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Sensitivity to interaural time difference and representation of azimuth in central nucleus of inferior colliculus in the barn owl

Peter Bremen · Iris Poganiatz · Mark von Campenhausen · Hermann Wagner

Abstract Standard electrophysiology and virtual auditory stimuli were used to investigate the influence of interaural time difference on the azimuthal tuning of neurons in the core and the lateral shell of the central nucleus of the inferior colliculus of the barn owl. The responses of the neurons to virtual azimuthal stimuli depended in a periodic way on azimuth. Fixation of the interaural time difference, while leaving all other spatial cues unchanged, caused a loss of periodicity and a broadening of azimuthal tuning. This effect was studied in more detail in neurons of the core. The azimuthal range tested and the frequency selectivity of the neurons were additional parameters influencing the changes induced by fixating the interaural time difference. The addition of an interaural time difference to the virtual stimuli resulted in a shift of the tuning curves that correlated with the interaural time difference added. In this condition, tuning strength did not change. These results suggest that interaural time difference is an important determinant of azimuthal tuning in all neurons of the core and lateral shell of the central nucleus of the inferior colliculus, and is the only determinant in many of the neurons from the core.

Abbreviations

ABL	Average binaural level
$AddT_x$	Manipulated virtual stimuli with additional ITD with x denoting the value of the additional ITD
FixT1–FixT4	Different types of virtual stimuli with fixed ITD
HRIR	Head related impulse response
HRTF	Head related transfer function
IC	Inferior colliculus
ICC	Central nucleus of the IC
ICCc	Core of the ICC
ICCls	Lateral shell of the ICC
ICX	External nucleus of the IC
ILD	Interaural level difference
IR	Impulse response
ITD	Interaural time difference
RAF	Rate azimuth function

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Introduction

Barn owls use interaural time difference (ITD) and interaural level difference (ILD) to localize sounds in azimuth and elevation, respectively (Moiseff and Konishi 1981; Moiseff 1989; Saberi et al. 1998, 1999). In this animal, these binaural cues are processed independently in anatomically separate auditory pathways (Moiseff and Konishi 1983; Takahashi et al. 1984; Takahashi and Konishi 1988) up to the inferior colliculus

(IC). The IC consists of a central nucleus (ICC), an external nucleus (ICX), and a superficial nucleus (Knudsen 1983; Wagner et al. 2003). The ICC can be divided into a core (ICCc), a lateral (ICCls) and a medial shell.

Neurons in the ICCc are narrowly tuned to frequency. The response threshold and the response strength to stimulation from the ipsi- or contralateral ear are similar. The neurons in ICCc are sensitive to ITD but not to ILD. When the ITD is varied, the response of the neurons changes in a cyclic manner (Wagner et al. 1987, 2002). Core neurons project to the ICCls (Takahashi et al. 1989). ICCls neurons are similar to ICCc neurons in their ITD sensitivity and tonotopic organization but are, in addition, tuned to ILD (Adolphs 1993; Mazer 1998). The ICCls, in turn, projects to the ICX where a map of auditory space was found (Knudsen and Konishi 1978a). The receptive fields of ICX neurons are limited in both azimuth and elevation. Therefore, these neurons were called space-specific neurons (Knudsen and Konishi 1978a). The responses of the space-specific neurons depend on both the ITD and ILD in a multiplicative way (Pena and Konishi 2001).

Behavioral studies have shown that ITD is the cue that determines azimuthal head turns (Moiseff and Konishi 1981; Moiseff 1989; Poganiatz et al. 2001). Lesion studies (Knudsen et al. 1993; Wagner 1993) as well as recordings from space-specific neurons of the ICX (Olsen et al. 1989; Brainard et al. 1992; Saberi et al. 1999) indirectly suggest an important role of ITD in representing azimuth. Furthermore, several studies directly showed a loss of azimuthal tuning in space-specific neurons after fixation of ITD (Euston and Takahashi 2002; Spezio and Takahashi 2003; Keller and Takahashi 2005). A study that tests the relation between ITD tuning and azimuth tuning in ICCc and ICCls directly is missing. This is the aim of the present study. While is seems clear from the evidence listed above that there should be a relation between ITD and azimuth in the tuning of the ICCc neurons, the interesting question tackled here is, how this relation looks like in quantitative terms. It should be noted that especially the study of ICCc neurons may have some advantages, because the responses of the neurons in ICCc are simpler and more related to single stimulus parameters than the responses of neurons in the ICX (Moiseff and Konishi 1983; Fujita and Konishi 1991).

The virtual space technique is a suitable method to investigate this question, because with this technique it is possible to simulate spatial sounds presented via earphones that are indistinguishable from free-field sounds (owl: Keller et al 1998; human: Wightman and

Kistler 1989a, b; cat: Rice et al. 1992; Tollin and Yin 2002) and to manipulate spatial cues independently from other cues of the sound signal (Nelken et al. 1998; Poganiatz et al. 2001; Poganiatz and Wagner 2001; Euston and Takahashi 2002; Spezio and Takahashi 2003). This independence makes it possible to draw conclusions about the role of these parameters in behavior and neuronal processing. The manipulations of virtual stimuli allowed us to demonstrate that ITD is an important determinant of azimuthal tuning in all neurons of the core and lateral shell of the central nucleus of the inferior colliculus, and is the only determinant in many of the neurons from the core.

Materials and methods

General procedures

Experiments were carried out with five captive-bred barn owls (F, M, J, O, and S). Each owl was used for several electrophysiological experiments. Experiments were performed under anaesthesia (Ketamine 4–20 mg/kg/h). Animals were tranquilized with Diazepam (Valium, 1 mg/kg/h). Atropine sulfate (0.05 mg/kg) was used to prevent salivation. At the beginning of an experiment a metal plate was chronically implanted on the animal's skull. This holder made it possible to fix the head of the birds in a constant position during the recordings. For the electrophysiological experiments the dorsal surface of the brain was exposed to allow the penetration into the brain of insulated tungsten microelectrodes (Frederick Haer Co., 3–15 MΩ). The electrodes were advanced through the brain from dorsal to ventral with a remote-controlled stepping motor. Action potentials from neurons were recorded extracellularly, amplified (M. Walsh Electronics) and passed to a computer and an audio-monitor for storage and acoustical online control, respectively. Initialization of acoustic stimulation and recording of spikes was performed with specific software (Brainwave Version 5.1 and Brainware Version 6.1.1). After the experiment the brain was covered with Vaseline, the hole in the skull was filled with dental cement, and the skin incision was closed.

Measurement of impulse responses and calculation of head-related transfer functions

Measurements were performed in two slightly different setups, setup 1 (owls: F, M) and setup 2 (owls J, O, S). Head-related impulse responses (HRIRs) were measured individually for each owl (for details see

Poganiatz et al. 2001). For recording impulse responses, the animal was anaesthetized, wrapped in a jacket, and placed in the center of a sound-attenuating chamber (2.4 m × 2.1 m × 2.7 m, IAC, double wall [setup 1], IAC 403A [setup 2]) in a natural posture. Impulse responses were measured inside the ear canal in front of the eardrum. The tip of a 4 cm long plastic tube, attached to a Sennheiser KE 4-211-2 microphone, was positioned 15 mm inside the ear canal of each ear.

To record HRIRs in setup 1, stimuli were presented from a loudspeaker that could be moved in elevation and azimuth on a semicircular vertical hoop. Computer generated clicks with a duration of 12 μs (<60 dB SPL, A-weighted) amplified by a HiFi-amplifier (DENON PMA-S10) were used for the measurement. The clicks were presented from a loudspeaker (TW6NG, 2–12 kHz: flat within ±3 dB, measured on axis) at a distance of 95 cm from the center of the owl's head. Reflections from the hoop and other distant objects in the sound chamber that could be detected in the recorded impulse responses as a delayed echo of the original transient signal were cut off by windowing (Hanning window, length 6 ms). Microphone signals were pre-amplified by custom-built amplifiers, low-pass filtered (Tucker Davis Technologies FT6, corner frequency 20 kHz) and converted to a digital signal (sampling rate 50 kHz, recording length: 1,024 samples) by a computer board (Data Translation DT2821). Recordings of 1,000 clicks were averaged for each of the 377 positions in space (for more details see Poganiatz et al. 2001).

For recordings in setup 2 we used a frequency sweep (20 Hz to 16 kHz logarithmically rising, 500 ms duration, 5 ms rise/fall time, five repetitions per position) to measure the IRs. Sweeps were created by a DA1 (Tucker Davis Technologies, Gainesville, FL, USA), amplified by a HiFi-amplifier (Yamaha AX-590) and emitted by a loudspeaker (Macaudio ML-103E, 2–12 kHz: flat within ±3 dB). The recorded microphone signals were pre-amplified by TDT-MA2 amplifiers, low-pass filtered (Tucker Davis Technologies FT6, cut-off frequency 20 kHz) and digitized by an AP2 computer board (Tucker Davis Technologies; sampling rate 100 kHz, recording length: 51,000 samples).

A reference measurement without the owl in place was performed to remove influences of the setup on our data. For the reference measurement, the microphones with the tubes were fixed in the center of the setup, arranged in parallel at a horizontal distance of 1 cm and pointed towards 0 azimuth and 0 elevation.

For the description of spatial positions we defined a spherical coordinate system that had its origin in the center of the owl's head. Zero degrees of elevation and 0° of azimuth were in front of the owl. Azimuth was measured as the angle between the midsagittal plane and the horizontal position of the loudspeaker. Angles on the left side of the animal were defined as negative. Elevation was measured as the angle between the horizontal plane through the owl's eyes and the vertical position of the loudspeaker. Angles in the lower hemifield were defined as negative.

Recordings in setup 1 were made from –60° to 60° in elevation and from –140° to 140° in azimuth. The range of recordings in setup 2 was from –70° to 70° in elevation and from –160° to 160° in azimuth. Resolution was 10° in both azimuth and elevation.

HRTFs were calculated according to standard methods as described, for example, in Wightman and Kistler (1989a, b), Keller et al. (1998) or Poganiatz et al. (2001).

Stimuli for electrophysiological experiments

For the acoustic stimulation in the electrophysiological experiments both non-virtual dichotic stimuli and virtual space stimuli were presented either monaurally or binaurally to the animals via earphones. Dichotic stimuli (white noise, band-pass noise or tones with an interaural time delay, an interaural level difference, a duration of 100 ms and rise/falls times of 5 ms) were produced with a computer controlled sound generating system (TDT System II).

Virtual stimuli had to be calculated before the electrophysiological experiments and were stored on computer disk before they were played via the TDT sound system.

Since we wanted to test the influence of different spatial cues of a sound on the spatial tuning of neurons, we did not only create normal virtual stimuli but also stimuli in which the ITD, the ILD and stimulus level across azimuth were manipulated while other parameters of the virtual sounds were not changed.

Interaural time differences were manipulated in two different ways. For the AddT$_x$ stimuli a constant time delay (x μs) was added to the right or left ear signals. In the FixT stimuli the ITDs were kept constant by shifting the HRIRs of both ears until the maximum of their cross-correlation function was at the desired position (Poganiatz et al. 2001). Because of the sampling rate of 100 kHz, ITDs were only fixed to multiple values of 10 μs with this method. The fixed HRIRs were stored on disk. Four types of FixT stimuli were used, each having a different manipulation of the sound level and spectrum. The average binaural level (ABL) was calculated as the sum of the root mean squared amplitudes of the HRTFs of the left and right

ear divided by two (Pena et al. 1996; Miller and Knudsen 1999; Euston and Takahashi 2002). This was done for all sampled spatial positions for the frequency range from 2 to 12 kHz (hereafter referred to as broadband noise or noise, BB) and for a number of 1/6-octave bands centered at several specific frequencies (hereafter referred to as band-limited noise and denoted by the corresponding center frequency, BL). The ABL-values obtained were used to scale the filtered stimuli so that the average of the right and left root mean squared amplitude was identical for all spatial locations. This resulted in the four subtypes of FixT-stimuli:

1. FixT1 = FixT$_{x–abl\ BB}$: ITD at x μs, no ABL correction, broad-band noise
2. FixT2 = FixT$_{x–abl\ BL}$: ITD at x μs, no ABL correction, band-limited noise
3. FixT3 = FixT$_{x+abl\ BB}$: ITD at x μs, ABL correction, broad-band noise
4. FixT4 = FixT$_{x+abl\ BL}$: ITD at x μs, ABL correction, band-limited noise

For the recordings in setup 1 only the FixT1 stimulus was available, while all 4 FixT stimulus types could be used in setup 2.

Data collection

Recordings were made from both the left and right ICs. The different areas of the IC could be identified by different typical tuning characteristics of the units (Knudsen and Konishi 1978b; Moiseff and Konishi 1983; Knudsen 1984; Takahashi and Konishi 1986; Wagner et al. 1987; Takahashi et al. 1989; Wagner 1990; Fujita and Konishi 1991; Adolphs 1993; Wagner et al. 2002). The search stimuli consisted of a sequence of broadband noise. In binaural stimuli, ITD or ILD were changed systematically. If an acoustically driven unit could be separated from the neuronal background activity, the recording program was started. Stimuli were presented about 10–30 dB above response threshold. Five to ten repetitions were recorded.

Typically, first the ILD (ITD) tuning of the unit was measured at the ITD (ILD) value at which the unit responded best as determined from the audio monitor. Next, the ITD (ILD) tuning was recorded at the ILD (ITD) at which the unit responded best; third, a frequency response function was recorded with tonal or band-limited stimuli. The energy density in the band-limited noise was the same as for the broadband noise when ITD and ILD tuning were recorded. In most units, an elevational tuning was recorded with virtual acoustic stimuli at an azimuth that evoked a high re-sponse, followed by the recording of the azimuthal tuning at the elevation where the unit responded best or at 0° elevation (if the unit was not tuned in elevation). Finally, azimuthal tuning curves were obtained with the different types of manipulated virtual stimuli.

Data analysis

It was possible to separate spikes of single units and multi units by online and offline cluster cutting with the recording software (setup 1: Brainwave (DataWave Technologies, Longmont, Colorado, USA); setup 2: Brainware (Tucker-Davis Technologies, Gainesville, Florida, USA). Further analysis was carried out with routines written in IDL (RSI, Boulder, USA) and MATLAB (The Mathworks, Ismaning, Germany). The spike numbers of each single stimulus presentation were used for statistical tests (Kruskal–Wallis test, $P < 0.01$). If the average spike rate of at least one of the different stimuli that were presented for the recording of a tuning curve was significantly different from the other spike rates, the tuning curve was classified as ''tuned'', otherwise it was classified as ''not tuned'', respectively. The advantage of the Kruskal–Wallis test over criteria derived from circular statistics is that it can be used independent of periodicity and without knowing the exact tuning frequency. We, furthermore, used the P value obtained in the Kruskal–Wallis test as a measure of tuning strength. Spike numbers were averaged and corrected for the spontaneous rate of the unit, which was determined from the spike rate recorded before stimulus onset. The trough-to-peak ratio was defined as the minimum response divided by the maximum and multiplied by 100.

Results

Spatial patterns of broadband ITD and ILD

Head-related transfer functions were obtained for all five owls individually. The time shifts between the HRIRs measured in the left and right ears for one position in space represent the ITD that a sound source generates naturally. The time shift between a pair of HRIRs can be assessed by cross correlation. Data analysis was accomplished by simple linear regression between ITD and azimuthal angles. ITDs changed linearly with azimuth in the frontal hemisphere as may be seen from the equally spaced iso-ITD lines (Fig. 1a). The linear equations were transformed to express ITD as a function of azimuth to enable a comparison of the data with earlier studies (Table 1).
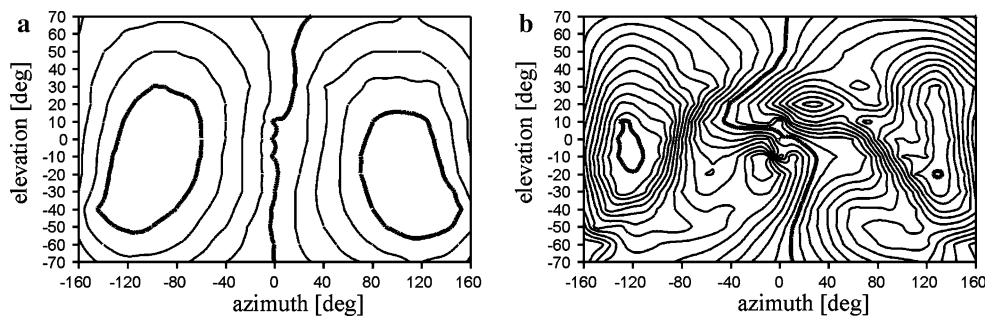
Fig. 1 Spatial patterns of broadband (2–12 kHz) ITDs (**a**) and ILDs (**b**) for owl O. The iso-ITD contour lines are drawn at intervals of 50 μs. Iso-ILD contour lines are drawn at intervals of 1 dB. Spatial positions are given in *spherical coordinates*. Zero degrees in azimuth and 0° in elevation are in the front of the owl. *Positive angles* denote the right or upper hemisphere, respectively. The *thick lines* mark the maximum, zero and minimum contour lines in each plot

For 0 azimuth an ITD of 0 ms is expected. The intercept values (Table 1) demonstrated that an ITD of 0 μs was only slightly shifted with respect to 0° azimuth in the external coordinate system, indicating that the owls were well aligned with the external coordinate system. The slope in the regression lines (Table 1) reveals that in the mean over all five owls 2.77 μs corresponded to 1° in azimuth. In other words, a change of ITD of 100 μs corresponded to a change in azimuth of 36.1 or about 40°.

The calculation of broad-band ILDs was done by subtracting the mean energy of the HRTFs in the frequency range from 2–12 kHz in dB of the left from the right ear. The spatial pattern of the ILDs was more complicated than the ITD pattern (Fig. 1b). Between ±30° azimuth and ±30° elevation the ILD changed systematically along a direction inclined by some 45° to the horizontal axis.

General observations in electrophysiological recordings

A total of 97 units (setup 1: 56, setup 2: 41) units were encountered in 19 experiments (setup 1: 6, setup 2: 13) with 5 animals. We recorded from 54 units (setup 1: 20, setup 2: 34) in ICCc and from 17 units (setup 1: 15, setup 2: 2) in ICCls. Twenty-six more units were located in ICC, but their allocation to either ICCc or ICCls remained unclear. Twenty-four units were clas-

Table 1 Relation between ITD and azimuth

Owl	Correlation coefficient	Slope (μs/deg)	Intercept (μs)
F	0.997	2.63	0.91
M	0.997	2.85	0.07
J	0.999	2.66	2.11
O	0.996	2.88	−18.95
S	1	2.85	−5.8

Elevation of 0°, $P < 0.0001$ for all linear fits

sified as single units; 73 units were classified as multi units. Because of the tonotopic arrangement and the maps of ITD of neurons in the brain areas investigated we did not expect significant differences between the results from multi and single units (Wagner et al. 1987). Therefore, we pooled single and multi unit data for the analysis, and identify them below as "units".

Responses of ICC units to dichotic and natural virtual stimuli

Units were classified as being located in ICCc if they exhibited tuning to ITD (Fig. 2a, b, g, h) and azimuth (Fig. 2 g, h) according to the Kruskal–Wallis test ($P < 0.01$) but not to ILD (Kruskal–Wallis test, $P > 0.01$) (Fig. 2c, d). These units were also sharply tuned to frequency (Fig. 2e, f). Monaurally, they were excited by stimulation from both the ipsi- and contra-lateral ears. The tuning to ITD showed a periodicity equivalent to the inverse of the unit's best frequency (Fig. 2b, f). For example, for the response shown in Fig. 2b, the period of the ITD tuning curve was 210 μs. The frequency of 4,762 Hz calculated from this period corresponds well to the unit's best frequency (Fig. 2f).

Some units were tuned to ITD and ILD (Kruskal–Wallis test, $P < 0.01$). These units showed phase ambiguity in the ITD tuning curve and a narrow frequency tuning (Fig. 3). Their response to monaural stimuli was characterized by excitation from the ear contralateral to the recording site and inhibition from the ipsilateral ear (Takahashi et al. 1989). Units with such clear response patterns were classified as units from the ICCls. The response of a typical unit of this class displayed in Fig. 3 was cyclic with the variation of the ITD (Fig. 3a) with a period of some 180 μs suggesting a best frequency around 5,500 Hz. The recorded best frequency was close to this frequency (Fig. 3c). The unit was broadly tuned to ILD (Fig. 3b).

Fig. 2 Tuning curves for a representative low-frequency (*left column*) and high-frequency (*right column*) ICCc unit to ITD (**a**, **b**), ILD (**c**, **d**), frequency (**e**, **f**) and (virtual) azimuth (**g**, **h**). Functions for one parameter were obtained by adjusting all other parameters to the unit's best values. Stimulus was noise for the responses shown in **a**–**d**, **g** and **h**. The stimulus was repeated five times. The spontaneous activity for the high-frequency unit was below 1 spike in five repetitions; for the low-frequency unit it amounted to about 19 spikes. Standard errors were typically smaller than 10% of the response at the maximal values
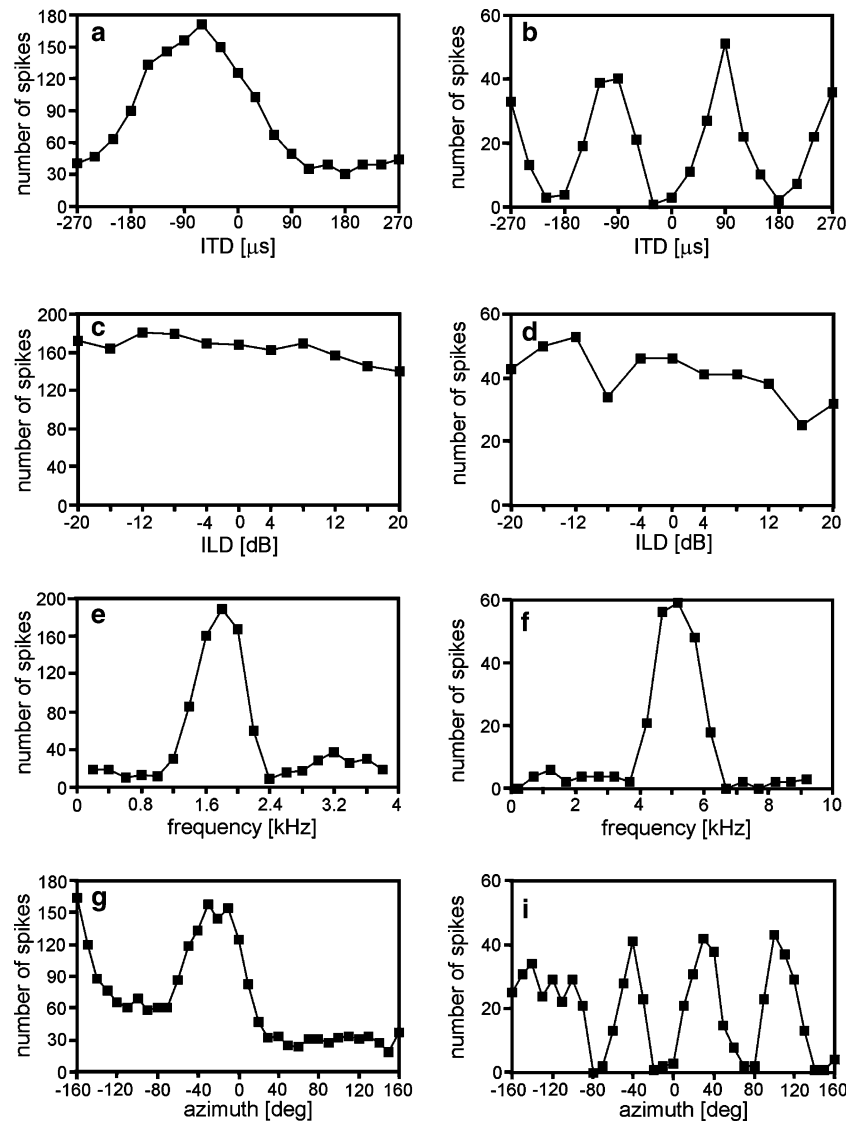
It was more difficult to classify units that exhibited a weak ILD tuning or did not show a clear excitatory or inhibitory ipsilateral input. To avoid a wrong classification that might influence statistics, such units were classified as having an unclear location within ICC.

The azimuthal tuning to normal virtual stimuli (RAF–rate azimuth function) was very similar to the ITD tuning in all ICC units (Fig. 2g, h). Response strength was equal (94 units tested in a Wilcoxon matched-pairs signed rank test, $P > 0.05$). A periodicity in the responses was seen with both stimuli. Response peaks and troughs occurred at equivalent positions. The latter could be quantified by fitting a sinusoid to the tuning curve. The periods read from the fits of the RAF and ITD tuning curve, respectively, were used to determine the relation between ITD and azimuth. The division of the period read from the ITD

tuning curve by the period read from the RAF yielded a stretch factor. The mean value of the stretch factor was 2.73 μs/deg (Fig. 4). This value corresponded well with the relation between ITD and measured in the HRTFs, which resulted in a mean value of 2.77 μs/deg (Table 1).

Responses of ICC units to FixT stimuli

We first tested the effect of fixation over a small range of azimuths (±50° around the response maximum in the azimuthal tuning curve) in the frontal hemisphere (Fig. 5). For example, Fig. 5a shows the response of a unit that varied in a cyclic way with both ITD and azimuth. The best ITD was at 30 μs, the best azimuth at 10°. Thus, the ITD was fixed to 30 μs, corresponding to the maximum response in the ITD tuning curve.

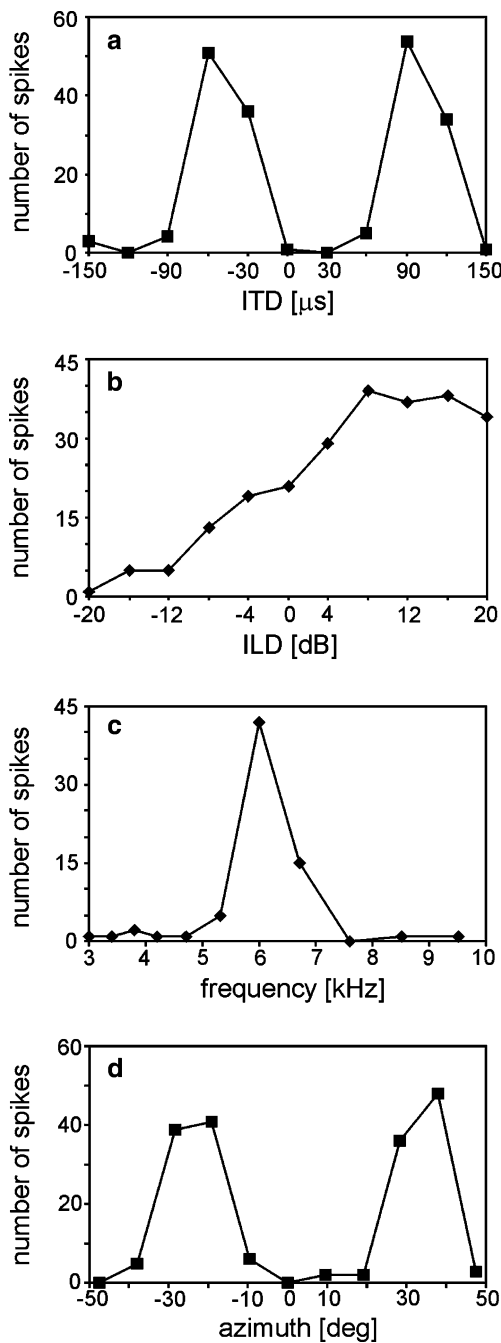**Fig. 3** Tuning curves for a representative ICCls unit. **a** ITD, **b** ILD, **c** frequency, **d** RAF tuning. ITD, RAF and ILD functions were obtained with noise stimuli. Other parameters and characteristics as in Fig. 2

When the FixT1 stimuli were presented, the response of the unit was no longer cyclic. Typically, response strength was close to the maximum response measured in the normal azimuthal tuning curve. In 54 cases the mean response to the FixT stimuli over all azimuths tested was compared with the maximal response in normal azimuthal tuning curve. The strength of the

mean response to the FixT stimuli was reduced to 81.2% compared with the maximal response in the normal azimuthal stimuli. It seemed, however, that the fixation of the ITD also clamped the response strength to the value measured at the corresponding azimuth in the normal azimuthal tuning curve. This hypothesis was further tested in the few cases ($N = 6$), in which the ITD was fixed to a value that was not close to the maximum response in the normal azimuthal tuning curve. Indeed, in these cases, the response corresponded again to the response measured in the normal tuning curve at that azimuth. Figure 5b shows an example in which the ITD was fixed to a value yielding about 70% of the maximal response in the azimuthal tuning curve. Indeed, the mean value of the FixT curve now was 71% of the maximal response in the normal azimuthal tuning curve. Despite their loss of periodicity in response to variation in stimulus azimuth, some units still showed significant tuning (Fig. 5c).

Three measures were used to assess the changes on ITD tuning induced by the fixation of ITD. First, we compared the trough-peak ratio in the FixT1 tuning curve with the trough-to-peak ratio in the normal (RAF) tuning curve. The trough-peak ratio increased in 47 out of 51 cases (Fig. 6), demonstrating that the fixation decreased the response modulation in the ITD curves. Second, we also used the P value in the Kruskal–Wallis test as a criterion for the effect of the fixation. The rational for using this test was that in normal RAF functions due to the strong tuning the P value should be low, while in the FixT curves the P value should increase. Indeed, the P value was higher in all FixT1 tuning curves than in the corresponding RAF tuning curves. This difference was highly significant (Fisher sign test, $N = 40$, $P < 0.01$). Although the P value in the Kruskal–Wallis test might increase, indicating an effect of the fixation of ITD, the units need not loose their tuning (Fig. 5c). Therefore, as third measure for the influence of fixing the ITD, we counted the number of units that lost tuning, i.e., the units that had a P value larger then 0.01 in the Kruskal–Wallis test. We found that 48 of 51 or 94% of the units (Table 2) lost tuning. Thus, all three measures yielded similar results, but the percentage seen with the third measure was remarkably similar to that observed with the first measure, the trough-to-peak ratio. The advantage of the third over the first measure is that the third measure is based on a statistical criterion. Therefore, the third measure was used in further tests to assess the effect of the fixation of the ITD.

The ITD tuning in ICCc and ICCls is similar, but the ILD tuning is different. Therefore, we investigated next whether fixating the ITD had different effects on
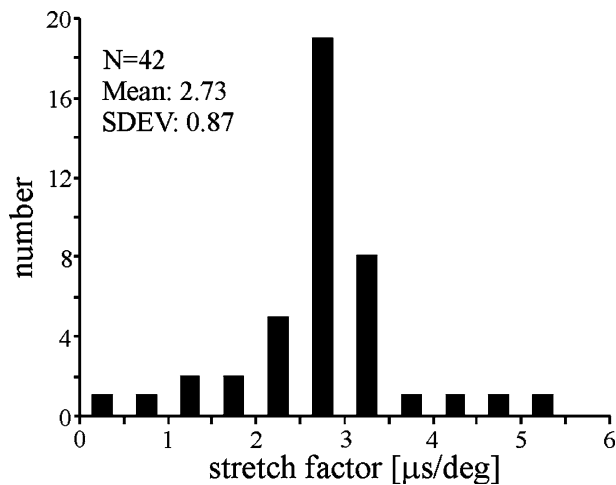
Fig. 4 Relation between ITD and azimuth in the neural responses. The plot shows the distribution of the stretch factor, specifying the relation between ITD and azimuth. For the calculation of the stretch factor the ITD and RAF functions were each fitted with a sinusoidal function. This was possible, because the responses had a periodic nature. This fit yielded the period of the response. The stretch factor was the period measured in the fitted ITD function divided by the period measured in the fitted RAF function. *N* Number of units, *Mean* mean value of stretch factor, *SDEV* standard deviation

ICCc and ICCls cells. We observed that units in the ICCls exhibited a similar response behavior as units in the ICCc (Fig. 5d). As in the recordings shown in Fig. 5a, the tuning of this single unit was high to both variations in ITD and azimuth, but disappeared after fixation of the ITD. For this comparison, we tested 20 cells from ICCc and 14 cells from ICCls. Seventeen cells from ICCc and 11 cells from ICCls lost tuning as judged by the Kruskal–Wallis test ($P < 0.01$). A χ^2 test did not reveal a difference in the number of cells that lost tuning between ICCc and ICCls ($P > 0.05$).

The effects described so far were found within a small range in the frontal hemisphere. We wondered whether similar changes would occur when a much larger range was regarded. Therefore we tested also ranges of –90 to +90 and –160 to +160° of azimuth. For example, the response of the cell shown in Fig. 7 to the FixT1 stimulus was found to be tuned according to the Kruskal–Wallis test ($P < 0.01$) when the whole range of –160 to +160° was considered, but not when the –90 to +90 range or the –50 to +50 ranges were analyzed. In our sample of 31 units from ICCc, fifteen (48%) lost tuning, if the FixT1 stimulus was used (Kruskal–Wallis test, $P < 0.01$; Table 2). This number increased to 90%, when only the range from –90 to +90 was taken into account (Table 2).

We concluded from these experiments that ITD plays an important role, but that other factors may also

influence the tuning in cases such as those shown in Figs. 5c and 6, in which the tuning became weaker after the fixation of ITD, but was not lost according to our statistical test. The increase in number of units that lost their tuning when the range analyzed was reduced from ±160° to ±90° and then to ±50° (Fig. 7; Table 2) suggested that stimulus level might play a role, because level varies considerably with azimuth. ICCc neurons have a dynamic range of some 20–30 dB (Wagner et al. 2002). We usually presented the stimuli some 10–30 dB above response threshold. Thus, we were in the steepest slope of the rate-level function, and changes in stimulus level could influence the response. Indeed, level varied some 20–30 dB within the azimuthal range tested (Fig. 1). In the next step we corrected for changes in stimulus level by compensating for the measured loss in gain (FixT3 stimulus).

The responses to the FixT3 stimuli resembled those seen with the FixT1 stimuli. The responses were usually independent of azimuth and corresponded well with the responses expected from the relation between ITD and azimuth in natural virtual stimuli. A typical example represents a unit with a best frequency of 3,333 Hz (Fig. 8a). In this case, the ITD was fixed to 150 μs, a value belonging to an azimuth of about 60°. While the response was tuned when the unit was stimulated with normal virtual stimuli, the tuning disappeared over the whole range from –160 to 160° after ITD fixation and ABL correction (FixT3 stimulus). A second example shows the response of a unit tuned to some 5,200 Hz (Fig. 8b). The response of this unit was periodic within the azimuthal range tested. The period (75°) suggested a frequency of some 4,800 Hz, close to the best frequency of the neuron. When this unit was tested with the FixT3 stimulus, it was tuned in the range of –160 to 160°, but was not tuned for the narrower ranges (Fig. 8b).

A total of 32 units were tested with the FixT3 stimulus. Again, the tuning as judged by the *P* value in the Kruskal–Wallis test became worse after fixation in all units compared with the normal situation, irrespective of the range tested. With regard to our second measure, 34% of the units lost the tuning, if the whole range was considered, but 75% lost the tuning, if the range from –90 to +90° was considered. Only 1 unit was tuned when the narrowest range, centered on 0 azimuth, was taken into account (Table 2). However, three units were still tuned when the center was set on the maximum of the response, which meant the inclusion of more peripheral angles. When the tuned units after the fixation in the FixT1 and FixT3 cases were compared, the level correction in the FixT3 cases did not further improve the *P* values in the Kruskal–Wallis
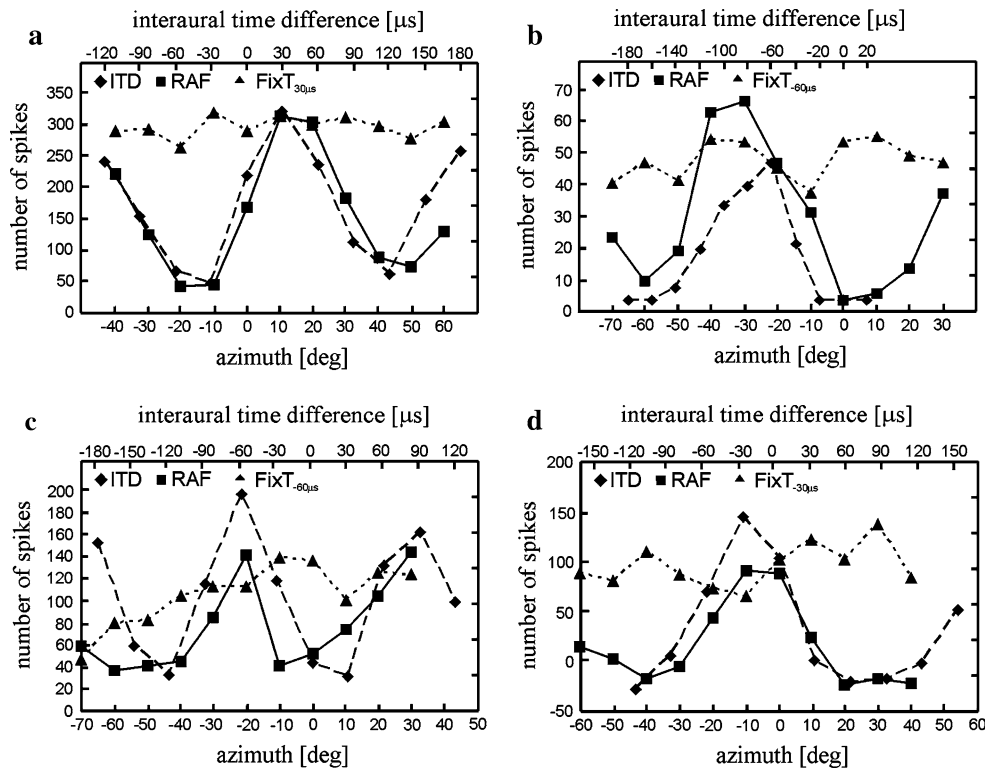
Fig. 5 Influence of fixing ITD. In **a–d** the ITD tuning curve (ITD), the normal azimuthal tuning curve (RAF) and the azimuthal tuning curve after fixation of the ITD (FixT1) are shown for 4 units, 3 from ICCc (**a–c**) and one from ICCls (**d**). **a** ITD was fixed to a value that corresponded to the maximum of the RAF function. The response to the FixT1 stimulus for all stimuli was about as high as the maximal response in the RAF curve. **b** ITD was fixed to a value that corresponded to a sub-maximal response in the RAF function. The response to the FixT1 stimulus for all stimuli was about as high as the corresponding response in the RAF curve, because an ITD of –60 µs correspond to about –20° in azimuth. **c** ITD was fixed to a value that corresponded to the maximum of the RAF function. The response to the FixT stimulus lost periodicity, but was still tuned after fixation. **d** ITD was fixed at the maximum of the ITD function. According to our criterion, the unit lost tuning after fixation of ITD. Other parameters and characteristics as in Fig. 2

test, independent of the ranges used for testing (all P values were above 0.05 in fisher sign tests).

In a next step we included the frequency selectivity of the units in the FixT stimuli leading to the FixT2 and FixT4 stimuli. Figure 9 depicts a unit tested with the FixT2-FixT4 stimuli. The response to RAF and FixT1 of this unit was already shown in Fig. 6. The best fre-

quency of the unit was at about 2,800 Hz, yielding a period of some 360 µs. Thus, response maxima in the RAF were expected to have a distance of some 130°. Indeed, two response maxima, one at –90° and the other at around 60°, were found when tested with natural virtual stimuli. This unit exhibited a broad peak between 60 and 180 µs (Fig. 6). The unit's tuning was significantly disrupted when stimulated with the FixT4 stimulus with ITD fixed to +60 µs and the restricted frequency range (Fig. 9c). For the three other FixT stimuli a "dip" around –20° remained that replicated the minimum of the RAF obtained with the natural stimulus (Figs. 6, 9a, b). With respect to the whole population of cells (17 tested with the FixT2 and 19 tested with the FixT4 stimulus), the use of the FixT2 and the FixT4 stimulus caused more units to lose their tuning than the FixT1 stimulus in the total range from –160 to +160° in azimuth was considered (Table 2). This was confirmed by a χ^2-test (FixT1–FixT2, $P < 0.05$ after Bonferroni correction, FixT1–FixT4, $P < 0.01$ after Bonferroni correction).

Table 2 Number of ICCc units that lost tuning with the FixT stimuli

Range (deg)	FixT1 (%)	FixT2 (%)	FixT3 (%)	FixT4 (%)
±50[a]	48/51 (94)	14/17 (82)	29/32 (88)	18/19 (95)
±50[b]	31/31 (100)	14/17 (82)	31/32 (97)	18/19 (95)
±90[b]	28/31 (90)	13/17 (76)	24/32 (75)	17/19 (89)
±160[b]	15/31 (48)	10/17 (59)	11/32 (34)	16/19 (84)

The decision level was $P < 0.01$ in a Kruskal–Wallis test

[a] Relative to the maximum response in the RAF

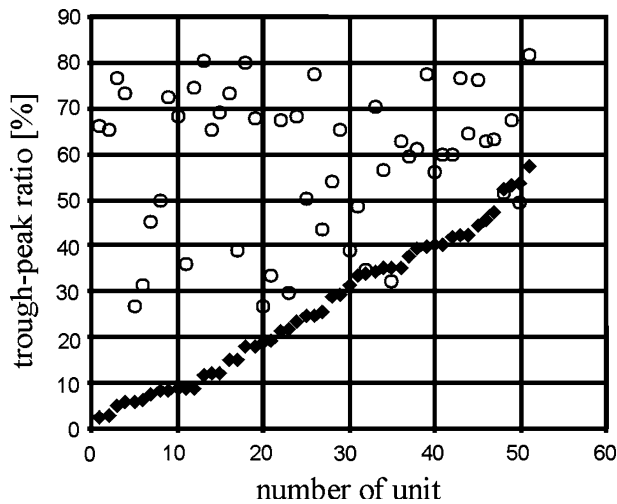[b] Relative to 0 azimuth (only data from setup 2)

Fig. 6 The effect of fixating ITD on the trough-peak ratio. In 51 units from the ICCc the trough peak-ratio in the RAF (*diamond*) and the FixT1 (*open circles*) are plotted. The data are aligned according to increasing trough-peak ratios in the RAF. The trough-peak ratio was defined as the number of spikes measured at the trough divided by the number of spikes measured at the peak of a response curve multiplied by 100. Note that the trough-peak ratio is higher in all but four cases for the FixT1 condition, indicating that the fixation of the ITD increased the minimal response in the tuning curve
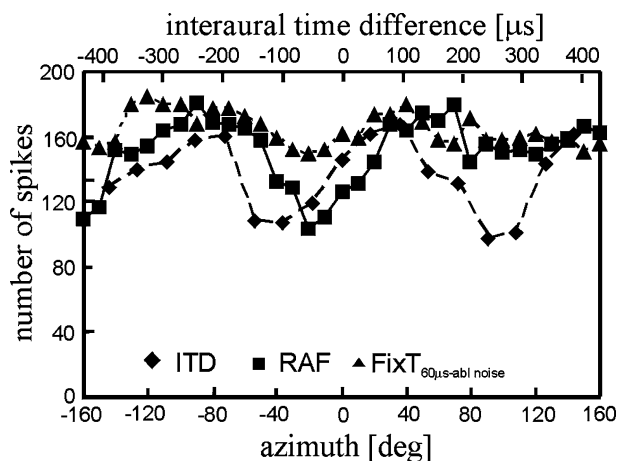

Fig. 7 Influence of the azimuthal range. This unit from ICCc was tuned to both variations of ITD and azimuth. After fixation of the ITD at 60 µs, the unit lost tuning, according to our criterion, for the restricted ranges, but not for the widest range considered. Other parameters and characteristics as in Fig. 2

Responses of ICC units to AddT stimuli

To further assess the importance of ITD, the units were tested with AddT stimuli. We hypothesized that the addition of an ITD should shift the tuning curve by a predictable amount, which may be read from the relation between ITD and azimuth in the normal tun-
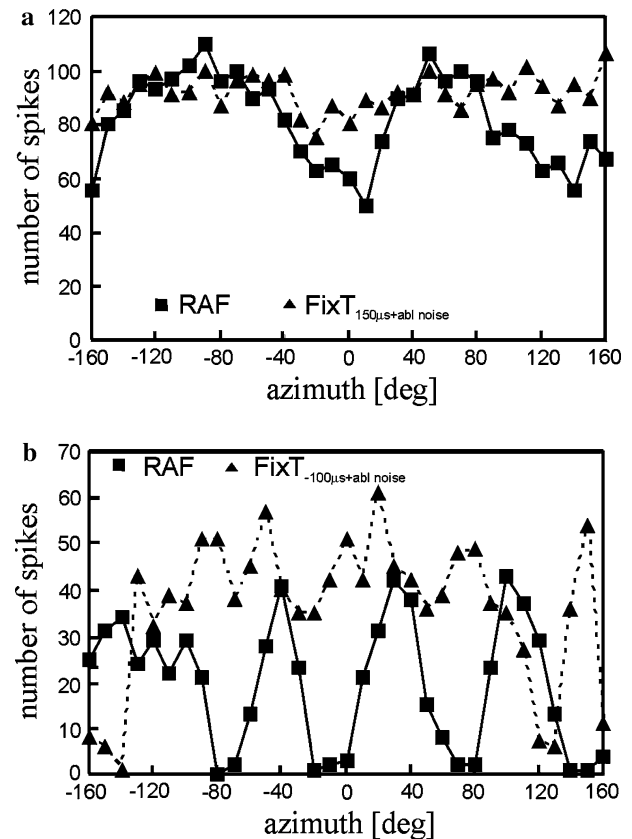

Fig. 8 The influence of correcting for average binaural level. RAFs and FixT3 tuning curves of two units from ICCc. **a** The ITD was fixed at 150 µs, close to the response maximum. The unit was classified as ''not tuned'' for –160° to 160° in azimuth (Kruskal–Wallis, $P < 0.01$). **b** The unit was classified as ''not tuned'' for –90° to 90° in azimuth (Kruskal–Wallis, $P < 0.01$; ITD fixed at –100 µs). Note the difference in frequency tuning in (**a**) and (**b**) as indicated by the different periodicity in the tuning curves. Other parameters and characteristics as in Fig. 2

ing curves. For example, the addition of an ITD of +100 µs should shift the curve by some 33–40° to the left.

Forty-seven tuning curves were obtained from 25 units in ICCc with AddT stimuli. Forty-two tuning curves were recorded using noise stimuli, while in the remaining five tuning curves tonal stimuli were applied. The introduction of an additional ITD led to a shift of the response maximum that corresponded to the ITD value (Fig. 10a, b). The tuning of the curves did not change in the two conditions as indicated by the lacking difference of the P values in the Kruskal–Wallis test (Fisher sign test, $N = 24$, $P > 0.05$).

To assess the shift, normal and shifted azimuthal tuning curves were cross-correlated. The maximum nearest to 0° in azimuth in the cross-correlation function represented the value of the induced shift. In three cases, peaks at equivalent positive and negative
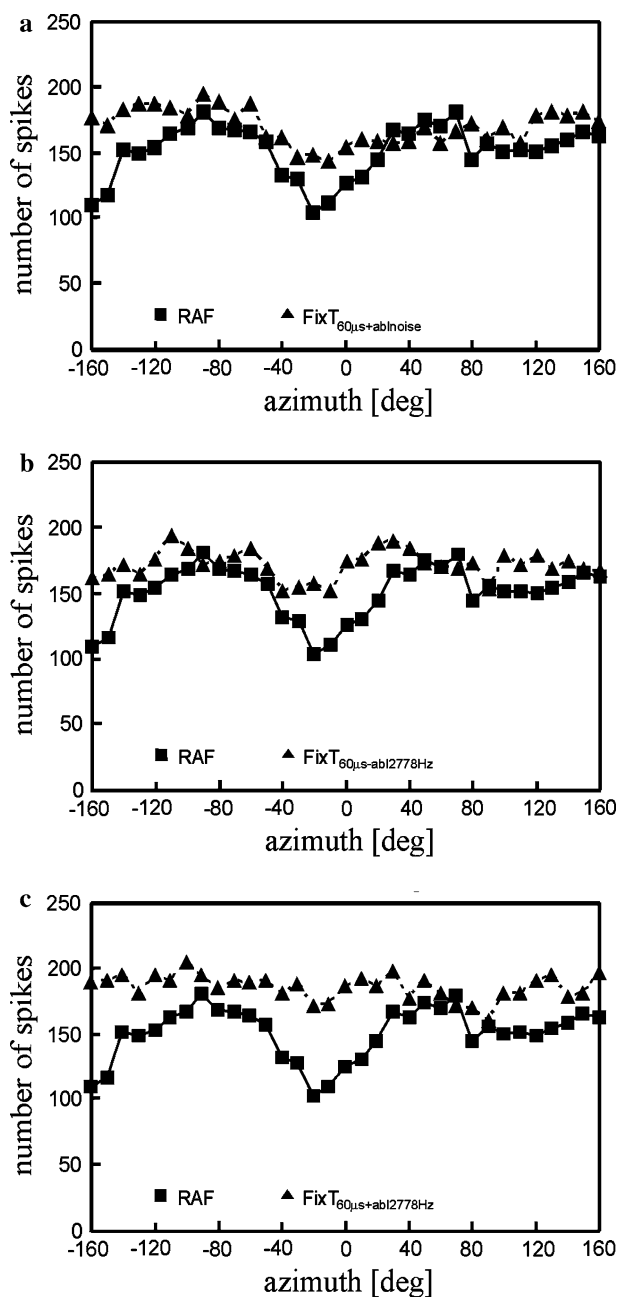
Fig. 9 Comparison of the response to the different FixT stimuli in one unit. In each plot the RAF for natural virtual stimuli (*squares*) is plotted together with one of the FixT stimulus types (*triangles*). **a** FixT3, **b** FixT2, **c** FixT4. Note that these are responses from the same unit as in Fig. 7. Other parameters and characteristics as in Fig. 2

Fig. 10 Effect of adding an ITD. Rate azimuth function of two ICCc units to normal virtual acoustic stimuli (*squares*) and stimuli with additional ITDs (*triangles*). **a** Responses of one ICCc recording site tested with +100 μs added-ITD. **b** Responses of a different ICCc recording site tested with –100 μs added-ITD. **c** Summary of shifts in response peaks for 47 tests (*diamonds*) at 25 recording sites when presented with various added-ITDs. *Solid line* indicates a 1:1 relationship, *dashed line* denotes the best linear fit. Other parameters and characteristics as in Fig. 2

azimuths were observed. In these cases the azimuths corresponding to the peaks with the higher correlation coefficients were chosen. The azimuth found by this procedure was multiplied with 2.73, the factor that represented the slope of the relation between ITD and azimuth as read from Fig. 4. The result was plotted together with the respective added ITD as a data point
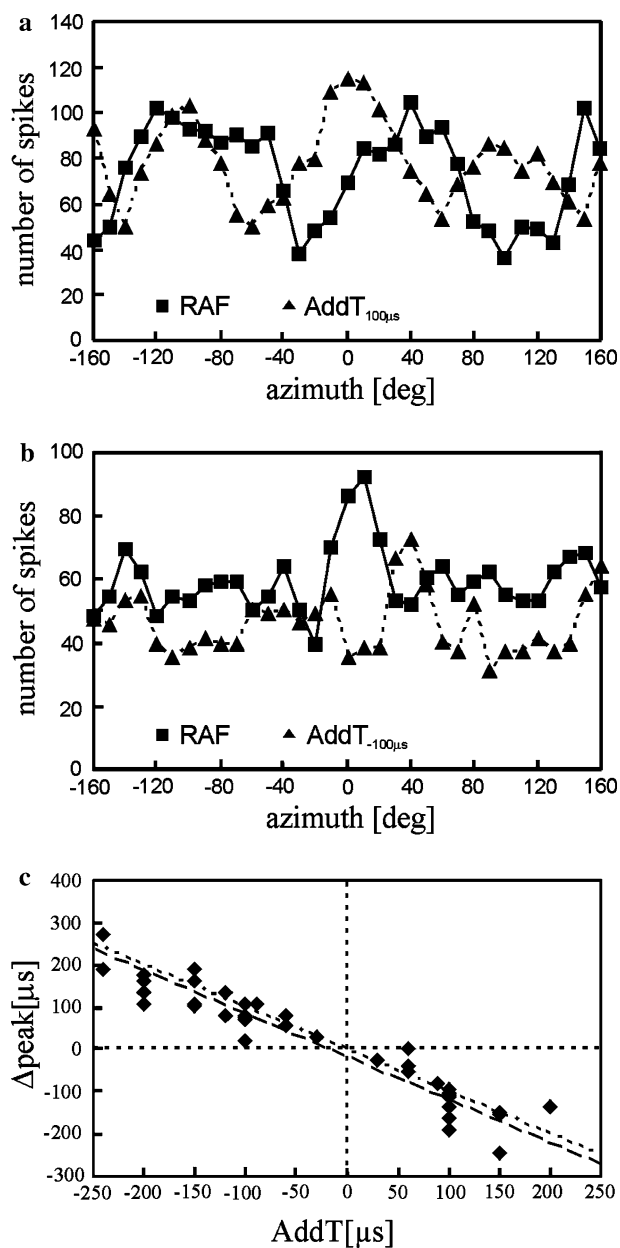
(Fig. 10c). This plot yielded a linear relation between the added ITD and the observed shift scattered around the following straight line: Observed shift (in μs) = $-15 - 1.02 \times$ AddT

Since the slope of the relation was close to –1 and the correlation was high (correlation coefficient 0.95),

the cause of the change in the AddT response curves compared with the normal RAF was the addition of the ITD.

Discussion

We stimulated neurons of the ICC in the barn owl with virtual acoustic stimuli and found similar tuning as with ITD stimulation. The azimuthal tuning of ICC neurons changed when the virtual acoustic stimuli were manipulated. When the ITD was fixed, the tuning worsened, while the neurons shifted their response in a predictable way when ITDs were added.

HRTF measurements and prediction of relation between ITD and azimuth

It was possible to replicate the linear relation between ITD and azimuth reported earlier (Olsen et al. 1989). The value of the slope of 2.77 µs/deg measured here was slightly larger than those determined by Olsen et al. (1989) (2.31 and 2.52 µs/deg). A very similar factor was obtained by comparing ITD and RAF tuning curves (Fig. 4). These observations, together with the obvious similarities of the tuning properties found in this study and many findings by others (Brainard et al. 1992; Keller et al. 1998; Poganiatz et al. 2001; Egnor 2001; Euston and Takahashi 2002), underlines the equivalence of free-field and virtual acoustic stimulation for use in electrophysiological and behavioral experiments in the barn owl. Furthermore, the straight and almost vertical Iso-ITD lines at least over much of the frontal hemisphere (see Fig. 1, see also Brainard et al. 1992; Olsen et al. 1989; Keller et al. 1998), were the basis for the expectation of a close relation between the neural responses to azimuth and ITD.

The influence of AddT stimuli on azimuthal tuning in ICC

Adding an ITD to the virtual stimuli caused a shift in the ITD curves. The shift of the azimuthal tuning curve induced by adding an ITD to the virtual stimuli could be predicted by the following assumption: the response of the units did not change in strength but shifted along the azimuthal axis by an amount that can be calculated from the relation between ITD and azimuth in the HRTFs. Thus, the prediction would be that behavioral experiments with AddT stimuli would yield a change in turning amplitude that can be calculated from the relation between ITD and azimuth without a change in localization precision. This prediction was indirectly

verified by Poganiatz et al. (2001): they fixed the ITD at 100 µs and tested virtual azimuths from –60 to +60°. These authors observed that the ITD was the only determinant of azimuthal turning amplitudes. Since in natural virtual azimuthal stimuli ITD varies with azimuth, the difference between the fixed ITD and the naturally occurring ITD might be interpreted as an added ITD. For example, a natural azimuthal stimulus of 20° has an ITD of about 50 µs. Therefore, for an azimuthal position of 20° fixing the ITD at 100 µs is equivalent to adding an ITD of 50 µs. If we view the fixed ITD as composed of a natural and an added ITD, the independence of the turning amplitude of the azimuthal position when the ITD was fixed suggests that natural and added ITD sum up to produce the head-turning amplitude. Since the iso-ITD lines are not totally straight and not exactly vertical, small differences between AddT-experiments and virtual stimuli without manipulation would be expected. But these might be difficult to determine, given the behavioral variability (Poganiatz et al. 2001).

The influence of FixT stimuli on azimuthal tuning in ICC

The influence of the fixation of the ITD on the azimuthal tuning curves was more complicated than the influence of adding an ITD. After fixation of the ITD, a decrease in tuning strength was observed. The typical change was a loss in the periodicity of the tuning curves. In many cases, tuning disappeared.

We started with a stimulus that did not correct for influences of stimulus level or frequency and observed an influence of fixating ITD in all units and a loss of tuning in many. Thus, the first conclusion was that any fixation of ITD had a dramatic effect on the tuning to ITD in the neurons of the ICC. Our results also indicated that ITD was the only spatial cue influencing azimuthal tuning in those units. This conclusion is supported by the observation that a change of ILD typically does not shift the best ITD (Wagner et al. 1987; Takahashi et al. 1989; Fujita and Konishi 1991; Wagner et al. 2002, 2005). Since not all units lost tuning according to our criterion, the FixT2, FixT3 and FixT4 stimuli were developed to test whether more units would lose tuning if stimulus level was adjusted or the frequency range was restricted. We did not observe an additional effect when we corrected for possible changes in stimulus amplitude with the FixT3 stimulus. This result was somewhat surprising, but it supports the conclusion that level cues do not influence the responses to ITD in neurons of the ICCc. However, when we limited the bandwidth of the stimulus to 1/6 octave

around a unit's best frequency an effect was observed when the widest range (–160 to 160°) was considered. Thus, the frequency selectivity of a neuron seems to be important in ITD tuning, especially for the signaling of large azimuthal values. This is consistent with the observation from HRTFs that the small differences in ITD between frequencies enlarge at peripheral azimuths.

In an elegant study, Euston and Takahashi (2002) investigated the contribution of level-difference cues to spatial receptive fields in space-specific neurons. They used an elaborated analytic and predictive tool, but reported similar observations as we do for ICC neurons. Specifically, they could predict the ILD alone spatial plots, curves in which ITD was fixed to the optimal value of a cell, with about 70–80% accuracy.

ITD is an important parameter for azimuthal tuning also in other animals (Yin and Kuwada 1984). The effect of fixing ITDs has also been studied in the cat (Nelken et al. 1998). In neurons of the auditory cortex of this animal a fixation of ITD to 0 resulted in a deterioration of elevational tuning without much influencing azimuthal tuning (Nelken et al. 1998). However, these experiments were carried out in high-frequency neurons. These neurons can utilize the ITD of the envelope, but not of the carrier. The situation may be different for low-frequency neurons in which the ITD of the carrier influences the response of the neurons. Despite the differences in the mechanisms underlying the detection of ITD (Brand et al. 2002; Hancock and Delgutte 2004; McAlpine et al. 2001), fixation of ITDs should result in similar effects.

The observation that the ITD is the only cue determining the tuning of the neurons in ICCc of the barn owl is consistent with the observation from behavioral experiments (Poganiatz et al. 2001). These demonstrated that after fixation of the ITD, the owl turned its head always to the position specified by the ITD. The other parameters characterizing a position of a sound source (ILD, frequency-specific cues) did not influence the azimuthal amplitude of head turns.

Wightman and Kistler (1992) produced virtual stimuli in which ITD and ILD cues signaled different directions for human psychoacoustic studies. They reported that subjects always followed the direction signaled by the ITD as long as low frequencies were included. Hartmann and Wittenberg (1996) described that contradictory ITD and ILD information in virtual sounds led to inside-the-head locatedness and lateralization of the sound at the side to which the ITD points. Tollin and Yin (2002) investigated the importance of ILD on the response properties of neurons in the lateral superior olive of the cat with a similar technique. Similar observations were made by Delgutte et al. (1999) for cells in the cat's inferior colliculus. Thus, in both mammals and birds, manipulation of cues in virtual auditory stimuli is a powerful means to study mechanisms of neural processing. Specifically, fixating ITDs (ILDs) or adding ITDs (ILDs) in virtual stimuli may help to unravel the neural mechanisms underlying neural computation and are indicative of the role of these parameters in sound localization.

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