HEARES 01597

# Coding of interaural time differences of transients in auditory cortex of *Rattus norvegicus*: Implications for the evolution of mammalian sound localization

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(Received 28 August 1990; accepted 20 February 1991)

We obtained quantitative evidence on the coding of interaural time differences (ITDs) of click stimuli by 40 single neurons in the auditory cortex of anesthetized albino rats. Most of the neurons (31/40) received an excitatory input from the contralateral ear, and an inhibitory input from the ipsilateral ear (El cells). These neurons expressed their sensitivity to ITDs in a sigmoidal relation between spike count and ITD, with maximal responses associated with contralateral-leading ITDs. The mean ITD dynamic range was 590  $\mu$ s. The dynamic ranges typically encompassed at least part of the behaviorally-relevant range (about  $\pm 130 \ \mu$ s). Variations in ITD from 130  $\mu$ s favoring one ear to 130  $\mu$ s favoring the other ear caused spike response rate changes, on average, of 29.5%. These data are similar to those previously presented for the central auditory systems of larger mammals, whose auditory localization acuity is significantly better than that of the rat. We argue, therefore, that the sound localization mechanisms based on transient ITDs have not evolved in a fashion that covaries with interaural distance, and that there exists a mismatch between the ITDs the rat will encounter in the free field, and the ITDs which are encoded by its nervous system. This may be one reason why sound localization acuity has a roughly inverse relation to interaural distance.

Sound localization; Auditory cortex; Rat; Evolution; Interaural time difference

# Introduction

One set of stimulus cues used to locate sound sources in the azimuthal plane derives from differences in the travel times of the sound to the two ears. These interaural time differences (ITDs) fall into two broad categories. First, there are arrival time disparities for the transient content of the sound (e.g., signal onset: Middlebrooks and Green, 1989). Second, there are steadystate phase differences in the signals at the two ears, which are resolvable by the nervous system for frequencies less than about 3000 Hz (Roth et al., 1980). The magnitudes of these cues are sensitive functions of sound source azimuth, at least for locations within about 45 degrees of the midline. Obviously, the magnitudes of the ITDs that the animal can encounter in the free-field (i.e., the behaviorally-relevant range) also depend on the animal's interaural distance, and therefore on its head size. In this respect, comparative studies have revealed that there is a roughly inverse relation between species' interaural distances and their localization acuities at the midline (Heffner and Heffner, 1982, 1988a).

A neurophysiological finding which appears to link the physical and behavioral data comes from studies of the neural coding of steady-state interaural phase differences. Briefly, when the range of interaural phase differences encoded by neurons of the central auditory pathway is expressed in units of time, the range is found to be independent of the species' head sizes (compare: Yin and Kuwada, 1983; Brugge and Merzenich, 1973; Stillman, 1971). The range of preferred (characteristic) delays, and therefore the range of ITDs over which spike rates vary from maximum to minimum, extends from about 500  $\mu$ s favoring one ear to 500  $\mu$ s favoring the other (Phillips and Brugge, 1985). Accordingly, the variation in spike rates driven by changes in ITD over the behaviorally-relevant range will be small for animals with small heads, but large for animals with large heads. It follows from this that large mammals have a closer match between the range of behaviorally-relevant ITDs and the range which is encoded by their nervous systems, a factor that could contribute to their superior localization acuity.

A line of evidence which is critical to this hypothesis concerns the neural coding of transient ITDs. If, as Phillips and Brugge (1985) imply, mammals have inher-

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ited ITD coding mechanisms common to both large and small species, then the range of transient ITDs encoded by animals with small heads should be similar to that for animals with larger heads. The answer to this question cannot be inferred from the data on coding of interaural phase differences, because different neural populations may be responsible for encoding the two ITD types (Caird and Klinke, 1987; Carney and Yin, 1989; Kuwada and Yin, 1983; Phillips and Brugge, 1985). Evidence on the range of transient ITDs encoded by the cat's nervous system has recently been presented (Carney and Yin, 1989; Caird and Klinke, 1987; Kitzes et al., 1980), but fewer parametric data have been presented for smaller mammals. Pollak (1988) has described in detail the ITD sensitivity of midbrain neurons in the Mexican free-tailed bat (Tadarida brasiliensis mexicana), but neither the behavioral sensitivity of this species to ITDs, nor its free-field localization acuity in the azimuthal plane is, to our knowledge, known.

In this report, we describe the coding of transient ITDs by single neurons in the auditory cortex of the albino rat (Rattus norvegicus). This species has a relatively poor midline localization acuity (about 13 degrees of azimuth: Heffner and Heffner, 1985; Kavanagh and Kelly, 1986; Kelly, 1980). The rat's interaural distance is about 3.5 cm, although our measurement of the shortest path length around the head is closer to 4.0 cm. Based on a sound travel time of 29  $\mu$ s/cm, this predicts a maximum ITD in the order of 116  $\mu$ s, although calculations based on a spherical head model (see Mills, 1972) predict a maximum ITD of 130  $\mu$ s. This value is still much smaller than that for the cat, whose interaural distance supports measurable ITDs in excess of 400 µs (Roth et al., 1980), and whose midline localization acuity is closer to 5 degrees of azimuth (Heffner and Heffner, 1988b; Martin and Webster, 1987). Our studies show that the rat's neural ITD functions encode ITDs over about a  $\pm 500 \ \mu s$  range, centered near zero, which is comparable to that previously described for cats. Our observations thus support the hypothesis that the neural mechanisms for sound localization based on binaural time differences have not evolved in a fashion which covaries with head size, and that for small mammals, there is a mismatch between the range of ITDs which the head size can generate and the range which is encoded by the nervous system.

## Methods

With the exception of the stimulus paradigm, all procedures were identical to those described in an earlier report (Phillips and Kelly, 1989). Briefly, 15 adult male albino Wistar rats were surgically anesthetized with Equithesin (3 ml/kg, after Sally and Kelly, 1988), and the left auditory cortex was exposed. The pinnae were left intact, and calibrated stimulus delivery systems (earphones built into custom designed housings) were snugly fitted into the external auditory meatuses. Although we did no systematic physiological mapping of the cortex, all single neurons were recorded from the region previously described as the primary field (Sally and Kelly, 1988; Kelly and Sally, 1988). Extracellular responses were recorded using insulated tungsten microelectrodes advanced perpendicularly through the dura mater using a micromanipulator. A Bak window discriminator was used to generate 'acceptance' pulses from spikes of selected amplitude and waveform. These pulses were timed relative to stimulus onset using a Tracor-Northern TN-1550 multichannel scaler. This device provided peri-stimulus time histograms, spike count and modal latency data on responses to a pre-set number of stimulus presentations.

The binaural studies all used 50  $\mu$ s condensation click stimuli presented at rates from 1/s to 1/0.7 s. Data collected were responses to blocks of 30 to 50 clicks presented monaurally to the contralateral ear, monaurally to the ipsilateral ear, and binaurally with manually set interaural time differences (ITDs). The ITDs tested varied between neurons, because our main goal was to define the ITD 'dynamic range' (see below) in each neuron, and this range itself varied between neurons. Almost all cells were tested with ITDs ranging from 500  $\mu$ s favoring the ipsilateral ear (i.e., the ipsilateral click leading the contralateral one) to 500  $\mu$ s favoring the contralateral ear, but we frequently extended the range of ITDs, sometimes by milliseconds. This was done either to define the ITD dynamic range more completely, or to address questions of underlying mechanism (see below).

### Results

Data were collected from 40 neurons. One neuron with a strongly nonmonotonic intensity profile for pure tones was unresponsive to clicks, and it has been excluded from what follows. Eight neurons were designated 'EE' cells, because click stimuli presented to each ear separately evoked at least modest spike numbers. ITD functions for two of these neurons are shown in Fig. 1. For each of these cells, the click amplitudes at the two ears were set to evoke monaural responses of roughly equivalent strength. In neuron JD11–7 (Fig. 1B), monaural stimuli of any amplitude evoked only low spike counts, so that it might properly be classified as 'PB' (predominantly binaural, after Kitzes et al., 1980). The ITD functions of these two cells are representative of our EE cell sample in three respects. First, responses to binaural stimuli with small ( $\leq 500 \ \mu$ s)



Fig. 1. Spike count-vs-ITD functions for two neurons that received a net excitatory input from each ear. The click amplitudes at each ear were set to evoke suprathreshold, but submaximal, monaural responses of comparable strength. Note that for binaural stimuli, response strength can exceed the sum of the monaural responses, particularly when the ITD favors the contralateral ear.

ITDs favoring the contralateral ear often evoked responses of greater strength than did binaural stimuli with the same magnitude ITDs favoring the ipsilateral ear when click levels were set at or slightly above threshold. When click levels were set to evoke saturated monaural responses, ITD functions were usually flat. Second, when the monaural components of the stimulus evoked submaximal responses, the binaural responses to signals with 0  $\mu$ s ITD were stronger than those to either ear alone. Third, if the ITD was extended sufficiently, the response facilitation provided by the interaction of afferent events from the two ears was reduced and in some cases eliminated (Fig. 1B).

Neurons that were excited by contralateral clicks, unresponsive to ipsilateral clicks, and suppressed in response to binaural clicks, were the most common cells in our sample (N = 31). Following convention, we refer to such cells as 'EI' neurons. For ITDs less than about 1 ms, ITD functions for these neurons had roughly sigmoidal shapes. Spike counts were high when the ITD favored the contralateral ear, and low for the converse binaural configuration.

Fig. 2 presents data on two of these neurons. For each of them, ITD functions were obtained for contralateral clicks paired with ipsilateral clicks of three or four different amplitudes (Figs. 2A and B, respectively). These ipsilateral levels ranged upwards from 0 dB relative to the contralateral click amplitude in the same neuron. In Fig. 2, responses have been expressed as percent maximum to facilitate scaling of dynamic ranges across neurons and stimulus conditions.

The ITD functions of both neurons were steep over their central portions. When the ITD was such that the ipsilateral click was lagging, response rates were high. In contrast, when the ITD favored the ipsilateral ear significantly, response rates fell to zero. Within neurons, the effect of increasing the relative amplitude of the ipsilateral clicks was to displace the ITD function leftwards (see also Pollak, 1988). This likely reflects the fact that as the ipsilateral click amplitude is increased,



Fig. 2. Normalized spike count-vs-ITD functions for two EI neurons. In each case, data are plotted for responses to a single contralateral click level paired with ipsilateral clicks whose relative levels are specified in the inset. Note that as the relative level of the ipsilateral clicks is increased, the ITD function is displaced left-wards.

the latent period of the inhibitory response shortens relative to that of the contralateral, excitatory one. The latency advantage conferred to the inhibitory input has the consequence that smaller ITDs favoring that ear are required to bring the excitatory and inhibitory afferent events into coincidence, thus suppressing the response to the contralateral click. Average time-intensity trading ratios (i.e., the temporal shift expressed as a ratio to the amplitude increment that brought it about) measured from the midpoints of ITD curves were generally in the range from 15 to 50  $\mu$ s/dB. This range presumably reflects the slopes of the inhibitory latency-intensity functions, which may vary within or between neurons. Within neurons, the variation in slope with different click levels would follow from the nonlinearity of latency-intensity functions over click amplitude ranges used to assess the slope.

On average, ipsilateral-leading ITDs brought about a maximum of 82.2% (SD = 14.7%) reduction in spike count (measured from the maximum count seen in the function). For each of the 31 EI neurons in the sample, we measured the 80% ITD dynamic range, i.e., the range of ITDs over which spike counts fell from 90% to 10% of maximum (from 90% to minimum rate in neurons whose ITD functions did not fall to 10% of maximum). In neurons for which we had obtained multiple ITD functions, dynamic ranges were measured from the function most closely centered around zero ITD. In most cases, these functions were obtained using stimuli that differed by less than 10 dB at the two ears.



Fig. 3. Horizontal lines depict the 80% ITD dynamic ranges for each of the 31 EI neurons in the sample. Vertical shaded area depicts the behaviorally-relevant range of ITDs for an adult rat, calculated using a spherical head model. Note that while most neurons had ITD dynamic ranges which encroached on, or encompassed, the behaviorally-relevant range, the neural ranges are typically much broader.



Fig. 4. Detailed data on neuron JD15-7. Panel A shows normalized spike count-vs-ITD functions for a single contralateral click level paired with each of four ipsilateral click levels. Panel B shows the responses of the same neuron to a broader range of ipsilateral-leading ITDs. Note that the response rate of the neuron is more deeply suppressed by the more intense ipsilateral clicks.

The 31 measured dynamic ranges are shown as horizontal lines in Fig. 3. The mean ITD dynamic range was 590  $\mu$ s (SD = 244  $\mu$ s). The stippled area of Fig. 3 represents the behaviorally-relevant range of ITDs for an adult rat of 3.5 cm interaural separation, calculated using the spherical head model (Mills, 1972). It is clear that while most neurons had dynamic ranges that encroached on or encompassed the behaviorallyrelevant range of ITDs, many of the neuronal dynamic ranges were broader than it, or offset from it. We measured, for each neuron in the EI sample, the percentage change in spike count which occurred in the ITD range from  $-130 \ \mu$ s to  $+130 \ \mu$ s. The mean change was 29.5% (SD = 18.7%).

Finally, Fig. 4 presents data on neuron JD15–7, which was studied with the broadest range of ITDs of all cells in our sample. The purpose of the experiments on this neuron was to determine the duration of the inhibitory input evoked by the ipsilateral clicks. We reasoned that by providing a sufficiently long delay favoring the ipsilateral stimulus, the trailing edge of

the inhibitory neural event could be defined by the recovery in the magnitude of the excitatory response evoked by the contralateral click (see also Carney and Yin, 1989; Pollak, 1988).

Fig. 4A shows this neuron's responses to ITDs between -1.6 and +1.5 ms, for clicks presented at a single contralateral level paired with ipsilateral clicks whose levels were between 5 and 35 dB greater. The family of ITD functions shows the same general pattern of behavior as those illustrated for two other EI cells in Fig. 2: the curves were broadly sigmoidal in shape, and were displaced leftwards with increases in the relative level of the ipsilateral stimuli. Fig. 4B shows the effect of long ipsilateral lead times on the response of the neuron to binaural clicks, and for stimuli of two relative click levels. When the ipsilateral clicks were only 5 dB more intense than the contralateral ones, the response to the pair declined steeply over ITDs from 0 to 1 ms (favoring the ipsilateral ear). The binaural response improved with further increments in ipsilateral click lead-time, and was within 20% of maximum when the ITD was close to 4 ms. For ipsilateral clicks 35 dB more intense than the contralateral ones with which they were paired, the descending arm of the ITD function was shifted leftwards, the depth of the suppression was 35% greater, and the left-leading ITD required for recovery to within 20% of maximum spike count was closer to 6 ms.

### Discussion

Cortical auditory neurons in Rattus norvegicus encode the ITD of binaural click stimuli in a fashion similar to that previously described for neurons in the cat's inferior colliculus (Caird and Klinke, 1987), the bat's inferior colliculus (Pollak, 1988), and the cortex of chinchillas (Benson and Teas, 1976). In EI cells, the ITD functions are typically sigmoidal in shape, with maximal responses for ITDs favoring the contralateral ear, a characteristic which extends to ITD functions for tonal stimuli in some cat cortical neurons (Kitzes et al., 1980). The ITD dynamic ranges of rat EI neurons, while often encompassing at least part of the behaviorally-relevant ITD range of  $\pm 130 \ \mu s$ , typically were wider than that range. Overall, the population of EI neurons had a dynamic range that extended from about  $-500 \ \mu s$  to  $+400 \ \mu s$ . This range is comparable to that seen in the click responses described for other species. and it matches that seen in response to steady-state ITDs in the cat's inferior colliculus (Yin and Kuwada, 1983), the kangaroo rat's inferior colliculus (Stillman, 1971) and the monkey's primary auditory cortex (Brugge and Merzenich, 1973).

These data indicate that there exists a mismatch between the range of ITDs available to the rat for binaural sound localization, and the range of ITDs encoded by its nervous system. Indeed, this study found that, on average, the change in firing rate across ITDs spanning the width of the rat's behaviorally-relevant range was only 29.5%. From this, one can conclude that the ITD stimulus information available to the rat does not effect changes in neural response rate large enough to support fine azimuthal discriminations. This may be one factor contributing to the rat's relatively poor acuity for sound localization in the azimuthal plane (Heffner and Heffner, 1985; Kavanagh and Kelly, 1986; Kelly, 1980).

Pollak (1988) similarly pointed out that in Tadarida, the behaviorally-relevant range of ITDs was very small (at most  $\pm 30 \ \mu$ s), and possibly inconsequential to neural response rates, for the same reasons as argued here. Pollak (1988) pointed out, however, that although Tadarida's head might not generate significant ITDs, it does generate significant interaural intensity differences (IIDs) for high frequency sounds. Through the latency-intensity relation, these could be large enough to bring about discrepancies in input latencies at the binaural comparator as large as the ITDs usually employed in his (and our) physiological studies of binaural time sensitivity. He further predicted that sensitivity to these interaural 'latency' differences (our term) might support a much better azimuthal acuity than predicted on the basis of binaural time cues alone.

This argument is based on considerations not fundamentally different from those expressed previously by Kitzes and his colleagues (1978, 1980), i.e., that by means of the latency-intensity relation, an IID can generate a very large asynchrony in the monaural inputs to the binaural comparator. Note, however, that this argument does not dispute the fact that the physical stimulus information available to the small-headed mammal is relatively impoverished: it simply provides an account of how large differences in the timing of the neural signals from the two ears might arise and contribute to the neural coding of IIDs. It remains the case that larger mammals reap the benefits of both the interaural 'latency' difference provided by any IID, and the advantage of larger, encodable, ITDs.

From the standpoint of the binaural comparator, it is not entirely clear how the physical ITDs at the ears and the IID-evoked interaural 'latency' differences might jointly shape sensitivity to sound source azimuth. The issue is complicated by two factors. One is that the binaural comparison relies as much on the relative amplitudes of the monaural inputs as it does on their temporal coincidence. In our Fig. 4B, note that the higher ipsilateral click level produced a 35% deeper modulation of response rate than did the lower onc. To the extent that behavioral discrimination performance relies on a difference in spike rates evoked by differing signals (e.g., Phillips, 1987; Phillips and Hall, 1990), the deeper the modulation of spike rates in the ITD function, the more salient is the neural representation on which the behavioral discrimination is based. A second, and related factor is that the IID-evoked input timing difference is compounded with one in the temporal precision of the transient response. Unlike the case with physical ITDs, the IID-evoked timing differences are consequences of the latency-intensity relation, and for every prolongation of the latent period, there is an increase in the imprecision with which the stimulus event is timed (Phillips and Hall, 1990). The ability of the IID-delayed input to interact with the leading response may depend on its temporal precision, especially for transient signals near threshold.

Thus, notwithstanding the general 'IID-induces-ITD' argument, we are left with the fact that the physical cues available to the small-headed mammal are impoverished by comparison with those for larger animals. Our study has shown that both the single neuron and the population response to transient ITDs in the rat's cortex has a dynamic range similar to that seen in larger mammals. We therefore conclude that the set of binaural localization mechanisms seen in mammals for coding transient ITDs has not evolved in a fashion that covaries with head size, and that this is one reason why rats and other small mammals have poor sound localization acuity.

## Acknowledgements

We thank Sharon L. Sally for technical assistance. The research was supported by NSERC of Canada Grants to JBK and to DPP.

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