for neurons that synchronized significantly to the beat frequency of a binaural-beat stimulus (Rayleigh test of uniformity, P < 0.001) (Mardia 1972) and thus followed dynamic changes in ITD (Fig. 2A, left) and for those that failed to do so (Fig. 2B, left).

The tendency of a neuron to be peak or trough type was quantified by plotting the mean interaural phases of the responses.
sponses against frequency (Fig. 2, A and B, right) and fitting the phases with a straight line (see METHODS). The intercept of the line with the ordinate is called the characteristic phase (CP) (Yin and Kuwada 1983b) (values at top right in Fig. 2, A and B, right). The CP is ideally 0 cycles for peak-type neurons and 0.5 cycles for trough-type neurons. The slope of the fit is a quantitative measure of the “characteristic delay” (CD) for the neuron (in Fig. 2, A and B, left; values at top left in Fig. 2, A and B, right) (Rose et al. 1966; Yin and Kuwada 1983b), which in turn is a measure of the encoded ITD. The CP and CD are only well defined when the phases change linearly with frequency. For this reason, we only calculated the CP and CD of neurons that satisfied the statistical linearity criterion of Yin and Kuwada (1983b) (P < 0.005). About 70% of the neurons (25/35 neurons) satisfied this criterion.

The CPs of neurons in the sample confirmed that most were of the peak type (Fig. 3). Most CPs were closer to 0 than 0.5 cycles (left of dashed line 19/25 neurons). There was no peak in the CP distribution at 0.5 cycles corresponding to trough-type neurons. There were, however, a few neurons with CPs nearer 0.5 than 0 cycles (right of dashed line 6/25), which were, therefore nominally trough type.

Most neurons in the VNLLm-encoded ITDs within the estimated free-field range of the rabbit (∼ ± 300 μs) (Heffner and Masterton 1980). The encoded ITD was assessed using two measures, the CD (Fig. 4A) and the composite peak delay (Fig. 4B). The composite peak delay is a measure of the average ITD that elicits maximal discharge (Kuwada et al. 1987) (see METHODS) and is related to the CD via the CP and the best frequency of the neuron (Fitzpatrick et al. 2000). The CDs of all peak-type neurons (19/19 neurons; Fig. 4A, filled bars) and nearly 90% of their composite peak delays (17/19 neurons, Fig. 4B, filled bars) lay within the free-field range (horizontal bracket). The CDs and composite peak delays of the nominally trough-type neurons were distributed across the corresponding overall distributions (Fig. 4, A and B, open bars). Both the CDs and the composite peak delays were weakly biased toward ipsilateral delays; that is, ITDs associated with sounds in the contralateral hemifield.

Sensitivity to ITDs in noise

When tested with interaurally delayed noise, most neurons exhibited a central peak, responding strongly near 0 ms ITD and more weakly at longer delays (21/26 neurons, Fig. 5, A and B). A few neurons responded minimally near 0 ms ITD and more strongly at larger delays (3/26 neurons, not illustrated). The response to noise as a function of ITD differed slightly from the response to tones averaged across frequency. The response to noise was compared with the response to tones by constructing a composite delay curve (Fig. 5, A and B, heavy line; see METHODS). In other auditory centers, the composite delay curve has been shown to be similar to the response to noise as a function of ITD (Fitzpatrick et al. 2000; Palmer et al. 2002).

FIG. 4. Encoding of ITDs. A: distribution of the CD. B: distribution of the composite peak delay. Calculation of composite delay curves and the derivation of the composite peak delay are described in METHODS. •, peak-type neurons. ○, nominal trough-type neurons as indicated by their CPs. Brackets above histograms, estimated free-field range of the rabbit. n = 25.

FIG. 5. Comparison of responses to noise and to tones as a function of ITD. A and B: comparisons of the responses of 2 neurons. Response to noise was calculated over the full stimulus duration. C: comparison of the locations of peaks in responses to noise and in composite curves (n = 16). Comparisons were only made when peaks were evident in response to noise. The best delay in response to noise was calculated by a parabolic fit to the upper 50% of the peak. Dashed line, line of equality. D: distribution of best delays to noise. n = 21.
1990; Yin and Chan 1990; Yin et al. 1986). For some neurons in the VNLLm, this was true as well (e.g., Fig. 5A). For other neurons, the centroid of the peak in response to noise was at more ipsilateral delays than that of the composite peak delay (Fig. 5B). Across neurons that exhibited a central peak in response to interaurally delayed noise, the best delays to noise (see legend of Fig. 5) tended to be at slightly more negative ITDs than the composite peak delay (Fig. 5C). The best delays to noise strongly favored negative ITDs, i.e., those associated with the contralateral sound field (Fig. 5D; 18/21 neurons).

The temporal pattern of the response to noise also differed from that to tones (Fig. 6). Most neurons in the VNLLm responded to tones at the optimal ITD with an onset response (e.g., Fig. 6, A and B, top). With frozen noise (see METHODS) at the same ITD and similar sound pressure level, there was also a sustained component consisting of multiple peaks that were typically irregularly spaced (e.g., Fig. 6, A and B, bottom). A quantitative comparison confirmed the difference in response to tones and noise (Fig. 6C). Nearly all neurons for which data on both tones and noise were available (n = 19) responded to binaural tones with almost no sustained discharge (filled bars). In contrast, the response to binaural noise always had a sustained component, which was typically > 10 imp/s (open bars).

In some neurons, comparing the responses to frozen noise and running noise demonstrated that the peaks in the discharge pattern were responses to features in the noise (Fig. 7, A and B). In these neurons, the peaks in their peristimulus-time histograms (PSTHs) to frozen noise (e.g., Fig. 7, A and B, top) were absent in the PSTH to running noise (see METHODS; Fig. 7, A and B, bottom). To quantitatively compare the difference in response between frozen and running noise across neurons, a coefficient of variation (CV) of the sustained discharge rate was calculated for both responses (Fig. 7C). This CV was a measure of the irregularity of the discharge pattern (Fig. 7, legend). For all responses for which comparisons were available, the CV was less for running noise than for frozen noise. Thus the peaks in the discharge pattern in response to frozen noise were responses to transient features in the noise.
Sensitivity to ITDs is conveyed from lower centers

Sensitivity to ITDs in the VNLLm is a result of ascending influences as indicated by the latencies of its neurons. The latency to contralateral tone bursts was 8 ± 0.8 ms (median ± semi-interquartile range, n = 43), which is only slightly longer than the latency of the VNLL as a whole (median = 7 ms) (Batra and Fitzpatrick 1999). The small difference is largely accounted for by the lower best frequencies of neurons in the present sample of VNLLm neurons as compared with the entire VNLL, and by the longer travel time (~0.9 ms) for low frequencies along the basilar membrane (Anderson et al. 1971; Goldstein et al. 1971; Joris and Yin 1992). For comparison, the time required for neural signals to ascend to the inferior colliculus was estimated from the latencies of a sample of high-frequency neurons in the inferior colliculus (best frequencies: ≥2 kHz) that were used in a previous study (Batra et al. 1993). The median latency in this sample was 10.5 ms (48 neurons), several milliseconds longer than latencies in the VNLLm.

Other evidence indicates that sensitivity to ITDs is not generated within the VNLLm. We have previously shown that neurons that are primary sites for the integration of monaural inputs, such as those in the SOC, synchronize strongly to the tones at either ear during a binaural-beat stimulus (Batra et al. 1997b). An example of the responses of a neuron in the SOC exhibiting synchrony consistent with primary binaural interaction is shown in Fig. 8A. These responses obey a convolution principle. The SCs for synchrony to the ipsilateral tone (Fig. 8A, dashed line) and the contralateral tone (light line) typically exceed the interaural SC (circles). Furthermore the product of the SCs for synchrony to the waveforms (heavy line) equals the interaural SC. Neurons that inherit sensitivity to ITDs may mimic their inputs closely enough to meet these criteria, but neurons that fail them are unlikely to be primary sites of binaural convergence.

We were only able to apply the technique we used in the SOC to the minority of neurons in the VNLLm that followed the dynamic changes in ITD produced by binaural-beat stimuli. Few of these neurons synchronized significantly (P < 0.001, Rayleigh test of uniformity) (Mardia 1972) to both the ipsilateral and contralateral tones (4/15 neurons). Even in these few neurons, the product of the SCs to the ipsilateral and contralateral tones was less than the interaural SC. The responses shown in Fig. 8B are from a neuron which exhibited some of the strongest synchrony to ipsilateral and contralateral tones. At many frequencies, the SC to the tone at one or the other ear (dashed and light lines) was greater than the interaural SC (circles). At all frequencies, however, the product of the SCs to the tones (heavy lines) was less than the interaural SC. Thus the responses of the neurons that followed dynamic changes in ITD (15/15) indicated that the VNLLm was not a site of primary binaural interaction.

Most neurons in our sample did not follow dynamic changes in ITD and also did not respond to ipsilateral stimulation. In these neurons, we only compared the contralateral SC, obtained from the response to contralateral tones, with the interaural SC. The responses of these neurons were often just a single action potential, so poor synchrony indicated that the variation in latency of the action potential was large compared with a period of the tone. Even in an onset neuron, tight locking should be necessary to generate a sensitivity to ITDs.

In most neurons that did not follow dynamic changes to ITD (e.g., Fig. 9A), the SC to the contralateral tone was not significant (middle), yet these neurons were strongly modulated by the ITD (right; 23/31 neurons). In a few neurons (e.g., Fig. 9B),
the SC to the contralateral tone was significant (8/31) but in half of these was less than the interaural SC. Thus >90% of the neurons in our sample that were adequately tested (42/46 neurons) failed to obey the convolution principle for coincidence detectors. The remainder may have failed this criterion as well, but this matter could not be settled in the absence of some measure of the ipsilateral SC. All eight neurons at marked sites within the VNLLm failed to obey the convolution principle. These results, coupled with the relatively short latency of most neurons in the VNLLm, imply that these neurons inherit their sensitivity to ITDs from a station lower in the brain stem, most likely the SOC.

**Excitatory input to contralateral sounds**

The ITD-sensitive neurons of the VNLLm differed from the neurons of the SOC not only in their poor synchrony to tones but also in their onset response. The onset response could be produced by an inhibitory input that suppressed later responses. Alternatively, it could be the result of an excitatory input that, when activated by contralateral tones, elicited an onset response in the VNLLm. The amplitude of the onset response could then be modulated by an additional input or inputs carrying information about ITDs. We reasoned that if a delayed inhibitory input were present, then the latency would be determined by the ITD-sensitive input, whereas if an excitatory contralateral input were present, then the latency of the response would be determined by the contralateral input.

In most neurons tested over a wide range of ITDs with tones (e.g., Fig. 10, A and B), the latency of the response relative to the contralateral tone was invariant as a function of the ITD (Fig. 10A, B, ●), whereas the latency relative to the ipsilateral tone varied linearly (Fig. 10A, B, ○). In these neurons, the latency tracked the contralateral tone, so the response seemed to be primarily due to a contralateral excitatory input. A few neurons followed a different pattern, the clearest example of which is illustrated (Fig. 10C). The latency of this neuron tended to track the trailing tone, suggesting that it responded primarily to an ITD-sensitive input.

The tendency of the latency to track the ipsilateral or contralateral tone was quantified using the slopes of linear least squares fits (Fig. 10, A–C, . . . , and --→). The slopes of the fits clustered around 0 when latencies were measured with respect to the contralateral stimulus (Fig. 10D, filled bars) and around 1 when measured with respect to the ipsilateral stimulus (open bars). Even for the neuron that tracked the later arriving tone (Fig. 10C), there was a stronger tendency for the latency to track the contralateral tone, as indicated by the shallower slope of the fit. Thus for the most part, the latencies of responses to binaural stimulation were controlled by the timing of the contralateral stimulus.

When combined with our earlier conclusion that the VNLLm inherits its sensitivity to ITDs, the constant latency to contralateral tones supports the idea that the neurons of the VNLLm receive at least two excitatory inputs: a contralateral input that determines the latency of the response and a typically subthreshold ITD-sensitive input that modulates the amplitude of the response but does not strongly influence the latency.

The lack of influence of the ITD on latency was all the more surprising because the ITD-sensitive input appeared to be transmitted more rapidly than the contralateral input (Fig. 11).

**Facilitation and suppression**

Depending on the ITD, binaural stimulation could enhance or suppress the response to contralateral stimulation. In some neurons, stimulation at the optimal ITD elicited a response well above the response to contralateral stimulation alone (Fig. 11, arrowhead). In other neurons, there was little facilitation at the optimal ITD (Fig. 12A). In most neurons, the contralateral response was strongly suppressed by binaural stimulation at the least favorable ITD (Figs. 11 and 12A). Ipsilateral stimulation alone typically produced no significant response (Fig. 12, A, B, C).
left-pointing arrowhead). The strength of facilitation varied widely (Fig. 12B, solid bars), ranging from near 0 to over 100%. In contrast, nearly 90% of neurons (28/32 neurons) were suppressed strongly (>80%) at unfavorable ITDs (Fig. 12B, open bars).

In at least some neurons, the degree of facilitation depended on the intensity level used (Fig. 12C). Near threshold, the response at the optimal ITD (Fig. 12C, triangle) was greater than that to contralateral stimulation (Fig. 12C, open circle), implying that facilitation was strong. At higher sound levels, the response at the optimal ITD first increased and then declined, so that it could be less than the response to contralateral stimulation. Thus at high sound levels the responses of some neurons showed either weaker facilitation or outright suppression (4/6 neurons). At the least favorable ITD, responses were always considerably less than that to contralateral stimulation, implying that suppression was strong at all sound levels (Fig. 12C, inverted triangle). Thus the neurons that exhibited weak facilitation but were tested at only one sound level may have exhibited stronger facilitation at a lower sound level.

D I S C U S S I O N

Implications for behavior

We have demonstrated that although neurons of the VNLLm respond transiently to tones, the response to noise is sustained and resembles that to a sequence of onsets. Neural responses of this type were hypothesized to exist by Hartmann (1983) to explain the abilities of listeners to localize sounds when reflections were present. He found that in this situation listeners localized tones more accurately when the tone had a sharp onset. When asked to localize noise, they were able to do so accurately even when the onset was gradual. Hartmann hypothesized that the binaural system responded to noise as if it were a sequence of transients. In this paper, we have demonstrated that the neurons of the VNLLm exhibit just such a response to noise.

The heavier weight that listeners assign to the onset of a tone is believed to underlie the Franssen effect (Franssen 1962; Hartmann and Rakerd 1989), an acoustic illusion. In this effect, listeners in a room with reflective surfaces are presented with sounds from two speakers at different locations. The first speaker emits a brief sound that has a sharp onset followed by a gradual decline to offset. During the gradual decline, the sound from the second speaker is gradually turned on. Listeners localize the ongoing sound from the second speaker to the first speaker. The Franssen effect occurs with tones but not with noise (Hartmann and Rakerd 1989; Yost et al. 1997). There are parallels between these psychophysical observations and our neural results in the VNLLm. The tendency to localize tones using only the onset corresponds to the transient neural response that we observed. The ability to localize ongoing noise corresponds to the sustained neural response to this stimulus. What is not explained by our results is the persistence of localization to the first speaker in the Franssen effect. Presumably, this relies on prolonged retention of information about the onset in some higher center.

Neurons with properties similar to those present in the VNLLm appear to exist at higher stations of the auditory pathway as well, suggesting that the VNLLm may represent the start of a pathway for encoding the ITDs of transients. Neurons in the inferior colliculus (Yin and Kuwada 1983a) and auditory cortex (Reale and Brugge 1990) have been reported that are sensitive to ITDs, respond transiently to tones, and do not follow dynamic changes in ITD. It should be noted, however, that these neurons were encountered in animals that were

![FIG. 11. Responses of 2 neurons as a function of ITD over a wide range. Arrowheads, responses to contralateral stimulation alone. Frequency was 1 kHz for both neurons. Sound levels (dB SPL): A, 60; B, 70.](Image)

![FIG. 12. Facilitation and suppression. A: responses of a neuron exhibiting chiefly suppression. Right and left pointing arrowheads, responses to contralateral and ipsilateral stimulation, respectively. B: distribution of facilitation (n = 35) and suppression (n = 32). Suppression could not be assessed in 3 neurons because they were not driven by contralateral stimuli. C: facilitation and suppression of the same neuron as in A as a function of average sound pressure level. Triangles and inverted triangles, responses at a favorable and an unfavorable ITD, respectively. Circles, responses to contralateral tones. Frequency in A and C, 700 Hz. Sound level in A, 60 dB SPL. Favorable and unfavorable ITDs in C, 280, −430 μs.](Image)

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anesthetized. Anesthesia tends to make responses more transient, both in the inferior colliculus (Kuwada et al. 1989) and in the auditory cortex (Fitzpatrick et al. 2000). Furthermore, administration of anesthesia can abolish the sensitivity of neurons in the auditory cortex to dynamically changing ITDs while leaving a residual sensitivity to static ITDs (Fitzpatrick et al. 2000). Thus the proportion of transiently responding neurons in the colliculus and auditory cortex is lower than published studies suggest, though a small number do appear to be present (personal observations).

Comparison with the SOC

We have provided evidence that the VNLLm inherits sensitivity to ITDs from a site lower in the auditory pathway. The most likely source is the SOC. Both the LSO and the MSO project to the medial part of the VNLL but not to the lateral part (Glendenning et al. 1981; Henkel and Spangler 1983). The limited projection of the MSO and the LSO to the lateral part of the VNLL supports our earlier inference that the ITD-sensitive neurons are located only in the medial subdivision.

A key difference between the SOC and the VNLLm is the weaker phase locking of neurons in the VNLLm to tones. Phase locking in the SOC has been widely reported (Batra et al. 1997b; Crow et al. 1978; Moushegian et al. 1964; Spitzer and Semple 1995; Yin and Chan 1990) and is usually strong. The strength of phase locking for many neurons in the SOC is related by a convolution principle to the range of interaural phase differences over which a neuron exhibits an elevated discharge. In higher centers such as the inferior colliculus, auditory thalamus, and the cortex, few neurons phase lock to tones (Aitkin and Webster 1972; Kuwada et al. 1984; Rouiller et al. 1979; Stanford et al. 1992; Wallace et al. 2000). Those that do so fail to satisfy the convolution principle (personal observations). The ITD-sensitive neurons of the VNLL also phase lock weakly and fail to satisfy the convolution principle, leaving the SOC as the sole site at which monaural inputs appear to converge to generate a sensitivity to ITDs.

Peak-type responses such as we have observed in the VNLLm have been associated with the MSO in a number of species (cat: Yin and Chan 1990; gerbil: Spitzer and Semple 1995; rabbit: Batra et al. 1997a; Mexican free-tailed bat: Grothe and Park 1998). In both the MSO (or equivalently, in peak-type neurons of the SOC) and the VNLLm, the ITDs that elicit maximal discharge are mainly within the free-field range. In the MSO, there is a strong preference for ITDs associated with the contralateral sound field. In the VNLLm, this preference was strong in response to noise, but weaker when tested with tones. Even so, there was no clear statistical difference in the means of either the distributions of the CD or the composite peak delay between the VNLLm and the MSO [t-test between present data and those of Batra et al. (1997a), \( P > 0.05 \)]. Thus in most measures of sensitivity to ITD, responses in the VNLLm resemble those in the MSO.

The small but consistent difference between the best delay to noise and the composite peak delay for neurons in the VNLLm indicates a degree of nonlinear processing. This suggests that neural processing increases the preference of neurons for ITDs associated with the contralateral sound field. A similar difference is present in responses of neurons in the inferior colliculus and auditory cortex (Fig. 7 of Yin et al. 1986; Figs. 6 and 7 of Palmer et al. 1990; Fig. 4 of Fitzpatrick et al. 2000). Thus any such process most likely occurs at an early stage of binaural processing, possibly the SOC.

Another key difference between the VNLLm and the SOC is the onset response to tones. This onset response is unlikely to be a result of cellular properties of neurons in the VNLLm even though some neurons of the VNLL do display an onset response to injected current (Wu 1999). It is unclear how such properties would induce a neuron to produce an onset response when receiving a train of action potentials conveying information about tones but a sustained response when the action potentials encode a noise stimulus. It seems more likely that the suprathreshold contralateral input we have inferred confers the discharge pattern on the neuron as well as controlling its latency. This discharge pattern could then be modulated by a subthreshold input from the MSO.

In addition to the two excitatory inputs, there is also likely to be a third, inhibitory input. The presence of this input is suggested by the suppression present at unfavorable ITDs. Such suppression is observed in the MSO (Goldberg and Brown 1969; Grothe and Park 1998; Spitzer and Semple 1995; Yin and Chan 1990). However, the input from the MSO to neurons of the VNLLm appears to be subthreshold, so it is difficult to see how this suppression could be echoed in the VNLLm. It is more likely that the suppression is caused by an inhibitory input that is active at ITDs far from zero. The source of this inhibition could be the LSO, which contains a population of low-frequency neurons sensitive to ITDs (Batra et al. 1997b; Finlayson and Caspary 1991; Tollin et al. 2000). These neurons are of the trough type, discharging maximally at ITDs that are typically unfavorable for neurons of the VNLLm. Some neurons of the LSO appear to use glycine (Glendenning et al. 1992; Saint Marie et al. 1989; Wenthold et al. 1987), a transmitter that is typically inhibitory. There is evidence that the LSO projects to the VNLLm (Glendenning et al. 1981).

In conclusion, the neurons of the VNLLm may be important for localizing sounds in environments containing reflections. Their responses suggest a complex set of inputs that confer the particular properties seen.

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