Title:
Spectral composition of concurrent noise affects neuronal sensitivity to interaural time differences of tones in the dorsal nucleus of the lateral lemniscus

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Abstract

We are regularly exposed to several concurrent sounds, producing a mixture of binaural cues. The neuronal mechanisms underlying the localization of concurrent sounds are not well understood. The major binaural cues for localizing low-frequency sounds in the horizontal plane are interaural time differences (ITDs). Auditory brainstem neurons encode ITDs by firing maximally in response to “favorable” ITDs and weakly or not at all in response to “unfavorable” ITDs. We recorded from ITD-sensitive neurons in the dorsal nucleus of the lateral lemniscus (DNLL) while presenting pure tones at different ITDs embedded in noise. We found that increasing levels of concurrent white noise suppressed the maximal response rate to tones with favorable ITDs and slightly enhanced the response rate to tones with unfavorable ITDs. Nevertheless, most of the neurons maintained ITD-sensitivity to tones even for noise intensities equal to that of the tone. Using concurrent noise with a spectral composition in which the neuron’s excitatory frequencies are omitted reduced the maximal response similar as obtained with concurrent white noise. This finding indicates that the decrease of the maximal rate is mediated by suppressive cross-frequency interactions, which we also observed during monaural stimulation with additional white noise. In contrast, the enhancement of the firing rate to tones at unfavorable ITD might be due to early binaural interactions (e.g. at the level of the superior olive). A simple simulation corroborates this interpretation. Taken together, these findings suggest that the spectral composition of a concurrent sound strongly influences the spatial processing of ITD-sensitive DNLL neurons.
Keywords:

Brainstem, interaural time differences, ITD, noise, sound localization
Introduction

In natural environments, sound stimuli are often complex and originate from a number of different sources. Obviously, our binaural auditory system is able to extract the relevant cues representing the positions of the sound sources amidst this complexity. Thus we can localize each of these sources and detect or segregate them based, among other cues, on spatial information (Culling and Summerfield, 1995; Darwin and Hukin, 1997; Drennan et al., 2003). A step towards the understanding of how concurrent sounds are processed is to investigate the perception of tones in the presence of a noise source. The detection and segregation of tones from background noise has been studied psychophysically (for review see: Blauert, 1983) and, furthermore, could be correlated to electrophysiological results (Langford, 1984; Caird et al., 1991; McAlpine et al., 1996; Jiang et al., 1997b; Jiang et al., 1997a; Palmer et al., 1999; Lane and Delgutte, 2005). But most of the work on sound localization has been performed for single sources and the localization of tones in background noise has not been thoroughly investigated. The small number of psychophysical studies showed that the capability to localize sounds in noise strongly depends on the location, the level, and the spectral components of the noise source (Cohen 1981, Cohen and Koehnke, 1982; Ito et al., 1982, Stern, Jr. et al., 1983; Good and Gilkey, 1996). However, the neuronal mechanisms underlying the localization of tones in background noise are not well understood.

In this study, we focused on the neuronal mechanisms underlying the localization of low-frequency tones (< 2000 Hz) in the presence of localizable noise. The most important spatial cue for low-frequency sounds in the horizontal plane is the difference in the arrival time of sound at the two ears, the interaural time difference (ITD) (Rayleigh, 1907). ITDs are processed by coincidence-detector neurons in the medial (MSO) and lateral superior olive (LSO) (Goldberg and Brown, 1969; Yin and Chan, 1990; Spitzer and Semple 1995, Batra et al. 1997, Brand et al. 2002, Tollin and Yin, 2005). These neurons receive precisely timed
monaural inputs from both ears. Both the strength as well as the exact timing of the monaural inputs determines the response rates of these coincidence-detector neurons. MSO and LSO neurons project to the dorsal nucleus of the lateral lemniscus (DNLL) (for review see: Oliver and Huerta 1992). Many DNLL neurons faithfully reflect the ITD sensitivity of their MSO and LSO inputs (Seidl and Grothe, 2005; Kuwada et al., 2006; Siveke et al., 2006). Therefore we used the population of ITD-sensitive DNLL neurons as an approach to studying binaural processing at the level of the coincidence-detectors.

We recorded from ITD-sensitive neurons in the DNLL of the anesthetized gerbil and found complex interaction between pure tones and noise. Furthermore the findings suggest that the spectral composition of a concurrent sound influences the processing of ITD-sensitive neurons.
Methods

Single neurons (N = 111) in the DNLL were recorded from Mongolian gerbils (Meriones unguiculatus) of both sexes two to three months of age. 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) and will only be described briefly here.

Animal preparation, recording procedures

The animals were anaesthetized by a physiological NaCl-solution containing ketamine (20 %) and xylacine (2 %). During recordings, the animal was placed in a sound-attenuated chamber and mounted in a custom-made stereotaxic 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. For electrode penetrations, a small hole was cut into the skull and the dura mater was removed extending 1.3 - 2.6 mm lateral to the midline and 0.5 - 0.8 mm caudal of the interaural axis. Micromanipulators were used to position the recording electrode. For some recordings the recording electrode was tilted 10° or 5° laterally.

Single-cell responses were recorded extracellularly using glass electrodes filled with 1M NaCl (~10 MΩ). 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 and filtered action potentials were fed into the computer via an A/D-converted (RP2-1, TDT-Tucker Davis Technologies, USA). Clear isolation of action potentials from a single neuron (signal to noise ratio > 5; see waveform of the recorded spikes in figure 3, 4, and 5) was
guaranteed by visual inspection (stable size and shape) on a spike-triggered oscilloscope and
by offline spike cluster analysis (Brainware, Jan Schnupp, TDT). Stimuli were generated at
50 kHz sampling rate by TDT System III. Digitally generated stimuli were converted to
analog signals (DA3-2/ RP2-1, TDT), attenuated (PA5, TDT) and delivered to the ear-phones
(Sony, Stereo Dynamic Earphones, MDR-EX70LP).

Stimuli

Stimuli were presented randomized with a repetition rate of 2 Hz. All binaural stimuli
were applied with an interaural intensity difference of 0 dB. Unless indicated otherwise,
stimulus duration was 200 ms plus 5 ms rise and fall times of a squared cosine. As search
stimulus we used uncorrelated binaural noise bursts. Using pure tones we first determined the
neurons characteristic frequency (CF) and absolute threshold audio-visually to set the
stimulus parameters subsequently controlled by the computer. The frequency that elicited
responses at the lowest sound intensity was defined as CF, the lowest sound intensity evoking
a noticeable response at CF as threshold. For all neurons both CF and threshold were later
confirmed by a careful offline analysis of the frequency versus level response areas (9
frequencies, step size CF/5, 10 dB steps). For a subpopulation of neurons, we additionally
measured the response threshold for noise stimulation by rate-level-functions (supplementary
figure). In some of these neurons the response to noise showed an increase already at the
threshold level for tones at BF with the same RMS.

Sensitivity to ITDs was assessed by measuring noise delay functions (NDFs) and tone
delay functions (TDFs) 20 dB above threshold to pure tones at CF (for details concerning the
relationship of levels for tone and noise stimulation see supplementary figure). The frequency,
which evoked the maximal response at a given neuron’s best ITD, we refer to as “best
frequency” (BF). For NDFs and TDFs we presented different ITDs over a range equivalent to
≥ 2 cycles of BF (step size BF/10). ITDs with the contralateral stimulus leading were defined as positive, ITDs with the ipsilateral stimulus leading as negative ITDs. TDFs were tested for five stimulus frequencies around BF. Each stimulus was repeated at least three times. NDFs were determined from 16 iterations. To obtain best ITDs the position of the peaks of the NDF or TDF at BF were estimated and used to compute the signals for further experiments.

For the first set of tone-in-noise experiments (used for figures 1 to 4) we presented a 100 ms tone at BF while varying the ITD. This stimulus was presented alone or embedded in a 250 ms Gaussian noise starting 10 ms before the tone. Assuming a neuronal delay of less than 20 ms to the DNLL, we defined and analyzed the neuronal response to the tone in the time window from 20 ms to 120 ms after onset of the tone. The binaurally correlated noise was varied in amplitude (noise level 20 dB below tone level and noise level equal to tone level) and ITD. The noise stimuli were applied with two different ITDs, 0 ms and the best ITD. In most of the neurons (n = 61) best ITDs were derived from the NDF. For 19 neurons the best ITDs were derived from the TDF. For a subgroup of neurons we additionally tested the monaural responses to the same tone-in-noise stimuli presented either ipsilaterally or contralaterally.

For the second set of tone-in-noise experiments (used for figure 5) we constructed neuron-specific spectrally adjusted “tuned” and “notched” noise stimuli. These were created online using the computer program Matlab (The MathWorks Inc., Natick, MA, USA). Tuned noise contained the frequency domain of the excitatory tuning curve, whereas notched noise was constructed as the difference between white noise and tuned noise, hence, reflecting the spectral areas outside the excitatory tuning curve of a given neuron. More specifically, we again determined response areas of neurons with eight repetitions of frequency versus level stimulations using pure tones at the best ITD at BF. From these frequency-versus-level response areas we determined the thresholds for all stimulated frequencies. The thresholds were defined as the intensity, which evoked 20 % of the maximal firing rate plus spontaneous
activity following Sutter et al. (1999). For frequencies other than the stimulated ones, thresholds were obtained by linear interpolations (figure 5B). The resulting threshold curve was used as a weighting function for the spectral content of notched and tuned noise. For notched noise spectral power was depressed proportional to this weighting function, whereas for tuned noise spectral power was depressed proportional to the maximal level minus the threshold curve. Therefore the weighting function, i.e. the threshold curve, was constructed such that the neurons still weakly responded to the notched noise. The overall sound intensities (root-mean-square value, RMS) of the three noise stimuli were chosen equal to the intensity (RMS) of the pure tone stimulus (20 dB above threshold). In contrast to the first set of tone-in-noise experiments, in the second set of experiments (used for figures 5) noise and tone were played in an overlapping sequence. The three noise stimuli were presented for 200 ms at the best ITD of the NDF. After 100 ms a 200 ms BF tone was added with varying ITD. The resulting stimulus sequence is: noise alone for 100 ms, tone and noise for 100 ms, and tone alone for 100 ms. To avoid overlapping of the responses, again assuming a neuronal delay of 20 ms, the time windows for the different sets of data were set as follows: the response to noise alone was derived for the interval from 20 to 100 ms, the response to tone and noise from 120 to 200 ms, and the response to the tone alone from 220 to 300 ms after stimulus onset. All tone and noise stimulus combinations were presented 10 to 20 times.

Data analysis

In the whole study all averaged quantities are denoted as mean ± standard error of the mean (SEM). Unless mentioned otherwise, significance was always determined by the Student’s two-tailed paired t-test with a level of significance $P < 0.05$.

Monaural tone and noise were defined as “excitatory” if the firing rate was significantly increased and as “inhibitory” if the firing rate was significantly decreased when
compared to the spontaneous rate. The vector strength of the monaural and binaural responses was calculated as described by Goldberg and Brown (1969).

Neurons were classified as ITD-sensitive if the Rayleigh test (Batschelet, 1991) showed a significant \( P < 0.001 \) deviation from a uniform distribution of response rates. The neuron’s mean interaural phase, eliciting the maximal spike rate, was calculated for each test frequency via a vector analysis following Yin and Kuwada (1983). We calculated the characteristic phase (CP) of the neurons using mean interaural phase versus frequency plots weighting each data point by the vector strength and the mean response (Kuwada et al., 1987; Spitzer and Semple, 1995). Peak-type neurons, described for the MSO, fire maximally at a characteristic ITD for which coincidence occurs. Trough-type neurons, described for the LSO, encode ITDs by being maximally suppressed at the ITD at which coincidence accrues. We defined peak-type neurons by an absolute CP of 0 to 0.25 cycles, trough-type neurons by an absolute CP of 0.25 to 0.5 cycles.

ITD-sensitivity of a single neuron is defined as the ability to respond with a different firing rate to different ITDs. Therefore we additionally measured the ITD-sensitivity of the neurons to tones in the presence of noise via the standard separation (D) of the response to the peak \( (R_p) \) and the trough \( (R_T) \) of the TDF (Sakitt, 1973). We used a modified version of the standard separation, described by Jiang et al. (1997a). This index gives a simple interpretation of discrimination that is independent of any assumptions about the underlying distributions. The calculation of D is described in the following equation:

\[
D = \frac{R_p - R_T}{\sqrt{SD(R_p) \times SD(R_T)}}.
\]

SD(\( R_p \)) and SD(\( R_T \)) denote the SDs of the respective response distributions. Random rating would produce \( D = 0 \) and perfect discrimination would produce an infinite D. We defined neurons as sensitive to ITDs, if D had a value above 2 (which is a quite conservative estimation).
Neuronal responses to combined tone-in-noise stimuli were classified as proposed by Jiang et al. (1997b) (see figure 7, schematic drawings). They presented correlated noise (ITD = 0, constant level) and measured the response rates to additional pure tones (signal) with increasing level. The signals were either presented with an ITD of zero (S₀) or phase inverted at one ear (Sₐ). If at some signal level the discharge rate to a combined tone-in-noise stimulus became one standard separation (D) larger than the discharge rate to noise alone, the neuron was classified as P-type (positive D-value). Conversely, a neuron was classified as N-type (negative D-value) if there existed a signal level at which the discharge rate to the tone-in-noise stimulus became lower than that to the noise alone. Since there are two stimulus conditions (S₀, Sₐ), each neuron was characterized by two letters (PP, PN, NP, NN). The first letter denoted the change in response for the signal S₀, the second one referred to Sₐ. In contrast to Jiang et al. (1997) in the present study we used stimuli with varying noise levels and a constant tone level. Thus we could not calculate standard separation as a function of the level of the pure tone. Instead we classified the neuron as P(N)-type, with respect to a significant increase or decrease in firing rate for the two tested noise levels independently (noise RMS equal to tone RMS and 20 dB below; ITD = 0). For all tested neurons, changes in firing rate were significant (P < 0.05).

Binaural correlation and model

The acoustic signals arriving at the ipsi- and contralateral ear were presented to the auditory nerve (AN) model by Tan and Carney (2003), which requires the characteristic frequency of the nerve fiber as a single parameter. In all simulations shown in this paper this characteristic frequency was chosen to be 1 kHz. The output of this model provides a firing probability per unit time. The resulting model outputs of the ipsi– and contralateral fibers are denoted by $a_{\text{ipsi}}(t)$ and $a_{\text{contra}}(t)$, respectively. These quantities were interpreted as proportional
to the presynaptic input rates to a coincidence-detector neuron in the superior olivary complex.

To quantify the amount of binaural correlations that are present in these input rates for different ITDs, we calculated their coefficient $r$ of correlation as:

$$r = \frac{\langle a_{\text{ipsi}} - \langle a_{\text{ipsi}} \rangle \rangle \langle a_{\text{contra}} - \langle a_{\text{contra}} \rangle \rangle}{\sqrt{\text{var}(a_{\text{ipsi}}) \cdot \text{var}(a_{\text{contra}})}}$$

in which

$$\langle a \rangle = \frac{1}{T} \int_0^T dt \, a(t)$$

denotes averaging over the duration $T$ of the stimulus (here $T = 100$ ms) and var is the variance over time. As a next step, to understand the subthreshold temporal summation of binaural synaptic inputs, we also assessed the temporal average $\left\langle \left( a_{\text{ipsi}} + a_{\text{contra}} \right)^2 \right\rangle$ of the squared binaural synaptic input rates (cf. Batra et al., 1997, Figure 12 A).

To also study subthreshold neuronal discharge rate we simulated two neuron models. Both were based on a simple integrate-and-fire mechanism (Gerstner and van Hemmen, 1994) at which the ipsi- and contralateral input rates $a_{\text{ipsi}}$ and $a_{\text{contra}}$ are convolved with an epsp kernel:

$$\kappa(t) = \begin{cases} e^{-t/\tau_1} - e^{-t/\tau_2} & \text{for } t \geq 0, \tau_1 > \tau_2 \\
0 & \text{for } t < 0 \end{cases}$$

and $\kappa(t) = 0$ for $t < 0$ to yield a mean membrane potential:

$$v(t) = \int_{t_0}^t dx \, \kappa(t-x) \left( a_{\text{ipsi}}(x) + a_{\text{contra}}(x-\Delta) \right).$$

Since synaptic inputs are of stochastic nature, we derived a noisy voltage trace by adding a Gaussian random variable $\eta$ to the mean input rates $a_{\text{ipsi/contra}}$. The variance of $\eta$ (in a small time interval of length $dt$) was set to a value of $a(t)dt/N$ as it would be expected from $N$ independent AN fibers per ear firing with Poisson statistics. Here, we assumed $N = 200$. Each
time the noisy membrane potential hit a threshold \( \theta \), the neuron generates an action potential and the voltage is reset to its resting potential \( v = 0 \). To limit the instantaneous firing rate to 200 Hz, we additionally introduced a refractory time of 5 ms. The shape \( \kappa \) of the excitatory postsynaptic potential was modeled using an exponential decay time \( \tau_1 \) of 200 µs and an exponential rise time \( \tau_2 \) of 100 µs (compare: Scott et al., 2005). The contralateral input was delayed by \( \Delta = 150 \) µs. This model we refer to as Jeffress-type model, since it incorporated a combination of coincidence detection and temporal delay (Jeffress, 1948). The firing threshold \( \theta \) of this neuron was adjusted to obtain a mean maximal firing rate of about 60 Hz for pure tone stimulation. In the second neuron model, we did not use a contralateral temporal delay, i.e., \( \Delta = 0 \). Instead, we added phase-locked contralaterally driven inhibition which is able to delay the effective contralateral excitation, if it arrives shortly before this excitation (Brand et al., 2002). The inhibitory kinetics was modeled with the same kernel \( \kappa \) as the excitation except that it was multiplied with a constant factor \( g = 2/3 \). To obtain the same best ITD as for the Jeffress-type model, the contralateral inhibition was modeled to arrive \( \Delta = 150 \) µs before excitation (Leibold and van Hemmen, 2005). The noise in the inhibitory inputs was determined by assuming \( N = 100 \). The resulting subthreshold dynamics of the membrane potential \( v \) is thus expressed by the convolution integral:

\[
v(t) = \int_{t_0}^{t} dx \kappa(t-x) \left( a_{\text{ipsi}}(x) + a_{\text{contra}}(x) - ga_{\text{contra}}(x+\Delta) \right).
\]

The firing threshold \( \theta \) was adjusted to obtain similar firing rates as for the previous model.

All TDFs of the spiking neuron models shown in Figure 6 were derived from 100 repetitions of the auditory stimulus.
Results

Data presented here were derived from single cell recordings from 111 ITD-sensitive DNLL neurons. We first studied the effect of different levels and ITDs of white noise on the response to tones presented at different ITDs (N = 80). To differentiate between effects arising from monaural processes and those caused by binaural interactions at the coincidence-detectors in MSO and LSO, we also investigated the monaural responses to tones in noise (N = 32) as well as the binaural responses to tones with spectrally adjusted noise (N = 31). Since these recordings suggested that lateral frequency integration decreases the response to tones, we compared our experimental data for narrow band noise stimuli with numerical simulations of a model of a coincidence-detector neuron.

Effects of binaural noise on tone delay functions

ITD-sensitive neurons show a distinctive maximum and minimum in their response to a favorable and an unfavorable ITD, respectively. To study the effects of noise on the ITD processing of pure tones, we focused on these two prominent response features evoked by the favorable and the unfavorable ITD. We used white noise at two different levels: one with the same level (RMS) as the tone and the other one 20 dB lower, corresponding to the threshold level for tones at BF.

Adding this noise to tones at favorable and unfavorable ITDs affected the maximal and minimal responses in opposite directions (figure 1). Noise suppressed the response to the favorable ITD (figure 1A) but slightly increased the response to the unfavorable ITD of the pure tone (figure 1B). Both effects became stronger with an increasing level of noise. All of these effects were statistically significant (P < 0.001) for the higher level of noise. For the lower level of noise the decrease of the response to the favorable ITD of the pure tone with noise at best ITD (figure 1A2) was significant (P < 0.001). The change of the TDFs was
measured for two different ITDs of the noise stimulus. If the ITD of the noise (noise level =
tone level) was set to 0 µs, which evoked an intermediate firing rate for most of the neurons,
the peak response was decreased to 46 ± 5.9 % \((P < 0.001)\) of the peak response to pure tone
stimulations (117 ± 7.4 spikes/s) (figure 1A2, left). The trough response was significantly
increased from 2.7 ± 0.5 % to 4.7 ± 0.8 % of the peak response to pure tone stimulation \((P =
0.044)\) (figure 1B2, left). If the ITD of the noise (noise level = tone level) was set to the best
ITD, the average peak responses were reduced to about 62 ± 6.6 % \((P < 0.001)\) (figure 1A2,
right) and the trough response statistically significantly increased from 2 ± 0.5 % to 6.1 ± 1 %
of the peak response to the pure tone stimulation \((P < 0.001)\) (figure 1B2, right). The effects
of the noise on the firing rate to tones at favorable and unfavorable ITDs did not differ
between peak- and trough-type ITD-sensitive neurons. The average responses to unfavorable
ITDs for both types are shown in figure 1B3.

To investigate how the noise-induced changes of peak and trough firing rates
influence ITD-sensitivity of the neurons, we calculated the standard separation \((D)\) of the
responses to the tone at favorable and unfavorable ITD (figure 2, see methods). Even for large
D-values, a considerable fraction of the neurons remains ITD-sensitive under all noise
conditions tested (figure 2A). The percentage of ITD-sensitive neurons was a decreasing
function of noise level, but was rather independent of the ITD of the noise (figure 2A). If we
applied a conservative separation threshold of \(D > 2\) we found that 96 % \((77/80)\) of the
neurons remained ITD-sensitive to tones when the noise was presented at ITD = 0 and 97 %
\((72/74)\) of the neurons remained sensitive for noise presented at best ITD. These fractions
were obtained presenting additional noise with intensities 20 dB below the tone level. If the
noise was presented at the same level as the tones the fractions were reduced to 71 % \((57/80)\)
for noise with ITD = 0 and 74 % \((55/74)\) for noise presented at best ITD (figure 2). Hence,
the ITD-sensitivity of DNLL neurons to tones showed a high robustness against additional
noise.
From a different point of view, the pure tone reduces or enhances the response to white noise. Therefore in addition to the question of how noise effects the localization of pure tones, we also addressed how the location of pure tones affected the response to noise. This was quantified through the differences between the average response rate to the noise alone and the response rate with additional tones at favorable or unfavorable ITDs. We refer to these differences as tone-induced reduction and tone-induced enhancement of the response to noise (figure 3A). On average with increasing noise level the response to noise increased \((P < 0.001)\) (figure 3B) but the tone-induced enhancement significantly decreased \((P < 0.001)\). Furthermore, with increasing noise levels, the increase of the response to noise alone was much stronger (figure 3B) than the increase of the response to the combination of noise and tones at unfavorable ITD (figure 1B). Therefore in contrast to the tone-induced enhancement the tone-induced reduction got stronger with increasing noise level \((P < 0.001)\) (figure 3C). The effects of tones on the responses to noise were independent of whether the neuron was a peak- or a trough-type neuron (compare figure 3C and 3D left and right). All described changes shown in figure 3 were significant for both levels of noise.

To conclude, white noise presented at levels up to equal that of the tone decreased the maximal response to tones at favorable ITDs, but the minimal response at the unfavorable ITD slightly increased. The strong tone-induced reduction of the response to noise accounted for the robustness of the ITD-sensitivity against additional noise.

Monaural contributions to the noise-induced effects on tone delay functions

To distinguish which of the noise-induced effects on TDFs are due to binaural interactions at the level of the coincidence-detectors in the superior olivary complex and which can be explained independently of binaural interactions we also recorded responses of DNLL neurons to monaural tones in monaural noise. The neuronal discharge rate (see raster
plots figure 4A left panel) evoked by monaural excitation was generally lower than that to binaural stimulation at the best ITD of the neurons. Nevertheless a considerable number of the ITD-sensitive DNLL neurons were significantly excited by contra- (27/32; 84 %) or ipsilaterally (19/32; 59 %) applied pure tones (example shown in figure 4A, average response in figure 4B, black bars). Adding monaural noise to the monaurally presented tones on average decreased the responses for both, ipsi- \((P < 0.001)\) and for contralateral stimulations \((P = 0.055)\) (figure 4B).

The temporal structure of the firing pattern was quantified by the vector strength of phase locking to the pure tone stimulus. The vector strength was slightly lower for monaural as for binaural stimulations (see phase plots figure 4A, right panel). Moreover, phase locking slightly decreased by adding noise, both in monaural and binaural stimulations (figure 4C).

The relative decrease of monaural response rates was similar to the noise-induced decrease of the responses at favorable ITDs obtained with binaural stimuli. Therefore, we hypothesize that the noise-induced reduction of the binaural response to tones at favorable ITDs has the same origin as the decrease of the monaurally evoked firing rates. On the other hand, the small but significant increase of the binaural response to tones with unfavorable ITD with increasing noise level could not be attributed to any of the monaural effects. Thus the tone-induced reduction of noise responses was likely to originate from binaural interaction at the coincidence-detectors at the level of the superior olivary complex.

Effects of notched noise and tuned noise on TDFs

The response rate of ITD-sensitive coincidence-detector neurons can be influenced by the frequency composition of the stimulus as well as the binaural correlations of their inputs. To distinguish the observed effects of noise on the TDFs in terms of these two mechanisms, we used three different noise stimuli: white noise, notched noise, and tuned noise. Notched
noise should mainly stimulate the frequency components a neuron is not excited by. Tuned noise was intended to cover the excitatory spectral components. All three noise stimuli were presented at best ITD and at the same level (RMS) as the pure tones.

As shown in the example in figure 5, notched noise consists of frequencies the neuron was only weakly responding to (see methods and figure 5A and 5B). Therefore the response to notched noise was smaller than the response to white noise (figure 5C). Consistent with this example the average responses to notched noise (23.8 ± 3.5 spikes/s) were significantly smaller (P < 0.001) than these to white noise (31.8 ± 3.6 spikes/s) (figure 5D). The effects of notched noise on the response to tones at favorable as well as at unfavorable ITDs were very similar to the effects of white noise (single response in figure 5C; average response in figure 5E); The responses to favorable ITDs were decreased, whereas the responses to unfavorable ITDs of the tones were slightly increased by adding both white noise or notched noise. Since the response to white noise was stronger than that to notched noise, the tone-induced enhancement at favorable ITDs was smaller and the tone-induced reduction at unfavorable ITDs was stronger in the white noise condition (figure 5F and 5G). Taken together, although the tone-induced effects were slightly different, notched noise and white noise had similar impact on TDFs.

Tuned noise was constructed from frequencies strongly exciting the neuron (see methods and figure 5A and 5B). Therefore the responses to the tuned noise (average response: 99.0 ± 6.9 spikes/sec) were stronger than the average response to white noise (P < 0.001) (figure 5C, figure 5D). Adding tuned noise to a tone with favorable ITD on average slightly but not significantly (P = 0.21) enhanced the response rate by 5 % (figure 5E, left), in contrast to white or notched noise, which decreased the response rate. Furthermore tuned noise also elevated the firing rate for tones at unfavorable ITDs (figure 5E, right). Despite a small increase of the response to the favorable ITD with increasing the level of tuned noise (figure 5E), the tone-induced enhancement was decreased and the tone-induced reduction of the noise
was increased (figure 5F); the latter effects were a direct consequence of the strongly increased response to tuned noise alone (dark gray dashed line in figure 5C).

Although the responses to the different spectral noise composites showed clear differences, the proportion of neurons which were sensitive to ITDs was almost unchanged when the noise level for each condition was equal to the tone level. For tuned noise, all neurons remained ITD-sensitive, whereas 77% (24/31) of the neurons (figure 5G) remained ITD-sensitive for both notched and white noise. Importantly, while the response rate to tones strongly depended on the spectral components of the added noise, the ITD-sensitivity to the tone was preserved with all different types of added noise.

We note that all three types of noise stimuli were presented at best ITD and with the same RMS as the RMS of the pure tones. The effective levels of these different types of noise for a particular neuron may thus be very different. In particular the effective level of the spectrally shaped noises, which are composed of fewer spectral components as the white noise, will presumably be higher. The conclusions of our paper, however, refer to changes of firing rates in dependence of noise intensity for each different type of noise separately. Therefore, though we might underestimate the effective level of the notched or tuned noise, the general trends are supposed to be the same.

Simulated effect of the noise level on binaural correlations

Tuned noise had been constructed in order to reduce cross-frequency interactions or effects caused by lateral suppression. We thus assumed the NDFs derived from tuned noise stimulation to be largely inherited from the coincidence-detector neurons in the superior olivary complex within the same frequency channel. To understand the neuronal responses to tuned noise, we investigated how binaural correlations are temporally processed and translated to firing rates in a neuronal model receiving input from a single frequency channel.
We therefore derived binaural input rates of the coincidence-detector neurons from feeding
the acoustic stimuli into the AN model of Tan and Carney (Tan and Carney, 2003) for a
characteristic frequency of 1 kHz. However, before studying a cellular model we first
calculated the coefficient of correlation between the binaural input rates as a function of pure
tone ITD (figure 6A1). As expected, with increasing noise level, the coefficient of correlation
becomes less dependent on the pure tone ITD and saturates at a constant value of 1. The
coefficient of correlation thus is not a good model for the discharge rate of the coincidence
neuron since it cannot explain the noise-induced increase in the peak rate, though it might
qualitatively explain the increase of the trough firing rate (figure 6A2).

As a next step to also include subthreshold integration of the binaural signal we
calculated the temporal average of the squared input rates and interpret this as a firing rate
(figure 6B). Energy models like such are long and widely used in visual (e.g., Adelson and
Bergen, 1985) and auditory systems neuroscience (Batra et al. 1997; Gollisch, 2006) and
incorporate the probably simplest non-linearity. The outcomes of this model show that an
increase of the noise level yields an increase in both the response to the favorable as well as
the unfavorable ITD and hence at least qualitatively can account for the observed in-vivo
responses. The sound intensity (20 dB above neuronal threshold) of the tuned noise used in
the experiment roughly corresponded to a noise level of 30 dB SPL (above standard threshold
of audibility) in the model. Consistent with our empirical DNLL data for tuned noise
stimulation, the peak response at 30 dB SPL (in the model) was slightly enhanced as
compared to the peak response obtained from pure tone stimulation. However, the increase of
the trough response was considerably larger than that observed in the data. The latter
discrepancy could be resolved by applying the input rates to simple integrate-and-fire-type
spiking neuron models (figure 6CD). As a result of the threshold non-linearity, the trough
firing rate at 30 dB SPL was only slightly enhanced as compared to the trough of the TDF.
The best ITD of the model neurons was shifted to 0.15 ms to match the averaged best ITDs of recorded DNLL units. In the first model (figure 6C) this shift was achieved by an additional temporal delay of contralateral excitatory inputs that might arise from longer axonal conduction. This way of shifting the best ITD dates back to the model of neuronal ITD representation by Jeffress (1948). Recently, another computational model of how to neuronally encode ITDs has been proposed by Brand et al. (2002), who showed that phase-locked inhibition evoked by inputs to the contralateral ear can also induce a shift of the best ITD if this inhibition arrives slightly earlier. We also implemented a model using contralateral phase-locked inhibition (figure 6D) to test whether the mechanism that accounts for the peak shift is crucial to explain the effects of tuning noise upon the TDFs of a coincidence-detector neuron. However, the phase-locked inhibition model exhibits both peak and trough firing rates with a virtually identical dependence on noise intensity as the Jeffress-type model (compare figure 6C and 6D). Hence our modeling cannot make a prediction on the mechanism of the peak shift.

To conclude, our models show that additional binaurally correlated noise does not reduce the peak firing rate of the TDF as noise intensity increases. The model thus corroborates the interpretation that the suppressive across-frequency interactions resulting in a reduction of the peak firing rate under notched and white noise stimulations are due to either inhibitory or binaurally uncorrelated contributions from lateral frequency bands. A second conclusion from our models is that the increase of the firing rate at the trough of the TDF with increasing noise level can be explained by a simple binaural coincidence-detector acting on binaural AN inputs. For the AN model by Tan and Carney (2003), the threshold noise intensity of about 30 dB SPL, at which the trough firing rate starts to linearly increase, is in good quantitative agreement with our DNLL data.
Discussion

The present study investigated the effect of a concurrent noise source on the sensitivity of DNLL neurons to ITDs of pure tones and vice versa. Although the neurons were responsive to binaural white noise, we found that, for the combination of white noise and pure tone, the neuronal response to the tones at best ITD decreased with additional noise. The response to unfavorable ITD slightly increased with additional noise. However, for all tested noise levels (up to RMS-identical tone and noise levels) it remained below the firing rate evoked by the noise stimulus alone. From a different point of view, a pure tone at unfavorable ITD could thus be considered to reduce the response to white noise.

The decrease of the response to a tone at favorable ITDs and the increase of the response to tones at unfavorable ITDs can be explained by two different mechanisms: monaural across-frequency interactions and temporal summation at the level of the coincidence-detector.

The influence of noise on TDFs was strongly dependent on the spectral composition of the noise. Notched noise, which was constructed to specifically stimulate suppressive side bands, had similar effects on TDFs as white noise. In contrast, tuned noise, which consists primarily of excitatory spectral components, did not suppress the neuronal discharge rate evoked by a pure tone at favorable ITD. Therefore these results support the hypothesis that the suppression of the response to favorable ITDs results from a spectral integration with a dominating role of suppressive side bands. The fact that noise presented at levels below excitatory thresholds for pure tones stimulation effected response rates to TDFs indicates sub-threshold across-frequency interactions. The lateral suppression, however, could already occur prior to the binaural processing stage, e.g. in the cochlear nucleus or in the cochlea. Our monaural data also showed a decrease in the response to tones with increasing level of
additional noise. This strengthens the idea that lateral suppression decreases the response to tones at favorable ITDs with increasing noise level.

Lateral suppression, however, cannot explain the observed small increase of the response to the unfavorable ITDs. Hence, the increase of the response to unfavorable ITDs by adding noise is likely to result from binaural interactions at the level of the coincidence-detector in the superior olivary complex. Simulations of simple coincidence-detector models receiving input from a single frequency channel corroborate this interpretation. In these models, adding binaural noise results in an increase of both the trough and the peak firing rate.

Comparison with previous monaural studies

Neuronal responses to stimulations with tones in combination with noise have been electrophysiologically studied in monaural structures i.e. the auditory nerve (Kiang and Moxon, 1974; Rhode et al., 1978; Young and Barta, 1986) and the cochlear nucleus (Goldberg and Greenwood, 1966; Greenwood and Maruyama, 1965; Gai and Carney, 2006). There, neurons generally respond stronger to tonal stimuli than to noise stimuli and the response to a combination of tone and noise is weaker than the response to tones alone. Furthermore, Kiang and Moxon (1974) also showed substantial across-frequency interactions at the level of the auditory nerve. These findings are consistent with the results from monaural and binaural notched noise stimulations presented in this study (figure 4). Therefore part of the suppressive effects caused by spectral integration we observed in the DNLL with spectrally adjusted noise stimuli could be explained by mechanisms, which might take place already at the level of the cochlea.

Comparison with binaural studies on the detection of tones in noise
Previous psychophysical studies showed that noise substantially affects the ability to
detect pure tones and, moreover, that this ability is strongly influenced by the ITD of the tone
(for review see: Blauert, 1983): the detection threshold for tones with 0 ITD (S₀) in noise with
0 ITD (N₀) improves dramatically when the phase of the tone at one ear (Sₑ) is inverted.
These results correlate with change of the firing rate of single neurons in the inferior
colliculus (IC) (Caird et al., 1991; Jiang et al., 1997b; Jiang et al., 1997a; McAlpine et al.,
1996; Jiang et al., 1997b; Jiang et al., 1997a; for review see Palmer and Shackleton, 2002).
Furthermore, in these studies the neurons are classified according to their changes of the firing
rate to noise and tones (N₀S₀ or N₀Sₑ) with increasing tone intensity. Since the main focus of
our study was not detectability but rather localization of pure tones we varied the ITD of the
tones and used two different noise levels. We therefore cannot make statements on whether
the IC neuron’s detection capability is present at the level of the DNLL. However, for N₀S₀
versus N₀Sₑ stimulation we did the same classification for our set of 80 neurons as in the IC
literature (figure 7; Jiang et al., 1997b). While there were small differences between the
results for the two noise levels, most of the neurons (66/80 for noise level at 20 dB below tone
level, and 65/80 for noise level at tone level) showed an increase in the response to noise with
additional tones with zero ITD (S₀) (Type-PP or Type-PN). As in the IC a few neurons
showed a decrease in the response with additional tones at zero ITD (Type-NP or Type-NN).
Altogether the fractions are similar to those reported from the population of IC neurons
measured by Jiang and colleges (Jiang et al., 1997b). We thus conclude that the ITD-
dependent detectability of tones in noise shown in the IC reflects the one we observed on the
level of the DNLL. Since the DNLL is a mainly inhibitory nucleus and therefore almost
certainly not solely responsible for the features of IC neurons, the similarity indicates that the
superior olivary complex is the potential site providing the relevant computational
mechanisms.
Comparison with binaural studies on the localization of tones in noise

The psychophysical studies investigating the localization of tones in background noise showed that accuracy and discrimination ability declines with increasing level of background noise (Stern et al., 1983, Good and Gilkey, 1996). This finding is consistent with the single neuron responses we report in this study, since background noise reduces the discriminability of peak and trough firing rates and, hence, the fraction of ITD sensitive neurons (figure 2).

Furthermore, psychophysical studies have shown that, in contrast to the detection of pure tones, the ITD discrimination of a signal (pure tone or narrow band noise) is improved, if the ITD of the background noise has the same ITD as the signal (Cohan 1981, Ito et. al., 1982). In the present study, however, we only see a small reduction of ITD sensitive neurons if we change the noise ITD from best ITD to 0 ITD (figure 2). Our results therefore cannot provide a link between single cell recordings in the DNLL and psychophysics.

Functional relevance

Our data reveal a complex interaction between the concurrent sound sources, in our example of tones and noise. The overall firing rates of the ITD-sensitive DNLL neurons to tones are strongly modulated by noise and vice versa the firing rate to noise is strongly modulated by tones. Furthermore, we observed a complex interaction between the spatial and the spectral cues. Different values of the neuronal firing rate seem to encode different spectral properties of the acoustic stimulus composition. Therefore we hypothesize that in contrast to theses spectral cues, the spatial cues are encoded independently of the actual firing rate via activity patterns in a population of neurons (Jeffress, 1948; Fitzpatrick et al., 1997; Hancock and Delgutte, 2004; Harper and McAlpine, 2004; Stecker et al., 2005).
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Reference List:


Figure Legends:

Figure 1

Effects of increasing the level of white noise at 0 or best ITD on the response to tones at favorable (A) and unfavorable (B) ITD. A1, B1: Raster plots of a single-unit response to tones at favorable (+420 µs) and unfavorable ITD (-280 µs) with increasing noise at best ITD (neuron: 050106_07; BF = 750 Hz). Analysis windows with a standard delay of 10 ms after stimulus onset are displayed by the light gray area underlying the raster plots. The presentation of the tone is indicated by the black bar, the noise level by the color coded line below the plots. A2, B2-3: Summarized population statistics. The maximal and minimal firing rates of the TDFs with noise are normalized to neuron’s maximal response of the TDF and than averaged over the population. B3: minimal average firing rate to tones in noise at best ITD are shown separately for the peak and trough types. All of these effects were statistically significant (P < 0.001) for the higher level of noise. For the lower level of noise the decrease of the response to the favorable ITD of the pure tone with noise at best ITD (figure 1A2) was significant (P < 0.001). Error bars = standard error of the mean (SEM).
Figure 2

Effect of increasing white noise on the ITD-sensitivity of the neurons. ITD-sensitivity is measured by the standard separation $D$ of the response to tones at favorable and unfavorable ITD (A, B). A: The percentage of neurons defined as ITD sensitive versus D-value. The effects of increasing noise were similar for noise at 0 µs ITD (A2) or at best ITD (A1). B: Percentage of neurons classified as ITD-sensitive with $D > 1.5$. C: Percentage of neurons with significant vector strength (VS).
Figure 3

Effects of tones on the response to white noise with increasing level. A: Exemplary firing rates of a single-unit and calculation of the three measures from TDFs with increasing noise level (neuron: 151205_05; BF = 700 Hz; the shapes of the recorded action potentials on the right demonstrate a single cell recording). B-D: Summarized population statistics. B: The response to noise at best ITD increased with increasing level (). C: The enhancement of the response to noise induced by tones at favorable ITD decreased. D: The reduction of the response to noise induced by tones at unfavorable ITD increased with increasing noise level. All described changes were significant for both levels of noise. Error bars = standard error of the mean (SEM).
Monaural and binaural responses to tone in white noise. A: Raster plots and period histograms of single-unit responses to contralateral (A1), ipsilateral (A2), and binaural (A3) stimulations with tone and noise presented at the same time. The shapes of the recorded action potentials on the right demonstrate a single cell recording (neuron: 151205_02; BF = 800 Hz). The noise level was 20 dB below the tone level. B-C: Summarized population statistics. B: Average contralateral and ipsilateral responses to tone and noise stimulation decreases with increasing noise level. C: The average vector strength (VS) of the monaural and binaural responses is slightly decreased by additional noise. Error bars = standard error of the mean (SEM).
Figure 5

Effects of white, notched, and tuned noise on TDFs. From the frequency-versus-level response areas (A; neuron: 181006_04, BF = 1000 Hz) we calculated the neuron’s notched and tuned noise (B). C: Single-unit response to the three different types of noise at best ITD are shown in dashed lines. The error bar on the right side shows the standard error of the response to the noise. The TDFs with concurrent presented noise are shown with lines, the TDF without noise in a dotted line. (neuron: 061006_04, BF = 800 Hz). D-G: Summarized population statistics. D: The response to noise E: The maximal and minimal response to tones in noise F: The enhancement and reduction of the response to noise by tones. G: Although there are differences in the response rate the ITD-sensitivity to tones remained in more than 75 % of the neurons independent of the spectral component of the added noise. Error bars = standard error of the mean (SEM).
Figure 6

TDFs (left column) derived from models. Concurrent noise was applied with different levels and at best ITD. Gray levels encode the noise intensity from 10 (dark) to 50 dB SPL (light). Peak and trough firing rates as a function of noise level are depicted in the right column. The gray areas indicate the noise level used in the experiment. A: Coefficient of correlation between ipsi- and contralateral AN model responses. B: Mean squared binaural sum of AN rates (see Methods). C, D: Firing rates derived from simple neuronal threshold models of either Jeffress- (C) or phase-locked inhibition-type (D).
Figure 7

Different types of binaural masking. Comparison of our DNLL data with the population of IC neurons measured by Jiang et al. (1997b). The schematic drawings describe the responses underplaying the division into the different types.
Supplementary Figure

A: Power spectrum of stimuli used: tone alone, tone with noise (RMS 20dB below RMS of tone) and tone with noise (same RMS as tone). B: The “effective” level of the tone and noise stimuli with the same RMS in the most relevant frequency band (500-1500 Hz). A and B are measured using a FFT Network analyzer (Stanford Research System, USA). C: Rate-level functions of a randomly chosen subpopulation of neurons tested with either tone alone or noise alone.
Figure 1

A tone at favorable ITD

A1

A2

n = 80  n = 74

% TDF peak

0 20 40 60 80 100 120

ITD noise: 0 µs  best ITD

0 20 40 60 80 100 120 n = 80 n = 74

B tone at unfavorable ITD

B1

B2

% TDF peak

0 2 4 6 8

ITD noise: 0 µs  best ITD

0 2 4 6 8

spikes/s

spikes/s

0 115 230

0 115 230

ITD (µs)

ITD (µs)

ms 0 115 230

ms 0 115 230

no noise  noise = 20 dB below tone level  noise = tone level

--- spontaneous activity

no noise  noise = 20 dB below tone level  noise = tone level

--- spontaneous activity

peak-type  trough-type

n = 44  n = 30

n = 44  n = 30
Figure 2

A. ITD noise: 0 µs

B. % of neurons $D \times 2$

C. % of neurons sig. VS

- no noise
- noise = 20 dB below tone level
- noise = tone level

A1 ITD noise: 0 µs

A2 ITD noise: best ITD

B

C

N = 80

N = 74

ITD noise: 0 µs

best ITD

Figure 2

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Figure 3

A

B

N = 74

response to noise (B)

ITD (µs)

enhancement (C)

reduction (D)

response to noise (B)

response to noise (B)

N = 74

trough-type; peak-type

response to noise (Hz)

response to noise (Hz)

% TDF peak

% TDF peak

D

trough-type; peak-type;

n = 30

n = 44

% TDF peak

% TDF peak

-1200 -800 -400 0 400 800 1200

response to noise (Hz)

response to noise (Hz)

-1200 -800 -400 0 400 800 1200

enhancement (C)

reduction (D)

response to noise (B)

response to noise (B)

enhancement (C)

reduction (D)

response to noise (B)

enhancement (C)

reduction (D)

response to noise (B)

enhancement (C)

reduction (D)

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response to noise (B)

enhancement (C)

reduction (D)

response to noise (B)

enhancement (C)

reduction (D)

response to noise (B)

enhancement (C)

reduction (D)

response to noise (B)
Figure 4

A1

contra

A2

ipsi

A3

contra

+ipsi

ITD = +391 µs

B

contra

ipsi

monaural response (Hz)

0 115 230

spikes

0 1 2

0.5 1 0 500 µs

spikes

0 4 8 10 20 30

VS = 0.54

VS = 0.38

VS = 0.45

C

contra n = 27

ipsi n = 19

binaural n = 74

vector strength

0 0.2 0.4 0.6

no noise

noise = 20 dB below tone level

noise = tone level

spontaneous activity

Volt

contra ipsi

n = 27

n = 19

n = 74
Figure 5

A

B

C

D

E

F

G
Figure 6

A. Binaural AN correlation

B. Mean squared input rate

C. Jeffress firing rate (Hz)

D. Phase-locked inhibition

A_2

B_2

C_2

D_2