

# Variations on a Dexterous theme: Peripheral time–intensity trading

Philip X. Joris\*, Pascal Michelet, Tom P. Franken, Myles Mc Laughlin

Laboratory of Auditory Neurophysiology, K.U.Leuven Medical School, Campus Gasthuisberg O&N2, Herestraat 49 bus 1021, B-3000 Leuven, Belgium

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## Abstract

Sound pressure level changes can affect the timing of spiketrains. Timing of spiketrains is critical for sensitivity to interaural timing differences (ITDs). Interaural level differences (ILDs) can therefore affect the ITD cue. It has been hypothesized that ILDs may be coded indirectly through a peripheral conversion of level to time (but it should be cautioned that the changes in phase with SPL in low-CF AN fibers of the cat are more complicated) (Jeffress, L.A., 1948. A place theory of sound localization. *J. Comp. Physiol. Psychol.* 41, 35–39). We tested this conversion by recording from auditory nerve fibers to broadband noise at different SPLs. For each fiber, correlograms were constructed to compare timing to fine-structure across SPLs. We find generally a decrease in the time delay between spikes and the stimulus with increasing SPL. However, the magnitudes of the shift in time are surprisingly small, and dependent on characteristic frequency (CF): the largest shifts are approximately 10  $\mu$ s/dB and occur at the lowest CFs. Nevertheless, the effects of level on spike timing are systematic and of a magnitude to which the binaural system is sensitive. Thus, even though the results indicate that ILD is not traded for ITD in a simple way, the possibility that low-frequency ILDs affect the binaural percept via a peripheral level-to-time conversion cannot be excluded.

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## 1. Introduction

The “latency hypothesis” refers to the idea that sensitivity to interaural level differences (ILDs) arises through a peripheral conversion of sound level to latency of neural response, and that these latency shifts are subsequently detected by the neural mechanisms subserving the processing of interaural time differences (ITDs). The hypothesis was most famously put forward in a single paragraph of Jeffress’ celebrated paper (Jeffress, 1948), at a time when physiological knowledge of the auditory periphery was based on compound potentials. It was inspired by the psy-

chophysical phenomenon of “time–intensity trading” which shows that ILDs and ITDs can interact (Green and Henning, 1969; Moushegian and Jeffress, 1959), and the observation that the compound action potential shows a decrease in latency in the order of milliseconds with increasing SPL (review in Eggermont, 1976).

Dexter Irvine and colleagues tested the latency hypothesis in the lateral superior olive (LSO) with a particularly elegant paradigm. They found that, for some neurons, ITD- and ILD-sensitivity could be mapped onto each other using SPL-induced changes in latency measured on the same neurons (Irvine et al., 2001). Importantly, their study, as well as other preceding physiological studies that specifically addressed the latency hypothesis, focused on transient responses at high frequencies (Hirsch et al., 1985; Irvine et al., 1995, 2001; Park et al., 1996; Pollak, 1988; Yin et al., 1985), while Jeffress’ hypothesis was concerned with sensitivity to ongoing ITDs and ILDs at low frequencies.

Oddly, while the latency hypothesis is popular with physiologists, it no longer is with psychophysicists. This

*Abbreviations:* AN, auditory nerve; CF, characteristic frequency; ILD, interaural level difference; ITD, interaural time difference; LSO, lateral superior olive; SR, spontaneous rate

\* Corresponding author. Tel.: +32 16 34 57 41; fax: +32 16 34 59 93.

*E-mail addresses:* [philip.joris@med.kuleuven.be](mailto:philip.joris@med.kuleuven.be) (P.X. Joris), [pascal.michelet@student.kuleuven.be](mailto:pascal.michelet@student.kuleuven.be) (P. Michelet), [tom.franken@student.kuleuven.be](mailto:tom.franken@student.kuleuven.be) (T.P. Franken), [myles.mclaughlin@med.kuleuven.be](mailto:myles.mclaughlin@med.kuleuven.be) (M. Mc Laughlin).

situation seems to arise partly from the difference in emphasis just mentioned. Physiologically, it is important to distinguish three categories of temporal locking: to a waveform's onset, its fine-structure, and its envelope. There is ample evidence that the onset latency of auditory neural responses generally decreases with SPL. The decrease is typically on a millisecond time scale (Kiang et al., 1965; Kitzes et al., 1978), and is therefore large relative to the ITDs to which the binaural system is sensitive. Thus, in circumstances in which the onset response is important, ILD may indeed affect the magnitude of the peripheral neural representation of ITD, henceforth referred to as the "internal ITD" (see below). However, for sustained responses that are temporally locked to sustained stimuli, the effect of SPL is more complex. Early studies of the auditory nerve (AN) already showed that the phase of responses that are phase-locked to the ongoing fine-structure of low-frequency tones is rather stable as a function of intensity when the stimulus frequency equals the fiber's characteristic frequency (CF: frequency of lowest threshold) (Rose et al., 1967). For other frequencies, the extent and direction of the effect of SPL depends on the relationship of the tone's frequency to the fiber's CF, as shown in the classical study of Anderson et al. in the AN of the squirrel monkey (Anderson et al., 1971). For tones away from CF, increasing SPL causes a progressive phase lag (at frequencies below CF) or lead (at frequencies above CF). The relatively simple picture that emerged from the study of Anderson et al. is consistent with measurements of basilar membrane vibration at the cochlear base (reviewed by Robles and Ruggero (2001)) and is generally thought to reflect the compressive nonlinearity of the inner ear (but it should be cautioned that the changes in phase with SPL in low-CF AN fibers of the cat are more complicated: Allen, 1983; van der Heijden and Joris, 2006b). Thus, in response to pure tones, the timing of the response of AN fibers to stimulus onset behaves quantitatively and qualitatively different from the timing of the ongoing response. Similar observations have been made for most cell types in the cochlear nucleus (Kitzes et al., 1978; Lavine, 1971), as well as for ongoing temporal responses to the stimulus envelope (Joris et al., 2004; Møller, 1975).

What is known regarding the interaction of level and time in binaural neurons? While an ILD–ITD interaction is well-established for onset responses of binaural neurons and is relatively straightforward (Hirsch et al., 1985; Irvine et al., 1995, 2001; Park et al., 1996; Pollak, 1988; Yin et al., 1985), the situation is again more complex for ongoing responses. The effect of combinations of ILDs and ITDs on ongoing responses of binaural neurons has been studied both to low-frequency pure tones (Finlayson and Caspary, 1991; Goldberg and Brown, 1969; Joris and Yin, 1995; Kuwada and Yin, 1983; Palmer et al., 2007; Tollin and Yin, 2005; Viète et al., 1997; Yin and Kuwada, 1983; Yin and Chan, 1990) and to high-frequency amplitude-modulated tones (Batra et al., 1993; Joris and Yin, 1995). Clearly, even for sustained stimuli, ILDs and ITDs can

interact at the single neuron level in the sense of jointly affecting the output rate of binaural neurons. In many instances such cue interaction reflects a central mechanism (e.g. inhibition in the LSO) rather than a peripheral level-to-time conversion. We will concern ourselves here only with instances where the main effect of ILD is a phase shift of the low-frequency binaural response (Kuwada and Yin, 1983; Palmer et al., 2007; Viète et al., 1997; Yin and Kuwada, 1983).

In these reports, the binaural phase shifts were indeed interpreted as the reflection of a peripheral level-to-time conversion, but not necessarily of a kind consistent with the "simple" decrease in onset latency with SPL (i.e. as it occurs in the timing of the onset response). It is in fact unclear whether the mechanisms causing "simple" decreases in latency play any role at all in sustained binaural responses. Rather, the binaural shifts observed are reminiscent of the complex change in the cochlear transfer function with SPL already mentioned (Anderson et al., 1971; Robles and Ruggero, 2001). In a large sample of IC neurons (Yin and Kuwada, 1983), about two-thirds of the neurons studied showed binaural phase shifts in a direction opposite to that expected from a simple decrease in latency with SPL, and this seemed to be independent of stimulus frequency. An increasing phase lag with increasing SPL was also the predominant result in binaural neurons of the nucleus laminaris of the barn owl (Viète et al., 1997), but the slope of the phase shift depended on the relationship of frequency to CF and was largely consistent with phase shifts at the peripheral monaural level (Koppl, 1997; Viète et al., 1997), which in turn were similar to the shifts reported in the mammalian AN by Anderson et al. (1971). In contrast, in the IC of the guinea pig, Palmer et al. (2007) found predominantly decreasing phase lags with increasing SPLs (i.e. phase shifts consistent with a decrease in latency with SPL), but in some neurons both decreasing and increasing phase shifts were observed in a frequency-dependent pattern broadly reminiscent of the data of Anderson et al. (1971). In summary, most binaural data to sustained tones show level effects which run counter to the latency hypothesis, but the effects are variable across neurons and across studies.

Our interest and approach differ from previous studies in a number of respects. First, the latency hypothesis proposes a peripheral conversion of intensity to time. It can therefore be tested most directly at a peripheral level. We are mainly interested in effects on fine-structure and therefore choose to study AN fibers with low CF. Second, we studied responses to broadband Gaussian noise, which is a generic stimulus often used in binaural psychophysical studies, rather than to pure tones. As mentioned, previous AN studies with pure tones show a relatively complex pattern of phase changes with SPL (Allen, 1983; Anderson et al., 1971). This makes it difficult to predict the overall effect, across the AN array, of SPL on the timing of responses to tones and particularly to broadband stimuli. To obtain such an overview, we recorded from many AN

fibers to a single, sustained, broadband stimulus presented at different SPLs. Finally, there are various methods to characterize peripheral filtering with broadband stimuli (Carney and Yin, 1988; De Boer and Kuypers, 1968; Evans, 1977; Recio-Spinoso et al., 2005; van der Heijden and Joris, 2006a), which show that this filtering changes with overall level. However, these characterizations are in stimulus space rather than in neural space and their implications regarding the latency hypothesis are not straightforward. We wanted to graphically present the data in a format which is easily compared to findings from psychophysical, physiological, and computational studies. We therefore simply processed the recorded AN spike trains with a physiologically-inspired (Goldberg and Brown, 1969; Yin and Chan, 1990) coincidence analysis to create a “binaural display” as used in computational models (Stern and Trahiotis, 1997).

## 2. Materials and methods

Our general procedures are described in previous reports (Joris, 2003; Louage et al., 2004) and were approved by the K.U.Leuven Ethics Committee for Animal Experiments. Cats were anesthetised with pentobarbital. Micropipettes filled with 3 M NaCl were used to record from single fibers in the AN exposed via a dorsal approach. Calibrated sounds were delivered with a dynamic speaker via an ear-bar placed in the transected ear canal. Spikes were timed at 1  $\mu$ s resolution with a peak-detector. For each fiber encountered, we determined the CF with an automated tuning curve program. A Gaussian pseudorandom white noise stimulus (100 Hz–30 kHz) was delivered at a number of SPLs in two polarities, referred to as standard and inverted, typically with the following parameters: 1000 ms duration, repeated 50 times every 1200 or 1500 ms. Within a dataset, the SPL was constant and responses to the two stimulus polarities were collected one after the other, in random sequence. SPL was usually set to 60 or 70 dB in the first dataset collected, and in subsequent datasets the SPL was varied in arbitrary order chosen by the experimenter. In this report we limit ourselves to CFs < 2500 Hz.

To compare the timing of spikes at different SPLs, we constructed correlograms between spiketrains. The interest here is not the temporal response pattern within a fiber to a single stimulus condition (Joris, 2003; Louage et al., 2004) or across fibers to a single stimulus condition (Joris et al., 2006b), but within a fiber across multiple stimulus conditions, *in casu* SPLs. The procedure is the same as the one to calculate the “cross-stimulus autocorrelogram” (Fig. 3C in Joris, 2003) but with different SPLs taking the place of the different stimuli. Briefly, the timing of every spike in a set of spiketrains to one SPL is compared with all other spikes in a set of spiketrains (from the same fiber) to another SPL. The top spiketrains in Fig. 1 represent responses to a stimulus at a “test” SPL A, and are compared to spiketrains (Fig. 1, bottom) to the same stimulus but at a different “reference” SPL B. The responses at both SPLs

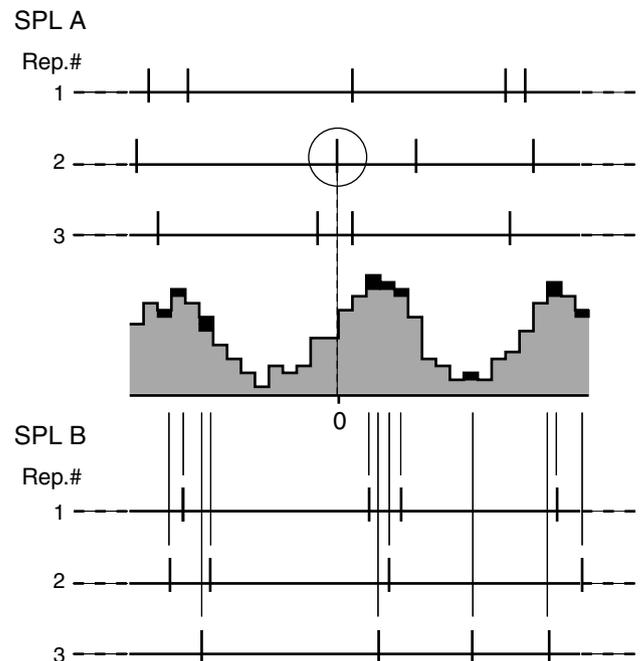


Fig. 1. Construction of correlograms to quantify delays between responses at different SPLs. The spiketrains on top depict the response of a fiber to three repetitions of a stimulus at SPL A. The lower spiketrains are obtained from the same fiber and to the same stimulus, but at SPL B. The timing of all spikes in response to SPL B, is determined relative to a spike selected in response to SPL A, and this is repeated for all spikes at SPL A. For each time interval between the spike in the upper panel and a spike in the lower panel, the histogram is increased by one count in one bin. The bandwidth of the correlogram equals the coincidence window.

show a periodicity and this is reflected as a modulation in the correlogram. In the context of this paper, the correlogram can be viewed as a conditional probability distribution for spikes in response to reference SPL B, given that a spike was discharged (by the same fiber) at time 0 in response to the same stimulus at test SPL A. A time delay in the response of one set of spiketrains relative to the other (e.g. as a consequence of a difference in SPL) causes a corresponding shift of the correlogram. In our convention, a shift towards positive delays indicates a lead of the response to the test SPL A relative to the spike trains in response to the reference SPL B. The main interest here is in crosscorrelograms (comparing responses of one fiber at different SPLs), but we also show some autocorrelograms (comparisons of responses at one SPL with themselves).

The advantage of using correlograms is, among other things (Joris et al., 2006a), that temporal relationships can be studied for responses to a variety of stimuli. For the issue at hand, it has the particular advantage that we can study the temporal relationships in the ongoing response, even for nonperiodic stimuli (like broadband noise) which are abundantly used in binaural psychophysical studies. Moreover, the correlograms provide an intuitive display of the output of a coincidence mechanism, and coincidence mechanisms in the olivary complex are a key feature of binaural interactions (Goldberg and Brown,

1969; Yin and Chan, 1990). Thus, the correlogram approach allows an assessment of the peripheral conversion of ILDs to “internal ITDs”, postulated in the latency hypothesis.

Although we analyze responses from monaural neurons, it is straightforward to view the correlograms from a binaural perspective. Let us assume that there would be two fibers, one in the left and one in the right AN, which would be identical in all their properties, and which would converge with an identical transmission delay on a coincidence detector which discharges only when it receives two spikes within a 50  $\mu$ s time window. If these two fibers would be presented with the same stimulus at the same SPL, the resulting correlogram would have a central peak at zero and would in fact be indistinguishable from an autocorrelogram for either fiber. On the other hand, if an ILD would be present and would cause a time delay of the spikes from one side relative to the other, the outcome would be something like Fig. 1.

The details of the computation of the correlograms can be found in Louage et al. (2004). The number of coincidences was counted in a 50  $\mu$ s window and was normalized for the average firing rate, number of presentations, and stimulus duration. Lack of stimulus-induced temporal structure results in a normalized count of 1. Larger counts indicate correlation; lower counts indicate anticorrelation. There is little doubt that the 50  $\mu$ s coincidence window is physiologically unrealistic: we choose the small value to be conservative (i.e. not to miss temporal structure in the spike trains), and to reveal small shifts in the main peaks of the correlograms. It will be seen that the shifts observed are so small that even a 50  $\mu$ s window results in visible quantization (e.g. Figs. 3–5). Longer windows result in a larger number of coincidences but do not affect the general shape of the correlograms as long as the window remains small relative to the periodicity in the correlogram.

### 3. Results

#### 3.1. Individual examples

Fig. 2 shows correlograms for noise responses at a test SPL of 50 dB and a reference SPL of 70 dB SPL, from a fiber with CF of 625 Hz. When the noise waveforms have the same polarity, the main feature of the correlogram is a large peak near 0 delay (Fig. 2A, solid line). This correlogram is very similar to the shuffled autocorrelograms (Joris, 2003; Louage et al., 2004) calculated from these same responses at 50 and 70 dB (not shown), except that the correlogram calculated here across SPLs is shifted: the maximum of the main peak (circle) is displaced slightly to the left of 0 delay, while shuffled autocorrelograms peak at 0 delay (see below, Figs. 3–5). This indicates that the response at 70 dB (the reference SPL) leads that at 50 dB by a fraction of a ms. Superimposed is the correlogram between anticorrelated noise tokens at 50 and 70 dB (Fig. 2A: thin line). This correlogram is anti-phasic with

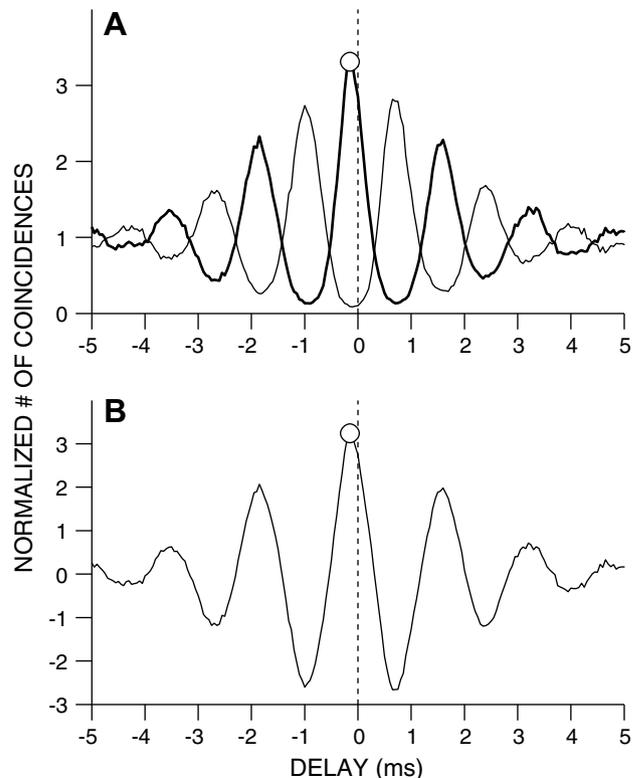


Fig. 2. Example of correlograms between noise responses at two SPLs (50|70) of one fiber. A: correlogram to noise waveforms of the same (thick line) or opposite (thin line) polarity. B: subtraction of the two correlograms in A yields the difcor. The circle indicates the delay between the spiketrains, at which the maximum number of coincidences occurs (here at  $-150 \mu$ s). CF was 625 Hz, SR 68 spikes/sec.

the other one, and has a central trough which is also slightly displaced from delay 0, toward negative delays. Subtraction of the latter correlogram from the former results in the “difcor” (Fig. 2B) which oscillates around a baseline of 0 coincidences and shows less rectification than the constituent correlograms. In the remainder of the analysis we will use difcors, but this is not critical to our conclusions. Note that, for difcors, a value of 0 indicates a lack of correlation between the spiketrains.

For each fiber a number of correlograms between different SPLs were calculated. The data for the same fiber as in Fig. 2 are shown in Fig. 3 for a reference SPL of 70 dB. Here, the difcors are stacked on a false y-axis: the intersection of the 0 count level with this false ordinate indicates the test SPL. For example, the second correlogram from the bottom is the difcor calculated from responses to noise at 50 dB compared to responses from the same fiber at 70 dB, also shown in Fig. 2B. We label this comparison “50|70”. The other difcors are for the 40|70, 60|70, 70|70, and 90|70 comparisons. The only “special” condition is 70|70 (thick line). The difcor at 70|70 is obtained from autocorrelograms (Joris, 2003; Louage et al., 2004) and peaks at 0 delay. The accompanying scale gives the true ordinate and maximum of the 70|70 condition, and applies to the other correlograms as well.

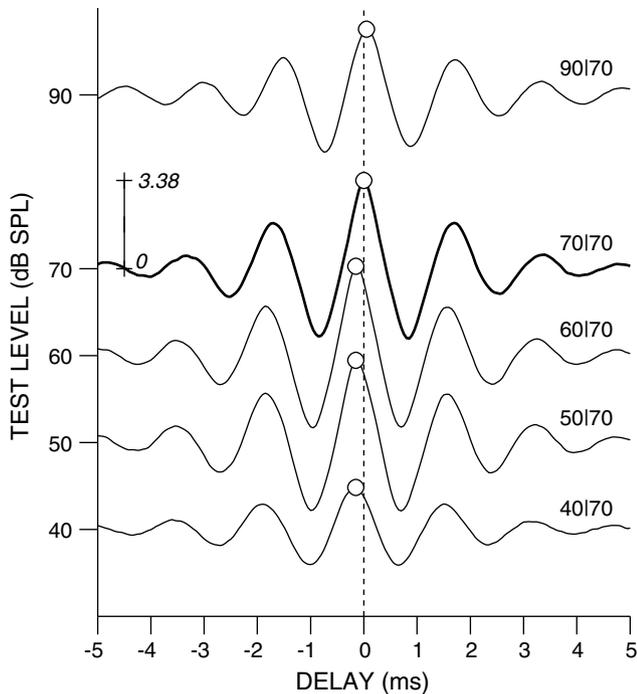


Fig. 3. A stack of difcors between responses at five different SPLs for one fiber, using the response at 70 dB as the reference. The correlograms are ordered for increasing test SPL (bottom to top), which is indicated on the y-axis. All correlograms have the same scale, which is indicated with the vertical line near the left of the 70|70 correlogram. The height of the scale bar (3.38) equals the maximum normalized number of coincidences for the 70|70 condition. A horizontal line of 0 coincidences indicates lack of correlation and intersects the y-axis at the test SPL value. Same fiber as Fig. 2: the difcor at 50|70 dB is the same as in Fig. 2B.

For the example of Fig. 3 all correlograms are rather similar, indicating that the temporal locking of the spike train to the local vibration of the basilar membrane is very similar across SPLs. The main feature of interest is the small shift of the correlogram on the delay axis. We quantify this shift by measuring the shift of the main peak, not only for simplicity but also for equivalence to the measure most frequently used on actual binaural responses (the best delay, e.g. Brand et al., 2002; Hancock and Delgutte, 2004; Joris et al., 2006b; McAlpine et al., 2001; Yin et al., 1986). For the correlogram stack in Fig. 3 the peak delays are  $-150$ ,  $-150$ ,  $-150$ ,  $0$ , and  $50$   $\mu$ s (bottom to top). These delays predict the “internal delays” that would be caused by ILDs of  $-20$ ,  $-10$ ,  $0$ , and  $10$  dB solely through cochlear conversion of level to time. Note that the sign of the ILD is arbitrary because these are in fact monaural responses.

More examples are shown in Fig. 4 for fibers with low spontaneous rate (low-SR,  $<18$  spikes/s, top row) and high-SR fibers ( $>18$  spikes/s, bottom row), at CFs spaced roughly an octave apart. The most striking finding is the similarity of the correlograms within fibers. Horizontal shifts are present but are small compared to the millisecond shifts in neural timing of onset responses (Irvine et al., 2001; Kitzes et al., 1978). In fact it is difficult to see the

effects on peak delay at the scale of Fig. 4. At the lowest CFs (left column), the peaks of the correlograms are shifted to the left (negative delays) for test levels  $<70$  dB (ILDs  $<0$ ), and to the right (positive delays) for test levels  $>70$  dB (ILDs  $>0$ ). This is in line with the latency hypothesis: raising SPL shifts the responses earlier in time. The same applies to the lower correlograms in the middle and right columns (test levels  $<70$  dB), which show small (or no) shifts toward negative delays. Unexpectedly, the top correlograms (test levels  $>70$  dB) in panels C, D, F also show shifts toward negative delays. Thus, relative to the response at 70 dB, the response at these higher SPLs is delayed, which runs counter to the latency hypothesis.

Although not the subject of this paper, there are several other interesting features in these correlograms besides the delays of the main peak. The correlograms are more oscillatory and often markedly asymmetric for the lower correlograms in each panel. For example, the lower correlograms in Fig. 4E and F (50|70 condition) are clearly more damped at positive than at negative delays. These features are consistent with sharper frequency selectivity at low SPLs. Correlograms of the two SR groups showed the general differences reported earlier (Louage et al., 2004) but did not differ with respect to the timing across SPLs, and are therefore not separately analysed in the remainder of this paper.

### 3.2. Population data

To zoom in on the most relevant range of delays and to provide an overview of the AN, we constructed population waterfall plots for different ILD conditions (Fig. 5). For example, Fig. 5A shows the central region ( $\pm 500$   $\mu$ s) of all available difcors for the 50|70 condition. The difcors are vertically arranged according to increasing CF. The circles are placed at the maxima of the correlograms. The curved dashed lines trace positive and negative delays at half the characteristic period (i.e. the inverse of the characteristic frequency,  $CF^{-1}$ ). The relevance of these “ $\pi$ -lines” is that in binaural neurons best delays are largely confined to values smaller than the so called  $\pi$ -limit or  $\pi$ -boundary (Hancock and Delgutte, 2004; Joris et al., 2006b; McAlpine et al., 1996, 2001). When there is no SPL difference (Fig. 5C), virtually all correlograms peak at a delay of 0 ms, as expected for autocorrelograms, showing the accuracy of the technique. The troughs flanking the central peaks coincide with the  $\pi$ -lines. This is entirely as expected, since the periodicity in autocorrelograms agrees well with the characteristic period (Louage et al., 2004) and the vertical placement of the correlograms in Fig. 5 is according to CF.

For SPLs lower than the reference SPL of 70 dB (Fig. 5A,B, negative ILDs), shifts towards negative delays occur, and the degree of shift decreases with increasing CF. Even the largest delays ( $-200$   $\mu$ s) are remarkable small. The direction of the delay is consistent with the latency hypothesis: the response at the higher SPL leads

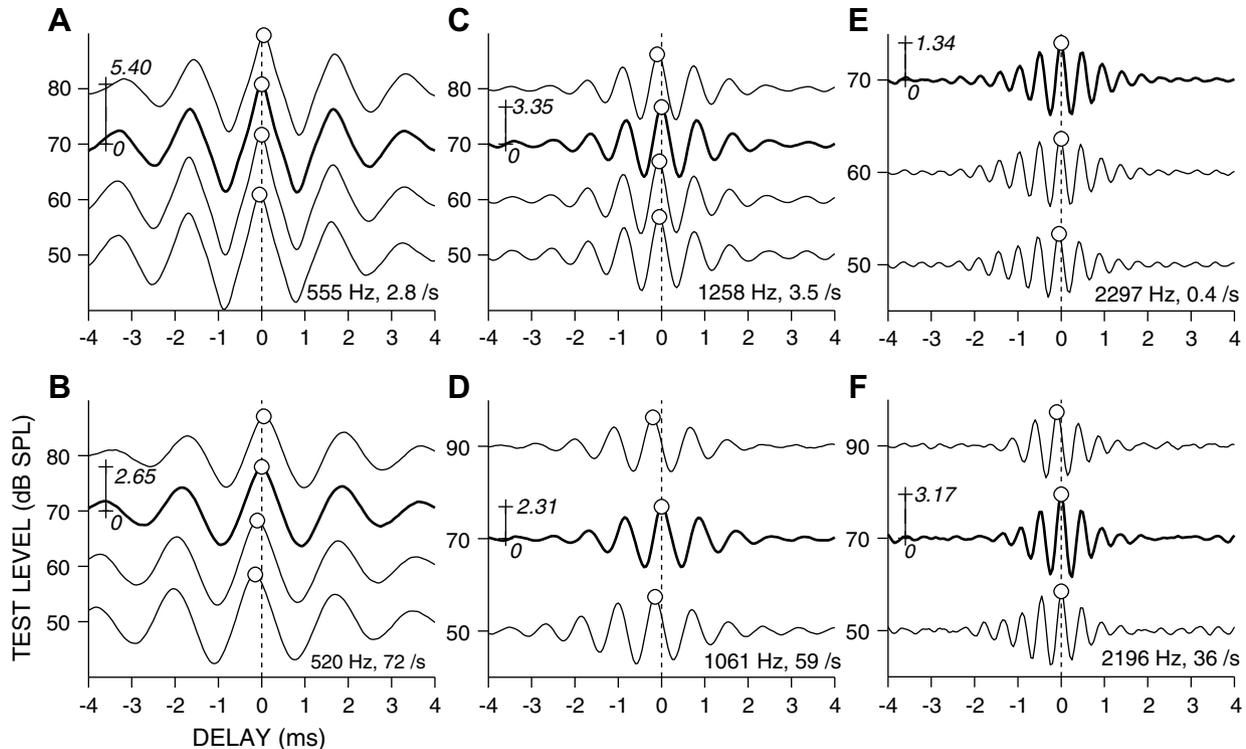


Fig. 4. Additional examples of difcors at different SPLs for 6 fibers. CF and SR are indicated in each panel. CF increases from left to right columns; top row shows results for low-SR fibers, bottom row for high-SR fibers. Conventions as in Fig. 3. Axis labels of panel B apply to all other panels.

in time. For SPLs higher than the reference SPL of 70 dB (Fig. 5D and E, positive ILDs) a more complex picture emerges, particularly so in the 90|70 condition. For CFs below approximately 750 Hz, the peaks shift towards positive delays of several hundred  $\mu$ s. Unexpectedly, for CFs above 1 kHz, the peaks shift toward negative delays of about  $-50$  to  $-100$   $\mu$ s. The latter shift is in a direction opposite to the latency hypothesis: the response at the higher SPL lags in time.

There are two ways to view the correlograms in the previous figures. They can be viewed as the output of a single, simple coincidence detector in response to external ITDs. Viewed this way, the shifts in the peak of the correlograms indicate how the ITD-curve of one coincidence detector would be affected by ILD, and in particular how the ILD can create an “internal delay”. Alternatively, the correlograms can be viewed as a binaural display akin to the so-called tau-frequency plane of binaural computational models (Breebaart et al., 2001; Colburn, 1996; Stern et al., 1988): the surface of this two-dimensional display gives the output of binaural neurons at different CFs and different internal delays. Viewed this way, the peaks indicate the binaural neurons that would be maximally responsive to a broadband noise which has an ITD = 0 and an ILD as indicated. Clearly, the presence of an ILD gives a pattern that is very different from the pattern caused by an external ITD. If the presence of an ILD  $\neq$  0 would be completely equivalent to a single external ITD  $\neq$  0 via a peripheral time-intensity trade, the correlograms in Fig. 5A, B, D,

E would be horizontally shifted versions of the correlogram of Fig. 5C (obtained for ILD = 0). For example, if an ILD of 10 dB would cause a consistent 100  $\mu$ s delay at all CFs, Fig. 4D would be similar to Fig. 4C but shifted rightward by 100  $\mu$ s. Such simple translational shifts were not observed.

#### 4. Discussion

Using a coincidence analysis, we examined the timing relationships between AN spike trains obtained in response to broadband noise at different SPLs. The most striking finding is that the temporal patterns are remarkably insensitive to SPL, with the vast majority of shifts restricted to 200  $\mu$ s or less (over the range studied of  $\pm 20$  dB relative to 70 dB). A given difference in SPL does not translate to a fixed difference in spike timing across CFs, but rather reveals a CF-dependent pattern. Interestingly, the time shifts are largest at frequencies where natural ILDs are smallest and close to zero except for nearby sources (Brunsgart and Rabinowitz, 1999).

While the effects of SPL on ongoing timing are small relative to the effects on onset timing (Irvine et al., 2001; Kiang et al., 1965; Kitzes et al., 1978) – by about an order of magnitude – the implications regarding human binaural hearing and time-intensity trading are not entirely clear. The data contradict a simple latency mechanism *à la* Jeffress, in that a single ILD does not generate a shift in the binaural display that is equivalent to a single ITD

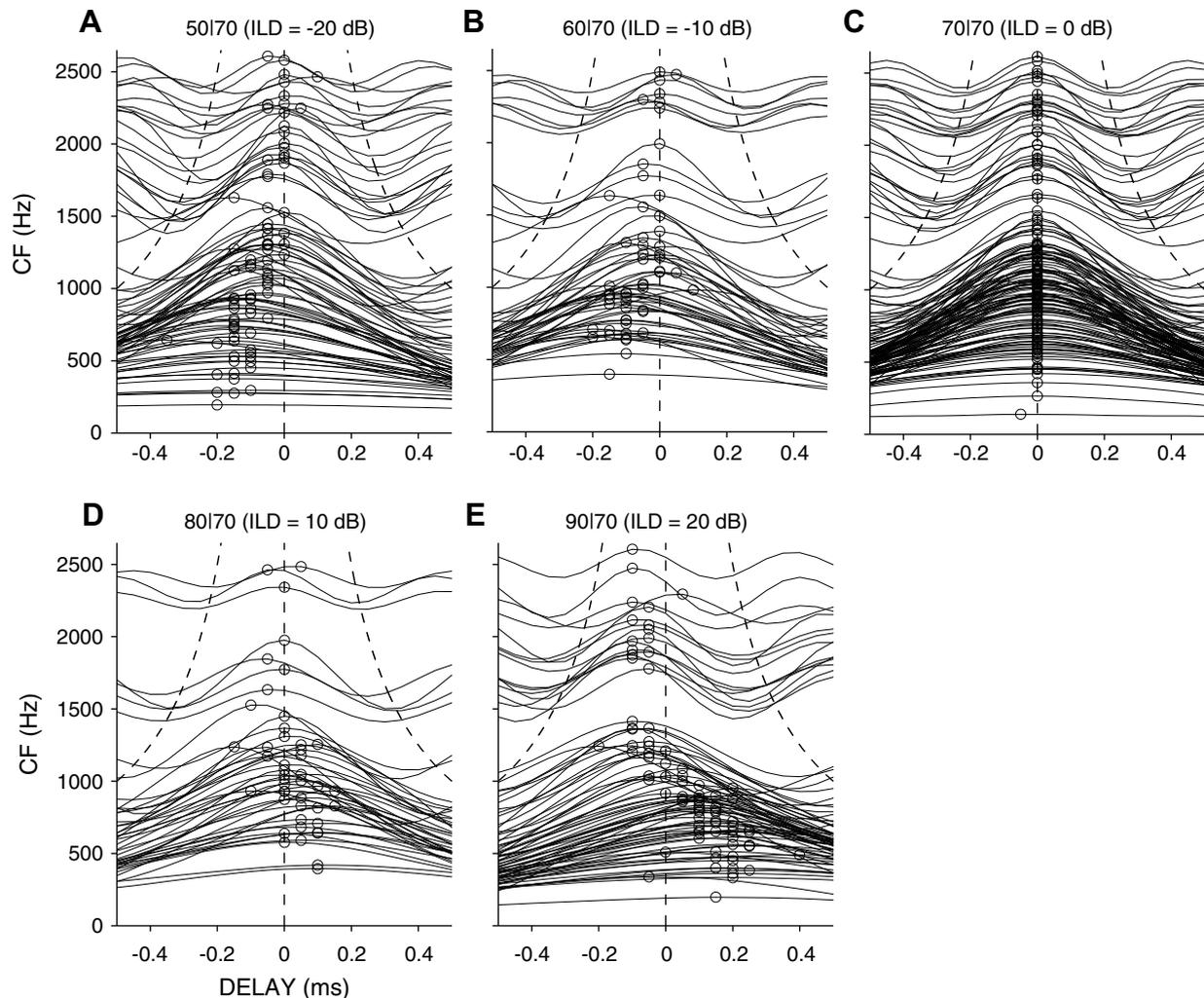


Fig. 5. Waterfall plots for different ILD conditions across a population of nerve fibers. Each panel shows the central portion of all available difcors at that ILD condition, positioned on the  $y$ -axis according to CF. For each difcor, a horizontal line of 0 coincidences would intersect the  $y$ -axis at the fiber's CF. The hyperbolic lines (dashed) indicate delays corresponding to half the characteristic period or  $(2CF)^{-1}$ .

(Fig. 5). This is also the conclusion of psychophysical studies (Domnitz, 1973; Domnitz and Colburn, 1977; Green, 1976; Hafter and Carrier, 1972; Trahiotis and Kappauf, 1978). However, even if the perception of ILDs at low frequencies can not be explained entirely by a peripheral conversion to a temporal cue, this does not imply that such a conversion does not play any role at all. Human sensitivity to ITDs is so acute that it can not be excluded that, at very low frequencies, even tiny effects of SPL on timing contribute to the perception of ILDs. The largest temporal shifts we measured physiologically are on the order of 100  $\mu$ s/10 dB (Fig. 5). We have not tested small SPL differences but there is no reason to doubt that this trading ratio can be interpolated to approximately 10  $\mu$ s/dB. Trading ratios measured psychophysically to low-frequency pure tones and low-pass clicks are extremely variable across studies and stimuli (a range of 1–300  $\mu$ s/dB is quoted by Durlach and Colburn (1978)) but are mostly in the range of 20–40  $\mu$ s/dB for low-pass clicks. However small, the shifts found here in the AN are systematic and are a significant

fraction of the effects measured behaviorally, and therefore the possibility that low-frequency ILDs affect the binaural percept via a peripheral level-to-time conversion cannot be excluded.

As always, these comparisons between physiology and perception are fraught with difficulties, not only of differences in species but also in stimuli: our physiological measures in cats are to sustained broadband noise, while the behavioral measures in humans are to tones and filtered clicks (we are not aware of psychophysical measurements of trading ratios to noise). Moreover, neither the psychophysical literature nor the physiological literature provide a consistent picture. Despite all these reservations, the interaction between ILDs and ITDs at low frequencies is an interesting phenomenon which needs a physiological explanation.

As mentioned higher, binaural recordings have shown interaction of ITD and ILD cues at the single neuron level (see INTRODUCTION for references). We are not aware of such data for responses to broadband noise,

except in the barn owl. (Viete et al., 1997) studied the effects of ILDs on ITD-sensitivity of neurons in the nucleus laminaris over a range of about  $-30$  to  $+40$  dB and for CFs between about 4.5 and 7.5 kHz. They found a shift on average of only  $0.71 \mu\text{s}/\text{dB}$  (also a phase advantage for the more intense ear). Trading ratios reported for binaural neurons in the mammalian MSO are  $8 \mu\text{s}/\text{dB}$  (Crow et al., 1978) and  $0.0016 \text{ cycle}/\text{dB}$  (Yin and Chan, 1990), and  $5.82 \mu\text{s}/\text{dB}$  in the IC (Kuwada and Yin, 1983; Yin and Kuwada, 1983), but the sign of these ratios is commonly opposed to that in humans (see INTRODUCTION).

We have not explored the mechanisms underlying the temporal shifts. Most likely the main determinant of the shift of the correlograms with SPL is the changing cochlear filter at the site of innervation. Basilar membrane and AN measurements to tones at different SPLs show a phase transfer function which pivots around CF, with maximal shifts of about a quarter of a cycle (Anderson et al., 1971; Robles and Ruggero, 2001). These characterizations actually predict that not the fine-structure, but rather the envelope of the correlograms should shift with SPL. The maximal shifts in fine-structure observed here are rarely larger than 0.1 cycle. Qualitative examination of the correlograms in Figs. 3 and 4, as well as a preliminary envelope analysis, suggest that shifts of the correlogram envelopes are also modest and of a magnitude similar to the shifts in fine-structure. The characterizations mentioned above (Anderson et al., 1971; Robles and Ruggero, 2001) therefore do not fit the responses of fibers innervating the apex of the cat cochlea, and this is corroborated by more direct estimates of filters at different SPLs (Allen, 1983; van der Heijden and Joris, 2006b). Interestingly, mechanical measurements in the cochlear base show a phase lag across frequencies at high SPLs (Ruggero et al., 1997): the “paradoxical” shift at high SPLs in our AN data (Fig. 5E) suggests that a similar phenomenon occurs at the cochlear apex.

We have examined the temporal relationships between spike trains obtained at different SPLs within single AN fibers. It is conceivable that low-frequency ILDs have larger effects on timing relationships between neurons of differing CF. Small differences in CF can have large effects on temporal correlation patterns (Bonham and Lewis, 1999; Joris et al., 2006b; Shamma, 1989), and we have preliminary evidence that such differences are present in the binaural system of cat and monkey (Joris and van der Heijden, 2007). Moreover, the characterization of changes in temporal coding with SPL is not only important in a binaural context. Carney and colleagues have argued that changes in temporal patterns with SPL across AN fibers may also be important in monaural hearing (Carney, 1994; Colburn et al., 2003; Heinz et al., 2001; Shamma, 1985). Examination of correlograms across fibers and SPLs (for an example see Fig. 10 in Joris et al., 2006a) would clarify the importance of peripheral level-to-time conversion from a wider perspective.

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## References

- Allen, J.B., 1983. Magnitude and phase-frequency response to single tones in the auditory nerve. *J. Acoust. Soc. Am.* 73, 2071–2092.
- Anderson, D.J., Rose, J.E., Hind, J.E., Brugge, J.F., 1971. Temporal position of discharges in single auditory nerve fibers within the cycle of a Sine-wave stimulus: frequency and intensity effects. *J. Acoust. Soc. Am.* 49, 1131–1139.
- Batra, R., Kuwada, S., Stanford, T.R., 1993. High-frequency neurons in the inferior colliculus that are sensitive to interaural delays of amplitude-modulated tones: evidence for dual binaural influences. *J. Neurophysiol.* 70, 64–80.
- Bonham, B.H., Lewis, E.R., 1999. Localization by interaural time difference (ITD): effects of interaural frequency mismatch. *J. Acoust. Soc. Am.* 106, 281–290.
- Brand, A., Behrend, O., Marquardt, T., McAlpine, D., Grothe, B., 2002. Precise inhibition is essential for microsecond interaural time difference coding. *Nature* 417, 543–547.
- Breebaart, J., van de Par, S., Kohlrausch, A., 2001. Binaural processing model based on contralateral inhibition. I. Model structure. *J. Acoust. Soc. Am.* 110, 1074–1088.
- Brungart, D.S., Rabinowitz, W.M., 1999. Auditory localization of nearby sources. Head-related transfer functions. *J. Acoust. Soc. Am.* 106, 1465–1479.
- Carney, L.H.C., 1994. Spatiotemporal encoding of sound level: models for normal encoding and recruitment of loudness. *Hear. Res.* 76, 31–44.
- Carney, L.H.C., Yin, T.C.T., 1988. Temporal coding of resonances by low-frequency auditory nerve fibers: single-fiber responses and a population model. *J. Neurophysiol.* 60, 1653–1677.
- Colburn, H.S., 1996. Computational models of binaural processing. In: Hawkins, H., McMullen, T. (Eds.), *Auditory Computation*. Springer, NY, pp. 332–400.
- Colburn, H.S., Carney, L.H., Heinz, M.G., 2003. Quantifying the information in the auditory-nerve responses for level discrimination. *JARO* 4, 294–311.
- Crow, G., Rupert, A.L., Moushegian, G., 1978. Phase locking in monaural and binaural medullary neurons: implications for binaural phenomena. *J. Acoust. Soc. Am.* 64, 493–501.
- De Boer, E., Kuyper, P., 1968. Triggered correlation. *IEEE Trans. Bio-Med. Eng.* 15, 169–179.
- Domnitz, R., 1973. The interaural time jnd as a simultaneous function of interaural time and interaural amplitude. *J. Acoust. Soc. Am.* 53, 1549–1552.
- Domnitz, R.H., Colburn, H.S., 1977. Lateral position and interaural discrimination. *J. Acoust. Soc. Am.* 61, 1586–1598.
- Durlach, N.I., Colburn, H.S., 1978. Binaural phenomena. In: Carterette, E., Friedman, M. (Eds.), *Handbook of Perception*, fourth ed. Academic Press, NY, pp. 365–465.
- Eggermont, J.J., 1976. Electrocochleography. In: Keidel, W.D., Neff, W.D. (Eds.), *Handbook of sensory physiology*, Vol. Auditory System. Springer, Berlin, pp. 625–705.
- Evans, E.F., 1977. Frequency selectivity at high signal levels of single units in cochlear nerve and nucleus. In: Evans, E.F., Wilson, J.P. (Eds.), *Psychophysics and Physiology of Hearing*. Academic, London, UK, pp. 185–192.

- Finlayson, P.G., Caspary, D.M., 1991. Low-frequency neurons in the lateral superior olive exhibit phase-sensitive binaural inhibition. *J. Neurophysiol.* 65, 598–605.
- Goldberg, J.M., Brown, P.B., 1969. Response of binaural neurons of dog superior olivary complex to dichotic tonal stimuli: some physiological mechanisms of sound localization. *J. Neurophysiol.* 22, 613–636.
- Green, D.M., 1976. *An Introduction to Hearing*. Lawrence Erlbaum Associates, NY.
- Green, D.M., Henning, G.B., 1969. Audition. *Ann. Rev. Psychol.* 20, 105–128.
- Hafer, E.R., Carrier, S.C., 1972. Binaural interaction in low-frequency stimuli: the inability to trade time and intensity completely. *J. Acoust. Soc. Am.* 51, 1852–1862.
- Hancock, K.E., Delgutte, B., 2004. A physiologically based model of interaural time difference discrimination. *J. Neurosci.* 24, 7110–7117.
- Heinz, M.G., Colburn, H.S., Carney, L.H.C., 2001. Rate and timing cues associated with the cochlear amplifier: level discrimination based on monaural cross-frequency coincidence detection. *J. Acoust. Soc. Am.* 110, 2065–2084.
- Hirsch, J.A., Chan, J.K., Yin, T.C.T., 1985. Responses of neurons in the Cat's superior colliculus to acoustic stimuli. I. Monaural and binaural response properties. *J. Neurophysiol.* 53, 726–745.
- Irvine, D.R., Park, V.N., Mattingley, J.B., 1995. Responses of neurons in the inferior colliculus of the rat to interaural time and intensity differences in transient stimuli: implications for the latency hypothesis. *Hear. Res.* 85, 127–141.
- Irvine, D.R., Park, V.N., McCormick, L., 2001. Mechanisms underlying the sensitivity of neurons in the lateral superior olive to interaural intensity differences. *J. Neurophysiol.* 86, 2647–2666.
- Jeffress, L.A., 1948. A place theory of sound localization. *J. Comp. Physiol. Psychol.* 41, 35–39.
- Joris, P.X., 2003. Interaural time sensitivity dominated by cochlea-induced envelope patterns. *J. Neurosci.* 23, 6345–6350.
- Joris, P.X., Yin, T.C.T., 1995. Envelope coding in the lateral superior olive. I. Sensitivity to interaural time differences. *J. Neurophysiol.* 73, 1043–1062.
- Joris, P.X., van der Heijden, M., 2007. Binaural responses match the cross-correlation of monaural inputs. *Assoc. Res. Otolaryngol. Abstr.* 30, 213.
- Joris, P.X., Schreiner, C.E., Rees, A., 2004. Neural processing of amplitude-modulated sounds. *Physiol. Rev.* 84, 541–577.
- Joris, P.X., Louage, D.H., Cardoen, L., van der Heijden, M., 2006a. Correlation index: a new metric to quantify temporal coding. *Hear. Res.*, 19–30.
- Joris, P.X., van de Sande, B., Louage, D.H., van der Heijden, M., 2006b. Binaural and cochlear disparities. *Proc. Natl. Acad. Sci. USA* 103, 12917–12922.
- Kiang, N.Y.S., Watanabe, T., Thomas, E.C., Clark, L.F. 1965. Discharge patterns of single fibers in the cat's auditory nerve. 35th ed. Research Monograph, No. 35, MIT Press, Cambridge.
- Kitzes, L.M., Gibson, M.M., Rose, J.E., Hind, J.E., 1978. Initial discharge latency and threshold considerations for some neurons in cochlear nuclear complex of the Cat. *J. Neurophysiol.* 41, 1165–1182.
- Koppl, C., 1997. Phase locking to high frequencies in the auditory nerve and cochlear nucleus magnocellularis of the barn owl, *Tyto alba*. *J. Neurosci.* 17, 3312–3321.
- Kuwada, S., Yin, T.C.T., 1983. Binaural interaction in low-frequency neurons in inferior colliculus of the Cat. I. Effects of long interaural delays, intensity, and repetition rate on interaural delay function. *J. Neurophysiol.* 50, 981–999.
- Lavine, R.A., 1971. Phase-locking in response of single neurons in cochlear nuclear complex of the cat to low-frequency tonal stimuli. *J. Neurophysiol.* 24, 467–483.
- Louage, D.H., van der Heijden, M., Joris, P.X., 2004. Temporal properties of responses to broadband noise in the auditory nerve. *J. Neurophysiol.* 91, 2051–2065.
- McAlpine, D., Jiang, D., Palmer, A., 1996. Interaural delay sensitivity and the classification of low best-frequency binaural responses in the inferior colliculus of the guinea pig. *Hear. Res.* 97, 136–152.
- McAlpine, D., Jiang, D., Palmer, A., 2001. A neural code for low-frequency sound localization in mammals. *Nat. Neurosci.* 4, 396–401.
- Møller, A.R., 1975. Latency of unit responses in cochlear nucleus determined in two different ways. *J. Neurophysiol.* 38, 812–821.
- Moushegian, G., Jeffress, L.A., 1959. Role of interaural time and intensity differences in the lateralization of low-frequency tones. *J. Acoust. Soc. Am.* 31, 1441–1445.
- Palmer, A.R., Liu, L., Shackleton, T.M., 2007. Changes in interaural time sensitivity with interaural level differences in the inferior colliculus. *Hear. Res.* 223, 105–113.
- Park, T.J., Grothe, B., Pollak, G.D., Schuller, G., Koch, U., 1996. Neural delays shape selectivity to interaural intensity differences in the lateral superior olive. *J. Neurosci.* 16, 6554–6566.
- Pollak, G.D., 1988. Time is traded for intensity in the bat's auditory system. *Hear. Res.* 36, 107–124.
- Recio-Spinoso, A., Temchin, A.N., van Dijk, P., Fan, Y.H., Ruggero, M.A., 2005. Wiener-kernel analysis of responses to noise of chinchilla auditory-nerve fibers. *J. Neurophysiol.* 93, 3615–3634.
- Robles, L., Ruggero, M.A., 2001. Mechanics of the mammalian cochlea. *Physiol. Rev.* 81, 1305–1352.
- Rose, J.E., Brugge, J.F., Anderson, D.J., Hind, J.E., 1967. Phase-locked response to low-frequency tones in single auditory nerve fibers of the squirrel monkey. *J. Neurophysiol.* 30, 769–793.
- Ruggero, M.A., Rich, N.C., Recio, A., Narayan, S.S., Robles, L., 1997. Basilar-membrane responses to tones at the base of the chinchilla cochlea. *J. Acoust. Soc. Am.* 101, 2151–2163.
- Shamma, S.A., 1985. Speech processing in the auditory system II: lateral inhibition and the central processing of speech evoked activity in the auditory nerve. *J. Acoust. Soc. Am.* 78, 1622–1632.
- Shamma, S.A., 1989. Stereausis: binaural processing without neural delays. *J. Acoust. Soc. Am.* 86, 989–1006.
- Stern, R.M., Trahiotis, C., 1997. Models of binaural perception. In: Gilkey, R., Anderson, T. (Eds.), *Binaural and Spatial Hearing in Real and Virtual Environments*. Lawrence Erlbaum Associates, Mahwah, NJ, pp. 499–531.
- Stern, R.M., Zeiberg, A.S., Trahiotis, C., 1988. Lateralization of complex binaural stimuli: A weighted-image model. *J. Acoust. Soc. Am.* 84, 156–165.
- Tollin, D.J., Yin, T.C., 2005. Interaural phase and level difference sensitivity in low-frequency neurons in the lateral superior olive. *J. Neurosci.* 25, 10648–10657.
- Trahiotis, C., Kappauf, W.E., 1978. Regression interpretation of differences in time-intensity trading ratios obtained in studies of laterality using the method of adjustment. *J. Acoust. Soc. Am.* 64, 1041–1047.
- van der Heijden, M., Joris, P.X., 2006a. Panoramic measurements of the apex of the cochlea. *J. Neurosci.* 26, 11462–11473.
- van der Heijden, M., Joris, P.X., 2006b. Effects of stimulus intensity on phase and amplitude characteristics of auditory nerve fibers. *Assoc. Res. Otolaryngol. Abstr.* 29, 28–29.
- Viete, S., Pena, J.L., Konishi, M., 1997. Effects of interaural intensity difference on the processing of interaural time difference in the owl's nucleus laminaris. *J. Neurosci.* 17, 1815–1824.
- Yin, T.C., Hirsch, J.A., Chan, J.C., 1985. Responses of neurons in the cat's superior colliculus to acoustic stimuli. II. A model of interaural intensity sensitivity. *J. Neurophysiol.* 53, 746–758.
- Yin, T.C.T., Kuwada, S., 1983. Binaural interaction in low-frequency neurons in inferior colliculus of the cat. II. Effects of changing rate and direction of interaural phase. *J. Neurophysiol.* 50, 1000–1018.
- Yin, T.C.T., Chan, J.K., 1990. Interaural time sensitivity in medial superior olive of cat. *J. Neurophysiol.* 64, 465–488.
- Yin, T.C.T., Chan, J.K., Irvine, D.R.F., 1986. Effects of interaural time delays of noise stimuli on low-frequency cells in the cat's inferior colliculus. I. Responses to wideband noise. *J. Neurophysiol.* 55, 280–300.