Title: Level dependent latency shifts quantified through binaural processing

Abbreviated title: Level-dependent latency shifts

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Abstract

The mammalian binaural system compares the timing of monaural inputs with microsecond precision. This temporal precision is required for localizing sounds in azimuth. However, temporal features of the monaural inputs, in particular their latencies, highly depend on the overall sound level. In a combined psychophysical, electrophysiological and modeling approach, we investigate how level-dependent latency shifts of the monaural responses are reflected in the perception and neural representation of interaural time differences. We exploit the sensitivity of the binaural system to the timing of high-frequency stimuli with binaurally incongruent envelopes. Using these novel stimuli, both the perceptually adjusted interaural time differences and the time differences extracted from electrophysiological recordings systematically depend on overall sound pressure level. The perceptual and electrophysiological time differences of the envelopes can be explained in an existing model of temporal integration only if a level-dependent firing threshold is added. Such an adjustment of firing threshold provides a temporally accurate neural code of the temporal structure of a stimulus and its binaural disparities independent of overall sound level.

Introduction

Precise temporal coding is the hallmark of the auditory system. Like no other sensory modality, the auditory system relies on the neural analysis of spike timing for both object localization and identification. At the same time, the peripheral auditory system has to cope with a huge variability in the loudness of sounds; the dynamic range of natural acoustic input spans at least five orders of magnitude. Several electrophysiological studies have shown that the processing of temporal features highly depends on the overall sound level (Joris and Yin 1992; Heil and Irvine 1997; Heil 1998; Wallace et al. 2002; Tollin and Yin 2005; Palmer and Shackleton 2009). Recent studies on temporal integration of sounds have revealed that neural
first-spike latency in the auditory nerve can be explained by the temporal integration of the stimulus pressure envelope (Heil and Neubauer 2003). With increasing sound level, the pressure-envelope amplitude increases and consequently, a shorter integration time is needed to exceed spiking threshold, i.e., the spiking latency decreases. It is unclear, however, whether this pressure-envelope integration is a sufficient descriptor for ongoing inputs to the binaural system at moderate or high sound levels.

In the binaural system, extraordinary temporal precision is required for the neural coincidence detection that underlies our capability to localize sounds in azimuth (Sandel et al. 1955). Experiments have demonstrated that neural tuning to interaural time differences (ITDs) in the medial superior olive is stable against changes of overall sound level and this level invariance is further stabilized at higher stages of the auditory system (Goldberg and Brown 1968; Pena et al. 1996; Cook et al. 2003; Pecka et al. 2010). Also psychophysically, it has been shown that sensitivity to ITDs is stable across a wide range of stimulus levels (Blauert 1997; Dreyer and Oxenham 2008). It has been proposed that level-dependent latency shifts may contribute to the processing of interaural intensity differences (IIDs, ‘latency hypothesis’), (Yin et al. 1985; Hirsch et al. 1985; Pollak 1988; Irvine et al. 1995; Joris and Yin 1995; Park et al. 1996; Park et al. 1997; Grothe and Park 2000; Irvine et al. 2001). However, level-dependent latency shifts should not interfere with binaural analysis as long as both monaural inputs are affected equally. The neural processing underlying this level-invariant encoding of temporal stimulus properties is still poorly understood, in particular since even phase locking, as a basic measure of precise temporal coding, is sensitive to changes in overall sound level in the auditory nerve (Joris et al. 2004). Such level dependence is also seen in the temporal encoding of the envelopes of high-frequency tones (Dreyer and Delgutte 2006).

In this study, we take advantage of the binaural system’s exquisite temporal sensitivity to quantify the temporal integration and the resulting perceptual and spike latency preceding binaural processing in the auditory brainstem. We exploit recent findings that interaural
envelope ITDs (eITDs) of high-frequency tones are binaurally analyzed with a precision similar to that of low-frequency tones (Bernstein and Trahiotis 2002). Physiological data obtained from the auditory midbrain support these psychophysical findings (Griffin et al. 2005). Interestingly, the envelopes of high-frequency tones can be manipulated in ways that the fine structure of low-frequency tones cannot: At high frequencies, stimuli can be constructed which carry different binaural temporal properties although they occupy the same frequency region in the two ears. We manipulated the envelope properties of high-frequency stimuli by changing the rise and fall times of the envelope and presented these stimuli at different sound levels. The experimental paradigm is illustrated in Fig. 1, which shows qualitatively how changes in the rise time and in the sound level of tone pips lead to shifts in latency. With increasing sound level, the latency difference induced by the difference in rise time converges to zero (cf. Fig. 1C). Using these new stimuli in a binaural experimental paradigm, we have directly quantified level-dependent latency shifts both psychophysically and electrophysiologically. The psychophysical and electrophysiological data show that even at the highest sound levels tested, the rise-time differences between the pips in the left and right ear are reflected in the eITDs. This result is inconsistent with current models of neural latency, even when cochlear compressive non-linearity is taken into account. This limitation can only be overcome by a level-dependent adjustment of firing threshold. Thus, in line with previous modeling- and in-vitro studies in birds (Kuba et al. 2002; Cook et al. 2003; Dasika et al. 2005; Kuznetsova et al. 2008), the current results indicate the importance of neural adaptation preceding binaural processing. Preliminary data of this study were presented at the 15th International Symposium in Hearing, Salamanca, Spain.
Methods

Rationale

The stimuli in this study were trains of tone pips. The pips consist of a high-frequency pure-tone carrier modulated with temporally asymmetric envelopes. If such a pip train is presented binaurally but temporally reversed in one ear, as illustrated in Fig. 1, it cannot be physically matched by simple interaural time shifts. Nevertheless, the binaural system can produce a reliable perceptual match that in turn reflects the way the stimulus envelopes are processed preceding binaural analysis. Note that although no physical match can be produced, we refer to the result of the perceptual match as the adjusted eITD. If the system is forced to produce a binaural match, one would expect that the eITD that produces a centralized binaural image does depend on overall sound level: if the sound level is low (solid lines in Fig. 1A), one would expect that the pips in the ear with the steeper rise time (black lines) have to be strongly delayed to compensate for the rise-time difference between the ears (large dT in Fig. 1B). If the sound level is high (dotted lines in Fig. 1A), one would expect that the overall latency decreases because the envelope integral exceeds the firing threshold earlier (Fig. 1B) but again the pips in the ear with the steeper rise time (black lines) have to be somewhat delayed to compensate for the rise-time difference between the ears (small dT in Fig. 1B). Thus with increasing sound level, not only the overall latency is expected to decrease, but also the latency difference elicited by the difference in rise time (Fig. 1C). Current models of neural latency predict that this latency difference approximates zero at high sound levels irrespective of the type of cochlear compressive non-linearity.
Psychophysics

Stimuli

For the psychophysics, the stimuli were trains of eight tone pips with a carrier frequency of 5 kHz. The interval between the pips was fixed at 10 ms. The pips consisted of a linear rise and decay without steady state. For the left-ear stimuli, the rise time was 1, 2, 4, or 8 ms, and the decay time was always double the rise time, resulting in tone pips with a duration of 3, 6, 12, or 24 ms. The pip trains in the right ear were either identical to the left-ear trains, or they were temporally reversed. To preclude residual carrier-periodicity related cues, the pure-tone carrier was refreshed for each ear and each stimulus with randomized phase. Experiments were run with a continuous background noise (8 dB SPL / Hz) low-pass filtered at 1500 Hz to preclude the binaural analysis of low-frequency aural distortion products. Stimuli were generated in Matlab (The Math Works Inc., Natick, MA, USA) at a sampling rate of 48 kHz and played via an RME-Audio DIGI 96/8 PST soundcard (Synthax, Haimhausen, Germany) into AKG K240 DF circumaural headphones (Vienna, Austria). The earphones were digitally equalized in magnitude and phase based on its binaural impulse responses measured on a Bruel and Kjaer 4153 artificial ear (Naerum, Denmark). The listeners were seated in a double-walled sound-attenuating booth (G+H Schallschutz, Ludwigshafen, Germany).

Procedure

In a two-alternative, forced-choice paradigm without feedback, listeners were asked to judge the lateralization of a test stimulus compared to a reference stimulus. The reference stimulus was always presented first. It consisted of a diotic pip train with identical rise and decay times in both ears and no eITD. The test stimulus followed the reference after a 500 ms pause and was presented with a variable eITD. For the first trial of each run, this variable eITD was set randomly in a range within ± 500 µs. In each trial, listeners judged whether the test stimulus
was lateralized left or right of the reference stimulus. In an adaptive procedure, the eITD of the test stimulus was changed to match the lateralization of the reverence stimulus. For the first and second reversal (a change in lateralization direction), eITD was changed in steps of 160 µs, for the third to fifth reversal, the step size was reduced to 80 µs, and for reversals six to eleven, it was reduced to 40 µs. The adjusted eITD in a given experimental run is given as the mean eITD across reversals six to eleven. Individual data are based on at least six runs per experimental condition. An experimental session consisted of three standard conditions and three test conditions in randomized order: In the standard condition, the test stimulus consisted also of a pip train with identical rise and decay times in the two ears. In the test condition, the pip train in the right ear was temporally reversed compared to the left ear, i.e., while pips in the left ear had a steep rise and shallow decay time, pips in the right ear had a shallow rise and a steep decay time.

Lateralization was measured as a function of the pip-train sensation level. For each listener, the absolute threshold for the reference stimulus was measured in an adaptive two-alternative, forced-choice experiment with feedback following a three-down, one-up paradigm. The level step size was 10, 5, and 2 dB for reversals 1 to 2, 3 to 5, and 6 to 11, respectively. Pip-train levels for the main experiment were based on the individual absolute thresholds for each listener and pip duration.

**Listeners**

At least four normal hearing listeners, aged between 21 and 35 of both genders took part in each experiment. Listeners for a pip duration of 6 ms were different from those that generated the data for the different pip durations.

**Electrophysiology**

Single-unit responses were recorded from two nuclei in the gerbil auditory brainstem, the LSO and the DNLL. Overall we chose to record single-neuron responses from the output
stage of the nucleus of interest, i.e., monaural responses from the LSO as an output stage of
the VCN and from the DNLL as an output stage of the MSO. Responses were collected from
high-frequency units which are insensitive to the carrier phase but which lock onto the
envelope period of the presented pip trains. The LSO recordings were performed to assess the
monaural inputs, not binaural processing, capitalizing on the fact that cochlear-nucleus
spherical bushy cells project both to the LSO and MSO and that the LSO faithfully preserves
the bushy-cell firing characteristics (cf. Magnusson et al. 2008; Hassfurth et al. 2009).
Consequently stimulation in the LSO was monaural from the ipsilateral side. In fact most
LSO units did not respond to binaural pip-train stimulation due to the inhibitory effect of the
contralateral ear. Assessment of binaural electrophysiological representation of the pip-train
stimuli is again based on the neural responses of the output stage, in this case the DNLL.

**Animals**

Recordings were obtained from 18 adult Mongolian gerbils (*Meriones unguiculatus*). They
were of both sexes, two to five months of age, and weighting between 50 and 90 g. Single
cells were recorded in two different brainstem nuclei, the LSO (n = 32), and the DNLL
(n = 50). All experiments were approved according to the German Tierschutzgesetz (AZ 55.2-
1-54-2531-57-05). The detailed methods in terms of surgical preparation, acoustic stimulus
delivery, stimulus calibration, and recording techniques have been described previously
(Siveke et al. 2006).

**Surgery**

The animals were anaesthetized by a physiological NaCl-solution containing ketamine (20 %)
and xylacine (2 %). The adequate state of the anaesthetized animal was ascertained regularly
throughout the experiment by testing the absence of motor reflexes and monitoring breathing
rate. To secure a constant state of anesthesia, supplementary doses of the same mixture were
given subcutaneously with a continuous rate of 1.7 µl/min or, in some experiments, 0.05-
0.1 ml every 30 min. Constant body temperature (37 – 39 °C) was maintained using a thermostatically controlled heating blanket. During recordings, the animal was placed in a sound-attenuated chamber and mounted in a custom-made stereotactic instrument allowing reproducible positioning of the skull (Schuller et al. 1986). Ear-molds were attached to the head allowing the insertion and fixation of earphones and probe-tube microphones. To gain access to the LSO, a craniotomy was performed lateral to midline of the skull and caudal to the posterior aspect of the transverse sinus. The underlying cerebellum was partially aspirated to expose the floor of the fourth ventricle. To gain access to the DNLL, a small craniotomy was performed lateral to the midline and caudal to the interaural axis. To access the LSO, electrode penetrations (tilted 20° rostrally) were performed 1.4-1.8 mm lateral to the midline and 4.3-4.7 mm caudal of the interaural axis, to access the DNLL, electrode penetrations (tilted 10° or 5° laterally) were performed 1.3-2.0 mm lateral to the midline and 0.5-0.8 mm caudal of the interaural axis.

**Recording procedure and general neural characterization**

Single-cell responses were recorded extracellularly using glass electrodes filled with 1M NaCl (~10 MΩ) or 2% Horseradish-peroxidase (HRP, Sigma-Aldrich, Germany) diluted in 10% NaCl. The recording electrode was advanced under remote control, using a motorized micromanipulator (Digimatic, Mitutoyo, Neuss, Germany) and a piezodrive (Inchworm controller 8200, EXFO Burleigh Products Group Inc, USA). The amplified (Toellner 7607, Herdecke, Germany) and filtered (VBF/3, Kemo, Beckenham, United Kingdom) action potentials were fed into the computer via an analog-to-digital converter (RP2-1, TDT-Tucker Davis Technologies, Alachua, USA). Clear isolation of action potentials from a single neuron (signal to noise ratio > 5; see waveform of the recorded spikes in the insets of Fig. 4B, Fig. 5B, and Fig. 7B) was guaranteed by visual inspection (stable size and shape) on a spike-triggered oscilloscope and by offline spike cluster analysis (Brainware, Jan Schnupp, TDT).
The recording sites of 24 of the 32 LSO neurons that we analyzed were marked with HRP that was ejected through the recording pipette via a current source (HV-TR 150; NPI, Tamm, Germany) using a current of 1 µA that was applied to the pipette for 1 min. DNLL recordings were made in locations that were verified to be within the DNLL in previous studies (Siveke et al. 2006). In three DNLL experiments, the last electrode position was marked by a current-induced lesion (5 mA for 5 seconds after a lethal injection of barbital had been applied) using metal electrodes (5 MΩ). Typical recording periods lasted 10-14 hours, after which animals were injected with a lethal dose of barbital. The animals in which a HRP injection or a current-induced lesion was performed, were perfused intracardially with heparinized physiological NaCl solution followed by 4 % paraformaldehyde solution. The brains were sectioned frontally and sections stained for HRP with diaminobenzidine, intensified by cytochrome and counterstained by standard protocol using Neutral Red. Sections of the current-induced lesions were Nissl-stained. The recording sites were verified using standard light microscopy.

Stimuli were generated at 48 kHz sampling rate in Matlab, converted to analog signals (RP2-1, TDT), attenuated (PA5, TDT) and delivered to the ear-phones (Sony MDR-EX70 LP, Tokyo, Japan). For general neural characterizations, stimulus duration was 200 ms plus 5 ms raised-cosine rise and fall times with a repetition period of 500 ms. As search stimulus, we used uncorrelated binaural noise bursts with an IID of 0 dB. Using pure tones, we first determined audio-visually the neuron’s characteristic frequency (CF) as that frequency which elicited a response at the lowest intensity, neuronal threshold (thr). For all neurons both CF and the corresponding thr were later confirmed by a careful offline analysis of the frequency versus level response areas (9 frequencies, step size CF/5, 10 dB steps) and rate level function at CF (8 dB steps). In the LSO, sensitivity to IIDs was assessed by presenting binaural tones at CF (ITD=0) with a combination of different IIDs (thr-30 to thr+20 dB, 10 dB steps) holding the excitatory (ipsilateral) ear constant at 20 dB above thr. Neurons were defined as
IID-sensitive if contralateral (inhibitory) stimulation reduced the maximal response elicited by ipsilateral (excitatory) stimulation by more than 50%. In the DNLL, sensitivity to eITDs was assessed by measuring noise delay functions (NDFs) presented with different ITDs over a range of ±3.5 ms (step size: 125 µs) determined from 2 to 16 repetitions. A unit was considered as eITD-sensitive if the noise-delay function was modulated by ≥ 50 % (i.e., if the minimum discharge rate was less than half of the maximum rate). The ITD eliciting maximal spike rate was defined as the neuron’s best ITD.

Pip-train stimulation

The pips consisted of the same envelopes as in the psychophysical experiments. The carrier frequency was set to the cell’s CF. The pips were presented in a 4-s train at a repetition rate of 40 Hz. Thus, one train consisted of 160 pips. For the LSO, five repetitions of the pip trains and temporally reversed pip trains were presented monaurally on the ipsilateral ear in a randomized sequence. Pip trains were presented with different pip durations (3, 6, 12, and 24 ms) and different sound levels (18 to 50 dB above threshold in 8 dB steps).

For the DNLL, the pip trains were presented binaurally (see inset of Fig. 8B). In the contralateral ear the temporal structure of the envelope was constant; in the ipsilateral ear the stimulation was identical to the LSO monaural stimulation, i.e., the temporal envelope of the pip train was equal to the contralateral side or temporally reversed. Furthermore in the ipsilateral ear, the inter-pip interval was used to generate time-variant eITDs: Within one second of pip-train stimulation, the delay of the ipsilateral pip was varied across a range spanning ± one quarter of the pip duration. This delay range was centered on the best ITD of the neuron. For a 40 Hz pip rate, the eITD range thus consisted of 40 different eITDs. As for the LSO stimulation, pip trains were presented at different pip durations and different sound levels above threshold.
**Analysis**

For all neurons recorded in the LSO and the DNLL, we first analyzed phase locking, quantified in terms of vector strength (Goldberg and Brown 1968) to the period of the pure-tone carrier and the envelope of the pips. Only neurons with significant phase locking to the envelope of the pips (see Figs. 5D and 8B) but not to the carrier (p < 0.01; Rayleigh test) were used for further analysis. To calculate the time shift in the period histograms recorded with the standard and time-reversed pips in the LSO, we performed a cross-correlation between the two histograms. A Gaussian was fitted to the cross-correlation function (Fig. 8C) and the lag of the maximum of the fit was taken as the time shift. The binaural DNLL response rates were plotted as a function of the eITD and fitted with a Gaussian for both standard and ipsilaterally reversed pip trains. The differences between the eITDs at which the two Gaussians had their maxima were taken as the eITD change. From the population of recorded neurons (N = 50) only the neuronal data with a correlation coefficient > 0.7 between the data and the Gaussian fits were used for further analysis (N = 30).

**Model fitting**

Two variants of the threshold integral model proposed by Heil and Neubauer (2003) were employed to fit the psychophysical and electrophysiological data. The model results were based on predicting the latencies $L_l$ and $L_r$ of the neuronal activities evoked by the acoustic stimuli at the left and right ear, respectively. The matched eITD was then derived from the binaural latency difference $L_r - L_l$. The threshold integrals $S(L)$ that were used for the latency prediction are described and explained in the Results section. The parameters of the models were obtained from a numerical fitting procedure. Using the MATLAB routine “fminsearch”, we minimized the root mean squared error

$$E = \sqrt{\frac{1}{N} \sum_{i=1}^{N} (\tau_i - \Delta t_i)^2}$$
between all measured eITD changes $\tau$ (all pip durations and sound-pressure levels) and the respective model predictions $\Delta t$. The fitting procedure was iterated for different starting values until the fit parameters converged. To have a better comparison between different experimental conditions we also give the relative error $\text{rel. err.} = E^2/\text{var}(\tau)$, which is the squared error normalized by the variance of the data.

**Results:**

The eITDs adjusted by the listeners to centralize the incongruent pip trains are shown in Fig. 2. Data are averaged across listeners; the error bars represent standard errors. At a sensation level of 20 dB, the listeners adjusted the temporally reversed 6-ms pip train in the right ear (with a 4 ms rise and 2 ms decay time) to start about 1150 $\mu$s earlier than the pip train in the left ear (with a 2 ms rise and 4 ms decay time). With this eITD, the perceived lateralization matched that of a diotic 6-ms pip train with 2 ms rise time and 4 ms decay time. With increasing sensation level, the adjusted eITD decreased monotonically but, even at a high sensation level of 60 dB, the listeners still required an eITD of about 580 $\mu$s to compensate for the different rise times in the two ears. Note that this experimental finding is in contrast to the expectation outlined in Fig. 1 and the corresponding text: based on this logic, one would expect that at a high sensation level, the rise-time difference is irrelevant. This would result in an adjusted eITD near zero $\mu$s, i.e., the incongruent pip trains should be perceived close to the center without an additional delay of the pip train with the steeper rise time.

Not surprisingly, the adjusted eITD systematically depended on the overall duration of the rise and decay times. The adjusted eITD increases with increasing overall pip duration for all sensation levels. However, in all conditions, even at the highest tested sensation levels, the adjusted eITD remained above 500 $\mu$s. Especially for the short tone-pip durations, the data
clearly show a floor effect, i.e. further increases in level do not lead to further decreases in adjusted eITD.

To study whether the eITD shifts can be explained by the level-dependent latency difference $L_L - L_R$, between the left and right-ear evoked neuronal activity, we employed two model variants of the pressure integrator proposed in Heil and Neubauer (2003). In contrast to the original model, in which latencies are predicted based on the sound pressure wave, we assume integration of the pressure envelope $e(t)$ of the sound wave. Then the binaural latencies $L_L$ and $L_R$ of action potentials are assumed to be determined by the threshold crossings of the respective integrated envelopes $S$ (Fig. 3A,B). Mathematically this maps to the implicit equation

$$\int_0^L \int [e(t)] e(t) \, dt = \Theta_0,$$

in which we allowed an additional exponent $k$ as a fit parameter. In the first model variant (called the ‘Latency model’, Fig. 3A) the threshold $\Theta$ is a constant and independent of sound level. This model thus has two fit parameters, $k$ and $\Theta$. In the second model variant (called ‘Latency model with level dependent firing threshold’ Fig. 3B) the threshold is a function of the signal level. Specifically we modeled the threshold as

$$\Theta = \Theta_0 + \Theta_1 a,$$

where $a$ denotes the amplitude of the envelope $e(t)$ in units of Pascal. The second model thus has three fit parameters, $k$, $\Theta_0$, and $\Theta_1$.

When comparing the best model fits to the psychophysically adjusted eITDs, we observed that the Latency model with a constant firing threshold cannot reproduce the large eITDs at high sound levels, although the model qualitatively fits the result in that longer pips produce larger eITDs (Fig. 3C). In contrast, the latency model variant that includes a level-dependent threshold can account for the saturation of adjusted eITDs at high sound levels (Fig. 3D). The best fit parameters of the first model variant were $k=1.21$, $\Theta = 0.0033$ (Fitting
error $E = 415 \, \mu s$, rel. err. $= 2.8$). The best fit parameters of the second model variant were $k=1.46$, $\Theta_0 = -9.4 \times 10^{-6}$ and $\Theta_1 = 0.0697/\text{Pa}$ (Fitting error: $E = 149 \, \mu s$, rel. err. $= 0.36$).

To measure the monaural inputs to the binaural system in the SOC, neural responses to ipsilateral pip trains were obtained from the LSO of the gerbil. We recorded from 32 cells with CFs between two and 13 kHz (mean: 4.7 kHz). Histological verifications of the recording sites are shown in Fig. 4A. All recorded cells were ipsilaterally excited and contralaterally inhibited, resulting in monotonic IID functions (Fig. 4B). When these cells were ipsilaterally stimulated with pip trains whose carrier matched the CF, the cells showed a sustained response (Fig. 5A) with no phase-locking to the carrier but stable phase locking to the envelope period (Fig. 5A, B, D). The period histograms in response to 6- ms pips (Fig. 5D) show that the spiking latency depends on the direction of the asymmetric envelope in that the cell fires earlier when the pip has a 2- ms rise and a 4- ms decay (black graphs in Fig. 5C, D). With increasing stimulation level, the response rate increases but the phase difference between the period histograms of the two envelope conditions decreases. This is quantified in the cross-correlograms of the period histograms in Fig. 5 E. The peaks in the cross-correlogram shifts from 810 $\mu s$ at a sound level of 26 dB above threshold to 357 $\mu s$ at 50 dB above threshold. This time shift is shown for the four different pip durations in Fig. 6A as a function of the sound level above threshold. Qualitatively similar to the psychophysically determined eITDs, the time shift increases with overall pip duration. For each pip duration, the time shift decreases with increasing sound level. Note that even at the highest sound level, the time shifts in the period histograms are still prominent. These main features are preserved in the LSO population average, shown with filled symbols in Fig. 6B. The error bars increase systematically with increasing pip duration. This may result from a less precise neural encoding of the much shallower envelopes of the longer-duration pips. Electrophysiological results from the gerbil LSO are in good agreement with the eITDs adjusted in the human psychophysical experiments, especially for the longer pip durations of 12 and 24 ms. For
shorter pip durations, the LSO data predict smaller eITD changes than observed psychophysically. The latency model with constant threshold (Heil and Neubauer 2003) is unable to predict the LSO data in that it cannot predict the relatively large time shifts seen at high sound levels. For the latency model with a level-dependent firing threshold, the fits to the LSO data capture the main trends but underestimate the time shifts measured at high levels for long pip durations. This is also reflected by the fitting errors $E = 607 \mu s$ (rel. err. = 0.28) for the latency model and $E = 533 \mu s$ (rel. err. = 0.22) for the latency model with level dependent firing threshold.

Recordings in the DNLL were obtained to get an estimate of how the gerbil’s binaural system evaluates the time shifts in the peripheral representation of the pip trains. Again, histological verifications of the recording sites are shown in Fig. 7A. We systematically searched for high-CF binaural units (between two and 17 kHz; mean: 5.1 kHz), which showed sensitivity to eITDs in response to interaurally correlated Gaussian noise. Examples of the noise-delay functions of such units are shown in Fig. 7B. A vector-strength analysis of the CF responses confirmed that the units did not show significant vector strength to CF tones. Unlike in the LSO, we used binaural pip trains but here, we introduced a 1-Hz binaural beat into the envelopes of the pip trains (see Methods) to quantify the effect of level dependent latency shifts onto binaural processing.

From the more than 90 cells recorded in the DNLL, only 50 responded reliably to the binaurally presented pip trains, i.e., they phase locked to the envelope period. Of these 50 cells, only 30 also responded to the binaural beat of the binaural pip trains, i.e., they phase locked to the binaural beat. In 20 of these 30 cells, we could determine the aurality: All 20 cells were excited with contralateral stimulation but 9 cells were excited also with ipsilateral stimulation (E/E), 8 cells responded irrespective of ipsilateral stimulation (E/0) and 3 cells were inhibited by ipsilateral stimulation (E/I). It should be noted that most of the high-CF E/I cells we found in the DNLL did not respond to our pip-train stimulations without additional
IIDs. The same was the case when we tried to stimulate LSO neurons with binaural pip train stimuli. However, in terms of eITDs and the level dependence of eITDs (see below), we found no differences between the different binaural cell types in the DNLL.

Exemplary data of a single DNLL cell are shown in Fig. 8. With binaural pip-train stimulation, this cell exhibited strong phase locking to the 25-ms envelope period. Moreover, this cell phase locked also to the 1-s binaural beat period. Both types of phase locking are seen in the raster plot (Fig. 8A). As in the LSO, the response rates increase with increasing sound level, but this increase was more pronounced for the time-reversed pips (shallow rise but steep decay, grey), which produced particularly weak responses at low levels. The binaural envelope beat was constructed to cover a range of ± one quarter of the pip duration within 1 s. Period histograms constructed with the envelope beat period of 1 s are shown in Fig. 8C. Since within each 1 s period, the envelope eITD changes linearly, the abscissa can be relabeled as an eITD axis. The neuronal responses to different eITDs are dependent on the pip-stimulus condition as well as on the overall sound level. To quantitatively analyze how the response rates depend on eITDs induced by the reversal of the ipsilateral pips, we fitted a Gaussian to the binaural-beat, period histograms derived from the two stimulus conditions and computed the time difference (Δt) between the maxima of these Gaussians. Like the LSO time shifts, also these DNLL time differences decrease with increasing sound level (Fig. 8C).

Figure 9A shows the time differences derived from the DNLL recordings for pip durations of 3, 6, and 12 ms. Unfortunately it was not possible to analyze the responses to 24 ms pips because first, the response rate was much smaller than for the shorter pips, and second, the eITD sensitivity of the DNLL cells was much worse for these longer pips. Population data are shown in Fig. 9B.

The time differences derived from the DNLL increase with pip duration and, for each pip duration, the time differences decrease with increasing sound level, but even at highest sound levels, the eITDs are significantly larger than zero (for the shortest pip duration and the
highest sound level, the mean eITD was 90 µs; SEM = 20 µs). The time shifts for high levels in the DNLL cannot be achieved with the latency model (Heil and Neubauer 2003) although the overall fitting errors are rather similar in both models (latency model: E = 153 µs, latency model with level-dependent threshold: E = 150 µs, rel. err. = 0.10 in both cases). In general, the observed time differences of the binaural DNLL responses are much smaller than the theoretically extracted time shifts for the monaural LSO data and also much smaller than observed psychophysically. However considering the different methods and experimental requirements the three datasets are in good qualitative agreement.

Discussion

We have presented a binaurally asymmetric, incongruent stimulus paradigm to quantify the level dependence of both perceptual and neural auditory response latencies. The paradigm exploits two key features of temporal auditory processing: the precise encoding of the envelopes of high-frequency carriers and the exquisite precision of eITD analysis. The used pip stimuli are composed of linear rise and fall times that constitute the envelope for a high-frequency sinusoidal carrier. The stimuli were investigated with respect to human binaural perception as well as their neuronal representations that are revealed by electrophysiological recordings from two different nuclei, the LSO and DNLL, of anesthetized gerbils. These three sets of experimental data are in qualitative agreement: an eITD induced by the binaural asymmetry of the envelopes decreases with decreasing rise time of the envelopes and with increasing sound level. Furthermore all three different experimental datasets showed, that the eITDs never decrease to zero but rather asymptote towards a particular eITD for the shortest rise times and most intense stimuli.

To check whether the observed eITDs can be explained by a current model of first-spike latency, we employed two variants of a spike-latency model by Heil and Neubauer (Heil and
Neubauer 2003; Heil et al. 2007) that was originally proposed to explain the level dependence of first spike latencies in the auditory nerve. While our experimental data are inconsistent with the latency model, the introduction of a level-dependent threshold into such a model gives a good qualitative match between all three datasets and model predictions.

Heil and Neubauer proposed a neural correlate of the pressure-envelope integration preceding spike generation to occur at the inner-hair cell, auditory-nerve synapse. Recent work has addressed the physiological basis of this pressure-envelope integration. In a constructive discourse, it was shown that the interplay between the stochasticity of synaptic events and a short time constant of synaptic transmission can explain the apparently long time constant of temporal integration at threshold (Krishna 2006; Meddis 2006a; Meddis 2006b). In contrast to the modeling work by Heil and Neubauer, Meddis’ (2006a) model also incorporated compressive non-linear processing in the inner ear. It is important to note that the threshold adjustment cannot be replaced by a simple static compression: Such a compressive non-linearity is often implemented by taking a power law of the pressure envelope (Oxenham and Moore 1994). In the latency model this power law would simply be compensated for by the fitting parameter $k$. Thus a static power-law compression alone shows not the experimentally observed effect on the binaural latency differences if it is not accompanied by a level-dependent threshold. More complex, dynamic compressive mechanisms (e.g., Dau et al. 1996; Tan and Carney 2003) may contribute to the hypothesized threshold adjustment.

Generality of the model. Although the latency model used in this paper is only one possible approximation to physiology, the conclusion that the experimentally observed saturation of eITDs at high sound intensities can only be explained by a level-dependent adjustment of neural latency, is more general: the observed eITD saturation cannot be explained by any model for which the latency converges to a level-independent minimal value as the pressure amplitude $a$ increases. For example, in the latency model used in this paper, a linear envelope increase $e \sim at$ results in a threshold integral $S \sim a^{1/2}L^{1+1}$ and, hence, the latency converges to its
minimum 0 according to $1/a^{k/(k+1)}$. In a more complex class of models, one may assume the
evelope to be additionally filtered by a leaky integrator. Then, the integral $S(L)$ increases
even slower than $L^{k+1}$, which would result in the latency to converge to 0 even faster than $1/a^{k/(k+1)}$. In yet another class of models (Heil et al. 2007) it was suggested to replace the
deterministic threshold by a probabilistic firing rate, which is modeled by the hazard function $R(L) \sim a^k L^k$. In such a model, the expected latency is computed via the integral

$$\langle L \rangle = \int dt \int t R(t) \exp \left[ -\int du R(u) \right] = \frac{C}{a^{1/(k+1)}},$$

in which C is a constant. Thus $L$ converges to its minimum value 0 like $1/a^{k/(k+1)}$. To conclude,
the eITD saturation observed here can only be explained by models with a firing threshold
adjusted to overall sound level. In the present paper this has been implemented via a level-
dependent threshold. A promising approach in modeling the current data has been pursued by
Ewert et al. (2010) who showed that level-dependent minimum latencies can be realized
through either feed-forward or feed-back mechanisms of neural adaptation. A recent attempt
in this direction represents the modeling work of Zilany et al. (2009). This model includes
long-term adaptation implemented with power-law dynamics and can thus capture relatively
long-term adaptation of the auditory nerve to stimuli with different sound levels. We tested
the Zilany et al. model by taking the simulated auditory-nerve output in response to pip-train
stimulation and performing a ‘binaural’ crosscorrelation similar to the analysis used for the
monaural LSO responses. The modeling results are shown together with the psychophysical
data in Fig. 10. Despite the fact that the model was in no way fitted to the data, the simulation
results capture the general trends of the psychophysical data. Thus, the current data highlight
the importance of including neural adaptation in models of binaural hearing.

Level dependence of temporal coding in the auditory nerve: Dreyer and Delgutte (2006)
showed that at the level of the cat auditory nerve, the temporal representation of transposed
tones, with an envelope modulation comparable to the current pip-trains, deteriorates with
increasing sound level. In contrast, the current data show that at the level of the gerbil LSO, the temporal representation of the pip-train envelopes does not deteriorate with increasing sound level. The current data are thus also in agreement with the psychophysical data showing that the sensitivity to eITDs elicited by transposed tones is stable over a wide range of sound levels (Dreyer and Oxenham 2008). These findings also argue for a refinement of temporal envelope encoding at the level of the cochlear nucleus, similar to the refinement of phase locking to pure tones (Joris et al. 2004).

Palmer and Shackleton (2009) have shown that the phase of phase-locked auditory-nerve responses to low-frequency pure tones varies systematically with sound level. A comparable effect is reflected in our data (cf. period histograms in Fig. 5B) obtained with the envelopes of high-frequency tones. While these phase shifts are consistent with a decrease in neural latency with increasing sound level, the level dependent phase shifts as such do not contribute to the level dependent eITDs reported here. We always used the same level on the two ears and thus the phase shifts would apply equally to both ears and cancel out for the eITD estimation.

Possible neural basis for the level-dependent threshold adjustment: The physiological basis of the level-dependent threshold proposed in this paper cannot be assessed in the framework of the present study. Our data reveal that the level dependent threshold adjustment is already present in the input to the SOC. The success of the published model by Heil and Neubauer (2003) to explain the level dependence of auditory-nerve first-spike latency points towards the cochlear nucleus as a neural stage of firing-threshold adjustment.

Experimental evidence for the adjustment of spiking to overall sound level has been seen in several previous studies: Gibson et al. (1985) showed that at the level of the cochlear nucleus, the level of simultaneous background noise strongly influences pure-tone rate-level functions. These authors contributed the observed effects to ‘two-tone suppression’, i.e., the effects of inhibitory sidebands. Dean et al. (2005) recently showed that comparable effects can be elicited not by frequency- but temporal interactions. Specifically, they showed that rate-level
functions of auditory-midbrain neurons can adapt to the statistics of sound-level fluctuations. In a follow-up study the authors showed that this adaptation can be described with time constants of a few hundred milliseconds (Dean et al. 2008). The fact that in the current psychophysical data, adaptation to overall sound level is evident with pip-train stimulation over little more than 100 ms suggests that similar processes may underlie our electrophysiological data. Note, however, that the current data do not allow speculation over the time constant for the threshold adjustment because both the psychophysical and electrophysiological experiments maintained the same sound level over several minutes of stimulation which precludes the analysis of an adjustment time constant.

Inconsistency of LSO and DNLL data: The level dependent eITD changes extracted from the monaural electrophysiological data recorded in the gerbil LSO are larger than the time shifts recorded in the gerbil DNLL with binaural stimulation. A possible reason for this discrepancy may lie in the different stimulation paradigms: The monaural data were recorded with static pip trains while for the binaural data, time-variant inter-pip intervals, creating a binaural beat, were recruited. This was necessary to accommodate the stimulation protocol within a realistic recording time. Although the beat frequency was only one Hertz, it is possible that the resulting motion cue may influence the eITD sensitivity. Hysteresis effects related to such motion cues were shown for binaural beats elicited with low-frequency pure tones in the mammalian IC (Spitzer and Semple 1993; McAlpine et al. 2000). Another possible reason is that the population characteristics of neurons are different in the DNLL and the LSO: The CFs of the two populations are similar, but their basic binaural properties were different: The LSO neurons were excited from the ipsilateral and inhibited from the contralateral side, where the majority of the DNLL neurons were binaurally excited, similar to neurons in the medial superior olive. It has been shown, that bushy cells in the anteroventral cochlear nucleus send collateral projections to the lateral and medial superior olive (Stotler 1953; Smith et al. 1993). Therefore we chose to record from ipsilaterally stimulated LSO cells, which are much easier...
to record from, assuming that the excitatory input to these cells is similar to the excitatory input to the medial superior olive. Finally DNLL data may deviate from the LSO data because the DNLL is not a principal stage of binaural envelope processing: There are multiple ascending binaural projections bypassing the DNLL, in which the envelopes of high-frequency sounds are accurately encoded (Oliver 2000; Pollak et al. 2003). Furthermore persistent inhibition as an important feature of DNLL binaural processing (Pecka et al. 2007) may interfere with the encoding of ongoing eITDs.

Envelope ITDs versus short-term IIDs: Any eITD is accompanied by a time-variant IID: an acoustic impulse that is presented first to the left ear and then, with a 300 µs delay to the right ear causes a strong leftward IID followed by an equally strong rightward IID. The overall IID is only zero when averaged across the stimulus duration. Previous studies on ITD-coding have shown, that overall IIDs have a substantial effect on the ITD-sensitivity especially at frequencies below and above BF (Kuwada and Yin 1983; Yin and Chan 1990; Viete et al. 1997; Palmer et al. 2007). While it has been shown that IID sensitivity improves with increasing duration (Blauert 1997), the time constant of perceptual IID analysis, i.e., its temporal resolution is entirely unclear. If we assume a long time constant of IID extraction (>20 ms), the IIDs generated by the current stimulation would be negligible. If however, the IID time constant is short, time variant IIDs are generated by the current stimuli. This would be the case for all high-frequency stimuli with an eITD. To address the question of the time scale of IID processing, it is conceivable to replicate the current psychophysical experiment asking listeners not to compensate the rise-time differences with an eITD but with an IID. Thus, the potential interaction of the current paradigm with IID extraction opens new opportunities to study the dynamics of binaural processing.

Relationship to the ‘latency hypothesis’: several studies have explored the hypothesis that high-frequency IIDs may be encoded not with interaural differences in spike rate but differences in spike latency (Yin et al. 1985; Hirsch et al. 1985; Pollak 1988; Irvine et al.)
al. (2001) showed that a relatively small proportion of neurons in the LSO encoded high-
frequency transient IIDs in terms of latency not rate differences. However, in the LSO of
awake bats, this proportion was much higher (Park et al. 1996). In line with previous data, the
current LSO data (cf. Fig. 5) show a decrease of spike latency with increasing sound level
with a trading ratio of about 77 µs/dB. However as outlined above, the current stimuli create
short-term time variant IIDs only if a short time constant of IID extraction is assumed. Based
on the results of Tollin and Yin (2005), such a short time constant of IID extraction appears
plausible. If these short-term IIDs were converted to changes in response latency, the resulting
latency shifts would interfere with the extraction of eITDs. The additional latency shifts
resulting from the interaural difference in rise time are superimposed on the level-dependent
latency shifts. Using the current stimulus paradigm, we cannot disambiguate these two types
of latency shifts.

In summary our experimental paradigm provides insights into the level dependence of neural
auditory latencies. Recruiting the temporal precision of the high-frequency binaural system,
the paradigm allows, for the first time, to quantify the level dependence of auditory neural
latencies perceptually. The psychophysical and electrophysiological data show that a modified
version of a spike-latency model, which includes an adjustment of firing threshold to overall
sound level, can account for the level-dependent perception and peripheral neural encoding of
transient sounds.

Figure captions

Figure 1: Illustration of the experimental paradigm. Binaural pip trains with different rise-and
fall times of the pip envelopes in the two ears (black = left ear; grey = right ear) were
presented to the listeners at different sound levels. Latency is determined by the point in time
where the envelope integral (lower panel) crosses firing threshold. At a low sound level (solid
lines) the latency is longer than at a high level (dotted lines). Also the difference in the
envelope rise time between the left and right ear is reflected in the latencies: The latency
difference dT decreases with increasing sound level. The experimental paradigm is based on
the assumption that these latency differences are compensated for by the eITDs that are
adjusted by the listeners.

Figure 2: Psychophysically adjusted eITDs as a function of sound level and pip duration. For
an exemplary pip duration of 6 ms, in the left ear, the pips rise within 2 ms and fall within
4 ms, in the right ear, the pips are reversed, i.e., they rise within 4 ms and fall within 2 ms.
The mean adjusted eITD decreases systematically with increasing sensation level. This
general pattern of results is found for all pip durations. Note that the adjusted eITDs do not
asymptote to zero even at high sound levels.

Figure 3: Explaining perceived eITDs by spike-latency models. (A) Because of the binaural
asymmetry, the envelope integrals $S(L)$ (black lines) at the left and right ear exhibit different
time courses. The integral at the left ear increases faster than that at the right ear,
corresponding to the different envelope rise times. The latency is predicted by the crossing of
a threshold $\Theta$ (dashed lines) and thus the latency at the left ear is shorter than that at the right
ear. The perceived eITD is predicted by the binaural latency difference $\Delta t$. If the sound level
is increased, both integrals are steeper (grey lines) and the latencies become shorter. The
binaural latency difference $\Delta t$ becomes almost arbitrarily short for high sound levels. (B)
Same as in A for the latency model with threshold adjustment. If the sound level is increased,
again the steepness of the integrals $S(L)$ increases but also the threshold increases. As a result
the reduction in latencies is less prominent than in the model with fixed threshold. The
predicted perceived eITD for high sound levels is considerably enhanced. (C) Summary of all
model fits for the published latency model (Dashed line shows psychophysics data from Fig.
2) Note the model could not be fitted such that it predicted reasonable data for the shortest pips at the lowest sensation level. Therefore, we have removed this data point. (D) Summary of all model fits for latency model with threshold adjustment (Dashed line: same as C).

Figure 4: Histological verification of a recording site and typical auditory responses in the lateral superior olive (LSO). (A) Nissl staining of the superior olivary complex (top), schematic drawing of the main nuclei (bottom). The lateral part is on the left and the medial on the right side. On the right, parts of the medial nucleus of the trapezoid body (MNTB) are visible. The typical band of aligned neurons of the medial superior olive (MSO) is in the middle of the picture, the U-shaped LSO with the HRP-injection site in the middle of the nucleus is on the left side. (B) Responses of six typical neurons in the LSO to IIDs. The shapes of the extracellularly recorded action potentials of two single neurons are shown as insets. Neurons in the LSO are typically excited from the ipsilateral and inhibited for the contralateral side. Positive IIDs indicate a higher sound pressure level at the ipsilateral side and evoke strong neuronal responses; negative IIDs indicate a higher sound pressure level at the contralateral side and evoke low or no responses.

Figure 5: Response of an example LSO neuron (CF = 3.5 kHz; thr = 20 dB SPL) to monaural pip train stimuli. (A) The raster plot shows the sustained response during the whole 4-s stimulus duration. To show the phase locking to the pip period (vertical lines), 500 ms in the middle of the stimulation are magnified in B. The electrophysiological traces on the right side show the clear separation of action potentials of the neuron (black) from the noise (grey). (C) Schematic diagram of the presented ipsilateral standard and the time reversed 6-ms pip. (D) Period histograms calculated from the ipsilateral responses to the standard (black) and the time reversed (grey) 6-ms pip trains are plotted for five different sound pressure levels ranging from 18 to 50 dB above neuronal threshold. (E) Related cross-correlations of the
period histograms are plotted as correlation index versus time shift. The time shift is derived from the time delay ($\Delta t$) of the correlation maximum as obtained from a Gaussian fit (black line).

Figure 6: Dependence of LSO time shifts on overall sound pressure level and pip duration.
(A) The time shift of the period histograms of a single LSO neuron (CF = 13 kHz; thr = 20 dB SPL) are plotted against the sound pressure level for a pip duration ranging from 24 ms (black) to 3 ms (light grey). B: Population responses ($N = 32$) are shown as the average time shift of the LSO neurons for the 24-ms pip (black dots; $n = 24$) the 12 ms pip (dark grey dots; $n = 29$) the 6-ms pip (grey dots; $n = 30$) and the 3-ms pip (light grey dots; $n = 29$). The error bars indicate the standard error of the mean (SEM). The latency-model (with threshold adjustment) fits to these data are shown as dotted lines; the psychophysical data (from Fig. 2) as solid lines using the same color code.

Figure 7: Histological verification of a recording site and typical auditory responses in the dorsal nucleus of the lateral lemniscus (DNLL). (A) The Nissl staining in the upper panel shows the crossing fibers of the lateral lemniscus (LL), the lower part shows a related schematic drawing. The DNLL with a small lesion is visible as a typically round shaped nucleus right below the border of the inferior colliculus (IC). (B) Responses of six typical DNLL neurons to noise stimuli presented with ITDs. Positive ITDs indicate, that the contralateral stimulus is leading, negative ITDs, that the ipsilateral stimulus is leading. eITD sensitive neurons with high best frequencies (>2 kHz) show a significantly stronger response to a neuron specific eITD. Shapes of action potentials of two single neurons are shown as insets.
Figure 8: Response of a DNLL neuron (CF = 3.6 kHz; thr = 25 dB SPL) to the binaural pip train stimuli. (A) The raster plot shows a defined acoustic response to a particular envelope eITD of the 6-ms pip train stimuli, which is, according to the “1 Hz beat” stimulation, repeated every second. (B) Period histograms for the standard (black) and the time reversed (grey) 6-ms binaural pips are plotted for five different sound pressure levels ranging from 18 dB to 50 dB above neuronal threshold. The time base for these period histograms is the pip repetition period, 25 ms. The schematic diagram of the presented binaural standard and the time-reversed pips are shown as insets. (C) The tuning of the neuron to a particular envelope eITD is revealed by the period histograms constructed with the envelope beat period of 1 s. Within each second of the envelope period the eITD changes linearly and the abscissa is relabeled as eITD axis. The eITD change (Δt) between the envelope period histograms obtained from the standard (black) and the time reversed pip stimulation is obtained by the difference between the shifts of the two histogram maxima obtained from Gaussian fits (dotted lines).

Figure 9: Dependence of DNLL eITD changes on overall sound pressure level and pip duration. (A) The eITD changes of the envelope period histograms of a single DNLL neuron (CF = 3.8 kHz; thr = 20 dB SPL) are plotted against the sound pressure level for pip durations ranging from 12 ms (black) to 3 ms (light grey). (B) Population responses (N = 30) are shown as the average eITD change of the DNLL neurons for the 12-ms pips (black dots; n = 11/22) the 6-ms pips (dark grey dots; n = 13/20) and the 3-ms pips (light grey dots; n = 15/17). The error bars indicate the standard error of the mean (SEM). The latency-model (with threshold adjustment) fits to these data are show as dotted lines; the psychophysical data (from Fig. 2) as solid lines using the same color code.
Figure 10: Simulation results based on the Zilany et al (2009) auditory-nerve model (dotted lines) compared to the current psychophysical data (solid lines). Although the model was not fitted to the data, the model predictions capture the general level dependence of the adjusted eITDs reasonably well.

Reference List


