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Mechanisms of sound localization in mammals: Ageing, dynamics and adaptation

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Chapter 1

General Introduction

Overview of thesis

Many mammals, including humans, assess differences in the timing and level of sounds at the two ears - interaural time differences (ITDs) and interaural level differences (ILDs), respectively - in order to determine the azimuthal location of the source (Rayleigh 1907). This ability can be critical to an animal's survival. Even though the evolutionary pressure to escape a predator or find prey by means of sound localization is no longer as important for humans, sound localization remains critical to every-day listening situations. Furthermore, the neural circuits for sound localization are also employed in other listening tasks. One example for human listeners is the ability to hear out a particular speaker in a noisy background, a phenomenon known as the "cocktail party effect" (Cherry 1953, Yin 2002).

Since the auditory scene is not static, but changes constantly as sources change their location, or the head is moved relative to these sources, the binaural cues are constantly updated. It is therefore incumbent on listeners to assess these changes, taking account of the acoustic environment in which they are listening. In addition to these more immediate changes in the acoustic environment, the auditory brain is also subject to changes that occur over a range of longer time-frames, encompassing developmental critical periods in early life (Kapfer et al. 2002, Seidl and Grothe 2005) and even the process of ageing (e.g. Gleich and Strutz 2002, Gleich et al. 2004). All of these factors can be considered with respect to neural plasticity which has, over the last two decades, become a major topic of interest in auditory research. As demonstrated in many fields of neuroscience, plasticity in neuronal networks permit adaptation to a modified environment (e.g. Ohzawa et al. 1982, Fairhall et al. 2001, Dean et al. 2005, Ulanowsky et al. 2004, Verhagen et al. 2007). The objective of this thesis is to elucidate the extent to which the neural circuits processing binaural localization cues (ITDs and ILDs) and their behavioral manifestations are plastic over a life-time (including the ageing process), dynamic and subject to adaptation. The ability of the mammalian auditory system to adapt to binaural localization cues over different time frames is investigated using three different approaches and species. This potentially provides for a

broad understanding of auditory brain mechanisms in mammals that contribute to survival and/or enhance communication.

Binaural mechanisms for sound localization

In the high-frequency range (generally above 2-3 kHz) mammals predominantly use ILDs to localize a sound source in azimuth. Here, the head acts to create an acoustic shadow, leading to a reduced sound level at the ear furthest from the sound source. Due to their longer wavelength, the shadowing effect of the head is negligible for low-frequency sounds. However, sound is able to "bend" around the head, generating differences in time of arrival at the two ears in the microsecond range, and ITDs of low-frequency sounds are accessible for processing by the auditory brain. This segregation into high- and low-frequency processes has been postulated in the duplex theory (Rayleigh 1907) and confirmed in subsequent morphological and physiological studies (e.g. Goldberg and Brown, 1968, 1969), although deviations from this general rule have been reported (e.g. Henning 1974, Tollin and Yin 2005).

Binaural cues for sound localization are first encoded in the brainstem, ILDs in the lateral superior olive (LSO) and ITDs in the medial superior olive (MSO; e.g. Yin 2002). The LSO receives excitatory inputs from the ipsilateral cochlear nucleus and glycinergic inhibitory inputs via the ipsilateral medial nucleus of the trapezoid body (MNTB) which itself is excitated by the contralateral cochlear nucleus (e.g. Glendenning et al. 1985). Furthermore, it has recently been suggested that, in addition to glycine, GABA might modulate the ILD-sensitivity of LSO neurons (Magnusson et al. 2008). It is generally accepted that the relative strength of the excitatory and inhibitory inputs determines the output of each LSO, and that the activation pattern across both LSOs indicates the location of the sound source (Park et al. 2004). The MSO is known to receive excitatory inputs from both cochlear nuclei and for almost five decades, a very elegant model of ITD processing based solely on such excitatory inputs (Jeffress, 1948) remained largely unchallenged. A critical feature of this model is that binaural neurons function as coincidence detectors, eliciting action potentials only when precisely-timed ("phase-locked") inputs from both ears coincide. Nevertheless, other features of the

model that suggest the form of the neural code for ITD are currently the topic of considerable debate. These features are 1) that each neuron in an iso-frequency (maximally sensitive to the same frequency) band within the ITD-encoding structure signals a different ITD by virtue of its peak response, and 2) that the difference in arrival of the sound at the two ears is compensated for axons of different path length, the so-called delay-lines, that innervate binaural neurons from each side. An array of coincidence detectors, fed by delay-lines of varying length could provide for a place code - a topographic map of ITDs - with different neurons uniquely encoding different source locations. Whilst the existence of a topographic arrangement of delay lines seems to hold true for birds, apart from controversially-received anatomical studies in the cat (Smith et al. 1993, Beckius et al. 1999), such an arrangement has not been demonstrated in mammals to date (see also review by Grothe 2003). Indeed, alternative mechanisms for ITD processing have been posited for mammals. A variation on the neural delay-line hypothesis favors cochlear disparities in frequency tuning on the ipsilateral and contralateral side (stereausis), as the means by which internal delays are generated (Schroeder 1977, Shamma et al. 1989). However, in contrast to these “hard-wired” means of assessing interaural delays, recent studies suggest a much more dynamic approach to ITD processing, one that depends on the relative activation of synaptic excitation and inhibition (for review see Grothe 2003, Joris and Yin 2007).

A major challenge to the Jeffress model came from electrophysiological studies in small mammals (guinea pig, gerbil and cat; McAlpine et al. 2001, Brand et al. 2002, Pecka et al. 2008, Hancock and Delgutte 2004), which indicated a frequency-dependent processing of ITDs. Neurons tuned to relatively low characteristic frequencies (CFs) were found to respond maximally to relatively long ITDs, whereas neurons tuned to relatively high CFs responded maximally to relatively short ITDs. This resulted in the peaks of ITD tuning curves lying at or beyond the physiological range of ITDs in many small mammals, with the consequence that the steepest slopes of the functions, where the change in neural activity is greatest for a given change in ITD, were positioned within the naturally-encountered range close to midline. These studies concluded that the slope of the function, rather than the peak, is responsible for sensitive ITD coding and

proposed a rate code for ITDs rather than a place code. Grothe and Sanes (1993) had already shown that, in addition to excitatory inputs, MSO neurons received glycinergic inhibitory inputs via the MNTB, and suggested these could play an important role in ITD processing. Subsequently, Brand et al. (2002) substantiated this suggestion by demonstrating *in vivo* an important role for glycine in setting a neuron's ITD tuning. In particular, they noted that the peak of the ITD function, which often lay beyond the naturally-encountered range, shifted to lie within the naturally-encountered range (close to zero µs ITD) upon application of the glycine antagonist strychnine. These findings raise the possibility that neural processing of ITDs is under dynamic control. Phase-locked inhibition from the ipsilateral MNTB (innervated by the contralateral cochlear nucleus) is presumed to lead in time the excitatory input from the contralateral ear, delaying and diminishing the net postsynaptic potential (PSP; Brand et al. 2002, Grothe et al. 2003 Pecka et al. 2008). On the ipsilateral side, a potentially lagging (relative to the excitation) inhibition derived from the lateral nucleus of the trapezoid body (LNTB) produces a shortened net PSP. By this means, the relative timing of these inputs accounts for the processing of the interaural delay (Brand et al. 2002, Grothe 2003). The existence of phase-locked inhibitory inputs to the MSO remained controversial, and an alternative model proposed that ITD tuning is generated by a morphological asymmetry in MSO neurons, delaying the arrival of one of the excitatory inputs, with the involvement of a tonic inhibition in fine tuning the ITD sensitivity (Zhou et al. 2005). However, a recent study confirmed the phase-locked nature of glycinergic inhibition (Pecka et al. 2008). These findings make the investigation of dynamic coding an interesting pursuit. This is particularly so given the possibility that the neural code for ITD changes from brainstem to cortex, with ITD-sensitive neurons becoming increasingly sensitive to the context in which ITDs are presented (Malone and Semple, 2002; Spitzer and Semple, 1993, 1995).

Means of investigation

Experiments were designed to examine the dynamics of spatial auditory processing, with respect to the influence of development, ageing and neural adaptability to the listening environment on the processing of binaural cues.

In **Chapter 2**, long-term adaptive effects are studied in the gerbil, a small mammal well adapted to processing low frequency sounds, and with a similar hearing range to humans, between 1 and 10 kHz (Ryan 1976). The effect of ageing and the effect of modified binaural cues during ontogenesis are examined in a behavioral experiment in which the spatial auditory resolution of gerbils with altered neural circuits is determined and compared with that of young animals raised under normal conditions (Maier and Klump 2008). The hypothesis under investigation is that modifications of binaural cues during development (Kapfer et al 2002), and the ageing process itself (Gleich and Strutz 2002, Gleich et al. 2004), lead to changes in the balance of excitation and inhibition in the binaural brainstem nuclei. The results are discussed with respect to possible compensatory mechanisms allowing for adaptation to altered circuits and functional deficits in binaural sound encoding structures.

In **Chapter 3**, short-term neural adaptation is studied in the responses of auditory neurons in the guinea pig midbrain, another small mammal with good low frequency hearing. Electrophysiological recordings demonstrate that the context in which spatial cues are presented may be a general property of neurons in the inferior colliculus (IC) (Spitzer and Semple 1993; McAlpine et al. 2000). This suggests a potential modification of ITD coding between MSO and midbrain. Of particular interest is the way in which ITD-sensitive neurons might alter their coding abilities dynamically to reflect the unfolding distribution of ITDs. Previous studies have shown that neurons are most informative about ITD on the slope of their rate-ITD functions (Shackleton et al 2003), and that these slopes generally lie within the naturally-encountered range (McAlpine et al 2001). Here, I examine whether ITD coding by IC neurons adapts to the statistics of a defined distribution of ITDs, assessing the extent to which the most informative region of a neuron's rate-ITD function shifts to accommodate the most commonly-occurring ITDs presented in a distribution. This was performed by conducting single-neuron recordings

in the IC of anaesthetized guinea pigs. Data are analyzed using estimation theory and discussed with respect to the extent of the requirement to adjust neural coding to take account of the dynamics of the spatial acoustic environment.

Whether adaptive coding at the level of single neurons has a correlate in human performance is examined in **Chapter 4** using a psychophysical paradigm. Discriminability (using d' analysis) was assessed for two consecutively presented binaural "target" sounds containing ITDs or ILDs, presented either with or without a preceding "adaptor" stimulus to determine whether performance in a discrimination task involving spatial cues is influenced by the context in which that cue is presented. Results are discussed in terms of potential interactions between ITDs and ILDs, and the influence of adaptor location on target discriminability.

The different models and techniques employed allow for a broad comparison of data as well as substantiating the conclusion that unifying principles of sound localization exist across species, and can be assessed, in the mammalian auditory system.

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Chapter 2

Effects of omni-directional noise exposure during hearing onset and age on auditory spatial resolution in the Mongolian gerbil (*Meriones unguiculatus*) – a behavioral approach

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Abstract

Inhibitory inputs to the binaural brainstem nuclei medial and lateral superior olives (MSO and LSO, respectively) are thought to be important for sound localization in mammals. Here, we investigate whether aged gerbils that typically exhibit degenerative changes in auditory nuclei providing inhibition to MSO and LSO show diminished localization ability. We also tested the localization ability in gerbils reared in omni-directional white noise during hearing onset, a treatment that affects the adjustment of inhibitory inputs to MSO neurons possibly resulting in weakened sensitivity to interaural time difference. Localization ability of both groups was compared to that of young gerbils raised under control conditions. Stimuli had a duration of 125 ms and were pure tones of 0.5, 1, 2, 4 and 8 kHz, 300-Hz-bands of noise centered at 0.5, 2 and 8 kHz or broad-band noise. Gerbils trained in a two-alternative-forced-choice procedure indicated if sounds were presented from the left or from the right by choosing the respective response compartment of a Y-shaped experimental setup. The minimum resolvable angle (MRA) was calculated as the minimum angle between two loudspeaker locations that a gerbil was able to discriminate. MRAs for aged gerbils were higher compared to controls, whereas MRAs of noise-reared gerbils did not differ from those of the control group. Results are discussed with respect to the progressive degeneration affecting the gerbil's auditory system, changes in the anatomical arrangement of inhibitory inputs on binaural neurons in the MSO, and hearing thresholds.

Introduction

The ability to localize the position of a sound source is critical to the survival of many species. For sound localization in the azimuthal plane mammals make use of differences in the level and timing of a sound reaching the two ears - interaural level and interaural time differences, i.e., ILDs and ITDs, respectively. These cues are not equally effective at all frequencies. In the high frequency range (e.g., for gerbils above 4 to 5 kHz) where the head is acoustically opaque, ILDs are the dominant localization cue and previous measurements of localization thresholds in gerbils suggest that an ILD of 4 dB may be sufficient for localizing single sound sources (Maier and Klump 2006). In the lower frequency range, however, the relatively small head-size of many small mammals provides only insufficient "acoustic shadowing" at the ear (except for near-field stimulation) and ILDs are vanishingly small (Rayleigh 1907, Shaw 1974, Yin 2002).

In the lower frequency range, many mammals have evolved the ability to detect differences in the timing of a sound in the order of just a few tens of microseconds. In the gerbil, the localization accuracy indicates that an ITD of 40 μs can be sufficient for localization (Maier and Klump 2006). The distinction between high- and low-frequency processes led to the duplex theory of binaural hearing (Rayleigh 1907) that has been supported, for example, by psychophysical studies in human listeners (Stevens and Newman 1936, Mills 1958, Mills 1960). Subsequent investigations (e.g. Boudreau and Tsuchitani 1968, Goldberg and Brown 1969) substantiated the duplex theory in the anatomical and physiological domains, with neurons in the lateral superior olive (LSO) of the superior olivary complex (SOC) specialized for processing ILDs, and those in the medial superior olive (MSO) and low-frequency part of the LSO (Tollin and Yin 2005) for ITDs.

Recent studies in the gerbil attributed the encoding of ITDs to an interaction of excitatory inputs from both cochlear nuclei and precisely timed inhibitory inputs, contralaterally derived via the medial nucleus of the trapezoid body (MNTB) and ipsilaterally via the lateral nucleus of the trapezoid body (LNTB, see review by Grothe 2003). The cellular mechanisms responsible for such precisely timed inhibitory processing remain controversial. Recent data (Magnusson et al. 2005, Donato and

McAlpine 2007) suggest that a combination of cellular mechanisms, including fast inhibitory time constants, are required to account for the speed with which timed inhibition appears to operate, as evidenced by the *in vivo* observations (Joris and Yin 1995, Joris 1996, Joris and Yin 1998, Tollin and Yin 2005). Kapfer et al. (2002) demonstrated that glycinergic synapses in the MSO undergo an experience dependent refinement process during hearing onset, and they suggested that this refinement has evolved as an adaptation for ITD coding in the submillisecond range. By rearing gerbils in omni-directional white noise the refinement process can be disrupted (Kapfer et al. 2002) possibly resulting in a lower sensitivity in MSO neurons to differences in ITD (Seidl and Grothe 2005). In the current study we investigated with psychophysical methods whether the disrupted refinement process of gerbils reared in omni-directional white noise is reflected in their sound localization ability.

Several studies reported that aged gerbils are subject to a degenerative disorder that causes lesions in the nuclei of the ascending auditory pathway including binaural nuclei (MNTB, MSO, LSO) (e.g. Gleich and Strutz 2002, Gleich et al. 2004, Faddis and McGinn 1997, Ostapoff and Morest 1989). Furthermore, old gerbils show a compromised temporal processing which has been attributed to reduced inhibition (Gleich et al. 2003, Hamann et al. 2004).

If this reduction in inhibition is also evidenced in the MNTB, it might be expected to influence the processing of binaural cues by neurons of the MSO and LSO, potentially reducing spatial processing capabilities. Here we examine, if binaural processing that also relies on functional inhibitory circuits is impaired by behaviorally determining minimum resolvable angles in the azimuthal plane.

Experimental Procedure

Sound localization experiment

Subjects

Seven gerbils (*Meriones unguiculatus*) reared in omni-directional white noise (noise-reared), four aged gerbils and nine gerbils raised under "normal" conditions (results of three of these individuals have been reported in Maier and Klump 2006) were trained to perform sound localization experiments in this study. During testing aged gerbils ranged from 32 to 51 months of age. The age of noise-reared and control gerbils ranged from three to eight months, and from four to 14 months, respectively. Animals were provided by the laboratories of Benedikt Grothe (LMU Munich, Germany), Otto Gleich (Regensburg, Germany) and Charles River laboratories. All animals originated from the Tumblebrook strain.

Animals were housed in individual cages (42x26x15 cm). Bedding consisted of wooden chippings (Raiffeisen) and shredded paper for burrowing. To keep the animals at an average 94.2 % of their ad libitum weight of 71.8 ± 12.6 g (mean ± SD) body weight was controlled daily during the entire training and testing. 20 mg pellets (Bioserve: Dustless Precision Pellets, Formula #FO163) were given as food reward during experiments. Additional rodent pellets (Altromin 1314) were fed to keep the animals' weights roughly constant. The access to water was unrestricted. The care and treatment of the animals was approved by the Bezirksregierung Weser-Ems and followed the NIH guide for the care and use of laboratory animals.

Noise exposure

A cage with gerbil pups and their mother was placed in a sound attenuated booth (100x80x80 cm^3) containing two pairs of loudspeakers in each wall (amounting to a total of 24). One speaker of each pair delivered the low the other the high frequency part of a white noise, generated by two analog noise generators (Rhode and Schwarz). Sound level was approximately 75 dB SPL (rms value, averaging time 30 s, determined with a

½-in Brüel & Kjær Type 4192 pressure field microphone placed in the middle of the cage), never exceeding 80 dB SPL. The booth and the stimulation scheme were similar to that used in the previous studies on the development of sound localization mechanisms in the gerbil (Kapfer et al. 2002, Seidl and Grothe 2005). Animals remained in the booth between postnatal days 10 and 25. Food and water supply was unrestricted. Gerbils were exposed to noise in the laboratory of Benedikt Grothe in Munich and were subsequently transported to our laboratory at Oldenburg.

Apparatus

Experiments were conducted in two sound-attenuating chambers (Industrial Acoustics type IAC 1204A and 403A, with internal dimensions 275x254x198 cm and 223x213x198 cm, respectively), whose inner walls were lined with a layer of sound-absorbing wedges (Illbruck Illsonic Waffel 70/125, mounted on Illbruck Plano type 50/0 SF). The wedges had an absorption coefficient of more than 0.99 for frequencies above 500 Hz. A 10-cm layer of polyurethane foam (25 kg / m^3) lined the floor. The noise reared and six control gerbils performed on a Y-shaped platform constructed from stainless steel mesh, the aged and three of the control gerbils in a Y-shaped cage constructed from wire mesh, fixed 100 cm above the floor on top of a stand. The platform and cage were composed of an entrance area (10x10x10 cm), leading to a podium (8x6x10 cm) where the gerbil sat waiting for stimulus presentations. Here, the sides of the cage allowed only for restricted head movements, whereas gerbils tested on the open platform were not so restrained. From the podium, the gerbil could run into the left or right arms of the Y (each 25x10x10 cm and separated by an angle of 90°) to indicate its response. The podium of the platform and cage was located in the center of a custom-built iron circle (radius 65 cm) on which six pairs of loudspeakers (Canton Plus XS) were mounted. Angular separation between the pairs of speakers on either side of the midline of the setup was 12°, 36°, 60°, 90°, 120° or 180° azimuth. Aged gerbils worked only with five speaker pairs (i.e., without the pair with an angular separation of 180°). The animals' whereabouts was registered by light-interrupting switches mounted in each compartment (entrance area, podium, left and right arms). A feeding dish was

mounted at the end of each of the two arms opposite to the podium, receiving food rewards via flexible tubes from two custom-built feeders mounted about 40 cm above the platform or cage. A feeder LED between the two arms served as visual feedback for the animals during experiments. The feeder LED was the only light source with a spectrum that was visible to the gerbils. A cluster of 28 LEDs (Conrad) was mounted above the listening podium, providing infrared light which is invisible for gerbils for an infrared sensitive camera that transmitted the picture to an observation monitor (Santec CCTV, Typ MM-12S).

Stimulus generation

All stimuli were generated using a Linux workstation (AMD Processor, Sound Blaster PCI 512, 44.1 kHz sampling rate) and passed through a programmable attenuator (PA4, Tucker Davis Technologies) before being amplified (Yamaha Stereo Amplifier A-520). After subsequent equalization (Technics Stereo Graphic Equalizer SH-8075), the maximum difference between any two speakers for frequencies used for presentations of pure tone and narrow-band noise was 8 dB. Since we employed a roving level with a range of 12 dB (see next paragraph), intensity differences between speakers could not provide a reliable cue for localization for pure tones or narrow band noise. In the case of broadband noise, the maximum difference between the level presented by any two speakers was 6.2 dB (range of frequencies 0.1 to 12 kHz), but narrow-band notches at a few specific frequencies were found that lead to differences of up to 18.2 dB between any two speakers. These notches did not affect testing with sine-wave or narrow-band noise stimuli. Due to the broad frequency range used for stimulation and a resulting broad excitation of the cochlea in which the regions of the basilar papilla corresponding to the narrow-band notches are well stimulated by the spectral energy close to the notch, it is unlikely that these notches could have provided a systematic cue for localization of broadband noise. Furthermore, the average differences in the transfer functions of sound presented from the different speakers were typically much smaller than the extreme values reported here. Via a Power Multiplexer (PM1, Tucker Davis Technologies) one of the 12 loudspeakers in the chamber could be

selected for signal presentation. By eliminating all DC offsets in the apparatus and switching when no signal was presented we made sure that no switching transients were available as unwarranted cues. Sound-pressure level (SPL) in the experimental setup was calibrated every morning with a sound level meter (Brüel & Kjær 2238 Mediator) with the microphone located at the position on the podium where the animal's head would normally be during the experiment just prior to stimulus presentation.

Pure tones with frequencies of 0.5, 1, 1.5, 2, 4 or 8 kHz, bands of noise 300 Hz wide centered at 0.5, 2 or 8 kHz and broad-band noise, limited by the transmission characteristic of the speakers (130 Hz – 21 kHz) were presented to the animals. All stimuli were of 125-ms duration including 25-ms Hanning ramps at stimulus onset and offset. This duration was sufficiently short to assure that the gerbils were forced to perform under open-loop condition, not allowing them to orient towards the location of the stimulus. Stimuli were presented with a mean overall level of 60 dB SPL that was randomly varied by ± 6 dB. 60 dB SPL corresponds to an average sensation level of 41, 54, 55, 57, 57 and 55 dB for frequencies of 0.5, 1, 1.5, 2, 4 and 8 kHz, respectively. These calculations are based on threshold data from Ryan (1976), which are also representative for young gerbils of the Tumblebrook strain (Klinge and Klump, personal communication).

Experimental procedures

Animals were trained by means of operant conditioning in a two-alternative-forced-choice (2-AFC) paradigm with food rewards (for details see Maier & Klump 2006). Gerbils initialized a random waiting interval of between 1 and 7 s upon jumping onto the podium. After the waiting interval was completed, a single stimulus was presented from one of the loudspeakers. Gerbils were trained to leave the podium and indicate if the stimulus was presented from the left or the right by entering the appropriate response compartment on the left or right side. If the gerbil responded correctly, the feeder LED was illuminated and the feeder on the appropriate side delivered a reward with a probability of 80 %. Following food delivery, the next trial was initiated. If the wrong response compartment was chosen, the next trial could not be initiated until a period of

3 s had elapsed. If a stimulus was missed, i.e. if the animal remained on the podium, a new trial was initiated after 3 s. If the subject missed a stimulus by leaving the podium but not breaking the light-interrupting switch in one of the response compartments, the trial ended after 5 s. The experimental protocol was monitored by the workstation using a custom program.

Discrimination thresholds for deriving the minimum resolvable angle (MRA) were determined using the method of constant stimuli. Sessions were comprised of 6 blocks of 12 trials or 9 blocks of 10 trials for noise reared and aged gerbils, respectively. In each block each of the loudspeakers was randomly activated. The first block of trials of each experimental session served as a “warm-up” period, during which only stimuli from the widest angle were presented. It was discarded from the analysis. Each session lasted between 20 and 30 min for noise-reared and control gerbils and between 30 to 60 min for aged gerbils.

Data analysis

The minimum resolvable angle (MRA) was determined from data collected within four sessions (240 trials for noise reared and the controls or 320 trials for aged gerbils). Psychometric functions were constructed combining stimulus presentations from left and right by plotting percent correct responses versus the angle between speaker pairs. In these four sessions noise reared and control animals had to respond to at least 14 of the 20 stimuli, presented via a certain speaker. Aged gerbils had to respond to 22 of 32 stimuli independent of whether they chose the correct or incorrect response compartment, otherwise a fifth session was conducted and the first session was discarded from the analysis. Experimental sessions were excluded from the analysis if the animal responded less than 80 % correct to stimuli presented via speakers that enclosed the widest angle (180° noise reared and normal, 120° aged; 21.5 %, 17.1 %, and 16.5 % of sessions excluded for noise-reared, aged and normal gerbils, respectively) and if the animal did cross the light interrupting switch in the response compartments to less than 75 % of all presented stimuli (0, 2 and 2 sessions excluded for noise-reared, aged and normal gerbils, respectively). The MRA was obtained by

means of linear interpolation of the data in the psychometric function as the angle resulting in 75 % correct responses.

Measurement of hearing thresholds

Subjects

Hearing thresholds were measured in four noise reared and five aged gerbils (*Meriones unguiculatus*). During testing, the age of the noise-reared gerbils ranged between 5 and 9 months, and the age of the old gerbils ranged from 35 to 53 months. Hearing thresholds of three of the four aged gerbils that took part in the sound localization experiment were evaluated. The fourth of these, plus all of the noise-reared gerbils, were returned to their laboratories of origin immediately following completion of the localization experiment and thresholds in these individuals could not be determined. Therefore, we tested noise-reared animals from the same strain, raised under the same conditions in the noise box as the gerbils tested in the localization experiment that were provided from the laboratory of Benedikt Grothe (LMU, München). Husbandry was consistent with that of the gerbils in the localization experiment (described earlier).

Apparatus

Hearing thresholds were measured in a sound-attenuating chamber (Industrial Acoustics type IAC 1204A, see 4.1.3) Experiments were carried out in a doughnut-shaped cage (outer diameter 30 cm, inner diameter 12 cm, constructed form wire mesh. The cage was mounted onto a chipboard (50x40x1.6 cm) covered with a layer of sound absorbing wedges (Illbruck Illsonic Waffel 70/125, mounted on Illbruck Plano type 50/0 SF) and inserted into stand consisting of metal bars (diameter 5 mm), 90 cm above the floor. The cage contained a podium where the gerbil sat waiting for stimulus presentations. An animal's presence on the podium was controlled by a double light-interrupting switch. A feeding dish was mounted 15 cm from the podium, receiving food rewards via a flexible tube from a custom-built feeder mounted about 60 cm above the cage. A feeder LED atop the feeding dish served as visual feedback for the animals

during experiments, a 20 W halogen light served as roomlight. Visual control of the experiments was enabled by a camera connected to an observation monitor (Santec CCTV, Typ MM-12S).

Stimulus generation

As for the sound localization experiment, a Linux workstation (AMD Processor, RME sound card Hammerfall DSP Multiface II, 44.1 kHz sampling rate, 16 bit) was used to generate stimuli. Subsequently they were passed through a programmable attenuator (PA5, Tucker Davis Technologies) and a supplemental manual attenuator (Texio Corporation) to set the required overall stimulus levels. After amplification (Harman/Kardon 6500) stimuli were presented via the loudspeaker (Canton Plus XS) in the booth mounted 60 cm above the center of the experimental cage. Sound-pressure level in the experimental setup was calibrated every morning with a sound level meter (Brüel & Kjær 2238 Mediator) with the microphone located at the position on the podium where the animal's head would normally be during the experiment just prior to stimulus presentation.

Pure tones with frequencies of 0.5, 2 or 8 kHz and broad-band noise, limited by the transmission characteristic of the speakers (130 Hz – 21 kHz) were presented to the animals. Stimuli had a duration of 800 ms including 25-ms Hanning ramps at stimulus onset and offset.

Experimental procedure

Hearing thresholds were measured by training animals in an operant conditioning Go/NoGo paradigm with food rewards. Gerbils initialized a variable waiting interval of between 1 and 7 s upon jumping onto the podium. After the waiting interval was completed, a single stimulus was presented via the loudspeaker. Gerbils were trained to jump off the podium if they perceived a stimulus (Go-condition) and expected to remain on the podium if they did not detect a stimulus (NoGo-condition). Hearing thresholds were measured employing the method of constant stimuli. Sessions were comprised of 11 blocks of 10 trials. The first 10 trials of each experimental session served as a "warm-

up" block, during which only the most salient, i.e. loudest, stimuli were presented. It was excluded from the analysis. Three trials in each block were so called "catch-trials" (30 % of all trials within a session) during which no stimulus was presented. These trials were used to determine an animal's false alarm rate. If an animal jumped off the podium upon stimulus presentation, the feeder LED was illuminated and it received a food reward with a probability of 80 %. Following food delivery, the next trial was initiated. If the animal missed a presented stimulus, i.e. remained on the podium, or left the podium during a "catch-trial", it could not initiate the next trial until a period of 3 s had elapsed. The experimental protocol was monitored by the workstation using a custom program. Each session lasted between 20 and 30 min.

Data analysis

Hearing thresholds were calculated from data collected within two valid sessions (100 trials each). Psychometric functions of each session were obtained by plotting percent correct responses versus decibels used. Signal detection theory was employed to determine hearing thresholds, applying a threshold criterion d' of 1.8. Individual thresholds were not allowed to differ more than 3 dB between sessions to be combined. Otherwise the first session was discarded from the analysis and a third session conducted. Experimental sessions were excluded from the analysis if the animal responded to less than 80 % go to the most salient stimuli and if the animal left the podium in more than 20 % of the "catch-trials".

Results

Sound localization

A total of 20 animals contributed to the current study. All animals were trained to perform a sound localization task employing a 2-alternative forced choice (2-AFC) paradigm. Gerbils raised under conditions of omni-directional noise ("noise-reared" – see Experimental procedures, N = 7) and six animals of the control group were tested on a platform that allowed head movements ("open setup"). Aged animals (N = 4) and three animals of the control group were tested in a cage allowing restricted head movements ("closed setup"). Although no significant differences in mean minimum resolvable angles (MRAs) between control animals in the two setups were observed ($P = 0.233$, $F_{1,76} = 1.706$; two-way repeated-measures ANOVA with stimulus type and groups of gerbils as factors), the variance in the MRA of control gerbils tested in the open setup was significantly larger compared to that of gerbils tested in the closed setup ($P < 0.001$, $F_{1,76} = 16.768$; Levene-test for homogeneity of variances). Therefore, in the following results obtained from the two setups will be described separately.

Pure tones

Minimum resolvable angles were measured for pure tones at 0.5, 1, 1.5, 2, 4 and 8 kHz for each group of gerbils.

Comparison of noise reared gerbils and young gerbils raised under control conditions:

No significant differences were observed in the average minimum resolvable angles (MRAs) between noise-reared gerbils and control animals measured using pure tones ($P = 0.158$, $F_{1,68} = 2.274$; general linear mixed model ANOVA with stimulus type and groups of gerbils as factors), nor between MRAs measured at different pure tone frequencies ($P = 0.183$, $F_{5,64} = 1.581$). For noise-reared animals, the smallest MRAs (23.1°±6.5°; mean ± standard deviation) were found using 1-kHz tones. MRAs for all other frequencies were higher, ranging from 29.5°±9.7° at 8 kHz to 35.8°±12.6° at 2 kHz (**Figure 1A**). In control animals, the smallest MRAs were observed for tones of 1 and

2 kHz (29.2°±11.8° and 28.8°±19.6°, respectively). MRAs for the remaining frequencies tested ranged from 38.0°±28.1° at 8 kHz to 71.4°±55.6° at 4 kHz (**Figure 1B**).

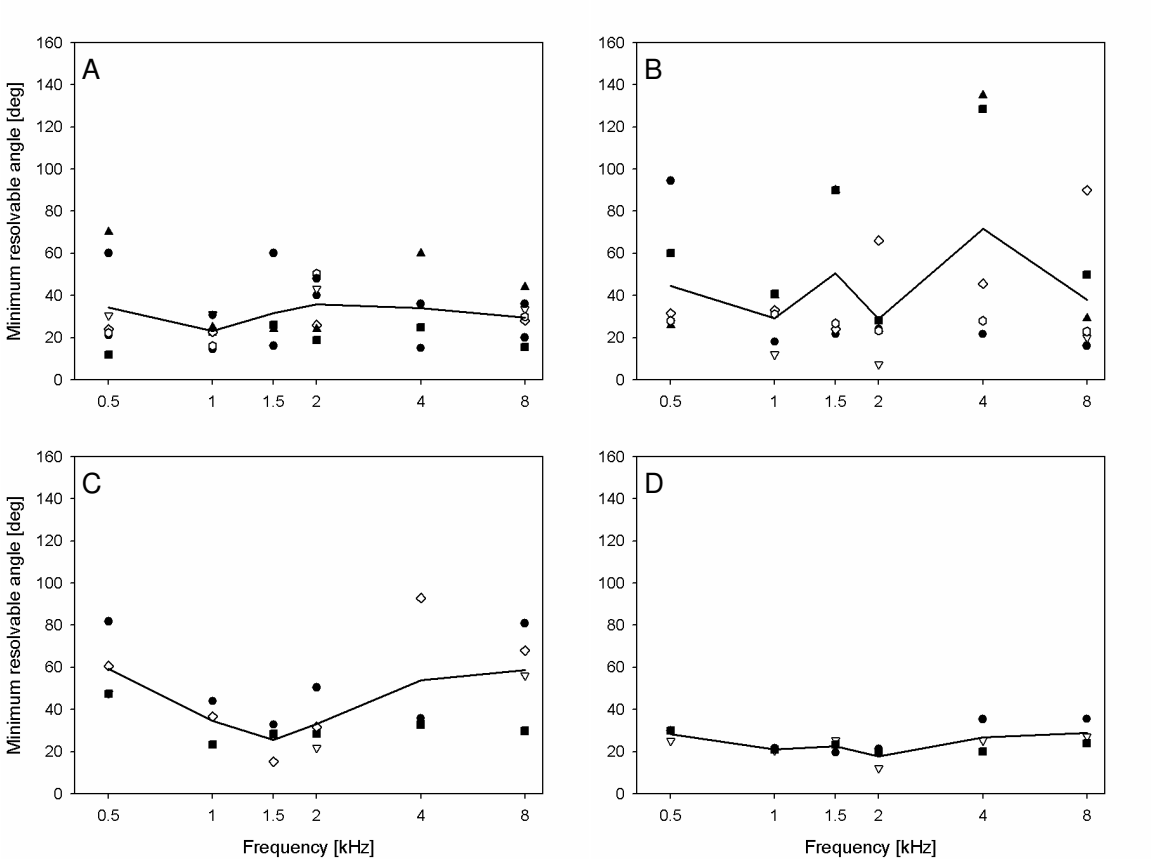

Figure 1: Minimum resolvable angles (MRAs) for localization of pure tones as a function of tone frequency: (**A**) MRAs for gerbils reared in omni-directional white noise (N = 7; open setup), (**B**) MRAs for the control group (N = 6; open setup), (**C**) MRAs for aged gerbils (N = 4; closed setup) and (**D**) MRAs for the control group (N = 3; closed setup). Thresholds of individual gerbils are identified by the differently shaped symbols. The lines indicate the mean MRA.

Overall MRAs measured in the open setup showed considerable variability. Standard deviations of noise-reared gerbils ranged from the relatively low 6.5° at 1 kHz to 21.9° at 0.5 kHz. Standard deviations in control animals ranged between 11.8° at 1 kHz to 55.6° at 4 kHz. Significant differences between standard deviations in both groups were observed for 1.5, 4 and 8 kHz ($P = 0.022$, $F_{1,7} = 8.576$; $P = 0.005$, $F_{1,7} =$

15.684 and P = 0.049, $F_{1,11}$ = 4.891, respectively; Levene-test for homogeneity of variances; both groups completed the same number of trials). Generally, controls showed higher standard deviations than noise-reared gerbils.

Comparison of aged gerbils and young gerbils raised under control conditions:

Aged animals were tested only in the closed setup. Here, average MRAs of aged gerbils differed significantly from those of control animals tested using the same setup (P = 0.039, $F_{1,37}$ = 7.939; General linear mixed model ANOVA with stimulus type and groups of gerbils as factors), with MRAs significantly higher in aged than in control animals at 0.5 and 8 kHz (P = 0.010 and P = 0.013, respectively; posthoc Tukey-test). In addition, significant differences between pure tone frequencies were evident (P = 0.013, $F_{5,33}$ = 3.761). For aged gerbils, MRAs were smallest between 1 and 2 kHz (34.6°±10.5°, 25.5°±9.1° and 33.1°±12.3° for 1, 1.5 and 2 kHz, respectively: **Figure 1C**), and higher below and above this frequency range (59.4°±16.2°, 53.8°±33.8° and 58.7°±21.8° for 0.5, 4 and 8 kHz, respectively), with MRAs for 0.5 kHz and 8 kHz significantly increased compared with 1.5 kHz (P < 0.05; posthoc Tukey-test). Control animals exhibited the smallest MRAs between 1 and 2 kHz (ranging from 17.8°±4.9° to 22.7°±2.9°). MRAs below and above were slightly higher; the widest angular separation between speaker pairs required was 28.8°±6.0° at 8 kHz (**Figure 1D**). None of these differences, however, were significant (P > 0.05; posthoc Tukey-test).

Generally, MRAs showed relatively little variability in animals tested in the closed setup. Aged animals showed, without exception, higher variability in their MRAs compared with control animals, with standard deviations ranging from 9.1° (1.5 kHz) to 33.8° (4 kHz) compared with values that ranged from 0.6° at 1 kHz to 7.7° at 4 kHz in control animals. These differences, however, were only significant at 4 kHz (P = 0.041, $F_{1,4}$ = 8.770,; Levene-test for equality of variances).

Narrow-band noise

Minimum resolvable angles were also measured using 300-Hz wide bands of noise.

Comparison of noise reared gerbils and young gerbils raised under control conditions:

Gerbils reared in omni-directional noise indicated correctly the location of speakers separated by, on average, 39.8°±40.2° and 28.9°±14.1° for center-frequencies of 0.5 and 2 kHz, respectively (**Figure 2A**). These values were not significantly different to those obtained in the control group (**Figure 2B**; 28.5°±18.2°at 0.5 kHz and 27.7°±14.2° at 2 kHz) and between different center-frequencies (general linear mixed model ANOVA with stimulus center-frequency and groups of gerbils as factors; P = 0.556, $F_{1,23}$ = 0.368 for group and P = 0.563, $F_{1,23}$ = 0.356 for frequency).

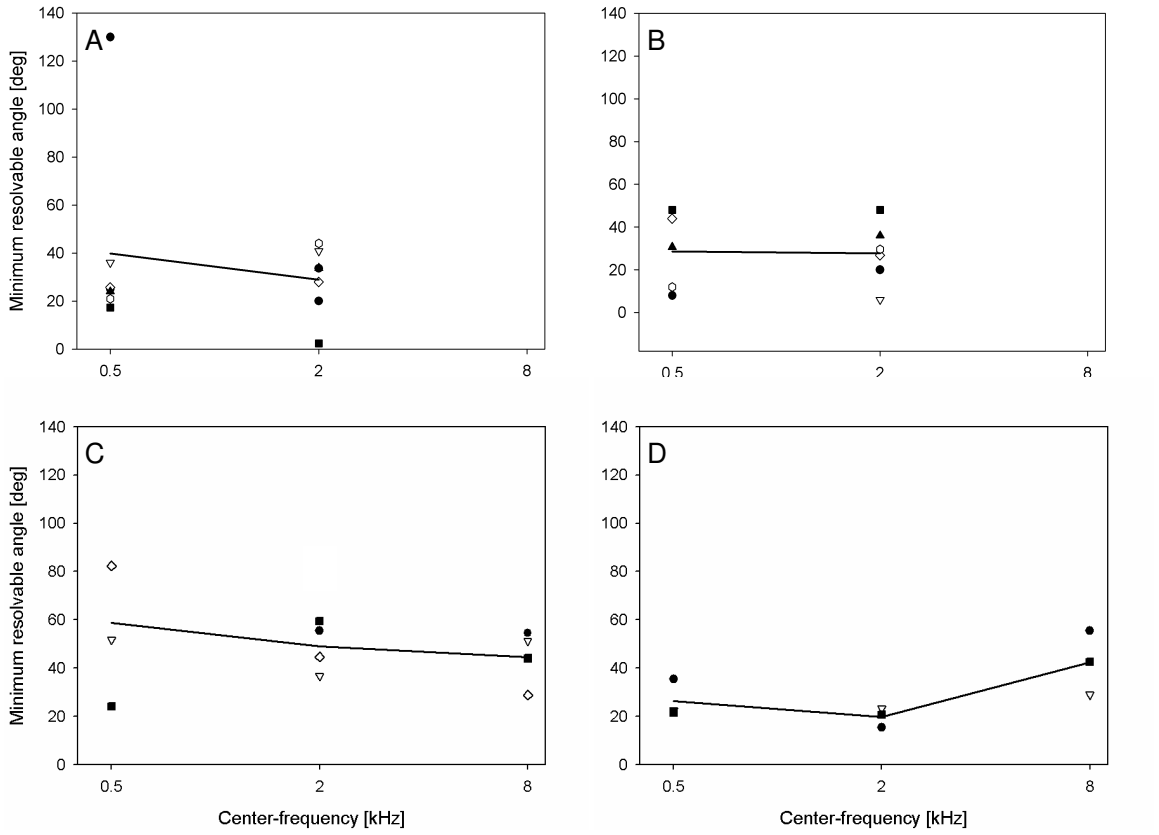

Figure 2: Minimum resolvable angles (MRAs) for localization of 300 Hz-wide bands of noise as a function of tone frequency: (**A**) MRAs for gerbils reared in omni-directional white noise (N = 7; open setup), (**B**) MRAs for the control group (N = 6; open setup), (**C**) MRAs for aged gerbils (N = 4; closed setup) and (**D**) MRAs for the control group (N = 3; closed setup). Thresholds of individual gerbils are identified by the differently shaped symbols. The lines indicate the mean MRA.

As for tones, standard deviations were relatively high at these (center) frequencies. However, no significant differences were evident between the variance in MRAs of noise-reared animals compared to control animals ($P = 0.436$, $F_{1,10} = 0.660$; $P = 0.822$, $F_{1,11} = 0.053$ for center-frequencies 0.5 and 2 kHz; Levene-test for homogeneity of variances).

Comparison of aged gerbils and young gerbils raised under control conditions:

In addition to center-frequencies of 0.5 and 2 kHz, animals in the closed setup were also tested for a center-frequency of 8 kHz. Aged animals required, on average, an angular separation for discriminating between two loudspeaker locations of 58.8°±26.8°, 49.1°±10.4° and 44.6°±11.4° for center-frequencies of 0.5, 2 and 8 kHz, respectively (**Figure 2C**). For control animals, MRAs for the same frequencies were 26.5°±7.8°, 19.7°±4.1° and 42.3°±13.3° (0.5, 2 and 8 kHz, respectively; **Figure 2D**). A general linear model ANOVA, with stimulus center-frequencies and groups of gerbils as factors, indicated MRAs for narrow-band noise to be significantly different for the two groups ($P = 0.013$, $F_{1,19} = 13.971$). Posthoc Tukey-tests revealed the MRAs at 0.5 and 2 kHz to be significantly higher in aged compared with control animals ($P = 0.013$ and $P = 0.022$, respectively; posthoc Tukey-test) with the exception of narrow-band noise centered at 8 kHz ($P = 0.840$; posthoc Tukey-test). No significant differences were observed for different center-frequencies ($P = 0.529$, $F_{2,18} = 0.680$; general linear model ANOVA with stimulus type and groups of gerbils as factors). Also no significant differences were evident between the variance in MRAs of aged animals compared to control animals (Levene-test for homogeneity of variances; $P = 0.085$, $F_{1,5} = 4.602$; $P = 0.300$, $F_{1,5} = 1.338$; $P = 0.901$, $F_{1,5} = 0.017$ for center-frequencies 0.5, 2 and 8 kHz, respectively).

Broad-band noise

The ability to localize broadband noise was also assessed for each group.

Comparison of noise reared gerbils and young gerbils raised under control conditions:

Noise-reared animals were able to localize broad-band noise presented via speakers separated by 37.8°±31.0°, (**Figure 3A**). This value did not differ significantly

from the MRA of 22.2° ± 16.5° of the control group (P = 0.295; t-test), nor did the standard deviations (Levene-test for homogeneity of variances; P > 0.324, $F_{1,11}$ = 1.067).

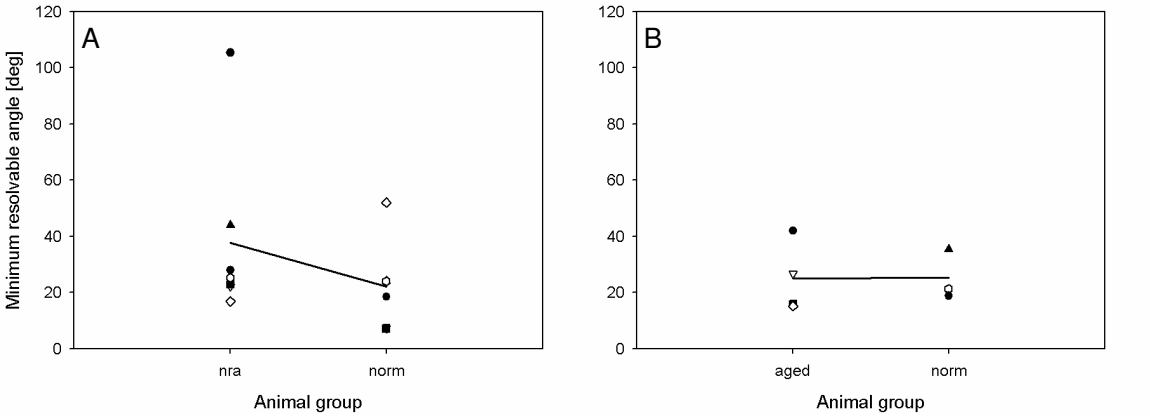

Figure 3: Minimum resolvable angles (MRAs) for localization of broad-band noise as a function of the group tested: (**A**) MRAs for gerbils reared in omni-directional white noise (N = 7; open setup) and for the control group (N = 6; open setup), (**B**) MRAs for aged gerbils (N = 4; closed setup) and MRAs for the control group (N = 3; closed setup). Thresholds of individual gerbils are identified by the differently shaped symbols. The lines indicate the mean MRA.

Comparison of aged gerbils and young gerbils raised under control conditions:

MRAs for aged animals (25°±12.5°; **Figure 3B**) did not differ significantly from those obtained in controls (25.2°±8.9°; P = 0.977, t-test). In addition, no significant differences were found between the standard deviations of both groups (P > 0.552, $F_{1,5}$ = 0.406; Levene-test for homogeneity of variances).

Hearing thresholds

Hearing thresholds of four noise-reared and five aged gerbils were measured for pure tones (0.5, 1, 2 and 8 kHz) and broad-band noise employing a GO/NoGo paradigm.

Noise-reared gerbils showed hearing thresholds of 4.0±1.5 dB for broad-band noise and 19.2±8.5 dB, -8.7±3.5 dB, -7.0±2.7 dB and -3.3±1.3 dB for pure tone frequencies of 0.5, 1, 2 and 8 kHz, respectively (**Figure 4A**). A two-way repeated-measures ANOVA with pure tone frequencies and animal groups as factors revealed no significant differences in hearing thresholds between noise-reared and four young control animals (Klinge and Klump, unpublished data). The thresholds of the noise-reared gerbils were similar or up to 13 dB more sensitive compared to the data obtained by Ryan (1976).

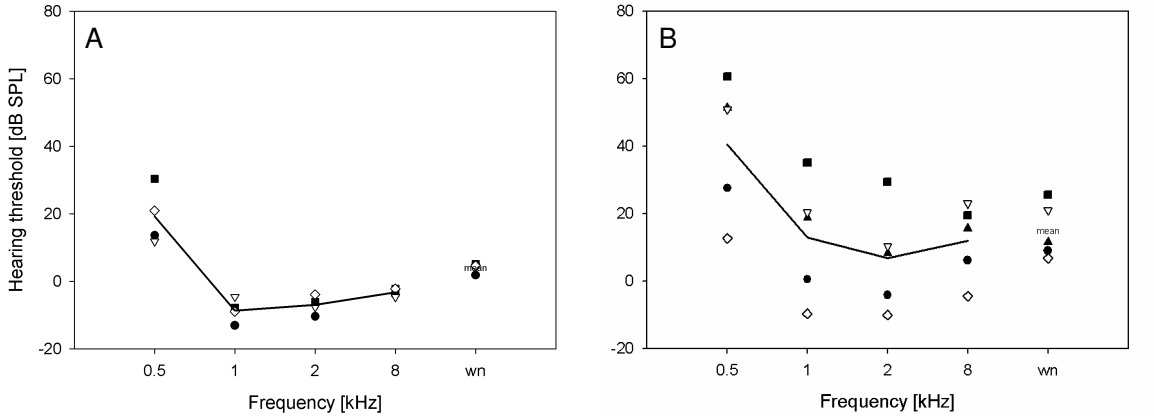

Figure 4: Hearing thresholds for pure tones and broad-band noise as a function of stimulus: (**A**) Hearing thresholds for gerbils reared in omni-directional white noise (N = 4) and (**B**) for aged gerbils (N = 5). Thresholds of individual gerbils are identified by the differently shaped symbols. For the three aged gerbils that also took part in the localization experiment, the symbols are matching those used in Figure 1C and 3B. The lines indicate the mean hearing threshold for pure tones. The mean threshold for broad-band noise is denoted by the word “mean”. The term “wn” is used to denote “white noise”.

For aged gerbils, hearing thresholds of 14.8±8.1 dB were obtained for broad-band noise and 40.6±19.8 dB, 13.0±17.7 dB, 6.7±15.3 dB and 11.9±11.1 dB for pure tone frequencies of 0.5, 1, 2 and 8 kHz, respectively (**Figure 4B**). There was a trend that in general hearing thresholds for pure tones differed from those of the control group described above (P = 0.061 for difference between groups; two-way repeated-measures

ANOVA with pure tone frequencies and animal groups as factors). A significant difference between both groups was found at a pure tone frequency of 0.5 kHz ($P = 0.014$, Tukey test) and a trend was observed at 1 kHz ($P = 0.055$, Tukey test).

Discussion

We investigated whether observed changes in the auditory system that may relate to inhibitory processing affect the sound-localization ability of gerbils. Minimum resolvable angles (MRAs) were measured in aged animals and compared with MRAs measured in a control group of young animals in a “closed setup” designed to minimize head movements. MRAs were also obtained in an “open setup” (in which a greater range of head-movements was permitted) for animals reared in omni-directional white noise during the onset of hearing and a control group of animals. Aged gerbils showed higher and/or more variable MRAs compared with MRAs measured in young gerbils raised under control conditions. No prominent differences were found between MRAs of noise-reared gerbils and their control group.

The effect of age on localization abilities in gerbils

Consistent with the impaired temporal processing previously observed in aged gerbils (e.g. Gleich et al. 2007) aged animals in our study exhibited increased MRAs in comparison to young controls. A likely contributing factor to reduced localization abilities in aged gerbils is the well-described and progressive degeneration of lower brainstem nuclei subserving sound localization in this species, characterized by progressive development of microcysts, vacuolar neural degeneration, and development of spongiform lesions (Ostapoff and Morest 1898, McGinn and Faddis 1998). First evident at the level of the cochlear nuclei, the degeneration affects other nuclei in the ascending auditory pathway with increasing age, including nuclei of the superior olivary complex in the brainstem, spreading as far as the inferior colliculus of the midbrain. A similar condition has been observed in the kangaroo rat (McGinn and Faddis 1997), a species closely-related to the gerbil. Occurrence of spongiform lesions in the cochlear nuclei, which provide excitatory input to MSO and the LSO, potentially distorts directional information, adding to localization errors. In addition, lesions of the medial nucleus of the trapezoid body (MNTB), functionally the main source of inhibitory input to both MSO and LSO, could also lead to errors in localization abilities. Such degeneration might account

for the increased MRAs at 0.5 and 8 kHz observed for aged gerbils in comparison to young controls.

A histological study investigating age-dependent changes in the MNTB of the gerbil, conducted with serial immuno-reactive staining for glycine (Gleich and Strutz 2002), showed a significant increase in the number and density of spongiform lesions in animals aged three years and older compared with younger animals. Lesions were particularly evident in the caudal division of the MNTB, systematically decreasing toward the rostral division, and were prominent by two years of age. The average size and diameter of these lesions increased significantly with age, accompanied by a significant reduction in soma size of MNTB neurons, although the rostro-caudal extent and total volume of the MNTB appears unaltered. With respect to binaural nuclei contributing to sound localization abilities, Gleich et al. (2004) reported that LSO neurons were significantly reduced in size in older animals, predominantly in high frequency regions (4 kHz and above). This could explain the increase in the MRA for 8 kHz. As with the MNTB, the number and density of LSO neurons, as well as the extent and volume of the LSO, was unaffected. In general, both the LSO and the MSO (which was also present in stained sections, but not examined in detail in that study) appeared less affected by lesions than was the MNTB (Gleich et al. 2004). Such an advanced pattern of lesions might provide an explanation to the observed increase of MRAs of aged gerbils compared to young controls in the present experiment.

Another factor that might influence localization ability in aged animals is the elevation in hearing thresholds that accompanies ageing. Behavioral measurements conducted with animals from the Regensburg, Germany breeding colony and animals bred in an independent colony in South Carolina, USA, revealed significant elevation, and increased variability, in hearing thresholds (tested at 2 and 10 kHz) in gerbils aged three years and older compared with young controls (Hamann et al. 2002). In our study, pure tone threshold at 0.5 kHz in aged animals was significantly higher than at all other frequencies and it was this frequency at which MRAs were also highest. Elevated gap-detection thresholds for broad-band noise, accompanied by increased variability, have also been demonstrated in aged gerbils suggesting impaired temporal processing in these animals (Hamann et al. 2004).

There was a trend for differences in MRAs between aged gerbils compared to their control group to diminish with increasing stimulus bandwidth. For pure tones and narrow bands of noise, aged gerbils showed significantly higher, and more variable, MRAs than the control group. That we did not observe differences in MRAs for broad-band noise could be explained by the increased number of localization cues available in the sounds with a broader bandwidth. In contrast to pure tones, broader bands of noise present the possibility of processing phase information across different frequency bands and exploiting envelope cues (Bernstein and Trahiotis 2002). The consistency of ITD information across frequency as stimulus bandwidth increases reduces the ambiguity of localization cues in humans (Trahiotis and Stern 1989) and barn-owls (Saberi et al. 1999), thereby enhancing localization accuracy. By extending the bandwidth to cover the frequency range over which both ITDs and ILDs are employed in localization tasks, this localization ambiguity is further reduced, enabling the animal to exploit the cue they can discriminate best. Broadening the bandwidth also provides the possibility of employing spectral cues for localization under conditions in which head movements are not completely restricted.

Our finding that MRAs for narrow-band noise centered at 0.5 and 2 kHz, but not for narrow-band noise centered at 8 kHz are significantly higher in aged animals compared with controls could indicate that compromised timing of inhibition is more ostensible for the processing of ITDs based on phase information than impaired inhibition *per se*. Gerbils, well adapted for low frequency hearing, use ITDs based on the neural representation of phase for sound localization at 0.5 and 2 kHz, a cue that probably does not play a large role at 8 kHz (Maier and Klump 2006). The finding that MRAs of aged gerbils to pure tones at 8 kHz are significantly higher than those of controls suggesting that localization for pure tones seems to be more strongly compromised than for narrow-band noise could be due to the impoverished cues of a pure tone stimulus (providing only intensity cues) compared to a narrow-band noise (providing envelope transients in addition to the intensity cues). The result that the MRA for narrow-band noise centered at 2 kHz in old animals is significantly higher than that for controls could indicate that also for this stimulus the representation of ITDs derived from the phase-locked neural response to the frequencies comprising the noise is

compromised (however, this effect was not significant for the MRA for 2-kHz pure tones).

Localization abilities of noise-reared gerbils

The hypothesis under investigation was that animals reared in omni-directional noise would have poorer localization abilities than animals raised under control conditions. Kapfer et al. (2002) reported altered inhibitory projections to MSO neurons in gerbils raised under a noise-exposure regime identical to that employed in this study. In particular, the normal developmental refinement of inhibitory inputs to the soma of MSO neurons, a refinement that is suggested to be critical for normal processing of ITDs, was interrupted. Before hearing onset, glycinergic inputs are distributed over somata and dendrites of the cells. Following the onset of hearing, between postnatal days 10 and 25 these inputs are gradually restricted to the somata.

In noise-reared animals, the gradual restriction to the somata was significantly reduced. The hypothesis that this may lead to compromised processing of binaural inputs was supported by patch-clamp recordings made *in vitro*, using MSO slices from noise-reared gerbils (Magnusson et al. 2005) and *in vivo* in single-unit recordings in the dorsal nucleus of the lateral lemniscus (Seidl and Grothe 2005). It has been argued that disruption of the experience-dependent refinement process of inhibitory synapses weakens the kinetics of the inhibition, impairing processing of ITDs in the sub-millisecond range (Kapfer et al. 2002). Such disruption to normal processing of ITDs at a cellular level inflicted through noise-exposure during the refinement period could result in reduced sound localization abilities.

However, in this study behaviorally determined MRAs of gerbils raised in omni-directional noise were not found to be greater than those of control animals. One reason might lie in the efficacy of the noise-rearing paradigm. In contrast to its sufficiency in the far field, noise-rearing is not as efficient in eliminating binaural cues in the near field (Withington-Wray et al. 1990). In addition, individual susceptibility to noise rearing could explain why MRAs in noise-reared gerbils are not significantly different from those of the control group. A factor contributing to the high variability observed in both noise-reared

and control animals tested on the open setup might be increased head movements. In this setup the gerbils' head was not necessarily centered close to the midline during stimulus presentation. The impact of the exact head position during the performance of a localization task is currently under investigation in our laboratory. Furthermore, animals were not tested immediately following noise-rearing, but within a period of two to seven month after noise-exposure. This was as a consequence of allowing the gerbils to reach maturity before training, which proves rather difficult in very young animals, and also to provide for a direct comparison with young controls of the same age that had been tested before. During the time period between rearing and the start of training the gerbils were exposed to a normal auditory environment in our laboratory. Since rearing in noise took place in a critical developmental period during infancy we believe the anatomical effects of disturbed refinement to be permanent (Kapfer et al. 2002). However, auditory experience acquired in this time frame might have benefited the development of compensatory mechanisms (discussed below) thereby contributing to our failure of observing an impairment of sound localization ability in noise-reared animals.

Another question with regard to the effects of noise-rearing concerns the number of ITD-sensitive neurons, with correctly adjusted inhibitory synapses, that are mandatory for an animal to faithfully localize a single sound in a quiet (sound-proof chamber) environment. Seidl and Grothe (2005) showed a disrupted distribution of ITD functions in noise-reared animals, but still a significant number of cells showed strong changes in the spike count across the small range of ±130 µs the gerbil would experience in an anechoic room. Hence, the consequences of noise-rearing leading to an unnatural distribution of ITD functions may only have behaviorally consequences under more difficult conditions, e.g. when multiple sound sources or masking noises are present. Further experiments are needed to evaluate this possibility.

A further possible explanation for the failure to observe reduced localization abilities in gerbils raised in noise relates to potential compensatory mechanisms that counteract the effects of the noise-exposure. A number of previous studies have investigated the plasticity of the auditory system to altered spatial cues, and reported evidence for compensatory strategies (Kacelnik et al. 2006, King et al. 2000, Parsons et

al. 1999; humans by Hofman et al. 1998, Wright and Zhang 2006, van Wanrooij and van Opstal 2005), that restore localization performance to control levels. Ferrets whose pinnae and conchae of the outer ear were removed during infancy, showed similar localization abilities to a control group in a relative localization, although these animals were significantly poorer in an absolute localization task in the horizontal plane employing short-duration stimuli (Parsons et al. 1999). Similar effects have been observed in ferrets following unilateral pinna occlusion during infancy (King et al. 2000, Kacelnik et al. 2006), and human subjects appear to adapt to altered spectral cues that arise following insertion of an ear-mold (Hofman et al. 1998).

Compensation strategies have also been observed in cats whose olivocochlear pathway connecting the superior olivary complex with the outer hair cells was ablated (May et al 2004). Functionally, this feedback loop enhances detection of auditory signals in noise, thereby improving neural coding. Cats subjected to lesioning were equally able as control animals to indicate a shift in elevation of a 200-ms burst of noise under conditions of quiet in a relative localization task. However, conducting the same task in broad-band masking noise resulted in significantly increased thresholds in lesioned, in comparison to control, animals. However, following weeks of constant training, lesioned cats also developed compensatory listening in this task, eventually reaching performance levels of control animals.

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Chapter 3

Adaptive coding of interaural time differences in the auditory midbrain

In preparation for submission to **Journal of Neuroscience** as: Maier JK, Harper NS, Dean I, Klump GM, McAlpine D: Adaptive coding of interaural time differences.

Abstract

Adaptation of sensory neurons to the prevailing environment is a widely accepted phenomenon. Here, we investigate adaptive coding to interaural time differences (ITDs), one of the cues used by mammals to localize sound sources in azimuth. ITDs are particularly suited to examining the site of adaptive mechanisms, as contributions from mechanisms below the level of binaural integration can be excluded. We recorded responses of single neurons in the inferior colliculus of anaesthetised guinea pigs to a continuous white-noise stimulus in which the ITD was randomly selected every 50 ms from a defined distribution. Distributions contained a high probability (80 %) range of ITDs, with the remaining ITDs presented with 20 % probability. Changes in neural gain and the shapes of rate-ITD functions were observed for different distributions of ITDs. Estimation theory revealed that adjustments of neural responses take account of the statistical distribution of ITDs, but only for stimulation with naturally-encountered ITDs, i.e. ITDs bounded by the guinea pig's head-width. The data suggest that implementing a coarse adaptation to the most prevalent ITDs alters the neural population code for ITD, so as to increase accuracy for the most-probably occurring ITDs. These data demonstrate a clear case of adaptive coding that arises in the central nervous system, as opposed to the sensory periphery.

Introduction

Sensory neurons across many modalities, and in a wide range of species, have been found to adjust their response to the statistical distribution of stimulus parameters. Such adaptive coding is suggested to adjust neural firing rates to code most effectively the current sensory environment (e.g. Ohzawa et al., 1982, Fairhall et al., 2001, Dean et al., 2005).

For primary sensory neurons, such as those in the fly visual system (Kurz, 2007), mechanisms residing at this early stage in processing clearly contribute to adaptive effects (although efferent influences cannot entirely be discounted). For non-primary neurons, however, it is reasonable to assume that adaptive coding reflects both processing intrinsic to a neuron as well as processing inherited from that neuron's inputs. Recently, Dean et al. (2005) demonstrated adaptive coding for sound intensity in the auditory midbrain, showing that accuracy of the neural population is improved near the most common sound levels, potentially ameliorating the "dynamic range problem" of auditory nerve fibers - most primary fibers saturate their responses at sound levels approximately 35 dB above absolute threshold, whereas the human hearing range encompasses some 120 dB. Although this demonstrates that adaptive processes enable adjustments to the prevailing auditory environment, the relative contributions of different brain centers to this adaptation can be difficult to ascertain; relatively few stimulus parameters exist that do not influence neural responsiveness at the very earliest stages of a sensory system. Here, we examine adaptive coding of interaural time differences (ITDs) - small differences in the timing of a sound at the two ears - a stimulus parameter for which neural sensitivity is entirely absent until three synaptic levels above the cochlear hair cells. Many mammalian species, including humans, rely on ITDs to determine the azimuthal location of a sound source in the low-frequency range (<1500 Hz). ITDs are first processed in the medial superior olive (MSO) of the brainstem, where individual neurons innervated by both cochlear nuclei act as coincidence detectors, responding maximally to the ITD that compensates for the difference in the time of transmission of a sound from the two ears (Jeffress 1948, Goldberg and Brown, 1968, 1969). The use of ITDs to investigate adaptive coding is particularly interesting as ITDs

constitute a stimulus parameter for which only central mechanisms underlie adaptation (**Figure 1**).

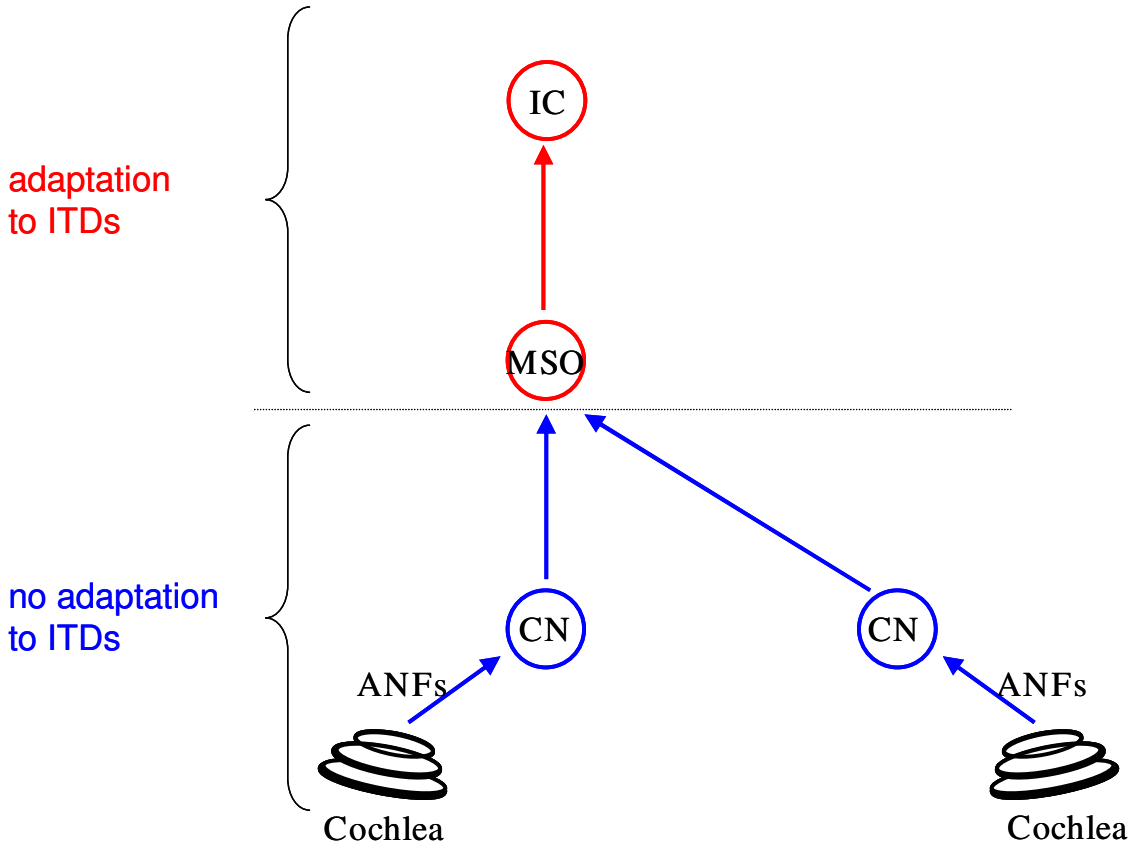

Figure 1: Excitatory pathway of the neural circuit involved in ITD processing. Auditory nuclei below the medial superior olive (MSO) - the site of binaural integration for timing differences between the ears - are unable to adapt to ITDs. ANF = auditory nerve fiber, CN = cochlear nucleus, IC = inferior colliculus, ITD = interaural time difference.

It has been demonstrated that neurons at or above the level of binaural integration appear to be insensitive to monaural changes in the phase of the stimulus fine-structure that, when applied binaurally, modulate the neural firing rate (Ingham and McAlpine, 2004). Here, we examine the ability of inferior colliculus (IC) neurons to adapt to the most prevalent ITDs in a defined distribution. We demonstrate, for a naturally-encountered range of ITDs, bounded by the guinea pig's head width, small shifts in the

slopes of neural rate-ITD functions towards the most commonly-occurring ITDs, when those ITDs were ipsilaterally-leading. In addition, the gain of rate-ITD functions tended to be higher the more ipsilaterally-leading were the commonly-occurring ITDs. Together, and taking both sides of the brain into account, these adaptive effects are suggestive of a limited but clear capacity for neural coding to adjust to better represent the most common ITDs in a distribution.

Methods

Surgical preparation.

Experiments were carried out in accordance with the guidelines of the UK Home Office, under control of the Animals (Scientific Procedures) Act 1986. Pigmented guinea pigs (*Cavia porcellus*) were anesthetised with a single dose of Urethane (Sigma-Aldrich, Poole, UK; 25 % solution of 0.9 % NaCl, 1 g/kg injected intraperitoneally). Subsequently an initial dose of analgesia was administered intramuscularly (0.1 ml Hypnorm; fentanyl citrate/fluanisone; Janssen-Cilag, High Wycome, UK) and supplemented as required during surgery and physiological recordings. To reduce bronchial secretions, 0.1 ml of Atropine sulphate was injected subcutaneously (Animalcare, York, UK; 0.6 mg/ml). Local anaesthesia during surgery was applied subcutaneously as needed using Lignocaine hydrochloride (2 % solution; Martindale Pharmaceuticals, Romford, UK). Depth of anaesthesia was assessed by means of the pedal withdrawal reflex. Body temperature was maintained at a core temperature of 37° using a thermostatically-controlled heating blanket and rectal probe (Harvard Apparatus, Kent, UK). After shaving the head, neck and torso, and following incision of the tragus, both ears were cleaned and the tympanic membrane inspected for damage. Following tracheotomy, the animal was transferred to a stereotactic frame with hollow ear speculae (modified from model 1730, David Kopf Instruments, Tujunga, CA) located within a sound attenuated booth (IAC, Winchester, UK). The surface of the skull was exposed, the head leveled stereotaxically and a craniotomy was performed (2-3 mm rostral and 1-4 mm lateral from the interaural axis). The dura mater enclosing the cortex was removed to allow for unhindered penetration of the electrode and the cranium was sealed with petroleum jelly. High acoustic-impedance tubes were sealed with petroleum jelly into each bulla to obtain pressure equalization of the middle ear. Custom-built ear phones were inserted into the hollow ear speculae fixating the animal's head, to form a sealed pressure-field sound delivery system. Single-unit extracellular recordings were carried out in the right IC using glass-coated microelectrodes of approximately 0.9 to 1 MΩ impedance (World Precision Instruments, Saratosa, FL). Electrodes were advanced dorsoventrally from

outside the booth by means of a piezo-electric stepper motor (Inchworm IW-700/710; Burleigh Instruments, Victor, NY).

Sound generation and presentation.

Stimuli were generated using Tucker Davis Technology digital (50kHz sampling rate) processing hardware (TDT, Alachua, FL; System III), TDT Brainware, Real Time Processor Visual design Studio (RPvds) and MATLAB software. Stimuli were attenuated (TDT, PA5), amplified (Beyerdynamic A150 Blueprint stereo-amplifier, Burgess Hill, UK) and presented via Beyerdynamic DT-48A (Burgess Hill, UK) loudspeakers, fitted and sealed with brass tube attachments to the hollow ear speculae. Probe-tube microphones (Knowles Acoustics FG3452, Burgess Hill, UK) inserted in the hollow specuale allowed for measurement of the stimuli at a distance of only a few millimeters from the tympanic membrane to ensure that the sounds delivered were well matched between the ears (within ±2 dB for frequencies below 2 kHz) . Probe-tube microphones were initially calibrated against a Brüel & Kjær $^1/_8$ in. microphone (Type 4136, Stevenage, UK).

Physiological recordings

Single units were isolated by presenting 50 ms pure tones of variable intensities and frequencies at a rate of 5/s. A neuron's characteristic frequency (CF) and threshold was determined audio-visually and confirmed by plotting a frequency-versus-level response area, extending 2 octaves above and 4 octaves below the estimated CF and between 10 and 90 dB attenuation, from the maximum system output of approximately 110 dB SPL (this range was sufficient to determine threshold in all cases; low CF neurons in the guinea pig IC tend to show relatively high thresholds, which accords with the species' audiogram) To assess sensitivity to ITDs a baseline function was obtained in response to 50 ms white noise bursts of various ITDs. Noise bursts were separated by 300 ms and presented in random interleaved order 20-40 dB above threshold (constant for a given cell). Each ITD was repeated ten times. If the unit proved to be ITD-sensitive the stimuli relevant for the experiment were presented (also at 20-40 dB

above threshold; constant for a given cell). These consisted of interaurally-delayed white noise of 5 s duration. Stimuli were repeated 75 times, with the ITD sequence randomized across repeats. The noise seed was also randomized across stimuli presented to the same neuron, and across neurons. ITDs ranged from -0.5 to +0.5 cycles with respect to neural CF, or were restricted to the maximum physiological range (±330 µs) suggested by Sterbing and Hartung (2003). ITDs were randomly chosen every 50 ms from a defined distribution, with a high-probability region, from which ITDs were selected with 0.8 probability (**Figure 2**).

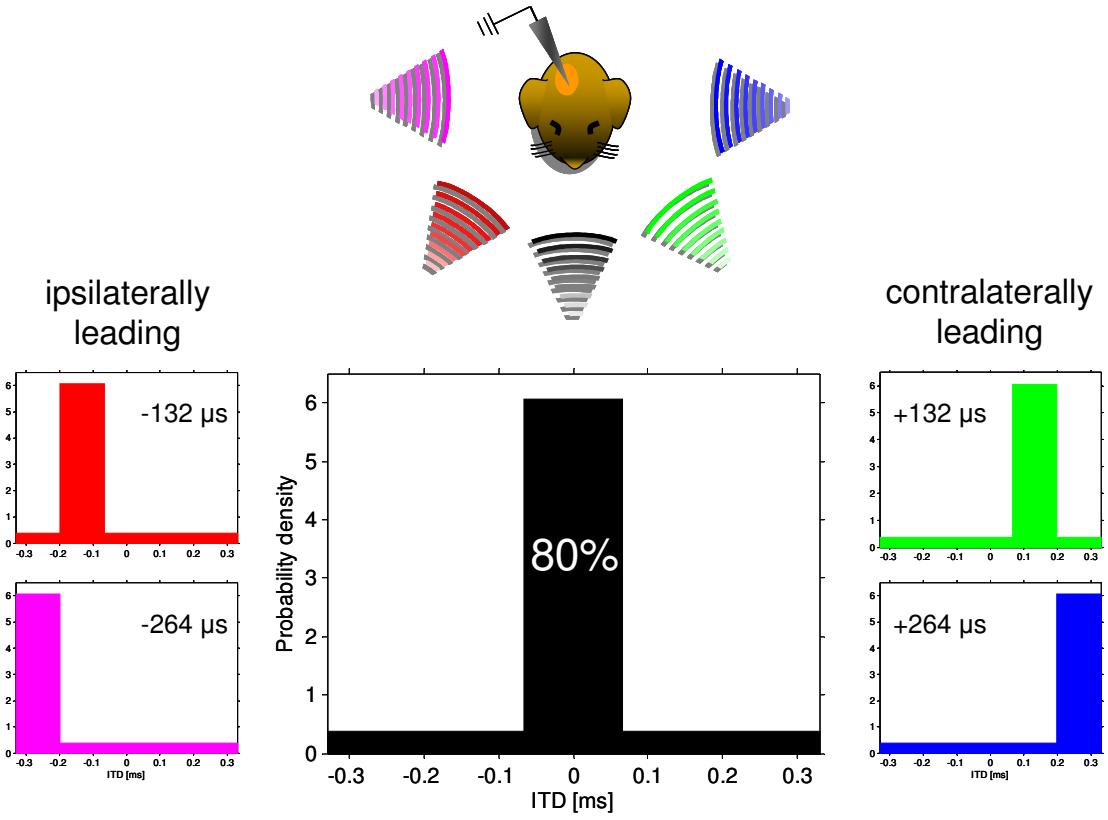

Figure 2: Number of 50ms presentations randomly chosen from a defined distribution, with a high-probability region from which ITDs were selected with 0.8 probability, as a function of ITD. Exemplified are distributions centered at 0 (black), -132 (red), +132 (green), -264 (pink) and +264 µs (blue) of ITD employed for stimulation over the naturally-encountered rage. Sketch shows stimulation relative to the recording site in the right IC.

Spike collection

Electrical activity from the microelectrode was transmitted via a headstage to a preamplifier (TDT Medusa RA16PA) where it was amplified and digitized at a sample rate of 25 kHz. Subsequently, the signal was transmitted via fiber-optic cable to an RA16 base station, where it was amplified and band-pass filtered (variable gain, 600 Hz high-pass filter, 3 kHz low-pass filter). Finally, the electrical signal was passed to TDT Brainware and action potentials exceeding a user-defined trigger level were recorded for analysis.

Data analysis

Using TDT Brainware, action potentials were sorted according to waveform characteristics to ensure that data were collected from a single neuron. Spike times were then exported to MATLAB 7.0 (The MathWorks, Natick, MA) for off-line analysis. Taking the neurons' latency into account, mean spike count for each ITD was calculated from every presentation of a given ITD in a given distribution (**Figure 3**). The probability $P_a[r|\tau]$ of neuron *a* giving *r* spikes to ITD τ was calculated. $P_a[r|\tau]$ was smoothed with a 2-D Gaussian, with standard deviations of 48 µs for the naturally-encountered range (or 0.08 cycles for presentation over a whole cycle re. neural CF) and 0.5 spikes. Fisher Information $f_a(\tau)$, for neuron *a* is given by the equation

$$f_a(\tau) = \sum_r P_a[r \mid \tau] \left(\frac{d \ln P_a[r \mid \tau]}{d\tau} \right)^2 \qquad (1)$$

Assuming that neurons generate spikes independently as indicated by low correlation in intrinsic spiking noise between IC neurons (Chechik et al., 2006; Popelar et al., 2003, Seshagiri and Delgutte 2003) the population Fisher Information $F(\tau)$ for *N* neurons can be approximated by the equation

$$F(\tau) = \sum_{a=1}^{N} f_a(\tau) \qquad (2)$$

Peak Fisher Information, indicating highest coding accuracy, tends to occur over the slopes of a function – the region of greatest change in neural activity.

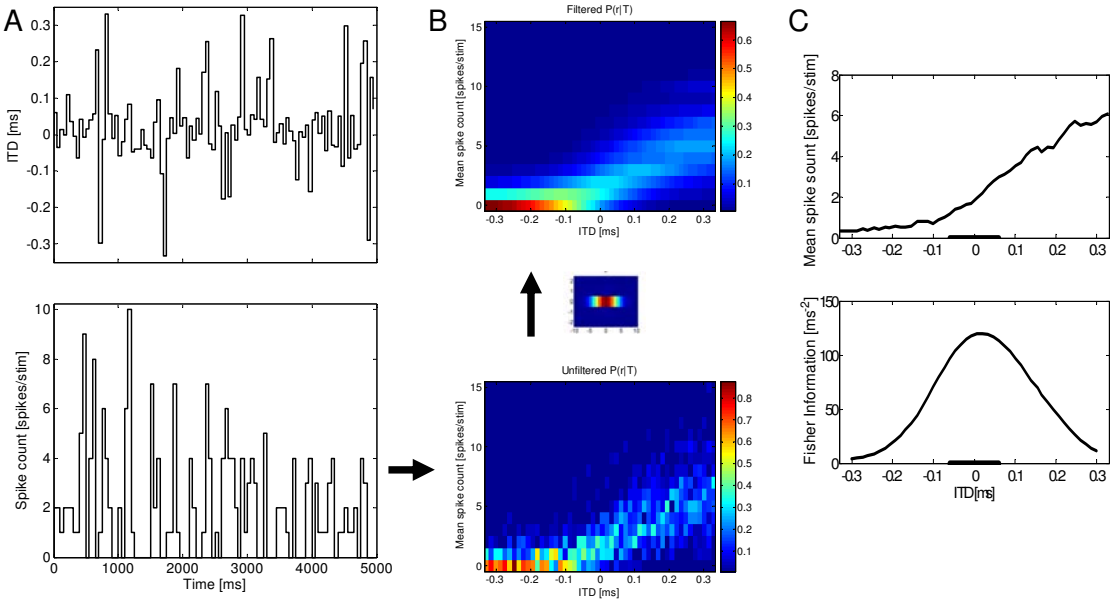

Figure 3: (**A**) ITDs presented with a high probability region centered at 0 µs ITD as a function of time and corresponding mean spike count. (**B**) Probability functions P*a*[*r*| *τ*] of a neuron, unfiltered and smoothed with a 2-D Gaussian, with standard deviations of 48 µs and 0.5 spikes, respectively. (**C**) Mean spike count and corresponding Fisher Information as a function of ITD. Peak Fisher Information, indicating highest coding accuracy, tends to occur over the slopes of a function – the region of greatest change in neural activity.

Fitting the rate-ITD functions

The spike count vs ITD functions of the neurons were fitted with by the function

$$g(\tau) = R\exp\left(A_1\sin(2\pi(\theta-\phi_1)) + A_2\sin(4\pi(\theta-\phi_2)) + A_3\sin(6\pi(\theta-\phi_3))\right) + B \qquad (3)$$

where θ is the interaural time difference τ expressed at a proportion of the period Q of the neurons characteristic frequency θ=τ/Q. All other parameters of the equation were varied to fit the data. The fitting was done by minimizing the least squared

difference between equation 3 and the measured rate-ITD function using the standard matlab program fminsearch.m. The normalized curves fits were produced by means of the formula

$$g_{norm}(\tau) = \frac{g(\tau) - g_{min}}{g_{max} - g_{min}} \quad (4)$$

where g_{min} is the minimum value of the curve fit over the range of the data, and g_{max} the maximum value of the curve fit over the range of the data.

Analysis of time course of adaptation.

The r.m.s. difference between the rate-ITD function of each 5 s sweep of interaurally-delayed white noise and the average function of the final 50 s of the stimulus was calculated over the high probability region. Subsequently a single exponential function was fitted to the r.m.s. data for each neuron to obtain a time constant for the decay in discharge rate. In cases where responses of neurons were better fitted to the r.m.s. data by a flat line, rather than an exponential decay ($P < 0.05$ to accept the exponential fit, F-test - due to the neural response not stabilizing but continuing to adjust throughout the stimulus presentation, the decay time constant of these neurons was designated 0.

Results

We assessed the sensitivity of IC neurons in the anesthetized guinea pig to statistical distributions of ITDs. A white noise stimulus of approximately 7 min duration was presented, during which the ITD was randomly chosen every 50 ms from a defined distribution, with a high-probability region (HPR) from which ITDs were selected with 0.8 probability. Responses were obtained from 37 neurons with respect to the maximum physiological range (±330 µs) reported for the guinea pig (Sterbing et al., 2003). In addition, responses were also obtained from 51 IC neurons for distributions of ITDs presented within a range of ± 0.5 cycles with respect to each neuron's characteristic frequency (CF), All neurons were sensitive to ongoing ITDs of the noise stimulus – no onset ITDs were present in the stimulus.

The effect of changing stimulus HPR on rate-ITD functions

The effect of changing the stimulus HPR on neural rate-ITD functions was examined for two ranges of ITDs. First, responses were obtained to stimuli in which ITDs were constrained to the guinea-pig's naturally-encountered range, to determine whether the low-frequency binaural system adapts to improve coding accuracy over the range of ITDs experienced under natural listening conditions. In this case, HPRs of each distribution were centered at -264, -132, 0, +132 or +264 µs. Second, in order to examine whether changes in neural coding for ITD instead scale to take account of a neuron's CF – generally considered a major determinant of the shape and periodicity of ITD functions (Yin and Kuwada 1983) - responses were also obtained to distributions of ITDs extending over a whole cycle re. neural CF, with HPRs centered at -0.4, -0.2, 0, +0.2 or +0.4 cycles.

The extent to which responses of IC neurons adapt to take account of the statistical distribution of ITDs, when ITDs are constrained to the naturally-encountered range is shown in **Figure 4**. The top row of **Figure 4** shows the mean responses recorded from three neurons where ITDs were drawn from distributions centered at -264, -132, 0, +132 or +264 µs. Rate-ITD functions in all plots were fitted with an

exponentiated sine-based curve (see Methods), allowing for better quantification of changes in neural response to different HPRs.

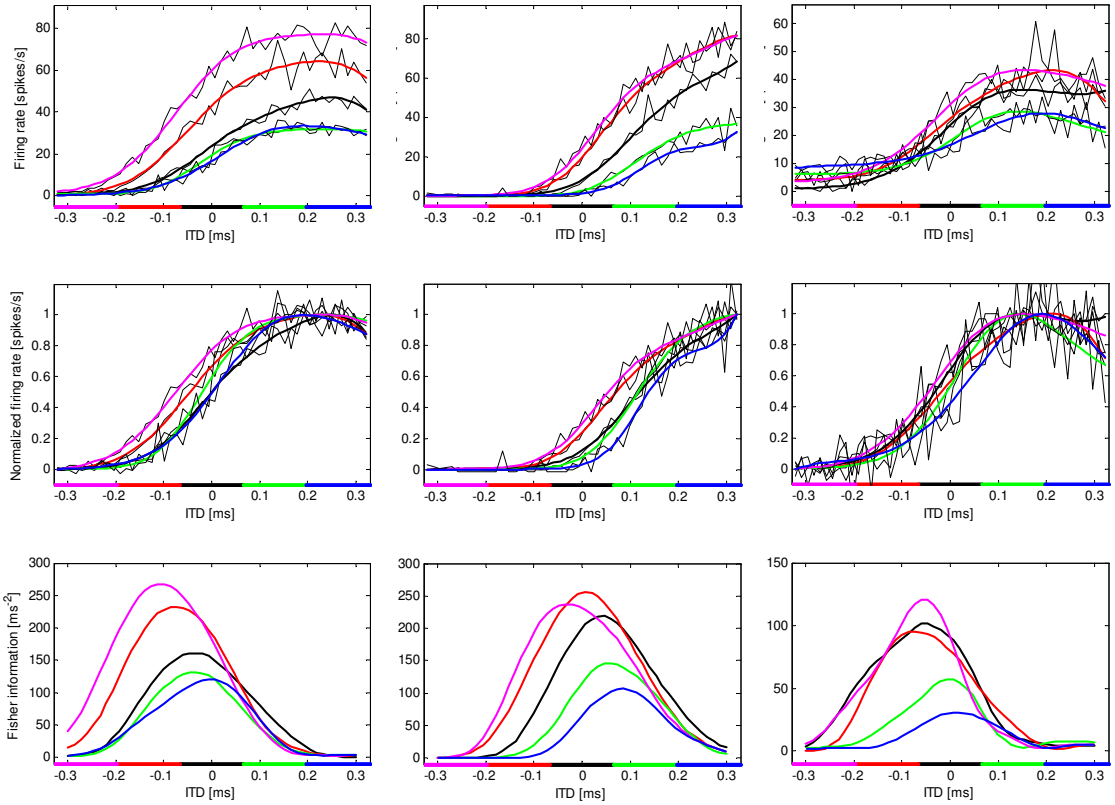

Figure 4: Top row: Spike rate-ITD functions and corresponding fits with an exponentiated sine based curve of three neurons stimulated over the maximum naturally-encountered range of ITDs (± 330 µs) with five different high probability regions. Middle row: Normalized data of neurons in top row. Bottom row: Single-neuron Fisher information corresponding to neurons shown in top row. Colors indicate position of stimulus high probability region and corresponding neural response.

Only the properties of rate-ITD functions that could be fitted significantly better than a flat line ($P < 0.05$, F-test; i.e. that were significant modulated with ITD) were taken into account. Rate-ITD functions showed highest gain when the HPR was positioned at ipsilaterally-leading (negative) ITDs (**Figure 4**, top row, magenta and red curve), and this fell systematically as the HPR was shifted towards contralateral ITDs.The top row of

Figure 5 shows responses of three neurons to stimuli in which ITDs were drawn from a distribution encompassing the full cycle of ITDs re. neural CF, with HPRs centered at -0.4, -0.2, 0, +0.2 or +0.4 cycles.

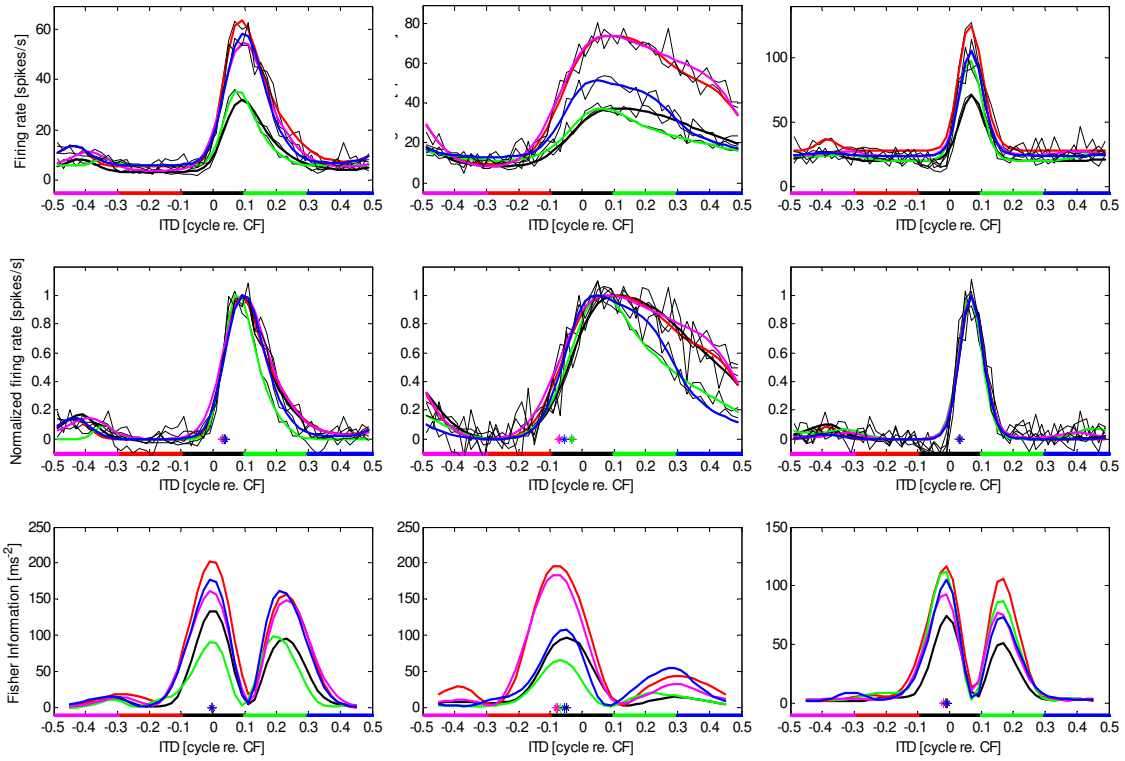

Figure 5: Top row: Spike rate-ITD functions and corresponding fits with an exponentiated sine based curve of three neurons stimulated over a full range of ITDs re. characteristic frequency (CF) with five different high probability regions. Middle row: Normalized data of neurons in top row. Bottom row: Single-neuron Fisher Information corresponding to neurons shown in top row. Colors indicate position of stimulus high probability region and corresponding neural response. Correspondingly colored asterisks denote the position of the steepest ipsilateral slope and peak Fisher Information on this slope in the middle and bottom row, respectively.

Here, firing rates were lowest when the HPR of the stimulus distribution was centered at 0 and +0.2 cycles (**Figure 5**; top row, black and green curve) in comparison to all other HPRs. The peaks of all rate-ITD functions were situated on the contralaterally-leading side relative to the recording site. Independent of the range of

ITDs, the observed pattern of responses with respect to the HPR is highly indicative of a multiplicative change in neural gain in which rate-ITD functions for different HPRs are multiplied or divided by a common factor (e.g. Mitchell and Silver, 2002). However, these gain changes seem more pronounced for stimulus presentation restricted to the physiological range.

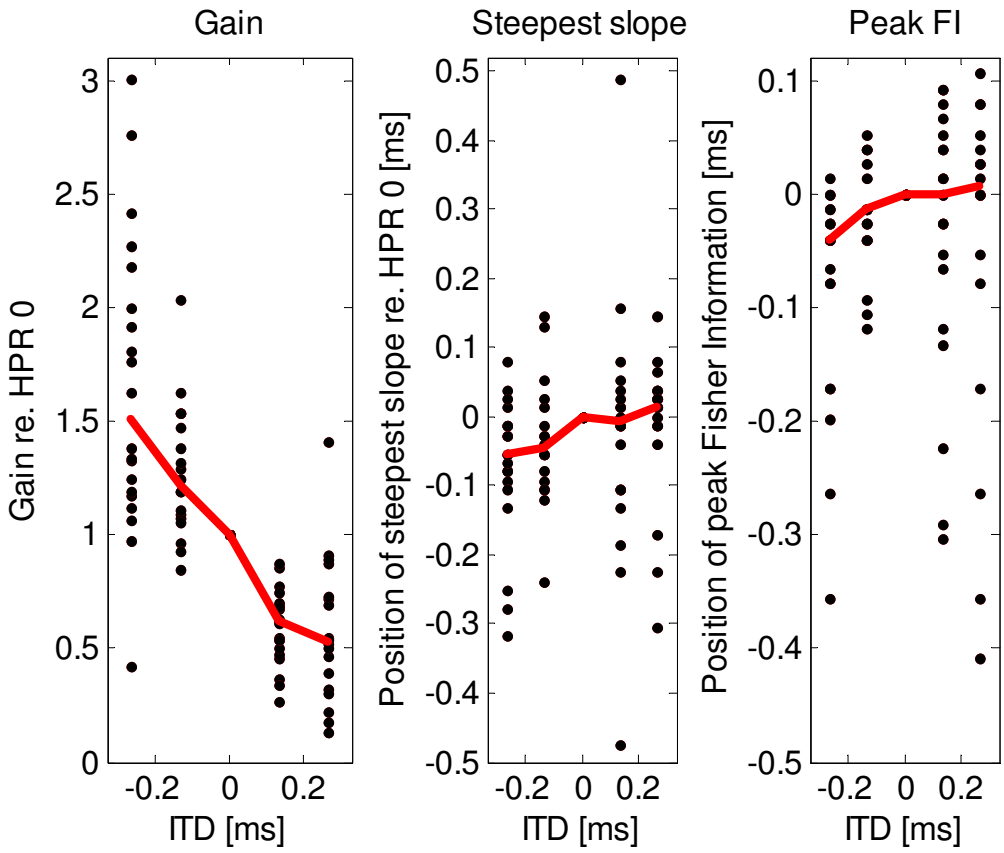

Figure 6: Left panel: Neural gain functions of a population of neurons stimulated over the naturally-encountered range (N = 23) at all HPRs as a proportion of the HPR centered at 0. Middle panel: Position of steepest slope of the rate-ITD function of all HPRs as a function of the position of steepest slope at the HPR centered at 0. Right panel: Position of peak Fisher Information of the rate-ITD functions of all HPRs as a function of the position of peak Fisher Information at the HPR centered at 0. Black symbol indicate individual data and the red line symbolizes the population mean.

In order to quantify these gain changes for the naturally-encountered range of ITDs, the dynamic response range (i.e. the difference between the maximum and minimum spike rate) of the rate-ITD functions to the different HPR stimuli were calculated as a proportion of the response range for the 0 µs stimulus, and plotted as function of the HPR (**Figure 6**). Similarly, this was performed for the full-cycle stimuli (**Figure 7**).

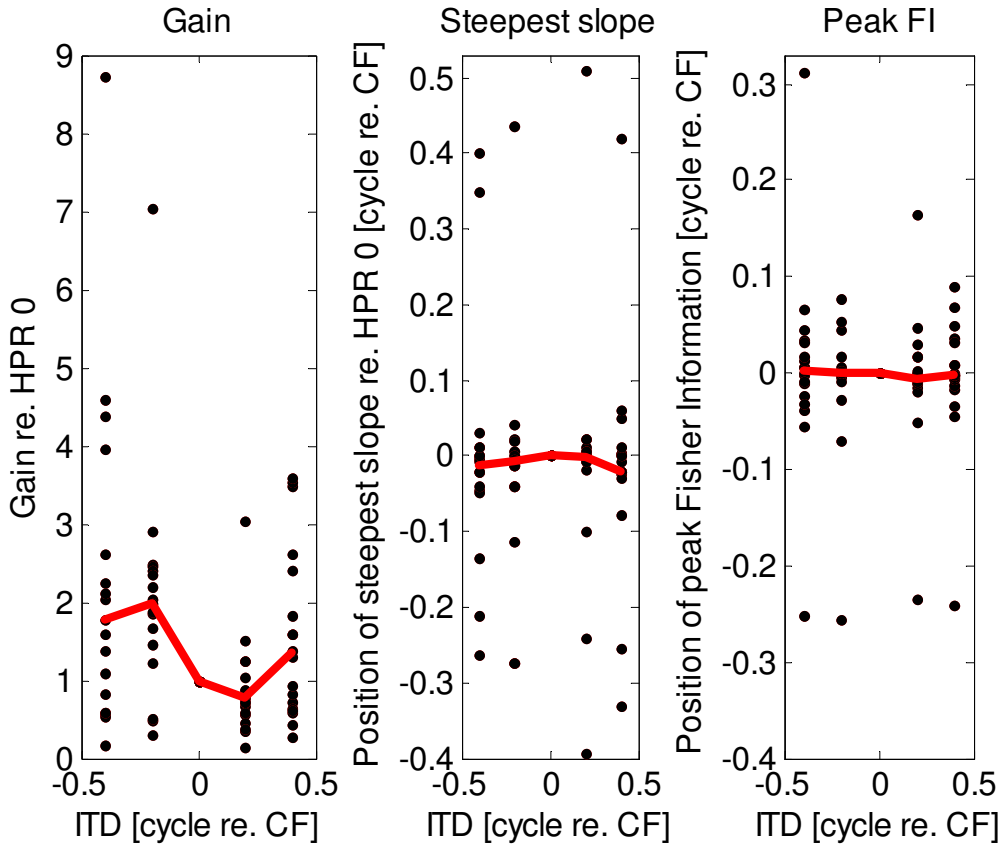

Figure 7: Left panel: Neural gain functions of a population of neurons stimulated over a whole range re. characteristic frequency (CF, N = 27) at all HPRs as a proportion of the HPR centered at 0. Middle panel: Position of steepest slope of the rate-ITD function of all HPRs as a function of the position of steepest slope at the HPR centered at 0. Right panel: Position of peak Fisher Information of the rate-ITD functions of all HPRs as a function of the position of peak Fisher Information at the HPR centered at 0. Black symbol indicate individual data and the red line symbolizes the population mean.

In both **Figure 6** and **7** each symbol depicts the gain for one neuron for the HPR indicated on the abscissa, and the red line shows the median gain. For stimulation restricted to the naturally-encountered range, gain increases as the HPR is shifted from contralateral to ipsilateral. Here, the median gain is significantly greater than one ($P < 0.05$, Wilcoxon signed-rank test) for ipsilaterally-centered HPRs, and significantly less than one ($P < 0.05$, Wilcoxon signed-rank test) for contralaterally centered HPRs. For stimulation over the full cycle, however, the median gain is only significantly greater than one for the HPR centered at -0.2 cycles ($P < 0.05$, Wilcoxon signed-rank test).

To test whether multiplicative gain changes constitute the only difference between the responses to different HPRs the exponentiated sine-based fits to the rate-ITD functions were normalized (see middle rows of Figs 4 and 5). Whereas the normalized fits overlap nearly perfectly for stimulus presentations over the full cycle, indicating only a change in gain, (**Figure 5**; middle row), the normalized fits for stimulus presentation restricted to the naturally-encountered range (**Figure 4**; middle row) show substantial differences in the shape of the function. Here, for ipsilaterally-centered HPRs (**Figure 4**; middle row, magenta and red curves) the slope of the rate-ITD function seems to shift ipsilaterally as compared with the rate-ITD function centered at 0 μs (thick black curves). For HPRs centered contralaterally (**Figure 4**; middle row, green and blue curves) the gain is low, thus the spike counts involved are smaller and normalized rate-ITD functions more variable. No significant shifts were observed for HPRs centered contralaterally.

The observed shifts of the slope of fits to the rate-ITD function are quantified in the middle panel of **Figures 6** and **7** for the naturally-encountered range and full cycle stimulation, respectively. The position of the steepest slope of the fit for stimulus distributions with HPRs of -264, -132, +132 or +264 μs for the naturally-encountered range (**Figure 6**), or -0.4, -0.2, +0.2 or +0.4 cycles for the whole cycle re. CF (**Figure 7**), is plotted as a function of the position of the steepest slope for the HPR centered at zero. Note that for the full cycle rate-ITD functions two slopes are normally evident, one either side of the peak ITD. To account for this only the steepest point on the ipsilaterally-facing slope is shown. Each symbol indicates the position of the steepest slope for one neuron for the HPR indicated on the abscissa. The red line shows the

median of the position of steepest slopes. No significant difference between the position of the steepest slope for different HPRs could be observed for full-cycle stimulation ($P > 0.05$, Wilcoxon signed-rank test). However, for stimulation restricted to the naturally-encountered range, the position of the steepest slope of the fitted rate-ITD functions for ipsilaterally-centered HPRs was shifted towards ipsilaterally-leading ITDs for most neurons. The median position of the steepest slope was significantly lower than zero ($P < 0.05$, Wilcoxon signed-rank test) for rate-ITD functions obtained in response to the most ipsilateral HPR (centered at -264 µs) only.

Adjustment of coding accuracy to statistical distributions of ITDs

Single neuron Fisher Information

In order to determine whether the observed changes in neural sensitivity associated with changes in the HPR of the stimulus distribution are accompanied by adjustments in the accuracy with which these neurons encode ITD we calculated the Fisher Information, a measure of coding accuracy, for the response of each neuron to the different distributions of ITDs. Assuming an optimal decoder, higher Fisher Information reflects higher coding accuracy, i.e. a more accurate representation of the ITD presented and, thus, a higher capacity to discriminate nearby ITDs. A reasonable approximation of Fisher Information for neurons is the square of the slope of the spike count-ITD function divided by the spike-count variance (Dean et al 2005). Thus, Fisher Information is high when the spike-count variance is low, and when the spike count changes steeply with changes in ITD. Since the variance in the neural spike counts recorded from IC neurons tended to be approximately proportional to the spike counts themselves, the peaks of the Fisher Information function were typically situated on the lower, rising portion of the slopes of the rate-ITD functions as illustrated in the bottom row of **Figures 4** and **5** for the naturally-encountered range and full-cycle stimulation, respectively.

We characterized the position of the peak Fisher Information across the population of neurons in the right panel of Figures 6 and 7. The position of the peak

Fisher Information evoked by stimulus distributions with HPRs centered at -264, -132 ,+132 or +264 μs for the naturally encountered range (**Figure 6**) or of -0.4, -0.2, +0.2 or +0.4 cycles for the full cycle re. CF, (**Figure 7**) is plotted as a function of the position of the peak Fisher Information evoked by the stimulus distribution with a HPR centered at zero. Each symbol denotes the position of the peak Fisher Information for one neuron at the HPR indicated along the abscissa. The red line shows the median position of peak Fisher Information. If the Fisher Information is indeed largely a result of the change in shape of the rate-ITD function, the peak Fisher Information should follow a similar pattern to the position of the steepest slope in the middle panel of **Figure 6** and **7**. Considering first the full-cycle data in **Figure 7**, consistent with the relatively minor changes in the gain and the shape of rate-ITD functions evoked by the different distributions of ITDs, no significant shifts in the position of peak Fisher Information for single neurons were observed for this mode of stimulation. In general, Fisher Information was found to be highest over the ipsilaterally-facing slope of the rate-ITD functions, as compared to the contralaterally-facing slope (**Figure 4** bottom row). This is consistent with several recent studies suggesting that the relatively steeper ipsilaterally-facing slopes of many ITD functions constitute the important feature of ITD-sensitive responses (McAlpine et al., 2001, Brand et al., 2002, Shackleton et al. 2004).

In contrast to stimulation with ITDs over the full cycle, most neurons stimulated over the naturally-encountered range of ITDs showed shifts in the position of their peak Fisher Information to accommodate the change in the HPR of the distribution. Note, however, that the shifts were not complete; peak Fisher Information did not shift to align completely with the centre of the HPR. Thus, although Fisher Information for individual neurons follows, to some extent, the HPR when the distribution of ITDs is restricted to the naturally-encountered range of ITDs, it does so only coarsely, and then only significantly so for HPRs centered at ipsilaterally-leading (negative) ITDs. The median peak Fisher Information was significantly more negative than zero ($P < 0.05$, Wilcoxon signed-rank test) only for the most ipsilaterally-leading (-264 μs) HPR rate-ITD functions. For all other HPRs, the median position of the peak Fisher Information was not significantly different to that for the HPR centered at 0 μs ($P<0.05$, Wilcoxon signed-rank test). The shifts observed for peak Fisher Information follow the same form as the shifts

in the steepest slope of rate-ITD functions, suggesting that the latter underlies the former.

Population Fisher Information

The responses of individual neurons could vary considerably in response to changing HPRs (see also Dean et al., 2005). To understand the implications of the diverse adjustments in rate-ITD functions for ITD coding, it is necessary to examine the response of the neural population. Evidence from many levels and modalities of the vertebrate nervous system suggests that information is represented by the activity of neuronal populations. For neurons with independent spike generators - a reasonable assumption for IC neurons (see Chechik et al. 2006; Popelar et al. 2003; Seshagiri and Delgutte 2003) – Fisher Information can be summed across neurons to produce a measure of coding accuracy for the population.

Population Fisher Information was first calculated for responses evoked by distributions of ITDs restricted to the naturally-encountered range, for HPRs centered at -264, -132, 0, +132, and +264 µs (**Figure 8A**; N = 23). For distributions with contralaterally-leading HPRs, population Fisher Information peaked around 0 µs ITD, and was generally lower in magnitude than for ipsilaterally-leading HPRs, reflecting the relative reduction in gain. Fisher Information was greatest for ipsilaterally-leading ITDs, and peak Fisher Information shifted towards ipsilaterally-leading ITDs as the HPR was shifted in this direction. Similar shifts in peak Fisher Information were observed for a larger population of neurons for distributions with HPRs centered at -132, 0, and +132 µs only (N = 37; data not shown). Assuming each neuron has a symmetric partner in the opposite IC, the population FI can be mirrored around zero, thus taking into account the neural representation of ITD in both brain hemispheres. For distributions in which ITDs were restricted to the naturally-encountered range, mirrored Fisher Information revealed that neurons shift their coding accuracy with respect to HPRs furthest away from the midline, but not for distributions centered at -132 or +132 µs (**Figure 8B**). For ITDs within approximately ±40 µs of zero, Fisher Information across both brain hemispheres indicates coding accuracy to be greatest when the ITD is most

likely to be drawn from the HPR centered at zero (**Figure 8B**, black curve). When the ITD exceeds ±40 µs, the pink and blue Fisher Information curves (those for HPRs centered at -264 or +264 µs) provide for the most accurate coding. Thus, at least for the HPRs centered at -264, 0, and + 264 µs, the resulting adaptive state of the neural population is most suited to code accurately the common ITDs in the stimulus. Note also that peak Fisher Information over all HPRs is roughly constant.

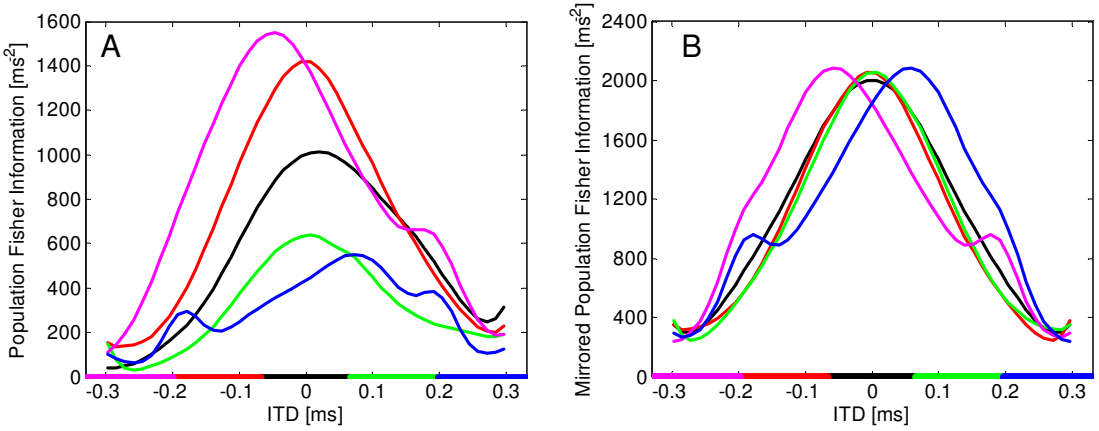

Figure 8: (**A**) Fisher Information for a population of 23 neurons stimulated with five different high probability distributions within the naturally-encountered range (**B**) Mirrored population Fisher Information of panel 8A assuming each neuron has a symmetric partner in the opposite IC. Colors indicate position of stimulus high probability region and corresponding neural response.

Assuming that ITD functions, when measured in cycles re. CF, roughly scale for, and are therefore independent of, CF, Fisher Information was pooled across all ITD functions obtained over a full cycle, and compared for different HPRs. Fisher Information calculated across 27 neurons in response to ITD distributions centered at 0, ±0.2 and ±0.4 cycles re. CF revealed Fisher Information to peak near zero for all distributions. This indicates that the magnitude of the Fisher Information for different HPRs is largely scaled when the HPRs are arranged across the full cycle (**Figure 9**). However, relative to the whole cycle, the position of the peak Fisher Information was largely unchanged.

This finding is confirmed for a larger population of neurons (N = 51, data not shown) in response to distributions of ITDs containing HPRs of -0.2, 0 and +0.2 cycles only.

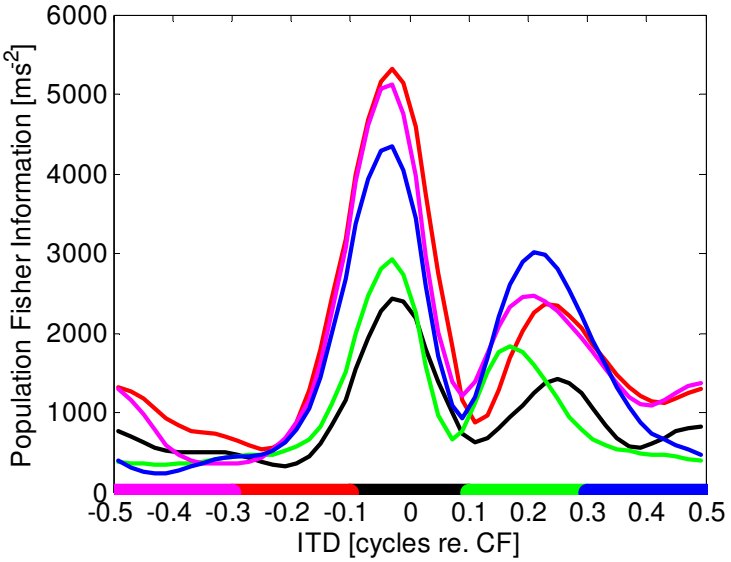

Figure 9: Fisher Information for a population of 27 neurons stimulated over a full cycle re. characteristic frequency for five different high probability distributions, respectively. Colors indicate position of stimulus high probability region and corresponding neural response.

Time course of neural adaptation

Finally, we examined the time course of the neural adaptation to statistical distributions of ITDs by plotting rate-ITD functions separately for consecutive 5 s sweeps, for stimulation within the naturally-encountered range of ITDs. The time elapsed for rate-ITD functions to reach a steady firing rate was obtained by calculating the root mean squared (r.m.s) difference between the rate-ITD function of each 50 ms segment and the mean rate-ITD function from the final 50 s of the stimulus (**Figure 10A**). The stimulus distribution chosen for this analysis was that with the HPR centered at 0. Single exponential decay functions were fitted to the r.m.s values for each neuron (**Figure 10B**) and only those fits that were significantly better than that to a flat line (using an F-test, see Methods) were considered further. For the HPR centered at 0 µs,

the median time required for the firing rates of these neurons to stabilize was 5.6 s (N = 17, **Figure 10C**). For the remaining neurons examined (N = 6), the response did not stabilize but continued to adjust throughout the stimulus presentation.

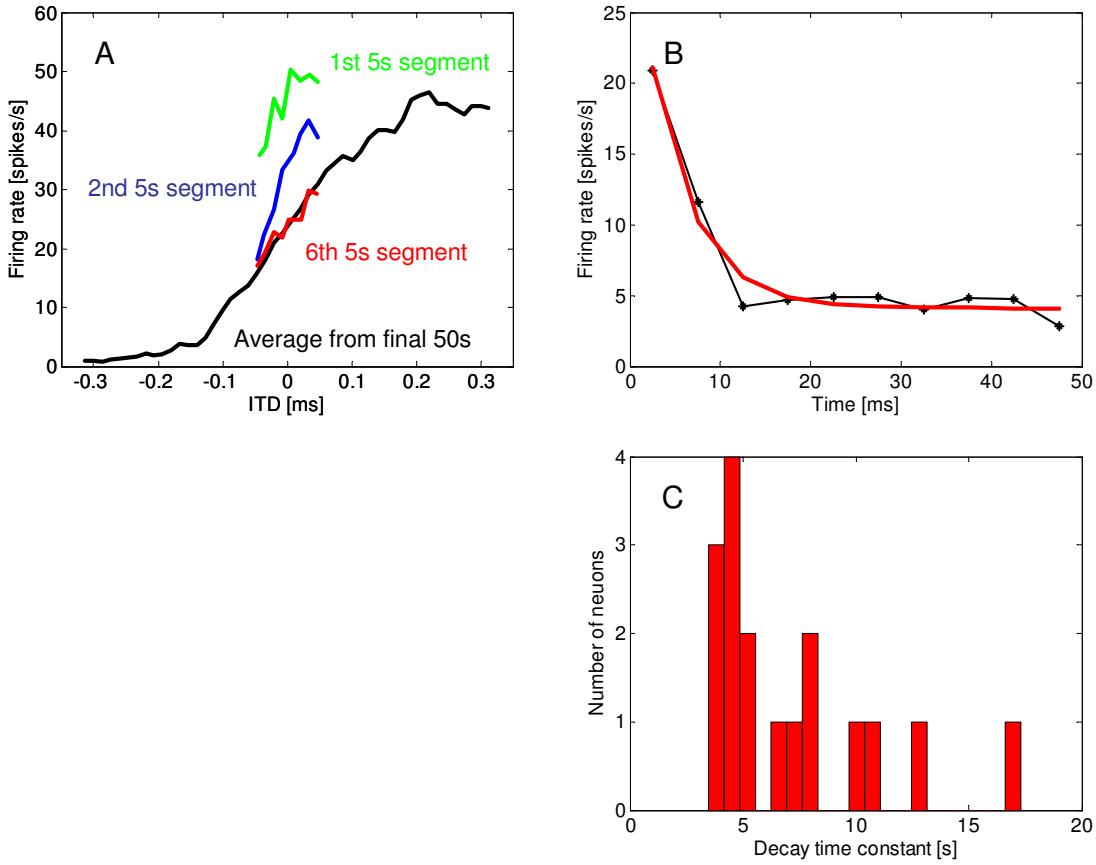

Figure 10: (**A**) Rate-ITD functions of a single neuron for presentation of 5 s stimulus sweeps over the high probability region of the stimulus distribution only, compared to the averaged function over the final 50 s of the stimulus. (**B**) Root-mean-squared (r.m.s.) differences between rate-ITD function of each 5 s sweep and the average function over the final 50 s of the stimulus for the same neuron as in A). Red line: Single exponential decay function, Tau = 4.8 s. (**C**) Histogram of decay time constant for the HPR centered at 0 (N = 17).

Discussion

We investigated the extent to which the responses of IC neurons adapt to the statistical distribution of ITDs, the major cue for sound-source localization in a wide range of species. Three main findings were observed. First, neurons adapt the gain and shape of their rate-ITD functions to take account of the statistical distribution of ITDs, resulting in a shift in peak Fisher Information towards the HPR in a stimulus distribution, at least for ipsilaterally-leading HPRs. An important aspect of this finding lies in being able to attribute any contribution to the adaptive effects of central brain mechanisms, and specifically those residing at or above the level of binaural integration. Second, adaptive coding to ITD is less apparent than is reported for IC neurons to sound level (Dean et al., 2005); rate-ITD functions were less mutable than were rate-level functions. For sound level, peak Fisher Information for the population shifted to lie at or just above the most probable sound levels for all distributions presented. This was not the case for peak Fisher Information with respect to ITD functions. Finally, the importance of examining coding for ITDs constrained to the naturally-encountered range is highlighted by the fact that only under such conditions were changes in responses observed that were consistent with an improvement in the accuracy with which the most commonly-occurring ITDs were coded.

Adaptation to stimulus statistics depends on position of HPR relative to peak ITD sensitivity

Although the width of ITD tuning functions depends on neural tuning for sound frequency, it is (largely) independent of frequency when considered in terms of interaural phase; i.e., when plotted as a function of the full cycle of ITDs re. CF. Given this essentially cyclic nature of delay functions, it is possible that adaptive coding mechanisms operate with respect to the full cycle, rather than to the relatively restricted range bounded by the guinea-pig's head-width. However, Fisher Information analysis revealed that IC neurons stimulated with ITDs over the full cycle re. CF did not show adjustments of coding accuracy useful in the context of the prevailing stimulus statistics.

Only by presenting ITDs restricted to the naturally-encountered range was any improvement in coding accuracy observed.

A potential mechanistic explanation for this is the location of the HPR with respect to a neuron's highest sensitivity to ITD. Over the full cycle re. CF, considerable reduction in gain was usually observed only for HPRs centered at 0 and +0.2, cycles re. CF, where most ITDs presented were at, or close to, a neuron's peak ITD-sensitivity (**Figure 5**, black and green curves). HPRs centered at -0.2, -0.4, and +0.4 cycles lay beyond the range of ITDs evoking substantial spike rates for the majority of neurons; here the relatively few occasions on which stimuli were presented at favorable ITDs evoked high spike counts (**Figure 5** magenta, red and blue curves). In contrast, ITDs restricted to the naturally-encountered range evoked adaptive effects possibly because, in this mode of stimulation, the HPRs were more finely-spaced across the sensitive slope of the ITD function, which tends to lie across midline ITD (i.e. around zero). However, such mechanistic explanations do not exclude the possibility that this adaptation has a functional relevance, whether these observations highlight the importance of ethologically-relevant stimuli or emphasize the relationship of the slope of the baseline ITD function and the position of the HPR in uncovering adaptive processes.

Neural gain control combined with shape changes of the rate-ITD functions can account for adaptive coding to ITD

The changes in neural response we observe could be produced by a number of known mechanisms, for example, intrinsic channel-based adaptation, synaptic depression or inhibitory circuitry, or a combination of these factors. One potential cause of the gain changes we report here may relate to the action of GABA-ergic inhibition. Ingham and McAlpine (2005) reported that ITD functions scaled largely multiplicatively when GABA-ergic inhibition was blocked (other than when spike rates clearly increased to saturation), and largely divisively when GABA itself was introduced. The scaling of the gain functions by GABA-ergic inhibition, coupled with the observation that ITD discrimination thresholds were altered (generally rising as GABA influences were up- or down-regulated), suggest a function for GABA-ergic inhibition in adaptive coding of ITD.

This suggests a potential mechanism underlying the gain changes observed in the current study. Inhibitory mechanisms might arise from extrinsic sources – the DNLL is known to contain ITD-sensitive neurons and sends an inhibitory GABA-ergic projection to the IC. Gain changes might also arise from the action of inhibitory inter-neurons intrinsic to the IC, or exist in the form of shunting inhibition reported by Mitchell and Silver (2003) in the cerebellum.

Although IC neurons scale multiplicatively in response to different HPRs, gain changes *per se* do not necessarily lead to informative changes in neural coding, as the neural responses to full-cycle stimulation demonstrates. In contrast, for naturally-encountered ITDs we also observed changes in the shape of the rate-ITD function which manifested as shifts of the position of steepest slope in response to different HPRs. Thus, mechanisms other than multiplicative gain must be invoked to account for the data, particularly as these shifts underlie the adjustments of the neural population's representation of ITD to encode most effectively the prevailing ITDs.

Emphasis of coding accuracy on ipsilateral side

Our observation that coding accuracy is greatest for ipsilaterally-leading sounds is at odds with the traditional view that sounds leading at one ear are processed by neurons in the opposite brain hemisphere. Nevertheless, single-neuron recordings in the IC demonstrate just-noticeable-differences (jnds) for static ITDs to be smallest on the ipsilaterally-leading side of ITD functions, despite the peak of the function being situated contralaterally (Shackleton et al., 2003). The smallest jnds, which indicate highest discriminability between two stimuli, were found at that part of the slope where the variance was relatively low and the slope relatively steep. This generally coincided with the position of the peak Fisher Information shown by neurons in our study. Thus, the highest coding accuracy occurs for ipsilaterally-leading ITDs independent of the statistical distribution of ITDs presented, confirming the observation of Shackleton et al. (2003) and suggesting it is robust to stimulus manipulations.

Assuming that population Fisher Information on one side of the brain is a mirror image of the other, presentations restricted to the naturally-encountered range suggest

relatively coarse changes in coding accuracy of the neural population in the auditory midbrain. A high-probability distribution leading on the left appears to be coded more by the population of neurons in the left (ipsilateral) IC than the right (**Figure 8B**, pink curve); i.e. the contribution to the total information is greater from the left IC than the right. Similarly, distributions leading on the right are coded more by neurons in the right (ipsilateral) IC (blue curve). Distributions centered at midline are coded employing neurons equally across both ICs (black curve). The possibility that ITD is coded by the activation of neural populations on both sides of the brain is consistent with recent views on the encoding of interaural time (McAlpine et al., 2001) and intensity (Park et al., 2004) differences.

Does adaptive coding change in the ascending auditory pathway?

Why is adaptive coding to ITD in IC neurons, although broadly consistent with that for sound level (Dean et al., 2005), less pronounced? As Dean et al. (2005) observed, rate-level functions do not shift to accommodate HPRs centered at sound levels below the threshold of baseline response functions. This is reflected in our data, where functions did not shift beyond the range of highest ITD sensitivity. Further, we observed less of a lateral shift in response functions for ITD than did Dean et al (2005) for sound level. ITD functions appear to rise from a relatively fixed location along the ITD axis. Notwithstanding the possibility that the neurons contributing to the responses reported by Dean et al (2005) are of a different type to those reported here, a plausible explanation for this difference lies in the number of synaptic stations at which adaptation 'accumulates' in the ascending auditory pathway. Adaptation to sound level may accumulate over several synaptic stages to the IC (and, indeed, may already be evident in the mechanical response of the middle ear). Adaptive coding for ITDs, which are first processed in the MSO one synaptic stage below the IC, may require further stages of processing before being more fully realized. It is worth noting that whereas MSO neurons sometimes show limited adaptation (Spitzer & Semple 1995, 1998) to the direction, centre and depth of auditory motion cues, recordings from the IC (Spitzer and Semple, 1993, 1998) and primary cortex (Malone et al., 2002) show substantially greater

adaptation. Adaptation at successive stages may serve to minimize the loss of coding accuracy or information that results between successive stages in the ascending pathway.

Can the observed adaptive coding for ITDs reflect requirements for behavioral performance?

In localization tasks, particularly in species for which visual cues also play a role, it may be important only to gauge to which side a sound source is located, reserving greatest acuity for sources on or near the midline as the head is moved to face the source (and the interaural cues are reset). This is consistent with the reported importance of midline positions (Mills 1958) and the results of a recently conducted psychoacoustic experiment in humans, where spatial discrimination was improved when target sequences were co-located with ITD-adaptor stimuli and deteriorated when adaptors and targets were presented from different locations (Maier et al. unpublished observations). These effects were most pronounced for midline ITDs. Thus, adjustment of the neural response to take account of the prevailing stimuli in an environment might only be informative for the most-laterally located sound sources. Consequently, adaptive coding for auditory spatial cues may be different to adaptive coding for sound intensity where sounds must be heard above a variable level of background noise, and adapting response functions to encode sound intensities at or just above the level of background noise provides a means of ensuring detection and maximum accuracy. Thus, adaptation to ITDs observed in IC neurons may reflect the likely behavior under natural listening conditions, where orienting towards the sound source requires high coding accuracy to be maintained for midline positions only (e.g. Gordon et al 2008).

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Chapter 4

Adaptation to interaural time differences improves discriminability of spatial cues

In preparation for submission as: Maier JK, McAlpine D, Klump GM, Pressnitzer D: Adaptation to interaural time differences improves discriminability of spatial cues.

Abstract

Single neuron recordings as well as behavioral studies indicate that the auditory system adapts to the prevailing binaural cues in an acoustic environment. In the present study discriminability of interaural time and level differences (ITDs and ILDs) was assessed for human listeners with and without preceding adaptation to ITDs. Stimuli, presented over headphones, were lateralized with reference ITDs of +400, 0 and -400 µs. Equivalent ILDs, measured beforehand in a matching procedure, allowed for the investigation of cue-specificity of adaptive effects. The ITD or ILD to be discriminated from the reference was adjusted individually to correspond to a d' of 2 for the non-adapted condition at all reference positions, as measured in preceding experiments. All stimuli were 800 Hz-wide bands of noise centered at 500 Hz and of 400 ms duration. The duration of the ITD adaptor was randomized between 1 and 2 s. We demonstrate that discriminability of both binaural cues is improved when adaptor and target are co-located, whereas it deteriorates when adaptor and target sequence are presented from deviating intracranial positions. Signal detection theory analysis suggests that the improved discriminability when adaptor and target are co-located is due to a sharpening of coding accuracy at the location of the adaptor, in the absence of a criterion shift. Further, spatial adaptation in human listeners seems to serve mainly improvement of discrimination around the midline. Finally, the transfer of adaptive effects between the binaural cues suggests that the representation of intracranial images generated by ITDs and ILDs is fused in the auditory brain before the site of adaptation.

Introduction

For sensory systems, adapting to stimulus statistics serves to increase information about the prevailing environmental conditions. Electrophysiological recordings have shown that the distribution of amplitudes of an ensemble of stimuli can influence the response characteristics of single neurons, and that this results in a more accurate encoding of the stimuli (e.g. Dean et al. 2005 for the auditory modality, Fairhall et al. 2001 for the visual modality). Improved coding efficiency by means of adaptation is also observed for stimulus characteristics other than amplitude (e.g. contrast gain adaptation; Ohzawa et al. 1982). Particularly relevant to the present study is that adaptation to the statistics of naturally-encountered interaural time differences (ITD) has been shown to alter the ITD tuning curves of inferior colliculus neurons, resulting in increased ITD coding accuracy (Maier et al. 2007). Many studies have investigated psychophysically the effects of adaptation to spatial location. Investigations of sensitivity to motion in the auditory system have lead to the discovery of a motion aftereffect (Kashino and Nishida 1998, Dong et al 1999). This phenomenon, paralleling a well-known observation from the visual system (e.g. McCullough 1965), is characterized by a perceived movement of a stationary target stimulus in the direction opposite to that of a preceding adaptor stimulus. The auditory motion aftereffect has been ascribed to adaptive processes in the central auditory system (Kashino and Nishida 1998, Carlile 2000). More recent studies concerned with adaptive processing of binaural localization cues - ITDs and interaural level differences (ILDs) - discovered a shift of the point of perceived centrality in the direction of preceding lateralized ITD or ILD adaptor tones, causing a change in lateralization judgment (Phillips and Hall 2005, Phillips et al. 2006). Finally, binaural enhancement following adaptation has recently been reported. In these experiments, a narrow spectral region could be made subjectively salient by changing its ITD compared to an adaptation period (Šerman et al. 2008). Nevertheless, few psychophysical experiments have investigated discrimination abilities of binaural localization cues following adaptation, or whether adaptive effects enhance information about the prevailing sensory environment. Spence and Driver (1994) observed that reaction times in a localization task were reduced when targets were preceded by

adaptor tones. Getzmann (2004) found an effect of adaptor on localization thresholds (minimum audible angle) for sounds presented in free-field.

Here, we used a psychophysical discrimination paradigm to investigate whether changes in spatial localization accuracy occur following adaptation to ITDs, and whether adaptation to ITDs transfers to the ILD cue. The experiments we present differ from the existing data in several important ways. First, we used the d' measure from signal detection theory (Green and Swets 1966, MacMillan 2001) to characterize localization discrimination thresholds. We used three different subjective locations (left, middle, right) that were produced by either ITDs or ILDs. In order to compare performance in all experimental conditions, we aimed at equalizing d' for all cues (ITD and ILD) and spatial positions, for each subject, when the test stimuli were presented without adaptation. Finally, we used relatively short adaptor sounds (1-2 s), as neural recordings have demonstrated that adaptation occurs in the range of tens to hundreds of milliseconds (Dean et al., in press) and relatively long target sounds (0.5 s).

Overall, the data indicate that adaptive effects are observed in the d' measure. Increased discriminability was found when adaptor and target shared the same location, while discriminability was decreased when the adaptor did not match the target. These effects were strongest at midline. Further, adaptation to ITD resulted in the same improvement in accuracy for both ITD and ILD. Results are discussed with respect to possible neural mechanisms underlying facilitation of source localization under natural listening conditions and potential sites at which such mechanisms could reside.

Methods

Subjects

Four subjects aged between 24 and 40 years participated in this study. All subjects showed normal audiograms (i.e. better then 20 dB HL at frequencies between 0.125 and 8 kHz in octave steps). Differences between ears were smaller than 5 dB HL for all subjects.

Stimulus generation and presentation

Stimuli were generated using customized Matlab programs on a personal computer (44.1 kHz sampling rate). Stimuli were passed into a sound-attenuating booth (Industrial Acoustics type IAC 1202A) and presented to the subjects over headphones (Sennheiser HDA 200) with a mean overall level of 68 dB SPL. Stimuli were lateralized with reference ITDs of 0 µs (middle), +400 µs (left) and -400 µs (right), and equivalent ILDs measured as described below. All stimuli were 800 Hz-wide bands of noise centered at 500 Hz and of 400 ms duration. The duration of the ITD adaptor was randomized between 1 and 2 s. Cosine ramps of 5 ms were applied to all stimuli. Inter-stimulus intervals within the target sequence as well as between target sequence and adaptor (where applicable) were of 500 ms duration, chosen to counteract binaural sluggishness. Inter-trial intervals were of 1.5 s duration.

Experimental procedures and data analysis

The experiment consisted of three preliminary steps, designed to adjust subjective location and discriminability between cues, followed by the main discrimination task. In Step 1, ILDs and ITDs were matched to produce similar subjective locations. In Step 2, discriminations thresholds were measured in all positions and for all cues using an adaptive procedure. In Step 3, a constant stimulus task was used to adjust d’ to a value of 2 at all positions and for all cues, for each subject individually. Finally, these values were used in Step 4 for the main task.

Step 1: Matching of ITDs and ILDs

ITD references were fixed at +400 µs, 0 µs, and -400 µs (left, middle, right), all with an ILD of 0 dB. In Step 1 ILD-equivalents to ITD references were determined, employing a subjective matching paradigm. Subjects could hear the reference ITD by activating a button on a computer screen via mouse-click, with a free number of repeats. They could also listen to the position of the ILD pointer (ITD always 0 µs, variable ILD) to be matched by activating a second button. The initial position of the ILD pointer was randomized from trial to trial. By pressing an arrow to the left or the right of the ILD pointer the ILD could be shifted to the left or the right in 2 dB steps, respectively. Each subject took part in 15 practice trials per reference. Subsequently the ILD-equivalent for each subject employed in the following steps of the experiment was determined by averaging the ILD values derived from 30 trials per ITD reference.

Differences in time-intensity-trading between subjects ranged from 7.19 dB to 16.13 dB (left), from 0.16 dB to 0.99 dB (middle) and from 5.44 dB to 14.31 dB (right).

Step 2: Measurement of just noticeable differences (jnds)

Following the reference matching task, jnds for the three ITD and ILD references were measured in a two-alternative-forced-choice (2-AFC) 3-down-1-up paradigm (d' corresponding to 1.16) with 8 reversals. The task was to indicate which of two noise bursts deviated from a previously presented reference-sound (XAB odd-one out task). Feedback was provided in the form of a red or green flashing button in case of an incorrect or correct answer, respectively. Jnds were determined by averaging over the last four reversals of five sessions. Each subject completed two practice sessions per reference.

Variations of jnds between subjects ranged from 38.73 µs to 138.74 µs and 2.95 dB to 5.89 dB (at left), from 29.27 µs to 83.6 µs and 1.56 dB to 5.27 dB (at middle) and from 44.81 µs to 114.05 µs 1.67 dB to 6.72 dB (at right), for discrimination of ITDs and ILDs, respectively. This relatively large variability is consistent with published jnd measurements (e.g. Mossop and Culling, 1998).

Step 3: Matching the ITD and ILD in the non-adapted condition to a d' of 2

The third step was designed to obtain a d' value of 2 for each subject and condition. The method of constant stimuli was used with a same-different task. For each subject, the difference between stimuli was a fixed number of jnds. Subjects had to indicate if two consecutively-presented noise bursts were the same or different. In trials in which a difference was introduced noise bursts were separated by 1 and 3 jnds for ITDs or by 1 and 2 jnds for ILDs. These differences were chosen after informal testing in order to bracket the value of d'=2. Both cues were presented interleaved within one session. Subjects completed one practice session followed by 12 experimental sessions comprised of 96 trials each (1152 trials per subject). Differences in ITD and ILD corresponding to d' of 2 were determined using linear interpolation.

The number of jnds for matching the ITD and ILD in the non-adapted condition to a d'-value of 2 ranged between 0.49 to 3.05 times jnd and 1.25 to 2.76 times jnd (at left), from 1.55 to 3.25 times jnd and 0.68 to 8.54 times jnd (at middle) and from 1.56 to 2.40 and 0.76 to 1.87 times jnd (at right) for ITD- and ILD-discrimination, respectively.

Step 4: Discrimination experiment (main task)

In the main experiment discriminability (d') was measured for ITD- and ILD-values determined in Step 3, with and without preceding adaptation to ITDs. Again subjects had to indicate if two consecutively-presented noise bursts were the same or different (**Figure 1**).

Subjects conducted 25 sessions comprising 192 trials each (4800 trials per subject). Because of the similarity of the task in Step 3 no practice session was conducted. Discriminability-index (d') and decision criterion (c) were measured using signal-detection theory with the following formulae:

$$d' = z(\text{hits}) - z(\text{false alarms}) \quad (1)$$

$$c = -0.5 * (z(\text{hits}) - z(\text{false alarms}) \quad (2)$$

where z denotes the number of standard deviations from the mean, hits the rate of detection of real differences in intracranial position and false alarms the rate of identical stimuli incorrectly classified as different.

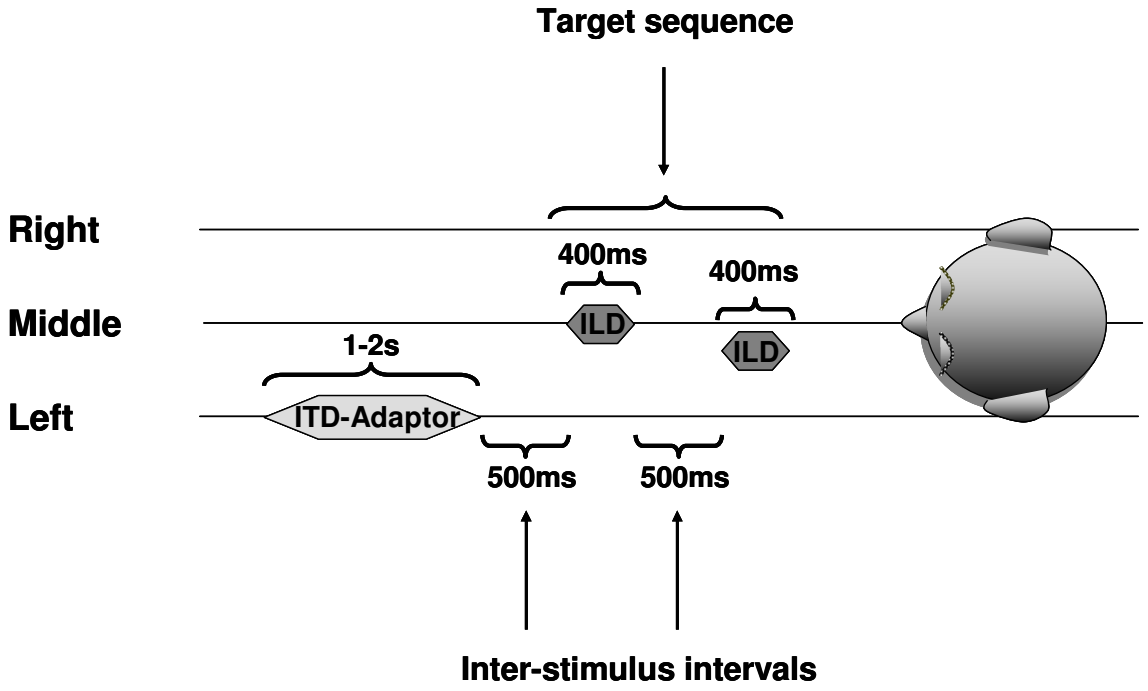

Figure 1: Example of a trial of the main experiment when adaptor and target sequence are presented from different positions. The adaptor is lateralized to the left, the target noise bursts to be discriminated are presented at midline (reference) and a fixed value of ITD corresponding to a d' of 2 away from midline, respectively. All stimuli were 800 Hz-wide bands of noise centered at 500 Hz and presented over headphones.

Results

A total of four subjects participated in the current study. Discriminability was assessed for sequential pairs of noise bursts (target) separated by a fixed value of ITD or ILD (see Methods, 19200 trials in total) with and without preceding adaptation to ITDs. The adaptor and the reference noise burst were presented randomly at ITDs of +400 µs, 0 µs, and -400 µs and the latter also at their respective ILD equivalents, hereafter referred to as left, middle and right, respectively.

Adaptor position influences discriminability for both binaural cues

Discriminability averaged over all subjects and target positions with respect to the type of adaptor condition (non-adapted, on-target position and away from target position) are shown in **Figure 2A**. Significant differences in discriminability were observed between adaptor conditions ($P = 0.025$, $F_{2,22} = 7.215$; GLMM ANOVA with adaptor condition and binaural cue as factors and subjects as random factors), whereas discrimination ability between binaural cues did not differ significantly ($P = 0.756$, $F_{1,23} = 0.116$). A subsequent Fisher LSD-test revealed discriminability to be significantly higher for the non-adapted compared to the away-from-target adaptor-condition for ITDs ($P = 0.020$) and for the on-target compared to the non-adapted adaptor-condition for ILDs ($P = 0.032$). Both binaural cues showed significantly better discriminability for the on-target than the away-from-target adaptor-condition ($P = 0.011$ and $P = 0.005$ for ITD and ILD, respectively).

The decision criterion averaged over all subjects and target positions with respect to the type of adaptor condition (non-adapted, on-target position and away from target) is shown in **Figure 2B**. A GLMM ANOVA with adaptor condition and binaural cue as factors and subjects as random factors revealed no significant shifts of the criterion between different adaptor conditions; $P = 0.292$, $F_{2,22} = 1.522$;) nor between the two binaural cues employed ($P = 0.880$, $F_{1,23} = 0.027$). Thus, it seems that adaptation influences sensory sensitivity only, whilst the decision criterion is unaffected.

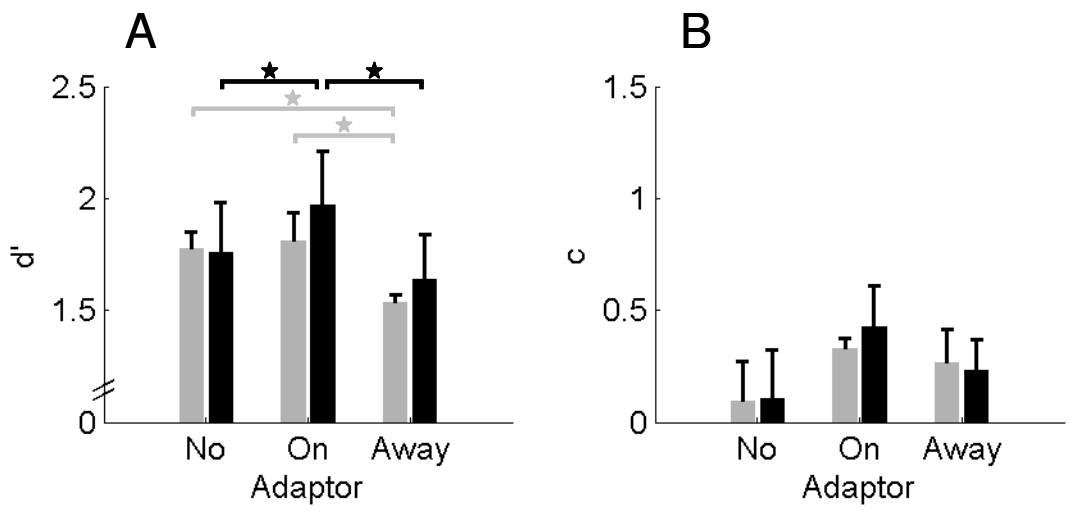

Figure 2: Mean discriminability d' (**A**) and mean decision criterion c (**B**) averaged over target locations are shown as a function of the adaptor condition (non-adapted, on-target position and away from target position). In this and all subsequent figures, error bars represent standard error of the mean. ITDs are depicted in grey, ILDs in black.

Analysis of Hits and False alarms

According to signal detection theory, an increase in discriminability could occur for two separate reasons: if real differences in the intracranial location of binaural cues were detected more often (increased hit-rate, i.e. two noise bursts correctly classified as different), and/or if identical stimuli were reported as different less often (fewer false alarms (FA), i.e. two noise bursts incorrectly classified as different). Hit-ratio (i.e. hit-rate normalized with respect to the non-adapted condition) and FA-ratio (i.e. FA-rate normalized with respect to the non-adapted condition) for each subject averaged over on-target and away from target location are shown as a function of the adaptor condition in **Figure 3A** and **B**, respectively. The effect of adaptor position on hit- and FA-rate is quite different. Hits tended to decrease for both on- and off- target adaptors with respect to the non-adapted condition. This difference was found to be significantly decreased for the co-located condition (right-tailed t-test, P = 0.017) and marginally significant for adaptation away from the target position (P = 0.051). In contrast, FAs were significantly decreased for the on-adaptor position only (P = 0.001), whereas adaptation away from

the target did not result in significant difference of FA-ratio compared to the non-adapted condition (P = 0.714). This pattern of results is observed for all subjects. Thus, the improved discriminability when adaptor and target are co-located (**Figure 2**) can be accounted for by a large decrease in FAs, that more than compensates a small decrease in hit rate that follows adaptation irrespective of the location of target and adaptor.

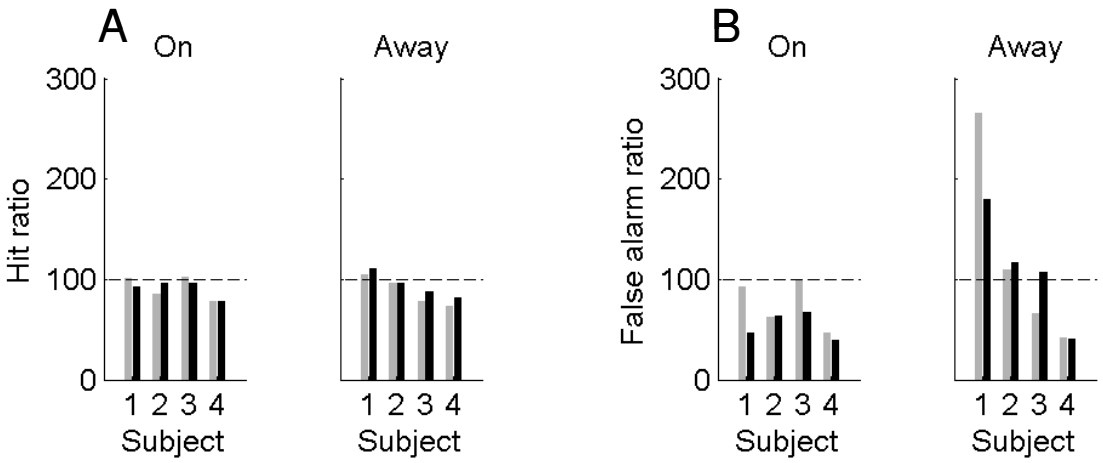

Figure 3: Hit- (**A**) and False alarm- (**B**) ratio (i.e. hit- and false alarm-rate normalized with respect to the non-adapted condition) for each subject averaged over on-target and away from target location as a function of the non-adapted condition. Values above 100 represent an increase after adaptation. ITDs are depicted in grey, ILDs in black.

Effect of absolute spatial location

Mean d'-value and standard error scored for each target position (left, middle and right) are plotted with respect to the adaptor position (none, left, middle and right) averaged over all subjects. Overall discriminability for midline targets (**Figure 4**, middle panel) tends to be higher when adaptor and target position were co-located than in the non-adapted condition and lower when adaptor and target position differed. The effects are somewhat obscured, however, because the d' adjustment procedure (Step 3, see Methods) did not produce an exact value of 2 for all subjects, most notably when the targets were located away from the midline position.

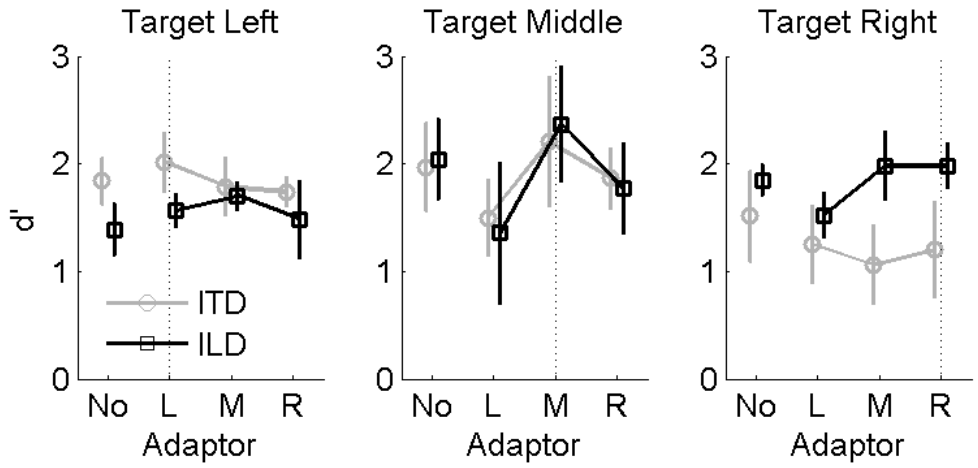

Figure 4: Mean discriminability and standard errors for each target location with respect to the adaptor location. ITDs are depicted in grey, ILDs in black.

To correct for this additional source of noise in the data, results were normalized with respect to the non-adapted condition at the same target location (**Figure 5**). Above zero d'-values indicate improved discriminability and below zero reduced discriminability compared to the non-adapted case. For the midline target (**Figure 5**, middle panel) normalized d' is above zero only for the condition when the adaptor is located in the middle and below zero when the adaptor is located to the left or the right, for both ITD- and ILD-discrimination. Discriminability for the adaptor position at the midline exceeds that for the adaptor located to the left on average by a normalized d'-value of 0.7 and 1.0, to the right by a normalized d'-value 0.3 and 0.6, for ITD-and ILD-discrimination, respectively. A less pronounced trend was observed for discrimination tasks performed on the left and the right (**Figure 5**, left and right panel, respectively). Adaptation to the left tends to increase discrimination on the left, whereas adaptation to the right tends to improve discrimination on the right. Again a GLMM ANOVA with target position, adaptor position and binaural cue as factors revealed no significant differences between d-values with respect to different binaural cues ($P = 0.204$, $F_{1,71} = 1.649$), to different target positions ($P = 0.064$, $F_{2,70} = 2.874$) and to different adaptor positions ($P = 0.060$, $F_{2,70} = 2.930$). However, discriminability for the last two factors comes close to significance.

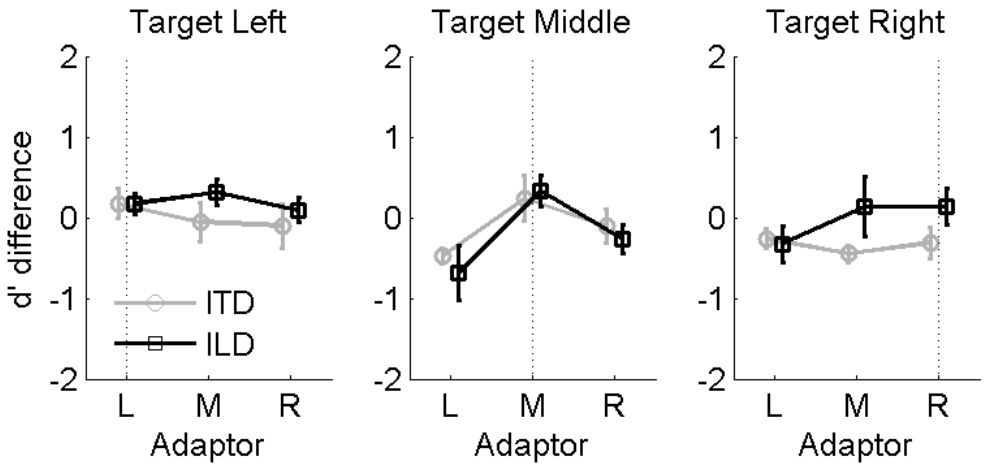

Figure 5: Mean discriminability and standard errors for each target location normalized for the non-adapted condition with respect to the adaptor location. ITDs are depicted in grey, ILDs in black.

Discussion

Investigating the effect of adaptation on discriminability of binaural cues in human listeners revealed three main findings. First, discriminability deteriorates when adaptor and target sequence are presented from different intracranial locations and tends to improve when co-located. The improvement is due to a large decrease in false-alarms when adaptor and target are co-located. Second, we observed that the effect of adaptation was larger for the midline position. Third, ITD adaptors influence discriminability of noise bursts separated by either an ITD or an ILD, with no difference between the two binaural cues.

Adaptation influences spatial discriminability

This is the first study of which we are aware that measured discriminability of intracranial location following adaptation, using signal detection theory (d') with a systematic crossing of binaural cues and subjective location. This required a careful adjustment of ILDs to ITDs to match the intracranial image for both cues, and their discriminability, making it possible to study whether or not adaptive effects are cue-specific. Our results show that discriminability of binaural cues averaged over all target positions improves significantly for co-location of adaptor and target position. This is consistent with findings of previous studies using different experimental methods that reported discrimination (e.g. Getzmann 2004, Hoormann et al. 2004, Sach 2000) reaction times (Spence and Driver 1994) or lateralization (e.g. Kashino and Nishida 1998) of target sounds following an adaptor cue. This common finding strongly suggests that even short-duration sounds can affect the perceived location of subsequent sounds, and that the effect is to improve location coding if all sounds are presented from the same subjective direction. Further, we observed that discriminability of binaural cues averaged over all target positions decreases significantly when the adaptor and the target sequence are presented from different positions.

Does adaptation benefit spatial attention?

One possible explanation for our observations is that the adaptor captured attention to a spatial location. This is suggested by the finding that adaptation to a spatial location had identical effects irrespective of whether the location cue was ITD or ILD. Adaptation at the target position may then be viewed as cueing the subject to where the task will have to be performed, while adaptation away from the target position produces a distraction. In this latter case the adaptor elicits a shift in attention, i.e. an orienting response, toward its spatial position, requiring the listener to re-orient to the target position, reducing discrimination ability. Kopčo et al. (2007) observed a reduction in spatial acuity employing a localization task following a distractor sound consistent with such a hypothesis, whereas Spence and Driver (1994) found a reduction in reaction times for correct cueing of the target position.

Our results, however, show several differences to previous experiments that used spatial cueing (Spence and Driver 1994). Since we employed headphones for stimulus presentation, the present study is concerned only with covert orienting, defined as a shift in attention in the absence of head or eye movements (e.g. Posner 1978, Spence and Driver 1994). Further, the adaptor was not indicative of target location, restricting the adaptive mechanism to exogenous orienting, attributable to a purely bottom-up process (e.g. Posner 1978). According to Spence and Driver's data (1994) from experiments measuring reaction times of binaural discrimination, exogenous orienting is effective for short inter-stimulus intervals (ISI) between adaptor and target (100 ms), but not for longer ISI (e.g. 400 ms). In the present study we observed significant adaptive (or distractive) effects for ISIs of 500ms between adaptor and target sequence, for a stimulus paradigm tapping into purely exogenous attention mechanisms. This discrepancy can possibly be accounted for by the different parameters measured in the present work and the study of Spence and Driver (1994) - discriminability and reaction times for discrimination, respectively. A further difference between the two studies are the much shorter stimulus durations (100 ms for both adaptor and target) in Spence and Driver (1994) compared to those used here (1-2 s and 400 ms for adaptor and target, respectively). Finally, we observed that hit rate was reduced even in the cases where

adaptor and target were in the same position. This seems difficult to interpret if the only effect of the adaptor was to capture attention at a specific spatial location.

Midline vs. lateral spatial positions

Differences in discriminability for different target positions (**Figure 5**) indicate that changes in discriminability with respect to different adaptor conditions occur predominantly for midline targets, whereas only trends can be observed for target sequences located to the left and to the right. A likely explanation for this finding might lie in the relative importance of central positions for sound localization, where auditory spatial resolution is most accurate (Mills 1958). Adaptation away from a midline target sequence causes a greater drop in discriminability than adaptation away from lateralized target sequences because it triggers a shift away from the position exhibiting the finest resolution. Under free-field listening conditions, one would expect an overt orienting response, i.e. a head-movement, toward the adaptor position, directing the majority of sensory organs toward the sound source for fine-tuning of the perceived location. Most mammals rely predominantly on their visual sense for localization, to the extent that width of the field of best vision is closely related to sound localization accuracy (Heffner 1997). In natural conditions, it may thus be argued that adaptor positions to the side would shift to become frontal because of overt orienting, which should then result in a pattern of discriminability observed for midline targets in the current, closed-field, study.

Possible neural correlates for the observed adaptive effects

The psychophysical observations we report here are compatible with recently-demonstrated effects of adaptation to spatial localization cues in an electrophysiological study of ITD-sensitive neurons in the guinea-pig inferior colliculus (IC). Such neurons appear to adapt their responses to take account of the statistical distribution of naturally-encountered ITDs. By such means, neural coding accuracy, as assessed by the population Fisher Information (FI) is improved (albeit coarsely) for the most commonly-occurring ITDs (Maier et al. 2007). A similar argument can be made for the psychophysical observations; discriminability of the intracranial locations of two

consecutive noise bursts, when co-located with a preceding adaptor, arises by means of a sharpening of information at the adaptor location. This would lead to an increase in coding accuracy at the adapted position and, due to the steeper slopes of the information function, to a decrease in information at the deviating target noise burst (**Figure 6A).** This might explain why false-alarm rates are reduced after adaptation (more precise encoding at the adapted position) but hit rates also decrease (less precise encoding at the deviating target noise position).

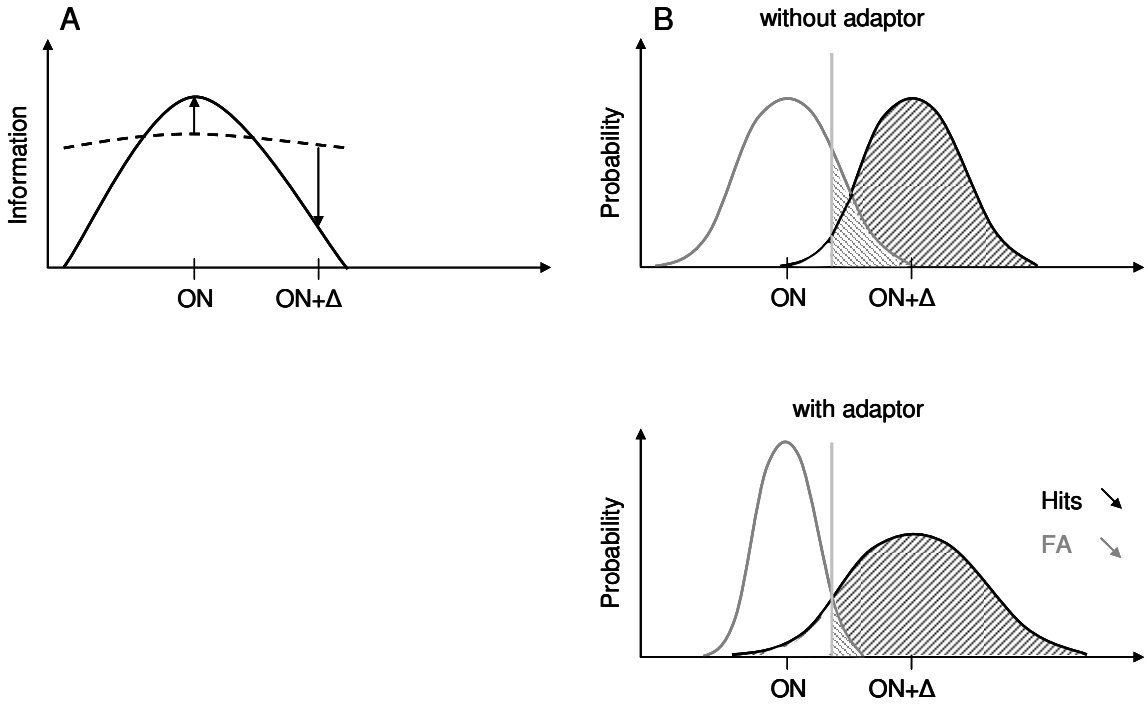

Figure 6: Model as to how adaptation may influence discriminability of binaural localization cues. (**A**) Fisher Information (FI, a measure of coding accuracy) is sharpened at the location of the adaptor. Dashed black line: FI without adaptation, solid black line: FI after adaptation. Arrows indicate increase and decrease of FI, respectively. (**B**) In a signal detection theory framework, the probability density function (PDF) along the decision axis is sharpened at the location of the adaptor, whereas the PDF of a deviating stimulus is broadened. Thereby, the probability of false alarms and hits is reduced but an increase in sensitivity is predicted, while the decision criterion remains unaffected. Dark gray and black curve PDFs for reference and deviant target noise burst, respectively. Dark gray dashed area and black dashed area: probability of false alarms and hits, respectively. Light gray line: criterion.

In terms of a signal detection theory framework, this translates into adaptation leading to a sharper probability distribution for the exact location of the adaptor and a broadening of the probability distribution of a deviating stimulus (**Figure 6B**). Again, this is consistent with the decreased number of both false alarms and hits in the co-located condition in the absence of a criterion shift (as indicated by statistical analysis). The proposed model requires a variance change of the probability distribution so that variances are unequal for signal and non-signal stimuli. Equal variances are the default assumption for the d' measure, for computational reasons, but asymmetric variances are fully compatible with the signal detection theory framework and can be observed experimentally (see Macmillan 2005, p.61).

That this mechanism seems to be more effective for locations around midline is also consistent with the electrophysiological observations (Maier et al. 2007). When the most commonly-presented ITDs lay within the range of approximately ±200 µs, highest coding accuracy, as assessed by FI, remained relatively constant at midline ITDs. Shifts in coding accuracy away from midline ITDs were not observed until the most common ITDs exceeded ±200 µs. This is also consistent with a recent report indicating high mutual information for midline ITDs in single-neuron responses of the guinea pig, where ITDs were presented in random order and with substantial intervals between consecutive presentations (Gordon et al. 2008). Thus, whether ITDs are roved randomly presented in the context of defined distributions in single-neuron studies (Maier et al. 2007), or presented as part of a psychophysical "adaptor-target" paradigm, resolution appears best around midline ITDs. Similarly, for ITDs located away from the midline, human discrimination performance is relatively unaffected by the location of the preceding adaptor.

Interaction between binaural cues

In addition to influencing the lateralization of ITD targets, ITD adaptors also appear able to influence discriminability of noise bursts lateralized by means of ILDs. This observation would be predicted by a top-down attentional effect of spatial cueing irrespective of the acoustic cue. However, as discussed above, the specific effect of

adaptation on hit and false alarm rate, together with a lack of shift in criterion, is inconsistent with such an interpretation (see section 4.1). The similar influence of the ITD adaptor on both binaural cues is, however, consistent with the notion that neural processing of ITDs and ILDs interacts in the auditory brain (e.g. Hari 1995, Phillips et al. 2006) such that, at some level of processing, there arises an integrated percept of auditory space, rather than the individual spatial (binaural) cues *per se*. Where in the brain this occurs, however, remains a matter of considerable debate.

A factor that definitely impacts on an integrated spatial percept is "time-intensity trading", the ability of one binaural cue to trade off against the other. Time-intensity trading is well established as a means of assessing the lateral extent of intracranial sound images. Studies in which subjects are given control of the time delay at each ear to centre the intracranial image of a non-zero ILD (e.g. Hafter and Jeffress 1968, Harris 1960) have an implicit assumption of such a trade, although the precise ratios of ITD and ILD required appear both subject and stimulus dependent.

Although often cast in terms of binaural processing, the earliest site at which time-intensity trading has been observed in the auditory pathway lies at the level of the auditory nerve (e.g. Heil 2004, Joris et al. 2008), where spike latencies appear highly dependent on intensity. However, the maximum trading ratio of 10 µs/dB demonstrated at this stage exists for only very low frequency sounds and no clear pattern of trading ratios could be found (Joris et al. 2008). Time-intensity trading has been observed at the level of the brainstem even though, classically, ITDs and ILDs are thought to be encoded by separate structures - the medial and lateral superior olive (MSO and LSO), respectively (for reviews see e.g. Grothe 2003, Yin 2002). However, the low-frequency limb of the LSO has been demonstrated to encode envelope ITDs (Joris and Yin, 1995, Tollin and Yin 2005) and neurons in the MSO are also assumed to process ILDs (Yin and Chan 1990). In general, these findings indicate that some blurring of the distinction of the early pathways encoding ITD and ILD exists (a conclusion reached by Joris and Yin 1995). A potential site at which the neural representations of ITDs and ILDs might converge is the inferior colliculus (IC) - the major auditory nucleus in the mammalian midbrain - which receives projections from MSO and LSO (Kuwada and Yin 1983, Yin and Kuwada 1983). Evidence for time-intensity trading has also been observed at the

level of the IC (the ITD- and ILD-sensitivity functions of equivalent ITD and ILD stimuli matched perfectly in 10 % and partially in 73 % of the 41 recorded neurons in Irvine et al 1995). Further possible candidates for the site of a common processor of binaural cues are the medial geniculate body (MGB) and fields in auditory cortex. Few studies have investigated the role of the MGB in encoding ITDs and ILDs (e.g. Jones et al. 2007). In contrast, processing of binaural cues in the auditory cortex has been studied extensively (e.g. Jenkins and Merzenich 1984, Stecker et al 2003, Stecker and Middlebrooks 2003). In particular the secondary auditory cortex contains areas in which merged sound localization cues might be processed (Stecker et al. 2005). However, it is not yet established whether the auditory cortex contains a final, common representation of auditory spatial cues, or whether this is achieved at higher associative cortices (Stecker et al. 2005).

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Chapter 5

Summary

Summary in English

Interaural time and level differences - ITDs and ILDs, respectively - are the main cues used to localize sound sources. They play an important role in the ability of animals, including humans, to orient and communicate. Understanding coding mechanisms, and the degree of neural plasticity in the binaural auditory system, potentially enables improvement in, or even the restoration of, localization accuracy *per se* as well as speech intelligibility. My thesis comprises three studies, employing different techniques in three mammalian species, in which I provide evidence that adaptation constitutes a unifying principle of the mammalian auditory pathways encoding sound localization. I demonstrate that binaural localization cues underlie constant dynamic control, enabling adaptation over long (in this case to modified circuits) and short (in this case to stimulus statistics) time frames and that the accuracy of sound localization deteriorates if this process is rendered non-functional (in this case by an ageing process). Together, these studies demonstrate the plastic nature of auditory spatial processing over different time scales.

In Chapter 2 I describe a behavioral experiment conducted to investigate dynamic processes including age-related functional deterioration and long-term adaptation with regard to auditory spatial resolution in the gerbil. In two experimental series, the sound localization ability of aged animals and animals reared in omni-directional noise (an acoustic environment designed to influence development of binaural neural circuits during ontogenesis) was assessed by measuring minimum resolvable angles and compared to respective control groups. Aged gerbils exhibited significantly reduced sound localization abilities compared to controls, and this is reasoned to arise from a functional deterioration caused by degeneration of neural substrates contributing to coding of binaural cues. In contrast, no significant differences in spatial resolution were found between noise-reared gerbils and those of their control group. This finding is attributed largely to compensatory mechanisms, by which the developing brain potentially circumvents impediments to normal routes of processing. Both experimental series indicate that auditory pathways encoding binaural localization cues are dynamic,

i.e. subject to developmental changes, including changes brought about by the ageing process.

In the second part of my thesis (Chapter 3) I focus on short-term adaptive mechanisms of binaural processing, investigating the ability of the mammalian auditory system to adapt in the millisecond range. For this purpose I recorded the responses of single-neurons in the inferior colliculus of the anaesthetized guinea pig to defined distributions of ITDs containing different high probability regions. Analysis using information theory indicates that inferior colliculus neurons respond to changes in ITD distributions by shifting the most sensitive portions of their ITD-functions towards the high probability region. However, this mechanism is subject to limitations, and adjustment of coding accuracy in the inferior colliculus is observed only for naturally-encountered stimuli leading at the ipsilateral (closer to the recording site) ear. The whole population of neurons seems to serve an improvement in information around midline locations.

Finally, in Chapter 4, I present data from a psychophysical experiment in which I investigate whether human listeners show similar adaptive behavior to that observed in single neuron recordings in Chapter 3. Using signal detection theory I measure discriminability for binaural sounds containing matched ITDs or ILDs, either with or without a preceding adaptor stimulus. Results show that adaptation to ITDs influences discriminability of both interaural cues in the same manner - suggesting a joint spatial percept at a yet to be determined level of the auditory pathway when encoding artificial binaural stimuli: Discrimination acuity with respect to the non-adapted condition is improved when adaptor and target sequence are co-located and deteriorates when presented from different intracranial locations. This observation can be explained by a sharpening of coding accuracy at the adapted location and reduced coding accuracy at any other location. Furthermore, discriminability at midline locations benefited most from the observed adaptive effects, consistent with results of single-neuron recordings in the guinea pig presented in Chapter 3.

Zusammenfassung auf Deutsch

Schallquellen werden überwiegend durch die Verarbeitung von interauralen Zeit- und Pegelunterschieden - ITDs und ILDs - lokalisiert. Solche bilateralen Reizunterschiede spielen eine wichtige Rolle für die Kommunikations- und Orientierungsleistungen von Tieren, einschliesslich des Menschen. Die Kodierungsmechanismen und das Ausmass neuraler Plastizität im binauralen auditorischen System zu verstehen befähigt uns möglicherweise sowohl die Lokalisationsgenauigkeit *per se* als auch die Sprachverständlichkeit zu verbessern oder sogar sie wiederherzustellen. Meine Doktorarbeit umfasst drei Themenkomplexe, in welchen unterschiedliche Techniken in drei verschiedenen Säugetierarten zur Anwendung kommen. Meine Untersuchungen zeigen, dass Adaption ein allgemeines Prinzip der die Schallokalisation kodierenden auditorischen Bahnen in Säugetieren darstellt. Ich veranschauliche, dass binaurale Reizunterschiede einer konstanten dynamischen Kontrolle unterliegen, die Adaption über lange (hier an modifizierte neuronale Verschaltung) und kurze (hier an verschiedene statistische Verteilungen eines Stimulus) Zeitrahmen ermöglicht. Weiterhin zeige ich, dass sich die Genauigkeit der Schalllokalisation verschlechtert, falls dieser Prozess nicht mehr funktionfähig ist (hier in Folge altersbedingter Funktionsverluste). Zusammen demonstrieren diese Studien die plastische Natur der auditorischen räumlichen Verarbeitung über verschiedene Zeitskalen.

In Kapitel 2 beschreibe ich ein Verhaltensexperiment, das durchgeführt wurde, um dynamische Prozesse einschliesslich altersbedingter Funktionsverluste und Langzeitadaption hinsichtlich der auditorischen räumlichen Auflösung der Rennmaus zu untersuchen. In zwei Versuchsserien wurde die Schalllokalisationsleistung (anhand der kleinsten akustisch auflösbaren Winkel) von alten Tieren und in omni-direktionalem weissen Rauschen aufgezogen Tieren (eine akustische Umgebung, dazu konzipiert, die Entwicklung der binauralen neuralen Verschaltung während der Ontogenese zu beeinflussen) errechnet und mit der ihrer jeweiligen Kontrollgruppe verglichen. Alte Rennmäuse wiesen im Vergleich zu ihrer Kontrollgruppe eine signifikant reduzierte

Fähigkeit zur Schalllokalisation auf. Dies wird auf eine funktionale Verschlechterung, verursacht durch eine Degeneration der neuralen Substrate, die zur Kodierung der binauralen Reizmerkmale beitragen, zurückgefuehrt. Im Gegensatz dazu wurden keine signifikanten Unterschiede zwischen der räumlichen Auflösung der im Rauschen aufgezogenen Rennmäuse und ihrer Kontrollgruppe gefunden. Dieses Ergebnis wird hauptsächlich Kompensationsmechanismen zugeschrieben, mittels welcher das sich entwicklelnde Gehirn möglicherweise Behinderungen der normalen Verarbeitungswege umgeht. Beide Versuchsserien deuten darauf hin, dass die für die Kodierung von binauralen Reizunterschieden zuständigen Bahnen dynamisch sind, d.h. entwicklungsbedingten Änderungen unterliegen, inclusive solcher, die durch den Alterungsprozess hervorgerufen werden.

Im zweiten Teil meiner Doktorarbeit (Kapitel 3) konzentriere ich mich auf Mechanismen der binauralen Verarbeitung, die der Kurzzeit-Adaption unterliegen, indem ich das auditorische System von Säugetiern auf seine Fähigkeit im Bereich von Millisekunden zu adaptieren hin untersuche. Zu diesem Zwecke habe ich Ableitungen der Antworten von einzelnen Neuronen im Colliculus inferior des anästhesierten Meerschweinchens zu definierten Verteilungen von ITDs mit verschiedenen Regionen höchster Wahrscheinlichkeit vorgenommen. Die Auswertung der Daten mittels Fisher Information deutet darauf hin, dass Neurone im Colliculus inferior auf Veränderungen der ITD Verteilung reagieren, indem sie den empfindlichsten Teil ihrer ITD-Funktionen in Richtung der Region höchster Wahrscheinlichkeit verschieben. Dieser Mechanismus unterliegt jedoch Einschränkungen, und eine Anpassung der Kodierungsgenauigkeit im Colliculus inferior wird nur für unter natürlichen Bedingungen wahrgenommene Stimuli beobachtet, die zeitlich am ipsilateralen (dem Ableitungsort zugewandten) Ohr führen. Die Gesamtpopulation der Neurone scheint einer Verbesserung der Information um mittige gelegene Schallquellen zu dienen.

Schliesslich, in Kapitel 4, präsentiere ich Daten eines psychoakustischen Experiments, in welchem ich untersuche, ob Menschen ein ähnlich adaptives Verhalten zeigen wie das in den Zellableitungen in Kapitel 3 beobachtete. Mittels der Signal-Entdeckungs-Theorie messe ich das Unterscheidungsvermögen für binauralen Schall, der aufeinander abgestimmte ITDs oder ILDs beinhaltet, entweder mit oder ohne

vorausgehenden Adaptor-Stimulus. Die Ergebnisse zeigen, dass Adaption an ITDs das Unterscheidungsvermögen von beiden interauralen Reizunterschieden in gleicher Weise beinflusst, was auf eine vereinte räumliche Wahrnehmung an einer noch zu bestimmenden Ebene der auditorischen Bahn hindeutet, wenn künstliche binaurale Stimuli kodiert werden: Die Unterscheidungsgenauigkeit im Hinblick auf die nicht-adaptierte Bedingung verbessert sich, wenn Adaptor und Zielsequenz sich an derselben Position befinden und verschlechtert sich, wenn sie von unterschiedlichen intracranialen Positionen präsentiert werden. Diese Beobachtung kann durch ein Schärfen der Kodierungsgenauigkeit an der adaptierten Position und eine Reduktion der Kodierungsgenaugkeit an allen anderen Positionen erklärt werden. Im Einklang mit den Ergebnissen der neuronalen Ableitungen im Meerschweinchen, die in Kapitel 3 aufgezeigt wurden, profitierte das Unterscheidungsvermögen ferner an mittig gelegenen Positionen am meisten von den bobachteten adaptiven Effekten.

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Curriculum Vitae

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Research activities

- Behavioural experiments investigating sound localization abilities in gerbils

- *In vivo* single-neuron electrophysiology in guinea pigs investigating midbrain responses to complex sound

- Human psychophysics investigating spatial hearing

Academic supervision

- Tuition of a two weekly practical course investigating the influence of head movements on sound localization abilities in the gerbil at the Physiology & Behaviour Group, Carl von Ossietzky University Oldenburg.

- Supervision of a two weekly practical course examining differences in sound localization accuracy in aged gerbils compared to young controls at the Physiology & Behaviour Group, Carl von Ossietzky University Oldenburg.

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- November 2006:- Seminar Speaker, SFB-Seminar, Otto-von-Guerike University Magdeburg, Germany.

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Publications

Refereed Articles:

Maier JK, Klump GM (2006) Resolution of azimuth sound localization in the Mongolian gerbil (*Meriones unguiculatus*). J. Acoust. Soc. Am. 119, 1029-1036.

Maier JK, Kindermann T, Grothe B, Klump GM (2008) Effects of omni-directional noise exposure during hearing onset and age on auditory spatial resolution in the Mongolian gerbil (*Meriones unguiculatus*) – a behavioral approach. Brain Res 1220:47-57.

Maier JK, Harper NS, Dean I, Klump GM, McAlpine D. Dynamics of ITD-sensitivity in the inferior colliculus: Adaptation to stimulus statistics of naturally-encountered ITDs. In preparation for submission to J. Neurosci.

Maier JK, McAlpine D, Klump GM, Pressnitzer D. Adaptation to interaural time differences improves discriminability of spatial cues. In preparation for submission.

Abstracts:

Maier JK, Klump GM (2005), Directional Hearing in the Gerbil (*Meriones unguiculatus*), 28th ARO Midwinter Meeting, New Orleans, USA.

Maier JK, Hoeffe T, Grothe B, Klump GM (2006), Effect of Rearing in Omnidirectional White Noise on the Auditory Resolution in Azimuth Sound Localization in the Mongolian Gerbil (*Meriones unguiculatus*), 29th ARO Midwinter Meeting, Baltimore, USA.

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Maier JK, McAlpine D, Klump GM, Pressnitzer D (2007) Adaptive coding of interaural time and level differences in the human brain: JNDs and interactions, Short Papers Meeting of the British Society of Audiology, UCL, United Kingdom.

Maier JK, McAlpine D, Klump GM, Pressnitzer D (2008), Coding of interaural time and level differences in the human brain: Adaptation and interactions? 31th ARO Midwinter Meeting, Phoenix, USA.

Erklärung

Gemäß § 10 Absatz (2) Punkt b) und c) der Promotionsordnung der Fakultät für Mathematik und Naturwissenschaften der Carl von Ossietzky Universität Oldenburg vom 10.12.2003 erkläre ich hiermit, dass ich die vorliegende Arbeit selbständig verfasst und nur die angegebenen Hilfsmittel benutzt habe. Die in Kapitel 2 beschriebene Studie ist bereits veröffentlicht, während die in Kapitel 3 und 4 beschriebenen Projekte zur Veröffentlichung vorbereitet sind (siehe Hinweise an den entsprechenden Stellen und Publikationsliste im Lebenslauf). Die Dissertation hat weder in ihrer Gesamtheit noch in Teilen einer anderen wissenschaftlichen Hochschule zur Begutachtung vorgelegen.

London, den

Julia Maier