The Processing of Low-Frequency Spatial Cues – A Behavioral Approach –

Andrea Lingner

Dissertation
an der Fakultät für Biologie
der Ludwig–Maximilians–Universität
München

vorgelegt von
Andrea Lingner

München, September 2010

Erstgutachter: ..... Prof. Dr. Benedikt Grothe

Zweitgutachter: ..... Prof. Dr. Lutz Wiegrebe

Tag der mündlichen Prüfung: 02.12.2010

Contents

Abbreviations

AVCN	anterior part of the ventral cochlear nucleus
BMLD	binaural masking level difference
CN	cochlear nucleus
DAS	dorsal acoustic stria
DCN	dorsal cochlear nucleus
DNLL	dorsal nucleus of the lateral lemniscus
ERB	equivalent rectangular bandwidth
GABA	gamma-amino-butyric acid
IAS	intermediate acoustic stria
IC	inferior colliculus
ILD	interaural level difference
ITD	interaural time difference
KA	kainic acid
LNTB	lateral nucleus of the trapezoid body
LSO	lateral superior olive
MNTB	medial nucleus of the trapezoid body
MRA	minimal resolvable angle
MSO	medial superior olive
NL	nucleus laminaris
PVCN	posterior part of the ventral cochlear nucleus
SNR	signal-to-noise ratio
SOC	superior olivary complex
TB	trapezoid body
VCN	ventral cochlear nucleus
2-AFC	two-alternative, forced-choice
6-AFC	six-alternative, forced-choice

List of Figures

Summary

The localization of sounds is an important feature to navigate in the environment. Especially for animals the ability to detect prey but also predators in close proximity is vitally important. To localize sounds, animals as well as humans mainly rely on two binaural cues, namely interaural time differences (ITDs) and interaural level discrepancies (ILDs). Generally spoken, ITDs are the unambiguous cue for localizing low-frequency sounds (up to around 1500 Hz in humans), whereas ILDs are unambiguous for high-frequency sound localization (over 1500 Hz in humans). The processing of ITDs and ILDs takes place in two brainstem nuclei, the medial and lateral superior olive (MSO and LSO). In general, the MSO processes mainly ITDs and the LSO processes mainly ILDs. The main objective of this thesis is the further understanding of ITD processing. An influential theoretical model introduced by Jeffress (1948) suggested that the representation of ITDs is performed by a place-code. That means, there is a topographic map within the ITD detection unit where each azimuthal space is encoded by one or a set of neurons. This model was shown to be accurately implemented in the ITD detection unit of birds. For a long time, it was assumed that ITD encoding in mammals works similar to that in birds. However, recent studies suggest that both the ITD representation and the underlying mechanism differs from that proposed by Jeffress. In mammals, it is assumed that ITDs are encoded by a rate-code. This means, ITDs are represented by differences in the firing rate of neurons. Recent physiological studies showed that the inhibitory inputs play a crucial role for the suggested ITD representation in mammals. Therefore, the main objective of this study is the further investigation of the ITD processing in a behavioral approach and to test the significance of inhibition for the behaviorally determined ITD sensitivity. The experiments for this study were performed in Mongolian gerbils. They are small rodents with extraordinary good low-frequency hearing, which is a fundamental prerequisite to process

ITDs.
The present study is divided into three parts. The first set of experiments revisited the ITD sensitivity of gerbils. Therefore, the minimal resolvable angle of gerbils was determined. That is, the ability to correctly classify a stimulus as presented either from left or right off midline. The mean minimal resolvable angle for all trained animals was approximately 16°. The resultant ITD sensitivity is with respect to the smaller head size comparable to that of human listeners. However, the localization of a sound without interfering background noise does not reflect a natural situation. Our surrounding environment is always composed of vitally important sounds embedded in various interfering background noises. Thus, for the second part of this thesis a more realistic approach was designed. For this, gerbils were trained to detect and localize a low-frequency noise embedded in two varying background noise conditions. The signal was presented at one out of six loudspeakers. The separation between neighboring loudspeakers was fixed at 35°. The signal-to-noise ratio was varied and the lowest signal-to-noise ratio needed to correctly detect the signal at one of the six speakers determined the threshold for each masker condition. This experiment was also carried out in humans. Results of this experiment showed that the detection thresholds of gerbils and humans were highly diverse. This suggests that there is a difference in the neural processing of low-frequency spatial cues. However, after simulating the auditory processing of the behavioral data with a numerical model, a difference in the processing can be presumably excluded. The last part of this thesis deals with the importance of the inhibitory inputs on MSO cells for behavioral ITD sensitivity. Therefore, the localization ability was determined before and after lesioning the medial nucleus of the geniculate body (MNTB). The MNTB is known to be the main source of inhibition to the MSO. Due to the very sophisticated method of lesioning, only two animals showed a partial lesion of the MNTB. Both of the animals showed an immediate impairment of their localization performance after surgery. It can be excluded that these effects were due to the surgical intervention, implying that the MNTB mediated inhibition plays presumably a crucial role in ITD processing. However, the localization performance recovered after a certain period of time. The most likely explanation for this recovery is a relearning of the localization under the altered conditions in the MSO.

Altogether, this thesis further strengthens the suitability of gerbils as an animal model to study human hearing. It was shown in this thesis that, additional to its already known excellent low-frequency hearing, being comparable to that of humans, gerbils seem to process ITDs in a similar manner to humans. Furthermore, this thesis encourages the already suggested importance of the inhibitory inputs for behavioral ITD sensitivity.

Zusammenfassung

Die Lokalisation von Schallquellen ist eine wichtige Fähigkeit, um sich in seiner Umwelt zu Recht zu finden. Die daraus resultierende Möglichkeit, Beute, aber auch mögliche Feinde, in seiner näheren Umgebungen zu detektieren, ist vor allem für Tiere überlebenswichtig. Tiere, wie auch Menschen, können die horizontale Position einer Schallquelle über kleinste Unterschiede in der Ankunftszeit des Schalls an den beiden Ohren, sog. interaurale Zeitunterschiede (ITDs), bestimmen. Darüber hinaus kann die Position einer Schallquelle aber auch über auftretende Lautstärkeunterschiede an den beiden Ohren bestimmt werden, sog. ILDs. Stark verallgemeinert kann man sagen, dass tieffrequente Schalle (für Menschen etwa bis zu 1500 Hz) mittels ITDs lokalisiert werden, hochfrequente Schalle (für Menschen über 1500 Hz) dagegen werden mit Hilfe von ILDs lokalisiert. Die Verarbeitung von ITDs und ILDs findet in zwei Hirnstammkernen statt, der medialen und lateralen oberen Olive (MSO und LSO). Allgemein gesprochen verarbeitet die MSO hauptsächlich ITDs, die LSO verarbeitet dagegen hauptsächlich ILDs. Schwerpunkt dieser Arbeit ist das weitere Verständnis von ITDs und deren Verarbeitung. Ein einflussreiches Model, vorgeschlagen von Jeffress 1948, besagt, dass die Repräsentation von ITDs, d.h. die Bestimmung der horizontalen Position eines Schalls, mit Hilfe eines so genannten “Place-Codes” stattfindet. Hierbei liegt eine topographische Karte im Gehirn vor, bei der die Position eines Schalls über die Position des aktivsten Neurons oder Neuronengruppe kodiert wird. Es konnte gezeigt werden, dass die Repräsentation von ITDs eben in dieser Art in Vögeln stattfindet. Lange Zeit wurde angenommen, dass die Repräsentation von ITDs in Säugetieren in der gleichen Art und Weise stattfindet. In jüngerer Vergangenheit konnte dies jedoch widerlegt werden. Die Repräsentation von ITDs in der MSO findet über einen so genannten “Rate-Code’ statt. Hierbei werden unterschiedliche ITDs, also unterschiedliche horizontale Positionen des Schalls, als eine Veränderung in der Feuerrate

dargestellt werden. Es häufen sich Hinweise, dass vor allem zeitlich sehr präzise hemmende Eingänge zur MSO die Grundlage der Repräsentation von ITDs in Säugern ist. Schwerpunkt dieser Arbeit ist die Untersuchung des Lokalisationsvermögens tieffrequenter Schalle, sprich die Verarbeitung von ITDs und die mögliche Rolle der Inhibition innerhalb dieses Prozesses in Verhaltensexperimenten. Die Experimente in dieser Arbeit werden an Wüstenrennmäusen durchgeführt, einem Kleinnagern mit einem außergewöhnlich guten tieffrequenten Hörvermögen. Dies ist eine wesentliche Vorraussetzung für die Verarbeitung von ITDs. Die vorliegende Arbeit ist in drei Teile gegliedert. Im ersten Teil der Arbeit wird die ITD Sensitivität von Wüstenrennmäusen bestimmt. Hierzu wird der kleinste Winkel zwischen zwei Lautsprechern bestimmt, den ein Tier gerade noch auflösen kann, d. h. den präsentierten Stimulus richtig als von links oder rechts kommend zuordnen kann. Der kleinste auflösbare Winkel aller 15 dressierten Tiere lag im Durchschnitt bei etwa 16°. Die daraus resultierende ITD Sensitivität ist, unter Berücksichtigung des kleineren Kopfes, in etwa vergleichbar mit der von Menschen. Dennoch entspricht die Lokalisation von Schallquellen ohne zusätzliche Störgeräusche nicht dem einer natürlichen Situation. Unsere auditorische Umgebung ist immer eine Mischung aus wichtigen Geräuschen, die eingebettet sind in verschiedene Hintergrundgeräusche. Deswegen wurde für den zweiten Teil dieser Arbeit ein anspruchvollerer Versuchsansatz angewendet. Hierzu wurden Wüstenrennmäuse dressiert, ein tieffrequentes Rauschen, welches vor einem von zwei Hintergrundmaskierern präsentiert wird, zu detektieren und lokalisieren. Das Zielsignal wurde aus einem von sechs vorhandenen Lautsprecher präsentiert. Der Winkel zwischen benachbarten Lautsprechern war fest bei 35°. Das Signal-Rausch-Verhältnis wurde variiert und die Detektionsschwelle als das Signal-Rausch Verhältnis festgelegt bei dem das Zielsignal gerade noch eindeutig an einem der sechs Lautsprecher detektiert wurde. Dieses Experiment wurde ebenfalls mit Menschen durchgeführt. Die Ergebnisse dieses Experiments ergaben sehr unterschiedliche Detektionsschwellen für Wüstenrennmäuse und Menschen. Dies lässt vermuten, dass hier eine unterschiedliche Verarbeitungsweise vorliegt. Nachdem die Verhaltensdaten jedoch mit Hilfe eines so genannten "numerical model of auditory processing“ simuliert wurden, konnten Unterschiede in der Verarbeitungsweise ausgeschlossen werden. Der letzte Teil der Arbeit beschäftigt sich schließlich mit den hemmenden Eingängen zur MSO und deren Relevanz für

die im Verhalten bestimmte ITD Sensitivität. Dazu wird ähnlich wie im ersten Experiment, das Lokalisationsvermögen von Wüstenrennmäusen bestimmt. Das Lokalisationsvermögen wird vor und nach der Läsion des medialen Nukleus des Trapezkörpers (MNTB) bestimmt. Der MNTB ist die Hauptquelle der Inhibition zur MSO. Auf Grund der sehr anspruchsvollen Durchführung der Läsion ist es nur gelungen, bei zwei Tieren eine teilweise Läsion des MNTBs zu setzen. Beide Tiere zeigten eine sofortige Verschlechterung in ihrem Lokalisationsvermögen, wobei ausgeschlossen werden konnte, dass dies Nachwirkungen des operativen Eingriffs waren. Das wiederum impliziert, dass die Inhibition höchstwahrscheinlich eine wichtige Rolle in der ITD Verarbeitung spielt. Dennoch muss erwähnt werden, dass sich das Lokalisationsvermögen der beiden Tiere nach einer gewissen Zeit wieder auf den Ausgangswert verbesserte. Diese Verbesserung ist höchstwahrscheinlich ein Wiedererlenen der Lokalisation unter veränderten Bedingungen in der MSO. Alles in allem kann diese Studie erneut die Verwendbarkeit von Wüstenrennmäusen als Tiermodel für menschliches Hören bekräftigen. Zusätzlich zu dem schon bekannten guten tieffrequenten Hörvermögen konnte gezeigt werden, dass Wüstenrennmäuse ITDs in ähnlicher Weise und Genauigkeit wie Menschen verarbeiten. Des Weiteren konnte die schon vermutete Wichtigkeit der Inhibition für die Lokalisation im sich verhaltenden Tier bestätigt werden.

1 Introduction

1.1 Sound Detection and Localization

Humans mainly rely on vision to orient in their environment. However, our surrounding environment is also composed of many ambient acoustic noises such as car engine noise, dog barking and of course human communication. These environmental sounds can entertain, annoy, but also alert us. To be able to react for example to a honking car, one has to be aware of its position. Furthermore, acoustical signals are an important part of human as well as animal communication. Especially for animals, the localization of prey and predators in close proximity, but also the localization of potential mating partners or the reaction to conspecific warning signals conducive to survival. Thus, detecting, but also localizing a sound source is vitally important, not only for animals, but also for humans. Humans are exceedingly good in detecting a change in sound source position. They are able to detect a sound source shift in azimuthal space of approximately 1°-3°. Trained persons can detect even lower shifts. However, such values often result from measurements in a very controlled experimental environment. But this only partially reflects our real environment, where we permanently have to deal with the localization of vitally important sounds in more or less noisy surroundings. Coping with this task - signal detection and localization in the presence of interfering sounds - is a further challenge for the auditory system. Psychophysical studies investigating the sound localization ability in dependency on the presented signal-to-noise ratio expectedly showed that the localization ability decreased with lower signal-to-noise ratios, thus higher levels of noise (Stern et al., 1983; Good and Gilkey, 1996). Furthermore, the study conducted by Good and colleagues successfully showed that the localization impairment is direction dependent. It was strongest for front/back judgments, followed by up/down judgments and left/right

judgments. Thus, humans are able to detect and localize sounds in presence of noise to a certain degree.
In the early 50's, Cherry was the first to describe this fact - the capability of humans and probably also other animals to focus on a single sound source in a mixture of varying background noise (Cherry, 1953). He termed this phenomenon the "cocktail party effect", as it is comparable to a cocktail party situation at which humans are able to separate a single person talking from a mixture of interfering voices, music, etc. Cherry already suggested various potential factors possibly facilitate sound source detection in noisy environments. Amongst others, he proposed that the spatial arrangement of both signal and interferers could play an important role in detecting and localizing a signal in such a noisy environment. In the following decades, a vast number of human psychophysical studies investigated the ability to detect speech sounds but also various other stimuli embedded in background noise in dependency of spatial location (for a review see Bronkhorst, 2000). In principle, detection thresholds were measured for different spatial arrangements of signal and maskers in the horizontal plane. These studies could confirm Cherry's suggestion by showing that the detection threshold for a signal co-located with the masker source is markedly higher than the detection threshold for spatially separated positions of signal and masker. In the recent literature, this phenomenon is referred to as spatial unmasking or spatial release from masking and is considered to be one of the main factors responsible for the cocktail party effect. In humans, the improvement of detection thresholds for speech signals and speech or speech-like interferers, is about 6-10 dB.
Signal detection in presence of a masker was also extensively studied by headphone presentations. Here, Licklider (1948) and Hirsh (1948) were the first to show that phase differences of the signal at the two ears lead to a detection improvement compared to a situation where the signal was in phase at the two ears. This phenomenon was later termed the binaural masking level difference (BMLD). As binaural phase differences also result from spatial variations of a low-frequency signal in free-field, BMLDs measured under headphones can be related to the spatial unmasking measured in free-field. In humans, BMLDs produced by phase variations of either signal or masker are as big as 9-15 dB. An overview of studies investigating the release from masking due to spatial information can be found in a review by Ebata (2003).

However, spatial unmasking is not unique to humans. A few studies in the past also investigated spatial unmasking in animals using psychophysical paradigms. Hine et al. (1994) demonstrated that the free-field detection threshold for a 500 Hz pure tone measured in ferrets (*Mustela putorius*) was markedly lower when two loudspeakers (one presenting signal and masker, the other masker alone) were separated by 180° compared to the situation where both loudspeakers were co-located. Dent et al. (1997) showed similar results for budgerigars (*Melopsittacus undulates*). Furthermore, mice also exhibit a better detection ability of a signal in noise if both sound sources were spatially separated (Ison and Agrawal, 1998). A recently published study by Holt and Schusterman (2007) has shown that not only land living animals are capable to benefit from spatial rearrangement in their localization ability, but also water living animals. They found that both harbor seals (*Phoca vitulina*) and California sea lions (*Zalophus californianus*) had lower thresholds for detecting pure tones (1 and 16 kHz) in noise when signal and masker were spatially separated. BMLDs measured under headphones in animals are, due to the experimental approach, rare. However, a few studies were able to determine the BMLDs in animals, showing that cats and rabbits exhibit a BMLD of approximately 8 dB when the phase of a 500 Hz signal in noise was inverted in one ear compared to the condition when the signal phase was the same in both ears (Wakeford and Robinson, 1974; Early et al., 2001). In humans, a similar approach induces a BMLD of about 12 dB. These studies show that both humans and animals are similarly able to deal with detection and localization of sounds in noisy environments, presumably using a similar solution to deal with the problem. However, a direct comparison of animals and humans tested in a comparable approach and stimulus is lacking so far, particularly to investigate underlying mechanisms.

For localizing sounds under controlled experimental conditions as well as in noisy environments, the auditory system needs to determine the position of the sound source. In contrast to other senses, for instance the visual system, the auditory system does not translate physical information about neighboring signal sources directly into a map of neighboring activation patterns of receptors, called the retinotopic map. That is, the localization of a stimulus position in the visual system can be determined directly from this topographic map. In the auditory system, no similar map is found. Therefore, determining a sound source position

depends on a computational mechanism in the ascending auditory pathway rather than mapping receptor activation as in the visual system. It has been shown that sound source detection is deteriorated while listening with one ear, even though relearning is possible under certain conditions (Kumpik et al., 2010). Thus, the information conveyed by both ears seems to be crucial for determining the sound source position via a computational mechanism. However, there is a difference between azimuthal and elevational sound source localization. For localizing sounds in the azimuthal plane, binaural cues are most important, but extracting information about elevational position is still feasible with monaural cues (King et al., 2001). Briefly, these monaural cues are introduced mainly by the direction-dependent filtering of the pinna and result in spectral modifications of the sound, depending on the sound source's position in elevational space (Gardner and Gardner, 1973; Blauert, 1997). That is, each position in elevational space is determined by an unambiguous spectral composition. This spectral composition is referred to as the head-related transfer function and can be measured for each point in elevational space. It is assumed that localization in the elevational plane involves individual learning and memory (Middlebrooks, 1992). The auditory system is assumed to compare templates - stored in memory, defining a position in space - with the actual incoming sound in order to determine the sound position. Recent work suggests, that for low-frequency sounds not only pinna filtering, but also reflections of torso and head add additional cues for sound source localization in the elevational plane (Algazi et al., 2001). The neural basis of spectral cue processing is not conclusively resolved. However, it is suggested that the processing takes place at a lower level of the ascending auditory pathway (May, 2000).

For localizing sounds in the azimuthal plane, a comparison between a template and the actual spectral composition of a sound is not necessary as the system can make use of binaural cues. Theories about binaural cues used to determine a sound source position in the azimuthal plane have a very long history. The first theory was already proposed in the late 19th century by Silvanus P. Thompson (Thompson, 1882) and about 30 years later approved by the British physicist John William Strutt, 3^{rd} Baron Rayleigh, better known as Lord Rayleigh (Strutt, 1907). They found that there were two binaural cues available to localize sound sources in the horizontal plane: interaural time differences (ITDs) and interaural level differences

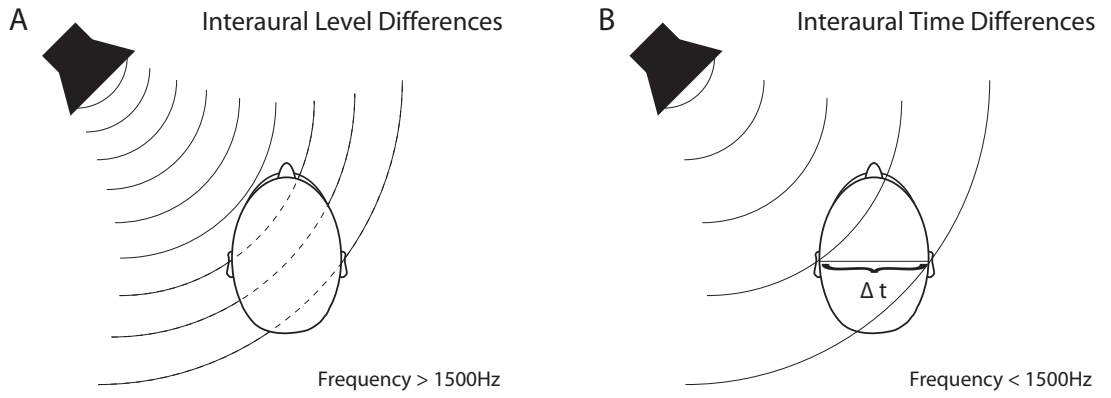

Figure 1.1: Duplex Theory of Sound Localization. Interaural level and time differences are the two binaural cues to localize sounds in the azimuthal plane. Interaural level differences emerge from the shadowing effect of the head, as shown in panel A. They are most effective for wave lengths shorter than the subjects' head. For humans, frequencies above approximately 1500 Hz lead to unambiguous interaural level differences. The unambiguous cue used to localize sounds with frequencies lower than approximately 1500 Hz is the interaural time difference. It results from minute differences in arrival times at both ears, as shown in panel B.

(ILDs). The explanation for the appearance of ITDs and ILDs is rather simple. Sound waves emerging from a sound source off midline with respect to the subjects' head, show the following behavior. The traveling sound wave reaches the ear closer to the sound source a few microseconds earlier than the ear farther away, resulting in minute differences in the arrival times at both ears, the ITDs (see Fig. 1.1B). Additionally, the traveling sound waves are 'hitting' the head and are thereby partially diffracted. This diffraction lowers the intensities at the ear farther away from the sound source compared to the closer one. Thus, ILDs are the result of shadowing effects of the head, but also torso and pinna (see Fig. 1.1A). Rayleigh also noticed in his very early experiments that due to the physical properties of sounds (wavelength and frequencies), ITDs and ILDs are not equally efficient for sound source localization. To produce detectable level differences, the emitted wavelengths have to be shorter than the inter ear distance (thus the head size). Sound waves tend to "bend" around the head with increasing wavelengths, thus lower frequencies, resulting in only little or no ILDs at all. Thus, ILDs are frequency dependent. For humans with an average head diameter of 18 cm, only frequencies above approximately 1500 Hz lead to unambiguous ILDs. Here, sounds with higher frequencies

(6000 Hz) produce ILDs as big as 20 dB in humans (Feddersen et al., 1957). For sounds with frequencies longer than the head's diameter - low-frequency sounds - ITDs play the crucial role in sound source localization. In contrast to ILDs, ITDs are frequency independent in a physical sense, however, there are limitations in the processing of ITDs for high frequency sounds. These limitations seem to appear already at the level of the inner hair cells (Palmer and Russell, 1986). In humans, ITDs can comprise several hundreds of microseconds (μs), ranging from 0 μs, for a sound source positioned straight ahead to approximately 650-700 μs for a sound source located 90° to one side (Feddersen et al., 1957). The unambiguousness of ILDs and ITDs for only certain frequencies was confirmed for pure tones by a simple free-field localization experiment 30 years later by Stevens and Newman (1936). They showed that localization ability in humans was constant for frequencies up to about 1000 Hz and over 4000 Hz. In between, they found an intense drop of localization ability with a minimum around 3000 Hz. This is the region where both binaural cues are presumably small (cf. Fig. 3 in Stevens and Newman, 1936). The simple theory about sound localization of low-frequency sounds via ITDs and high-frequency sounds via ILDs was later known as the "Duplex Theory" of sound localization and is in essence still valid today. That is, the classical separation of ITDs and ILDs for the localization of either low- or high-frequency sounds is rather simple, but valid for pure tones. However, the localization of complex sounds does not completely follow this separation of binaural cues. Already in the 1950s, and further confirmed in the 1970s, psychophysical studies showed that humans are able to localize complex high-frequency sounds on the basis of ITDs similarly accurate as low-frequency sounds (Klumpp and Eady, 1956; Henning, 1974; McFadden and Pasanen, 1976). For complex high-frequency sounds the auditory system is able to compare delays in the envelope of a given sound. For a review about localization of envelope ITDs see Bernstein (2001). But it is not only the complexity of a sound which leads to deviations in the classical view of localizing high and low-frequency sounds with either ILDs or ITDs, but also the distance of the sound source. Until 1990, it was assumed that the accuracy of localizing sounds does not depend on the distance between listener and sound source. However, there are enormous changes in the binaural cues for sound sources less than one meter away from the subject. The most prominent changes are found for ILDs whereas

ITDs are more or less distance independent. At 500 Hz, we would, according to the "Duplex Theory" expect no or at least negligible small ILDs. However, measurements at 500 Hz in the near field showed that the ILDs increased markedly from around 5 dB at 1 m to around 12 dB at 250 cm (Brungart and Rabinowitz, 1999). That shows that low-frequency sounds can also produce ILDs in dependency on the source position (Shinn-Cunningham et al., 2000). Thus, the "Duplex Theory" of sound localization is valid for pure tones in the far-field. However, the position of a sound source and also the complexity of sounds lead to deviations from the original classification of ITDs and ILDs for azimuthal sound localization. Nevertheless, ITDs and ILDs remain the two main cues to localize azimuthal sounds.

Generally spoken, there are two nuclei, belonging to the superior olivary complex (SOC), which is located in the brainstem, considered to be the neural correlates of our ability to process ITDs and ILDs. The medial superior olive (MSO) is assumed to be ITD sensitive (Masterton and Diamond, 1967; Goldberg and Brown, 1969; Yin and Chan, 1990; Grothe and Park, 1998; Brand et al., 2002), whereas the lateral superior olive (LSO) is assumed to be ILD sensitive (Boudreau and Tsuchitani, 1968; Tsuchitani and Boudreau, 1969).
Before auditory information reaches these two nuclei it has to be translated from the physical signal into a neuronal signal in the peripheral structures of the auditory pathway. Briefly, vibrations of the eardrum, induced by incoming sounds, are transmitted to the auditory portion of the inner ear, i.e. the cochlea. Within the cochlea, fluid-borne vibrations are converted into neural information by the hair cells, located in the Organ of Corti. Ascending nerve fibers from each ear further transmit this neural information to each cochlea nucleus (CN) separately. This is the first relay station of the ascending auditory pathway. The CN can be divided, based on both physiological and anatomical properties, into at least three parts (Rose et al., 1959; Osen, 1969): the ventral cochlea nucleus (VCN) with an anterior and posterior part, AVCN and PVCN, and the dorsal cochlea nucleus (DCN). After entering the CN, every auditory nerve fiber bifurcates, those carrying low-frequency information earlier than high-frequency ones. They systematically innervate all three subdivisions of the CN (Lorente de No, 1933). Various cell types are identifiable in these subdivisions. An overview of all cell types is given by Cant and Benson (2003). The important ones for sound localization are the globular and

spherical bushy cells. Both cell types are located in the VCN. The main projections of the spherical bushy cells terminate in the MSO and LSO (Stotler, 1953; Cant and Casseday, 1986; Shneiderman and Henkel, 1985). The main projections of the globular bushy cells terminate in the medial and lateral nucleus of the trapezoid body (MNTB and LNTB) (Friauf and Ostwald, 1988; Kuwabara et al., 1991; Smith et al., 1991). Generally, projections leaving the CN can be divided into three tracts: the dorsal acoustic stria (DAS) the intermediate acoustic stria (IAS) and trapezoid body (TB) or ventral acoustic stria (Barnes et al., 1943). For this introduction, I will focus on projections of the TB as this projection is involved in the innervation of LSO and MSO, shown in Fig. 1.2A and B, respectively. For clarity, pathways involving LSO and MSO will be discussed separately, beginning with the LSO circuitry.

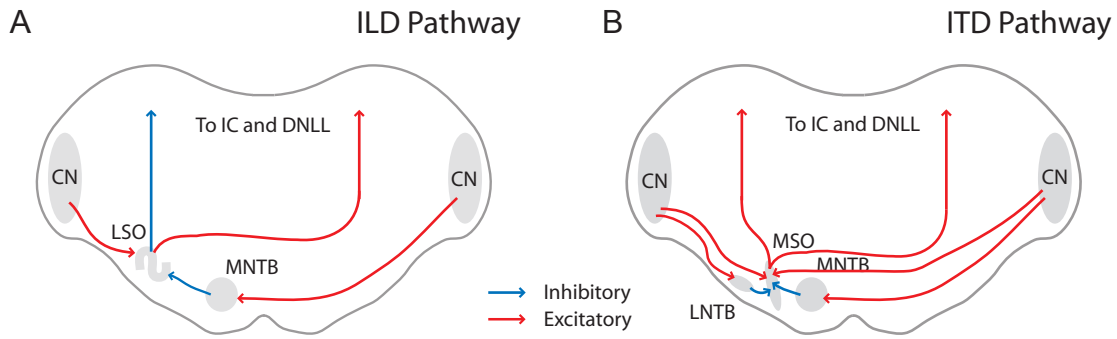

Figure 1.2: Schematic Innervation Pattern of LSO and MSO. The LSO receives direct excitatory inputs from the ipsilateral ear, inhibitory inputs are projected from the contralateral ear via the MNTB, as shown in panel A. The MSO receives direct excitatory inputs from both ears. Bilateral inhibitory inputs arise mainly from the contralateral side via the MNTB and to a lesser extent from the ipsilateral ear via the LNTB, as shown in panel B.

LSO neurons receive inputs from both CNs, thus these neurons are processing binaural information (Boudreau and Tsuchitani, 1968). Ipsilateral inputs are excitatory and reach the LSO directly from the spherical bushy cells located in the ipsilateral VCN (Stotler, 1953). Contralateral inputs arise from the globular bushy cells located in the contralateral VCN. These inputs are reaching the LSO via an indirect pathway. Globular bushy cells directly innervate the contralateral MNTB (Smith et al., 1991). The MNTB itself acts as a sign-inverter and thus forms inhibitory synapses on the LSO neurons. LSO neurons are so-called 'IE' cells, with

glycinergic inhibitory inputs carrying information from the contralateral ear and glutamatergic excitatory inputs carrying information from the ipsilateral ear. Information from the LSO is then conveyed both ipsi - and contralateral. Glycinergic inhibitory synapses form inputs on both the ipsilateral dorsal nucleus of the lateral lemniscus (DNLL, the only part of the lateral lemniscus receiving binaural information) and the inferior colliculus (IC), whereas glutamatergic, excitatory synapses form inputs on the contralateral DNLL and IC (Glendenning et al., 1992).
The circuitry computing ITDs involves the MSO as a main processing unit. Similar to the LSO, the MSO is the primary site receiving binaural information (Stotler, 1953). Inputs from each CN to the MSO consist of a set of inhibitory and excitatory fibers. Glutamatergic excitatory inputs arise directly from spherical bushy cells located in both VCNs (Stotler, 1953; Perkins, 1973). Glycinergic inhibitory inputs originate from the globular bushy cells located in both VCNs. They reach the MSO indirectly via two different pathways. Globular bushy cells located contralaterally to the MSO form synapses on the ipsilateral MNTB (Stotler, 1953; Smith et al., 1991). Based on the sign-inverter characteristics of the MNTB, these projections form inhibitory inputs. Globular bushy cells located in the ipsilateral VCN form excitatory synapses onto the ipsilateral LNTB (Smith et al., 1991). Analogous to the MNTB, this nucleus acts as an sign-inverter, thus forming inhibitory synapses onto the MSO. The MSO itself projects glutamatergic excitatory synapses to both left and right IC and the ipsilateral DNLL (Henkel and Spangler, 1983), also projecting finally to the IC. The majority of the ascending auditory projections, including ITD and ILD pathways, converge into this nucleus (Brunso-Bechtold et al., 1981; Oliver et al., 1995). The IC projects via the auditory thalamus to the auditory cortex. Thus, the IC is a major interface between the lower auditory brainstem and higher order centers in the auditory pathway.

However, the classification of ITD and ILD processing into two distinct pathways involving either MSO or LSO is oversimplified. For one, the MNTB as the source of glycinergig inhibition is involved in both pathways. Furthermore, it was shown that there is some overlap between ITD and ILD sensitivity of MSO and LSO (Caird and Klinke, 1983; Joris and Yin, 1995; Tollin and Yin, 2005). That is, the MSO also processes ILDs whereas the LSO also processes ITDs. A strict separation of the two binaural cues for localizing either low-frequency or high-frequency sounds

is also not supported by humans psychophysical data (see above). Another psychoacoustical phenomenon, called time intensity trading, describes the fact that ITDs can be compensated by ILDs and vice versa. That means, a signal presented with different arrival times over headphones produces an off-centered inter cranial image. However, if the lagging ear is more intense than the leading one, the off-centered image of the sound shifts back to a centered image. Thus, this phenomenon also supports a non-independent processing of ITDs and ILDs (Hafter et al., 1990; Joris and Yin, 1995)

After the introduction of the binaural cues to localize azimuthal sounds and the involved nuclei with the corresponding innervation circuitry, I will now present strategies to represent the binaural cues, and thus the position of a sound source, on neural level and the underlying mechanistic features. As the processing of ILDs will not be subject of this thesis, I will refrain from discussing it in more detail. For further information of this topic see a review of Tollin (2003).
Theories about the encoding of ITDs have a long history. Over forty years after the first fundamental theory about sound localization, Llyod Jeffres proposed a remarkable theory concerning azimuthal sound localization (Jeffress, 1948). In his research paper, he presented an encoding strategy and an underlying model explaining the basic features of ITD processing in the brain. Jeffress hypothesized that the ITD detection unit encodes all occurring ITDs via a so-called 'place-code' (also termed a 'labeled-line code'). That is, every neuron within this unit is most sensitive to a particular ITD in the horizontal space, resulting in an evenly distributed representation of different azimuthal position within the population of neurons. Thus, the sound source position is determined by the neuron with the maximal firing rate within the array of ITD sensitive neurons. This results in a topographic map of azimuthal space where a certain ITD sensitive neuron represents a certain position in space (see Fig. 1.3C). Such a topographic map is present for every frequency channel in the ITD detection unit. In his research paper, he also presented a theory of how this topographic map can be achieved. Simplified, this theory comprises three fundamental assumptions of how ITDs are transformed into a neural code, namely:

- Phase locking
- Coincidence detection

- Internal delay lines

According to Jeffress (1948), the translation of ITDs into place-code requires the ability to preserve the temporal information up to the ITD detection unit. Preserving temporal information is enabled by phase-locking of auditory neurons. Phase-locking is a special form of time-locking and describes the fact that the discharge rate occurs always at a particular phase of a stimulus (see Fig. 1.3A). Second, Jeffress postulated that there are neurons within the ITD detection unit performing a coincidence detection of two phase-locked binaural excitatory inputs. That is, these neurons only fire if both inputs are simultaneously active (see Fig. 1.3B). Last, Jeffress proposed that the axons reaching the neurons of the ITD detection unit are forming delay-lines or latter-like structures. That is, the lengths of the axons vary systematically for every innervated neuron and thus introduces different traveling times of the action potential from the ear to the different neurons (Fig. 1.3B). For example, a neuron, innervated by a longer axon coming from the right ear than the axon coming from the left ear, is sensitive to sound source positions in the right azimuthal space. Thus, this mechanism results in the representation of ITDs in a topographical map. That is, a defined place (the most active neuron) represents a defined ITD (the sound source position in the azimuthal space), a so-called place-code (Fig. 1.3C).

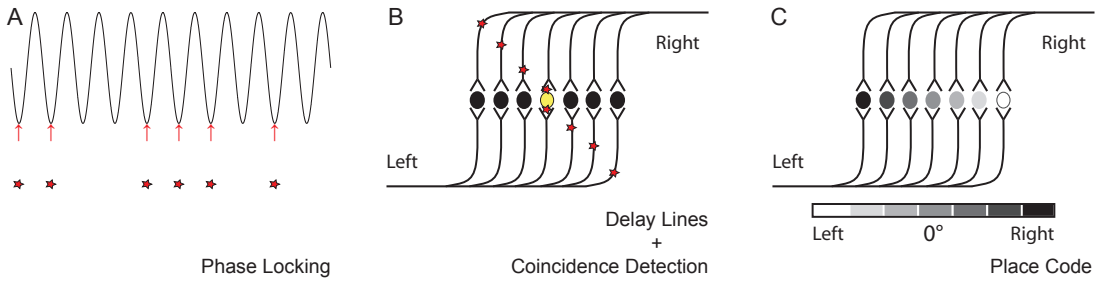

Figure 1.3: Jeffress-Model. The first model illustrating the transformation of ITDs into a neural code. Being able to detect time differences, a system must fire at the same point within a sound wave. Panel A shows an example for a phase-locked response to a sine wave. This phase-locked information from both ears is further transmitted via axons with variable length, forming so called delay-lines, to an array of coincidence detector neurons (panel B). This network of coincidence detectors and delay-lines results in a topographic representation of the azimuthal space (panel C).

Anatomical and also physiological studies showed that the nucleus laminaris

(NL), an avian brainstem nucleus receiving binaural inputs, possesses the main features proposed by Jeffress. That is, the NL is innervated by precisely-timed, excitatory inputs from both ears. The inputs arising from the contralateral ear form a delay-line pattern before reaching the NL (Parks and Rubel, 1975; Sullivan and Konishi, 1986; Carr and Konishi, 1988). It was also shown that neurons within the NL act as coincidence detectors, that is they only fire if both inputs are simultaneously active (Overholt et al., 1992). This led to the suggested place-code within the NL (Carr and Konishi, 1990). Thus, the proposed ITD encoding strategy by Jeffress is accurately implemented in the ITD detection unit of birds. Both anatomical and physiological results fit his suggestion. For a very long time, it was assumed that mammals also encode ITDs via a place-code as studies showed that the anatomical prerequisites for a place-code were also present in mammals. That is, MSO neurons were shown to possess binaural excitatory inputs, at which axons reaching the MSO are forming delay-lines (Smith et al., 1993; Beckius et al., 1999). However, the existence of delay-lines is questionable, particularly the results shown by Smith et al. demonstrate that most cells are not innervated by delay-line pattern. Both the questionability of delay-lines and recent physiological evidences (e.g. Brand et al., 2002) show that the processing of ITDs in the mammalian auditory system seems to differ from the model proposed by Jeffress. For one, studies examining the ITD representation in mammals lead to clear doubts about a place-code for ITDs in mammals (e.g. McAlpine et al., 2001). McAlpine and colleagues systematically investigated the existence of a place-code in guinea pigs. Based on the place-code suggested by Jeffress, it is expected that neurons, sensitive to ITDs, fire maximally for a certain, favored ITD. That is, every spatial location should be encoded by a set of neurons tuned to different, physiologically occurring ITDs. However, McAlpine and colleagues failed to find such neurons in the MSO. Contrary to their expectations, most of the ITD sensitive neurons had their the peak outside the physiologically occurring range of ITDs for guinea pigs, conflicting with the classical view of ITD encoding by place-code. Accordingly, a second theory about the encoding of ITDs in the mammalian brain was proposed. It was suggested, that ITD encoding is mediated via a so-called avarage rate-code in mammals. Given that the best ITD (maximum in firing rate) is located outside the physiological relevant range of ITDs the steepest slope (maximal

change in firing rate) of the ITD sensitive neuron is close to 0 ITD. Accordingly, a small change in ITD (i.e. azimuthal space) results in a big change of firing rate. Thus, the full range of ITDs is encoded by a change in firing rate rather than the maximal firing rate of neurons as proposed by Jeffress. This rate-code representation is implemented on each side of the brain in an inverse manner. That is, ITD sensitive neurons located in the right MSO fire maximally for ITDs corresponding to locations on the left hemifield. For ITD sensitive neurons in the left MSO, it is vice versa. Thus, the encoding of ITDs in mammals is achieved by comparing the relative activity of ITD sensitive neurons in the left and right MSO. This average rate-coding of ITDs is assumed to be the strategy in mammals.

Nowadays, it is believed that binaural inhibitory inputs to the MSO are a main part of the underlying mechanism for the just described ITD encoding strategy in mammals. The first hints about inhibitory inputs to the MSO can be traced back to the late 60's (Goldberg and Brown, 1969). The authors found beside neurons that had two excitatory inputs, also neurons that were innervated by one excitatory and one inhibitory input. Nevertheless, inhibition was not considered to play a role for the representation of ITDs in mammals for a long time. Starting in the early 90's, studies systematically investigated the input characteristics to the MSO. Amongst others, an *in-vitro* study conducted in gerbils could verify that there is prominent inhibition present in MSO neurons (Grothe and Sanes, 1993). The major source of these inhibitory inputs on MSO neurons is the MNTB, fewer inhibitory inputs come from the LNTB (Cant and Hyson, 1992; Grothe and Sanes, 1993; Kuwabara and Zook, 1992). The MNTB is innervated by globular bushy cells located in the VCN. They seem to be highly specialized for transmitting temporal information as they show an enhancement of phase-locking in their response compared to auditory nerve fibers (Joris et al., 1994; Joris et al., 1994). This leads to a sharpening of temporal information. Furthermore, axons of the globular bushy cells form the largest synapse within the auditory pathway - the Calyx of Held. It has been shown that this synapse performs a very fast and secure transmission of information (Wu and Kelly, 1993; Taschenberger and von Gersdorff, 2000; von Gersdorff and Borst, 2002), and thus preserves spike timing. In summary, this innervation circuitry and in particular the MNTB shows a very high degree of specialization for high-fidelity transmission of

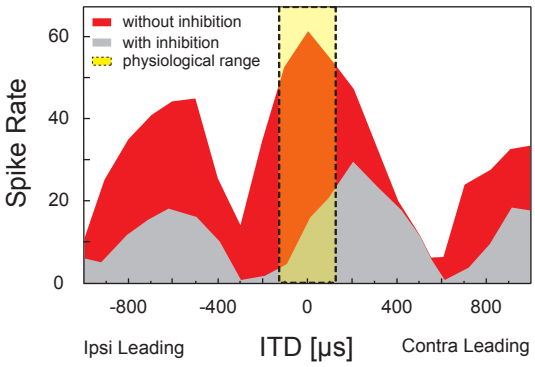

Figure 1.4: Effect of Strychnine on a MSO Neuron. Displayed is an ITD function of an exemplary MSO neuron, redrawn from Brand et al., 2002. The gray area depicts the spike rate recorded for each presented ITD under control condition (i.e. with inhibition). The peak of the ITD function is located outside the physiological range (yellow-shaded area), whereas the steepest slope of the function is found within the physiological range. The red area depicts the ITD function of the same neuron after blocking glycinergic inhibition with strychnine. Subsequently, the peak is shifted towards zero ITD and thus the steepest slope of the function is mainly outside the physiological range.

sounds, especially regarding its temporal information. Similar to the MNTB, the LNTB, as a minor source of inhibition to the MSO, also shows very specialized adaptations to perform a temporally precise processing (Spirou and Berrebi, 1996).

Although, all the above mentioned results indicate that the inhibition plays a major role in the underlying mechanism to represent ITDs in the mammalian brain, the first striking proof about the importance of inhibition for the ITD representation was presented at the beginning of the 21^{th} century. Brand et al. (2002) investigated the response properties of MSO neurons *in-vivo* before and after pharmacologically blocking the inhibitory inputs. ITD tuning curves recorded under control conditions (without pharmacological blocking) show the very characteristic shape already described by McAlpine and colleagues. The peak lies mostly outside the physiological range (approximately ± 135 μs for gerbils (Maki and Furukawa, 2005)), whereas the steepest slope is located near midline. After blocking the postsynaptic receptors with strychnine, the situation changed remarkably in that the peaks of the ITD functions shifted from outside the physiological range towards 0 ITD. Fig. 1.4 depicts the situation before and after blocking inhibitory inputs as presented in the study of Brand et al. The prominent increase of firing rate is an obvious effect of blocking inhibition. Thus, this study showed that inhibition to the MSO plays a crucial role in shaping the response of ITD sensitive neurons.

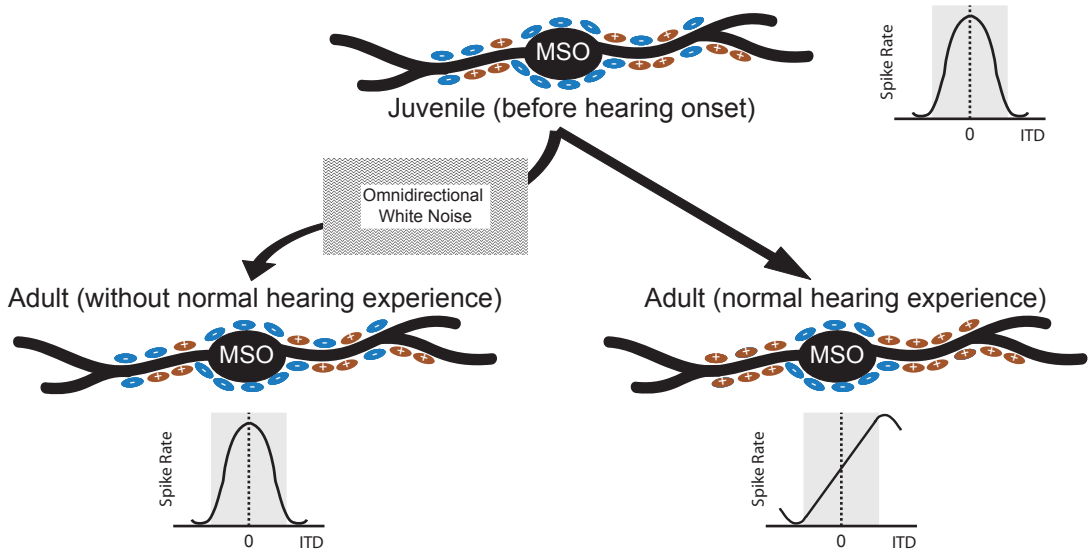

Figure 1.5: Maturation of Inhibitory Synapses in Gerbils. Inhibitory synapses in the MSO of gerbils undergo a refinement process after hearing onset. Before hearing onset, inhibitory inputs are distributed over soma and dendrites. A schematic drawing of the pattern and a corresponding ITD function are shown in the upper part. After the maturation process, inhibitory synapses are restricted to the soma of the cell (right side). This process leads to a shift in the ITD function, see small inset. The result of a disruption of the maturation process, e.g. by white noise-rearing, is depicted on the left side. The distribution of the inhibitory synapses is similar to that before hearing onset. Thus, the ITD function is also similar to that before hearing onset.

A study conducted by Kapfer et al. (2002) could further strengthen the importance of inhibition for the ITD representation. In this study, it has been shown that inhibitory inputs to the MSO undergo a refinement process after hearing onset. Before hearing onset, the inhibitory synapses are more evenly distributed over soma and axon than compared to the situation after hearing onset when the synapses are mainly found on the soma of MSO principle cells. This refinement process was shown to happen in gerbils, a low-frequency hearing specialist, however, not in rats. Furthermore, this study revealed that this refinement process is dependent on acoustic experience, particular the experience of spatial acoustic cues. It was possible to disrupt the refinement process by rearing gerbils in omni-directional white noise (see Fig. 1.5). This type of rearing is a method to avoid spatial acoustic experience in animals without damaging the cochlea or other peripheral structures (Withington-Wray et al., 1990). Thus, the refinement process depends on spatial

acoustic experience and is not present in animals that do not rely on ITDs to localize sounds (e.g. rats and bats). Whether this refinement process has impacts on the ITD encoding mechanism was shown a few years later by Seidl and Grothe (2005). They systematically investigated the response properties of ITD sensitive neurons before and after hearing onset of gerbils and compared these results to the response properties of ITD sensitive neurons of adult gerbils reared in omni-directional white noise. The results of this study showed that correct ITD tuning depends on the acoustic-dependent experience. Recorded ITD functions of noise-reared animals were similar those recorded before hearing onset (see small insets in Fig. 1.5). In summary, inhibitory inputs to the MSO and in particular their maturation process that is dependent on spatial acoustic experience, thus a direct adjustment with the outer world, seem to be crucial for the processing of ITDs. However, behavioral studies investigating the effect of a changed ITD representation due to the lack of inhibition on the localization ability are not available. One study in the past examined the effect of noise-rearing on the localization ability in gerbils. Noise-rearing is assumed to impair the localization ability as it avoids the maturation process of inhibitory inputs. However, the determined localization thresholds of noise-reared animals did not differ from those in control animals. Thus, impacts of non-existing inhibition on the localization ability need to be investigated.

1.2 Aim of the Current Study

The understanding of basic features of sensory systems is an important and fundamental part of research in the field of systemic neuroscience. Concerning the field of auditory neuroscience, research into detection and sound localization have played a prominent role. The physical cues that can be used to identify a sound source in the horizontal plane are already well investigated. In contrast to this, the mechanisms underlying the representation of these cues in the brain are not that well understood. To investigate the underlying mechanism of the ITD representation, this thesis uses the Mongolian gerbil as an animal model. Before studying mechanistic features of sound localization on neuronal network or cellular level, it is important to assign boundaries of a behaving system. Thus, this thesis deals with the research of sound localization and detection in a behavioral context. The main

objective of this thesis is to present results showing that the gerbil is an excellent animal model to investigate the neural processing of spatial tasks in the auditory system. The results of this thesis are divided into three parts. The first part of this study deals with the ability to use ITDs to localize low-frequency sounds in gerbils. The localization acuity of low-frequency sounds in gerbils was already tested in several other studies (Heffner and Heffner, 1988a; Maier and Klump, 2006; Maier et al., 2008). The resultant ITD sensitivity of gerbils found in these studies is conspicuously worse than that for humans. A smaller head-size, and thus consequently smaller available ITDs can not account for the difference in ITD sensitivity. One theory presented by Heffner (1997) states that differences in the ITD sensitivity amongst animals arise from differences in the field of best vision. He argued that sound source localization is important to guide visual attention to the source of interest and showed that there is a strong correlation between the width of the field of best vision and localization acuity. The narrower the field of best vision, the better the localization acuity was. However, it can be assumed that the gerbil's localization ability was underestimated by the previous studies, e.g. the procedure to investigate a threshold was rather unusual in one study(for more information see discussion). Therefore, we reassessed the ability to classify a low-pass filtered noise presented over two loudspeakers at various positions in the frontal field as either left or right. Results of this part will give us indications about localization precision of the gerbils' auditory system and whether it is comparable to humans or not. However, compared to an everyday situation where the surrounding sounds are always a mixture of important signals embedded in different kinds of noise, I used a rather simplified stimulus. Thus, in a second set of experiments, I investigated the detection and localization ability of gerbils with a more sophisticated stimulus set. This will provide more insights into the localization ability of gerbils. In these experiments, the animals had to detect a signal presented over one of six loudspeakers equally spaced around midline ($\pm 87.5°$) in presence of two different background noise interferers with varying signal-to-noise ratios. Such a stimulus set reflects a more natural situation for the auditory system, as the auditory system is always confronted with different, eventually vitally important sounds amongst interferers. This experiment was also performed with humans subjects. Thus, it is possible to directly compare the used animal model with humans. The first two ex-

periments will give indications about the ability of gerbils to process low-frequency spatial cues. A comparison to humans will show whether there are similarities or dissimilarities in the neural processing of low-frequency sounds in both a very basic and a more complex experimental environment.

After determining the behavioral processing of ITDs in two different behavioral approaches, the last part of this thesis will focus on the underlying mechanism, in particular the role of inhibition. It will present some interesting prospects of the importance of MNTB-mediated inhibition for sound localization. Recent electrophysiological studies demonstrated the importance of this inhibition for ITD representation on a neuronal level in mammals. Thus, it probably plays a key role in the localization of low-frequency sounds in a behavioral context. Therefore, we quantified the azimuthal low-frequency sound localization ability as described in experiment one, before and after lesioning the MNTB by injection of kainic acid. Resultant alteration in the behaviorally determined ITD sensitivity due to a modification of inhibition will probe the relevance of MNTB-mediated inhibition for the processing of ITDs.

1.3 Mongolian Gerbils and Auditory Research

Figure 1.6: Gerbil.

The experimental animal used in this study is the Mongolian gerbil (*Meriones unguiculatus*, referred to as gerbils, see Fig. 1.6). Exception is experiment 2, where experiments were also performed with human listeners. Gerbils are small rodents belonging to the subfamily of *Gerbillinae*. Their natural habitats are the semi-desert and steppe of Mongolia, North China and southern Russia. In their natural environment, these highly social animals live in family organizations of approximately 15-20 animals and inhabit subterraneous burrows, protecting themselves against extreme weather conditions (both heat and cold). Gerbils can be regarded as both diurnal and nocturnal animals with a sleep-wake cycle of about 2-4 hours. Nevertheless, there are great intra-species variations, with individuals being predominantly diurnal whereas other being predominantly nocturnal (Re-

finetti, 2006). A bigger part of their active phases, they spend foraging, feeding on seeds, fruits and roots; the required water is absorbed via food. Gerbils are an established experimental animal in biological research, especially in auditory research. Based on the advantage that there is a sizeable amount of data available due to their very pronounced low-frequency hearing ability, these small rodents are also a preferred animal-model for the investigation of auditory processing. The comparison of the audiogram of gerbils and man exhibit that both species have a very similar hearing threshold up to 8 kHz (Ryan, 1976). Above 8 kHz gerbils exhibit a slightly better hearing threshold than humans. Such a pronounced low-frequency hearing, as developed in gerbils, is rather unusual (Heffner et al., 2001). It is assumed that this low-frequency hearing results from a hypertrophied (enlargement of an organ or a tissue as a result of an increase in the size) middle ear cavity (Plassmann et al., 1987). Behaviorally, it is assumed that this low-frequency hearing is an adaptation to avoid predators (Lay, 1972). Furthermore, when feeling threatened, gerbils communicate by typically drumming with their hind feet on the sand, producing low-frequency sounds of about 1 kHz. They are interpreted as warning signals. Thus, low-frequency hearing is seen as an adaptation to their environmental conditions and seems to be vitally important for these small rodents. Beside their good low-frequency hearing, the gerbil auditory system is also very suitable for developmental studies. Gerbils are born deaf and do not hear airborne sounds before postnatal day 10. In addition, they also have a comparably short life-span of two to four years. This means that it is possible to study both changes between the immature and mature auditory system but also during changes of the auditory system due to aging processes (Sinnott and Mosqueda, 2003; Hamann et al., 2004; Gleich et al., 2007). In summary, it can be said that the gerbil is a small laboratory animal, which is assumed to be both suitable for electrophysiological and behavioral (Pecka et al., 2007; Schebesch et al., 2009; Wolf et al., 2010) experiments with a remarkable low-frequency hearing ability among small rodents and the possibility to study developmental changes due to their life-span. Particularly with regard to the objectives of this study, the good low-frequency hearing is an essential prerequisite to serve as animal model.

2 Material & Methods

2.1 Azimuthal Sound Localization

Animals

Experiments were performed with 15 adult gerbils, 4 males and 11 females. A maximum of 3 animals were housed together in a 71x46x31 cm^3 (length x width x height) cage, containing wooden chipping as bedding, a sleeping house and paper towels for nesting. Gerbils were kept under constant laboratory conditions with a 12 hour day/night rhythm, a temperature of 23° C and a humidity of 55 %. Gerbils were trained five consecutive days a week, followed by a break of two days. They had unrestricted water access the entire time. During training days, gerbils were food-deprived, receiving 20 mg-pellets (Dustless Precision Pellets Product# F0071; BIO-SERV; Frenchtown, New Jersey, USA) as reward for correct decisions in the experimental setup. On days without training, gerbils had unrestricted access to rodent dry food (ssniff Gerbil; ssniff Spezialdiäten GmbH; Soest, Germany). Body weight was controlled daily during the whole training period and ranged between 60 and 70 g. In case of a weight-loss animals received additional food supply.

Setup

Experiments were performed in a double-walled sound attenuated chamber (Industrial Acoustics Company GmbH, Niederkrüchten, Germany). Walls, ceiling and floor were covered with foam wedges (Industrial Acoustics Company GmbH, Niederkrüchten, Germany). Foam wedges were 40 cm in depth eliminating echoes for frequencies of more than approximately 250 Hz. Training took place in a circular arena, placed in the chamber. The arena had a diameter of 94 cm, enclosed by a wire mesh with a height of 29 cm; the floor was covered by carpet. A platform 3 cm

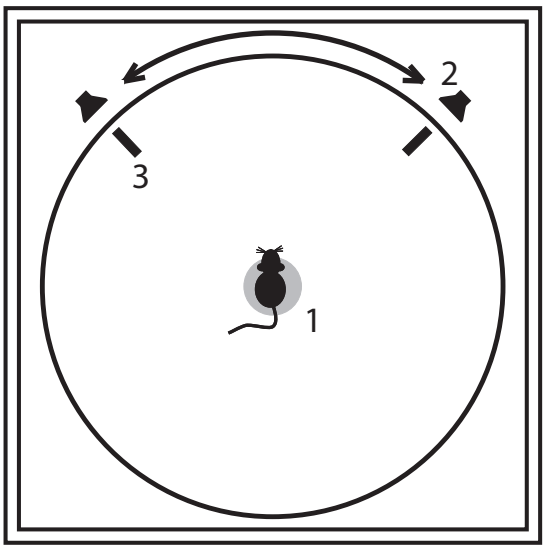

Figure 2.1: Setup of Experiment 1. Illustration of the setup used to determine the MRA of gerbils. The circular arena consists of a platform located in the center with a light barrier in front (1). Two movable loudspeakers (2) with an adjacent foot-switch and feeder (3) releasing a food-reward for correct decisions are mounted on a rail.

in height (9 cm in diameter) with a little ring arranged in front of it, was placed in the middle of the arena, serving as the starting position. Gerbils were trained to jump on the platform and position their nose within the ring. This guarantees a defined head position and moreover automatically starts a trial, as an internal light barrier was disrupted. Inner-diameter of the ring was 3 cm to ensure unrestricted sound transmission to the gerbils' ears. Two custom-made movable arms were mounted on a rail around the setup. Each arm consisted of a loudspeaker (Aura Sound, NSW1-205-8A, Santa Fe, CA, USA), a foot-switch, and a feeder, delivering pellets for correct decisions. A calibration routine was used to assure a similar flat frequency response from approximately 200 Hz to 10 kHz for each loudspeaker. The loudspeakers were moved to various angles around midline. The angle between the two speaker arms was varied from 105° to 5.5° as seen from the starting platform (intermediate steps: 60°, 45°, 35°, 30°, 25°, 20°, 15°, 10°, 7°). A schematic diagram of the setup is depicted in Fig. 2.1. A standard monitoring video system was installed directly above the setup to observe the gerbils' performance from outside the chamber. Four halogen light spots provided setup lighting.

Stimuli

The localization signal was a computer generated (MatLab, Mathworks, Natick, MA, USA) low-pass noise with a cut-off frequency of 1 and 1200 Hz, played back via a Delta 410 PCI Audio card (M-Audio, Hallbergmoos, Germany) at a sampling

rate of 22.05 kHz and amplified (Rotel, RB-976 MK II, Worthing, England) before being presented to the gerbils via the setup loudspeakers. The signal length was 125 ms. For every signal generation the spectral envelope was roved by ±6 dB. That is, the presentation level for frequencies between 1 and 1000 Hz (in 200 Hz increments) was roved by ±6 dB. To prevent extreme level changes within the stimuli due to the amplification or attenuation of the individual frequency parts, the change in level was implemented as slowly raising or falling within these steps. Moreover, to preclude the gerbils from using the overall presentation level, it was additionally roved by ±6 dB per trial.

Experimental Procedure

Gerbils were trained to lateralize a sound in a two-alternative, forced-choice (2-AFC) setup by means of operant conditioning using food pellets as positive reinforcement, examining the minimal resolvable angle (MRA) for each animal by varying the speaker separation. In order to guarantee a defined head position before each trial, the gerbils were trained to jump onto the platform located in the middle of the arena and position their nose into a little ring (ensuring a constant and controllable head position), interrupting a light barrier. Triggered by this interruption, a trial was started by presenting the signal from either the left or the right loudspeaker side. Gerbils learned to move towards the corresponding speaker and to press the foot-switch in front of that speaker. Gerbils had to execute this step within 15 s to complete one trial. Correct decisions within this time were rewarded with one food pellet, incorrect decisions remained unrewarded. Activation of a new trial within the 15 s time period without finishing the preceding trial (by pressing a foot-switch) was not possible. There was a timeout period of 20 s after incorrect trials; starting a new trial within this time period was not possible. An experimental session started with the presentation of five trials at the largest speaker separation (105°). The angle was then reduced to the next smaller speaker separation and another five trials were obtained. This procedure was followed down to the smallest speaker separation (5.5°) and the speaker separation was reset to its maximum. The entire training procedure was controlled automatically by a custom software (MatLab, The Mathworks, Natick, MA, USA) until the experimenter stopped the training session. Experimental sessions took place once a day between

1 to 5 pm and lasted in average between 30 to 60 min for each gerbil. Within this time period about 110 to 165 trials per gerbil could be obtained.

Data analysis

Data acquisition was completed after recording 64 trials per speaker separation, resulting in a total of 704 trials per gerbil. To determine a MRA I fitted the recorded psychometric functions with a sigmoidal function. The MRA was determined as the point where this function crossed the performance level of 62.5 %, corresponding to a significance level of $p<0.05$, on the basis of 64 trials (two-tailed binomial test in a 2-AFC with 64 trials per point).

2.2 Release from Masking

2.2.1 Gerbils

Animals

Experiments were performed with five male gerbils. To examine the effect of noise-rearing on the amount of spatial unmasking, three of the five gerbils were reared in omni-directional white noise (see section noise-rearing). The remaining two were reared under "normal" laboratory conditions, serving as control group. Each animal group was housed individually in a 71x46x31 cm^3 (length x width x height) cage, containing wooden chipping as bedding, a sleeping house and paper towels for nesting. Animal keeping was already described in the first experiment (see chapter 2.1, section 'Animals').

Noise-Rearing

All experiments were approved according to the German Tierschutzgesetz (55.2-1-54-2531-58-5). Gerbils were exposed to omni-directional white noise presented via 24 loudspeakers between postnatal day 10-25 (P10-P25). For that purpose a cage (23 x 38 x 20cm^3) with gerbil pups, aged P10, and the mother was placed in a sound-attenuated box (100 x 80 x 80 cm^3). Walls, ceiling and floor of this box were covered with foam and two pairs of loudspeakers were embedded in each of the six

sides. A speaker pair consisted of a low frequency and a high frequency speaker. Each of the loudspeaker pairs on one side presented white noise (bandwidth 30 Hz-600 kHz) from two individual analogous noise-generators (Rhode and Schwarz, Munich, Germany). The amplitude was approximately 80 dB SPL (rms value, averaging time 30s), causing no damage to neither the cochlea nor the primary centers (Withington-Wray et al., 1990). The gerbils had unrestricted access to water and food during the noise-rearing period. After this period, gerbils were returned to their normal environment.

Setup

Experiments were performed in a double-walled sound attenuated chamber (Industrial Acoustics Company GmbH, Niederkrüchten, Germany). Walls, ceiling and floor were covered with foam wedges (Industrial Acoustics Company GmbH, Niederkrüchten, Germany). Foam wedges were 40 cm in depth, eliminating echoes for frequencies of more than approximately 250 Hz. Training took place in a circular arena, placed in the chamber. A schematic diagram of the setup is depicted in Fig. 2.2. The arena had a diameter of 94 cm, enclosed by a wire mesh with a height of 29 cm; the floor was covered by carpet. A platform 3 cm in height (9 cm in diameter) with a little ring arranged in front of it was placed in the center of the arena, serving as starting position.

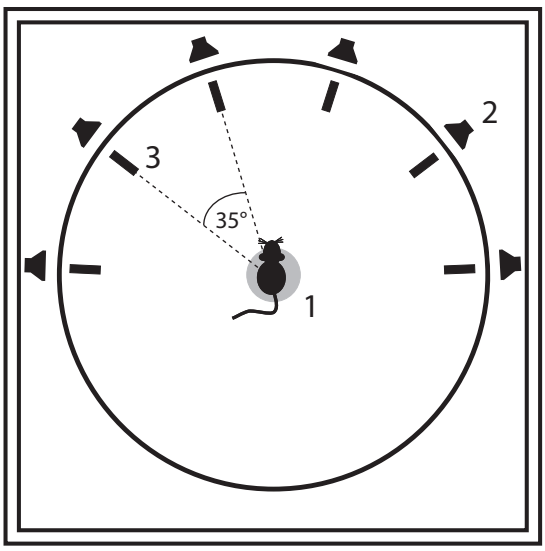

Figure 2.2: Setup of Experiment 2 (Gerbils). Illustration of the setup used to determine the release from masking of gerbils. The circular arena consists of a platform located in the center with a light barrier in front (1). Six loudspeaker fixed at a separation of 35° between neighboring speakers (2) with an adjacent foot-switch and feeder (3) releasing a food-reward for correct decisions are mounted on a rail.

Gerbils were trained to jump on the platform and position their nose within the

ring. This guarantees a defined head position and moreover starts a trial, as an internal light barrier was disrupted. Inner-diameter of the ring was 3 cm to ensure unrestricted sound transmission to the gerbils' ears. Six custom-made arms were mounted on a rail around the setup. Each arm consisted of a loudspeaker (Aura Sound, NSW1-205-8A, Santa Fe, CA, USA), a foot-switch, and a feeder, delivering pellets for correct decisions. A calibration routine was used to assure a similar flat frequency response from approximately 200 Hz to 10 kHz for each loudspeaker. Loudspeakers were positioned at $\pm 17.5°$, $\pm 52.5°$ and $\pm 87.5°$ off midline. This results in a separation of 35° for neighboring speakers and a separation of 175° for the two outer speakers. A video camera was installed directly above the setup, to observe the gerbils' performance from outside the chamber. Four halogen light spots provided setup lighting.

Stimuli

The stimuli used in this study consisted of six maskers and a signal. Both maskers and signal were low-pass filtered white noise with a cut-off frequency of 1 kHz. The maskers were played continuously from all six loudspeakers during the whole training session and the signal was added to one of the maskers at a randomly chosen loudspeaker. The maskers at the six speakers were presented under two conditions, either the maskers at the six speakers were correlated (that is six identical noises) or they were uncorrelated (that is six independently generated noises). Maskers were generated at a digital rms of 0.03 resulting in a sound-pressure level at the gerbils' starting position of approximately 60 dB SPL for the uncorrelated maskers and 68 dB SPL for the correlated maskers, respectively. The signal-to-noise-ratio (SNR) ranged from 24 dB to -6 dB in 3 dB steps. The stimuli were played back through a Delta 410 PCI Audio card (M-Audio, Germany) at a sampling rate of 22.05 kHz and amplified (Rotel, RB-976 MKII) before being presented to the gerbils via the loudspeakers. The maskers were produced with a duration of 10 s and played in a loop to assure continuous playback throughout the whole training session. The signal duration was 300 ms.

Experimental Procedure

From approximately P40 on, gerbils were trained to localize a sound in a six-alternative, forced-choice (6-AFC) paradigm by means of operant conditioning using food pellets as positive reinforcement. Psychometric functions were recorded to determine (I) detection thresholds for a presented signal while applying different background maskers and (II) effects of noise-rearing on these thresholds. In order to guarantee a defined head position in each trial, the gerbils were trained to jump onto the platform located in the middle of the arena and position their nose into a little ring, interrupting a light barrier. Triggered by this interruption, a trial was started by adding the signal to one of the six continuous maskers. Gerbils learned to move towards the signal speaker and to press the foot-switch in front of that speaker. Gerbils had to respond within 15 s to complete a trial. Correct decisions within this time were rewarded with a food pellet, incorrect decisions remained unrewarded. Activation of a new trial within the 15 s time period without finishing the preceding trial (by pressing a foot-switch) was not possible. There was no timeout between completed trials, regardless of the correctness of the trial. An experimental session started with six trials at the highest SNR, three trials for each of the two masker conditions. The SNR was then reduced by 3 dB and another six trials were obtained. This procedure was followed down to the lowest SNR and the SNR was reset to its maximum. The entire training procedure was controlled automatically by a custom software (MatLab, The Mathworks, Natick, MA, USA) until the experimenter stopped the training session. Experimental sessions took place once a day between 1 to 5 pm and lasted on average between 30 to 60 min for each gerbil. Within this time, about 70 to 130 trials per gerbil could be obtained.

Data analysis

Data acquisition for each gerbil was completed after recording at least 60 trials per SNR and masker condition, resulting in a total of at least 1320 trials per gerbil. To determine a detection threshold, I fitted the recorded psychometric functions with a sigmoidal function. Detection thresholds were determined as the point where this function crossed the performance level of 25 %, corresponding to a significance level of $p<0.05$, on the basis of 60 trials (two-tailed binomial test in 6-AFC task with 60 trials per point).

2.2.2 Humans

Subjects

Four human listeners (three male and one female, aged 26, 27, 31 and 32) participated in this study. These were the author and three other listeners. All subjects had experience with psychoacoustic tasks. Listeners participated voluntarily in this study and had normal hearing at audiometric frequencies between 250 Hz and 8000 Hz.

Setup

Ensuring comparable results between human and gerbil psychophysics, the loudspeakers of the human psychophysical setup were arranged similarly to the gerbil experimental setup. The subjects were seated in a double-walled sound attenuated chamber (Industrial Acoustics Company GmbH, Niederkrüchten, Germany) surrounded by a semi-circular loudspeaker array. Walls, ceiling and floor were covered with 20 cm foam wedges. Listeners were seated exactly in the middle of the loudspeaker array with their head fixed. Six loudspeakers (Canton XS.2, Weilrod, Germany) were mounted on this array at azimuths between -100° and +100° at 40° steps. Fig. 2.3 depicts the human experimental setup.

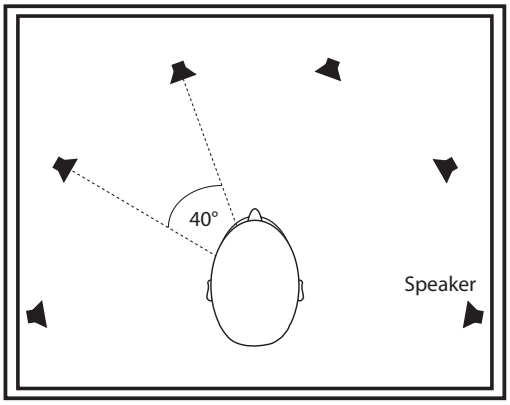

Figure 2.3: Setup of Experiment 2 (Human). Illustration of the setup used to determine the release from masking of humans. The setup consists of a centered chair and six loudspeaker fixed at a separation of 40° between neighboring speakers. In the human experiment correct and incorrect decisions were indicated visually via a touchscreen (not shown here).

Stimuli

We obtained data from two experimental test sessions in the human psychophysics. In the first experiment, we presented the same stimuli as used for the gerbil psychophysics. As for the gerbils, sound pressure level was set to 60 and 68 dB SPL

for uncorrelated and correlated maskers, respectively. The SNRs ranged from 9 to -15 dB in 3 dB steps. The second version of the experiment was identical to the first experiment, except that the low-pass cutoff frequency for both maskers and signal was reduced to 500 Hz. The masker sound pressure levels were preserved. Stimuli were generated in MatLab and digital-analog converted with a Motu PCI 424 board and Motu HD192 converters (Cambridge, MA, USA). Stimuli were then amplified (Rotel CI 9120, Halle, Germany) and presented via the loudspeakers.

Experimental Procedure

The experimental procedure was identical to that for the gerbils apart from the following differences: while the continuous maskers were already active, listeners triggered each trial and the presentation of a signal by pressing a button on a graphical user interface displayed on a touch screen. Listeners were required to respond from which of the six speakers the signal was presented by pressing one of six buttons arranged in a semi-circle on the touch screen. Visual feedback was provided after every trial. As in the gerbil experiments, psychometric functions for the two masker conditions were obtained using a non-adaptive one-interval, six-alternative, forced-choice procedure: An experimental run was started by presenting the signal with the highest SNR (9 dB). At this SNR, six trials were obtained for the uncorrelated-masker condition followed by six trials for the correlated-masker condition. The SNR was then reduced by 3 dB. This sequence was repeated until a minimum SNR of -15 dB was reached which finished the run. Listeners were free to decide how many runs they performed in an experimental session. A minimum of ten runs were acquired for each listener, yielding at least 60 trials per point on the psychometric functions for each of the two masker conditions. Data analysis was identical to that of the gerbils.

Data analysis

Psychometric functions for each listener were constructed out of the last six complete runs and thus, performance at the each SNR consisted of 60 trials. Detection thresholds were determined as the intersection of a sigmoidal fitted curve to the psychometric data and the significance level of 25 % ($p<0.05$, two-tailed binomial test).

2.2.3 Simulation

To develop an understanding for the deviations of masked thresholds between gerbils and humans, I have simulated the behavioral experiments in a numerical model of auditory processing. The model is divided into three stages: I) the auditory periphery, II) binaural processing and III) the decision device. A block diagram of the different stages of the model is shown in Fig. 2.4.

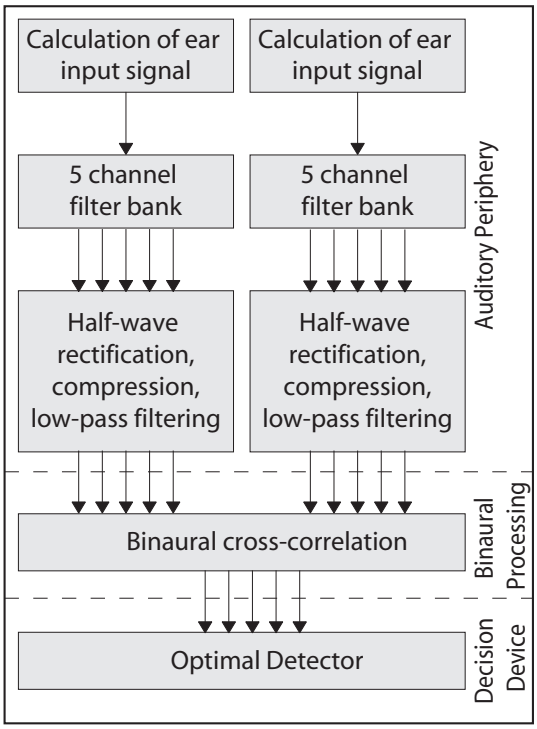

Figure 2.4: Block Diagram of the Model. Auditory periphery is modeled by calculating the input signal for each ear, sending the signal through a five channel filter bank and performing a half-wave rectification, compression and a low-pass filtering. Within the binaural processing, a cross-correlation of both monaural signals is performed. The resulting signal is then compared to internally stored templates in the last step of the model.

Auditory Periphery

For each ear, the sounds from the loudspeakers were added after the corresponding ITDs were applied. These ITDs depended on both the azimuthal position of each speaker and the subject's head size. The head diameter was set to 3.2 cm for gerbils and 18 cm for humans. The signals were then sent through a gammatone filter bank with five center frequencies equally spaced on a log frequency axis between 250 and 1000 Hz, simulating the apical (low-frequency) part of the basilar membrane. The model assumed different auditory-filter bandwidths for gerbils and humans: auditory-brainstem recordings from the gerbil have shown that low-frequency channels are broadly tuned (Siveke et al., 2008). While the equivalent

rectangular bandwidth (ERB) was taken to be 0.108 times the center frequency for humans (cf. Glasberg and Moore, 1994), the ERB was taken to be 0.8 times the center frequency in the gerbil. As a last step of the peripheral processing, the signal transduction at the inner hair cells was modeled as a half-wave rectifier, exponential compression with an exponent of 0.4 after Oxenham and Moore (1994) and a second order low-pass filter with a cut-off frequency of 1 kHz.

Binaural Processing

The second step of the model simulates binaural interactions by performing a cross-correlation between left ear and right ear signal. In contrast to the model published in Bernstein and Trahiotis (1996), the cross-correlation in this model was not normalized. No internal noise was added after the binaural cross-correlation.

Decision Device

A decision process was modeled using a so-called optimal detector as introduced by Dau et al. (1996): Analogous to the assumption that the subjects develop an internal representation of the above-threshold signal plus the masker and a representation of the masker alone, the model creates six signal-plus-masker templates, one for each possible signal position and a masker-only template. Corresponding to the different SNRs used to train the gerbils and humans, the SNR for the signal-plus-masker template was set to 36 dB for the gerbils and to 12 dB for the humans. To describe the differential effect of the signal onto the signal-plus-masker representation, the masker-only template was subtracted from each signal-plus-masker template. The resulting signal templates and masker-only templates were calculated separately for the two masker conditions. Internal noise was not added for the template generation. As in the psychophysical experiment, psychometric functions were generated by the model by presenting 180 repetitions of each stimulus with randomized signal position for each subject (gerbil or human), for each masker condition, and each SNR. The range of SNRs was 36 to -6 dB in 3 dB steps for gerbils and 24 to -18 dB in 3 dB steps for humans. The model calculated the internal representation of the signal-plus-masker, subtracted the masker-only template and calculated the cross-correlation of the resulting representation with each of the six signal templates. The model chooses the signal position where the cross-correlation

is maximal. Data analysis and presentation is identical to that of the experimental data.

2.3 Azimuthal Sound Localization and the MNTB

Setup, stimuli and experimental procedure were the same as in the first part of this thesis. Briefly, gerbils were trained to classify a low-pass filtered noise, presented over loudspeakers at various positions (ranging from 5.5° to 105°) as either left or right. The precision of the azimuthal sound localization was determined before and after lesioning the MNTB. For further information see chapter 2.1, sections 'Setup', 'Stimuli' and 'Experimental Procedure'.

Animals

Experiments were performed with 8 adult gerbils, three males and five females. Four animals received an injection of kainic acid (KA) to study lesioning effects on the behaviorally determined lateralization ability. Another three animals received an injection of a physiological sodium chloride solution (NaCl), serving as control group.

Surgery

All experiments were approved according to the German Tierschutzgesetz (AZ 55.2-1-54-2531-57-05). In preparation for the injection, animals were anesthetized by a subcutaneous injection (0.225ml/100g body weight) of a combination containing medetomidine (7%), midazolam (67%) and fentanyl (26%). During the whole surgery and injection procedure, a constant body temperature of 39°C was assured using a thermostatically controlled heating pad. To avoid water shortage and oxygen deficiency, animals were supplied with subcutan injections of NaCl twice (1 ml in total) and oxygen during the whole injection. The skull was carefully dissected by cutting the skin and removing tissue covering the skull. A metal rod, fixated with a UV-sensitive dental-restorative material (Charisma, Heraeus Kulzer, Hanau, Germany), was placed on the frontal part of the skull. This rod guarantees a defined position of the gerbils head in a stereotactical device (Schuller et al., 1986). The animal was transferred to a sound-attenuated recording chamber, the gerbil's

position within this chamber was then determined by stereotaxic landmarks on the surface of the skull (intersections of the bregmoid and lambdoid sutures with the sagittal suture in horizontal alignment, Loskota et al., 1974). According to the following stereotactic axis a small hole was drilled into the skull. Injections were made approximately 800μm lateral off midline (both left and right), 4046 - 4199 μm caudal with angle of 20° and 9000 - 9800μm deep into the tissue. The MNTB was targeted by a stereotactical and audio-visual approach through the cerebellum. A volume of 0.5μl KA (0.5mg/ml in physiological NaCl) was delivered within two to three minutes to each MNTB via manual pressure injection through a glass pipette. After injections the hole was filled with bone wax, the rod was removed and the skin was sutured. After surgery and surgical dressing the anesthesia was stopped with a combination (0.533ml/100g body weight) containing the competitive antagonist atipamezole (1.5%), flumazenil (75%) and naloxone (23.5%). Typical injection session lasted approximately 1.5 to 2 hours, including pre- and postoperative preparations. Retesting began within the next three days after surgery, depending on the individual constitution of the gerbils and lasted for at least two weeks.

Medication

Animals were treated with an analgesic medication (meloxicam, diluted in NaCl (1:20), 0.1ml/100g body weight) for the first three days after surgery and treated with antibiotics (enrofloxacin, diluted (1:3), 0.15ml/100g body weight) for the first five days after surgery. Wounds were checked daily.

Analyzing Timeschedule and Statistics

To investigate effects of the MNTB lesion on the behaviorally determined precision of localization ability and to furthermore be able to quantify these effects as either long- or short-term, data were analyzed in three different time windows. All windows contained 64 trials per speaker separation. Thus, the MRA of each time window was based on 704 trials per animal. A schematic timetable of the analyzing windows is depicted in Fig. 2.5. I determined the MRA for one time window immediately before the injection, that is I analyzed the last 64 trials recorded before the injection day for each speaker separation. To test whether the MRA changed over time after the injection, I determined the MRA for two different time win-

dows. Here I analyzed the very first 64 trials for each speaker separation recorded after the injection. For the second time window after the injection I analyzed the 64 trials per speaker separation recorded at the very end. None of the two time windows overlapped. For the control animals I additionally compared the MRA for a time window before the injection, after the injection and during the treatment of analgesic medication and antibiotics and a time window after the injection and after the treatment of analgesic medication and antibiotics.

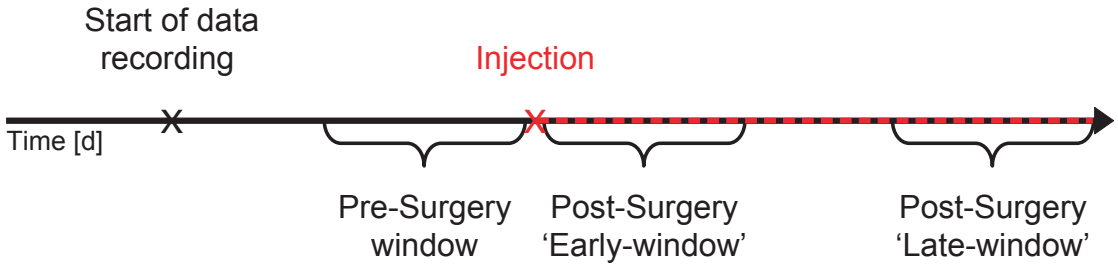

Figure 2.5: Analyzing Time Schedule. A schematic depiction of the time windows used to analyze the data. Data were analyzed within three different time windows: One immediately before the surgery ('Pre-Surgery window') to determine the individual ability with intact inhibition. One immediately after the surgery ('Post-Surgery Early-window') to determine effects on the localization ability after the lesion. And a last one at the end of data recording ('Post-Surgery Late-window') to see whether occurring effects can be classified as long-term effects.

Histology

After postoperative data recording, animals were sacrificed by a lethal injection of chloralhydrate (4% in NaCl) and perfused transcardially with Ringer solution and paraformaldehyde (4%). The fixated brain was cut in 50μm sections and stained with fluorescent Nissl using standard methods. Histological verifications of the extent of the lesions were made with light and confocal microscopy. Additionally, left-over MNTB cells were counted by a noninvolved payed student without any knowledge about the treatment of the animals. Histological verifications and cell counts are giving some indication about the extent of the lesion.

3 Results

3.1 Azimuthal Sound Localization

In the first experiments of the current thesis I investigated the localization ability of a low-frequency noise signal with a length of 125 ms in gerbils. Therefore, I determined MRAs by analyzing the lateralization performance at 11 different speaker separations ranging from 5.5° to 105° in the frontal hemisphere. 15 adult gerbils (4 males and 11 females) participated in this study, each of them had to fulfill at least 64 trials per speaker separation, thus each calculated MRA is based on 704 trials per animal. Psychometric function of all gerbils are shown in Fig. 3.1A-E. For claritiy only three animals are shown in one plot. As obvious from the data, all animals performed well with a minimum of 80% correct at the largest speaker separation. That is, all animals were able to learn the task and lateralized presented sounds as either left or right significantly correct at a speaker separation of 105°. Thus, I was able to analyze MRAs for all 15 animals shown in this figure. The MRA for each gerbil was determined by the intersection of the sigmoidal function fitted to the individual data and the significance level (dashed gray line at 62.5%). For example, gerbil 1 (black dots, Fig. 3.1A) achieved a MRA of approximately 21°. Individual MRAs of all 15 animals ranged from approximately 6° to 26°, with a mean MRA of 16.1°. Fig. 3.1F shows both mean and individual MRAs of all animals.

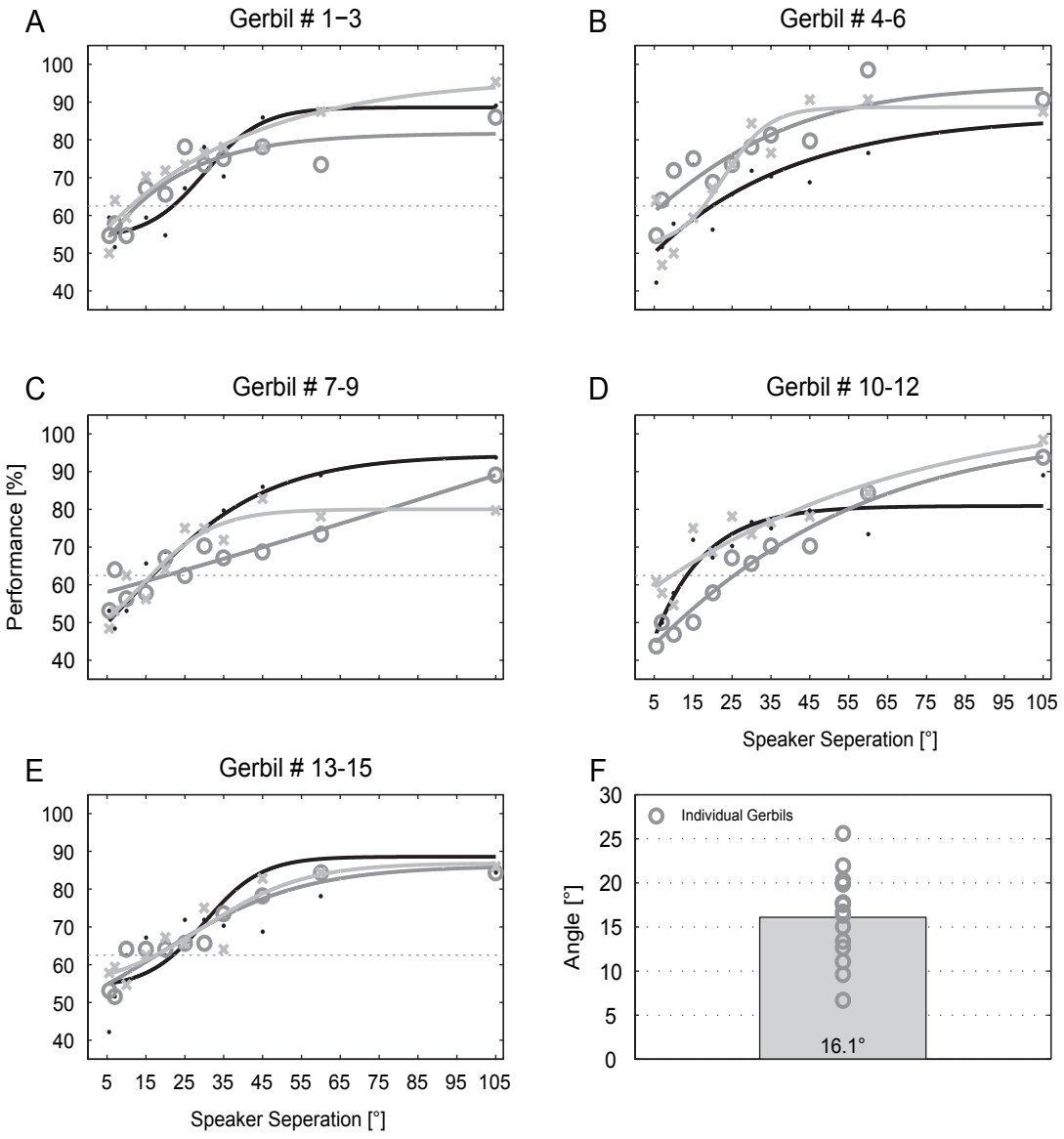

Figure 3.1: Azimuthal Sound Localization. Panel A-E show the localization ability for 15 animals at each speaker separation ranging from 5.5° to 105°. Symbols indicate the performance at each speaker separation for individual animals, solid lines indicate the sigmoidal function fitted to the corresponding data. The gray dashed line indicates the significance level of 62.5% ($p<0.05$, two-tailed binomial test in a 2-AFC with 64 trials per point). Panel F shows the mean MRA for all 15 animals. The gray open circles indicate the individual determined MRA of all 15 animals.

3.2 Release from Masking

In the second experiment, I investigated the detection threshold for a signal in two different masker conditions. This part was conducted with gerbils and humans. Exemplary psychometric functions for the signal detection are shown for one control and one noise-reared gerbil Fig. 3.2A. With the uncorrelated-masker condition, the detection threshold for the noise-reared gerbil is at a SNR of 0.1 dB and for the control gerbil at 0.9 dB. With the correlated-masker condition, the threshold increases to a SNR of 9 dB for the noise-reared gerbil and to 9.2 dB for the control gerbil. These individual data indicate that while detection thresholds differ strongly between masker conditions, they are independent of whether the gerbil was reared in a noisy environment or not.

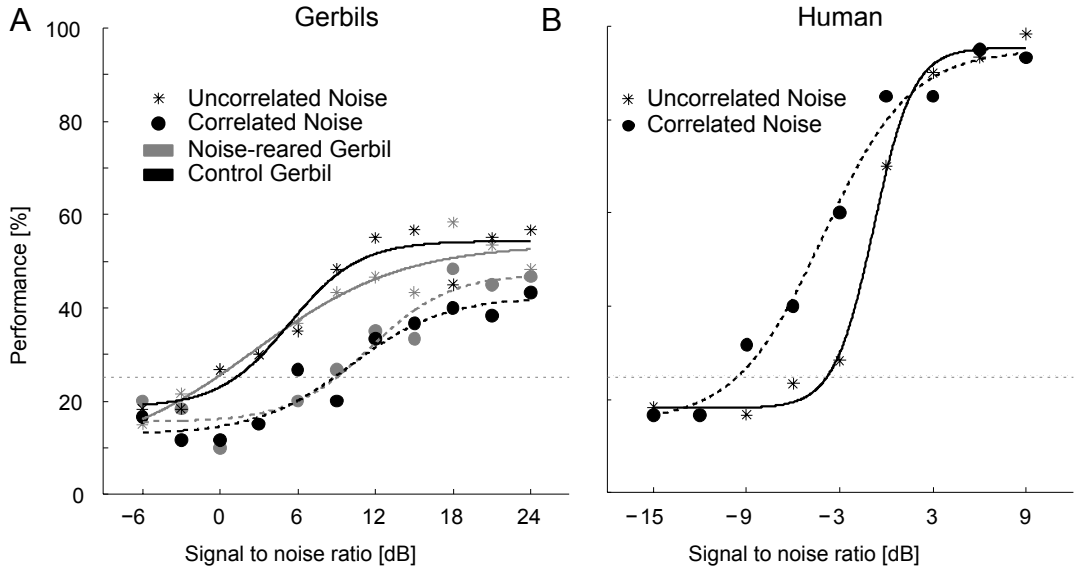

Figure 3.2: Exemplary Psychometric Function. Panel A depicts an exemplary psychometric function for one noise-reared (gray) and one control gerbil (black). Panel B depicts an exemplary psychometric function for one human listener. Symbols indicate the detection performance in percent correct at each SNR for each subject. Stars represent the detection performance in presence of the uncorrelated-masker condition, dots represent the detection performance in presence of the correlated-masker condition. Solid and dashed lines indicate the sigmoidal fitted function to the corresponding data. The gray dotted line depicts the significance level of 25% ($p<0.05$, two-tailed binomial test in a 6-AFC with 60 trials per point).

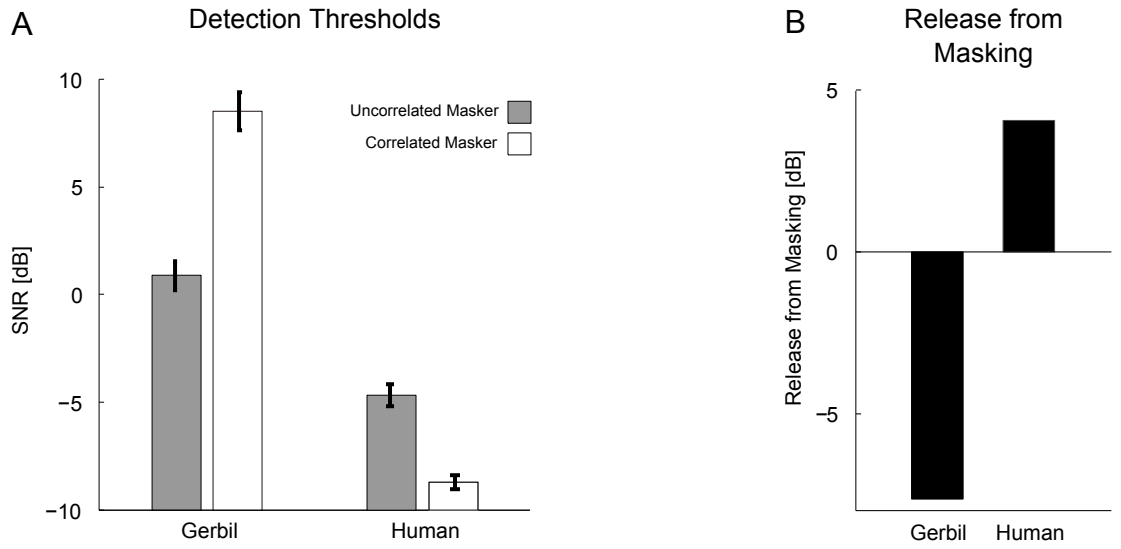

Figure 3.3: Detection Threshold and Release from Masking. The mean detection thresholds for gerbils and humans are shown in panel A. The gray bars represent mean detection thresholds in presence of the uncorrelated-masker condition, whereas the white bars represent the mean detection thresholds in presence of the correlated-masker condition. Errorbars depict one standard deviation. Panel B shows the release from masking for both gerbils and humans, assuming the uncorrelated-masker condition as reference.

A two-way ANOVA with the parameters 'masker condition' and 'noise-rearing' reveals a significant effect of the masker condition ($p<0.001$) but no effect of the noise rearing ($p=0.8090$). Consequently, noise-reared and control gerbils are grouped together for further data analysis. An exemplary psychometric function for one human listener is shown in Fig. 3.2B. The detection threshold for this listener is at a SNR of -3.8 dB and -9.5 dB for the uncorrelated- and correlated-masker condition, respectively. The mean detection thresholds for gerbils and humans are shown in Fig. 3.3A. For gerbils, a mean SNR of 0.9 dB and 8.5 dB was necessary to detect a signal in the uncorrelated- and correlated-masker condition, respectively. For humans, a mean SNR of -4.7 dB and -8.7 dB was necessary to detect a signal in the uncorrelated- and correlated-masker condition, respectively. Thus, first of all, humans showed an overall performance that is markedly better to that of gerbils. Furthermore, assuming the uncorrelated-masker condition as a reference, gerbils showed a masking release of -7.6 dB whereas humans showed a masking release of +4 dB (see Fig. 3.3B).

To understand the deviations of the release from masking between gerbils and

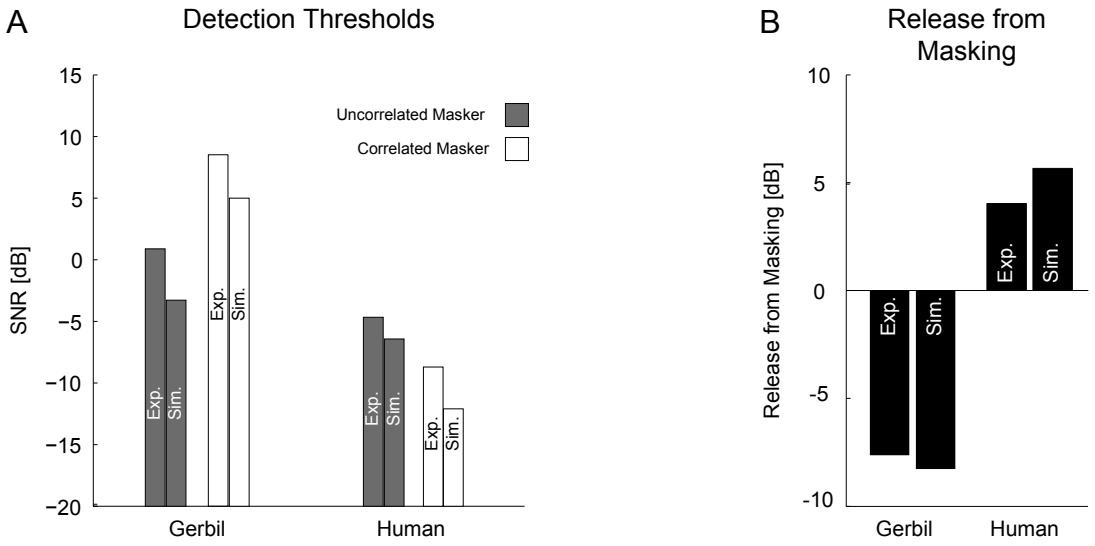

Figure 3.4: Detection Thresholds and Release from Masking as a Comparison to the Model. Detection thresholds for the experimental (Exp.) and simulated data (Sim.) for gerbils and humans are shown in panel A. The gray bars represent the mean detection thresholds in presence of the uncorrelated masker condition, whereas the white bars represent the mean detection thresholds in presence of the correlated masker condition. Panel B shows the release from masking calculated from the experimental and simulated data for both gerbils and humans, assuming the uncorrelated masker condition as reference.

humans, we created a numerical model of auditory processing, simulating the behavioral experiments. The comparisons of the detection thresholds measured in the experiments and those derived from the simulation are shown in Fig. 3.4A.

Overall, the simulation results follow the experimental data in that the detection thresholds are generally higher in gerbils than in humans. The effect of the masker condition, i.e. the release from masking, on the detection thresholds is qualitatively predicted by the model for both, gerbils and humans. A direct comparison of the release from masking is shown in Fig. 3.4B. The model correctly predicts a negative release from masking for gerbils and a positive release from masking for humans.

To further clarify the features of the model that guided its predictions, the inspection of the masker-only templates and signal templates is informative. In general, the task of detecting the signal superimposed on the maskers is easier for the humans than for the gerbils because the humans' head is bigger. The bigger head creates larger ITDs which create more dramatic changes of the binaural display

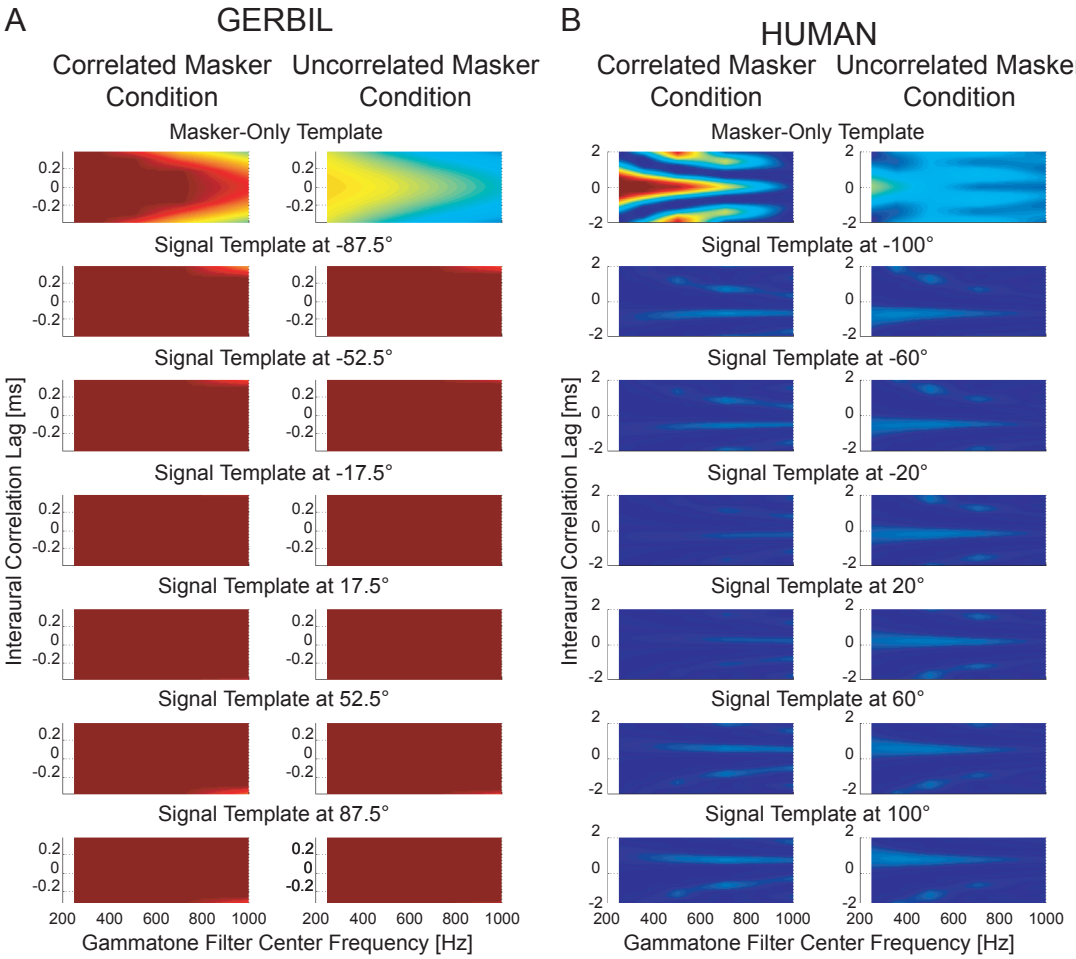

Figure 3.5: Simulated Masker-Only and Signal Templates. This figure shows the binaural excitation pattern of the simulated masker-only and signal templates as a function of the gammatone filter center frequency and interaural correlation lags for both masker conditions for gerbils (panel A) and humans (panel B). Upper row of each panel depicts the masker-only template; row 2-7 of each panel depict the signal templates for each corresponding loudspeaker separation. For further explanations of the differences in the binaural excitation pattern see text.

in the model. The signal templates in Fig. 3.5 (row 2-7) illustrate these changes. Note, that while in Fig. 3.5 the templates are plotted for a smaller range of interaural correlation lags in gerbils than in humans, the model predictions are based on the same range of lags (±2 ms), i.e. the binaural processing is identically implemented for gerbils and humans. Comparison of the masker-only templates for the gerbils (Fig. 3.5A, upper row) shows that the difference in the overall masker sound level between the correlated- and uncorrelated-condition is well reflected in the degree of binaural excitation. With correlated-masker condition (higher overall sound level), the excitation created by the maskers across the whole frequency and interaural-correlation range is higher than with uncorrelated-masker condition. Detecting the signal-induced change in the binaural representation (Fig. 3.5, rows 2-7) is more difficult when superimposed on a higher excitation background. In humans, the masker-only template for the correlated condition (Fig. 3.5B, upper row) show several horizontal ridges related to the center frequency of the gammatone filters. These ridges occur along the interaural correlation axis because the height of the side peaks increases with decreasing auditory-filter bandwidth. Thus, as the human auditory periphery was simulated with narrower filters, the side peaks are stronger. The signal-induced excitation superimposed on this masker representation creates stronger changes in this complex excitation pattern than in the gerbil which facilitates, in humans, the detection of the signal. The masker-only template in humans with uncorrelated-masker condition shows much less pronounced ridges. Consequently, detecting the signal-induced excitation superimposed on this less conspicuous masker excitation is more difficult. This results in deterioration of the detection threshold.

Humans were tested with a second set of stimuli using a reduced low-pass cutoff frequency of 500 Hz. The effect of lowering the cutoff frequency and a direct comparison of the simulated release from masking for both cutoff frequencies is shown in Fig. 3.6. Again assuming the uncorrelated masker condition as a reference, the experimentally determined release from masking decreased from about 4 dB at a cutoff frequency of 1000 Hz to about 2 dB at a cutoff frequency of 500 Hz. Similar to the experimental data, the model also followed this decrease in the release from masking as an effect of lowered cutoff frequency.

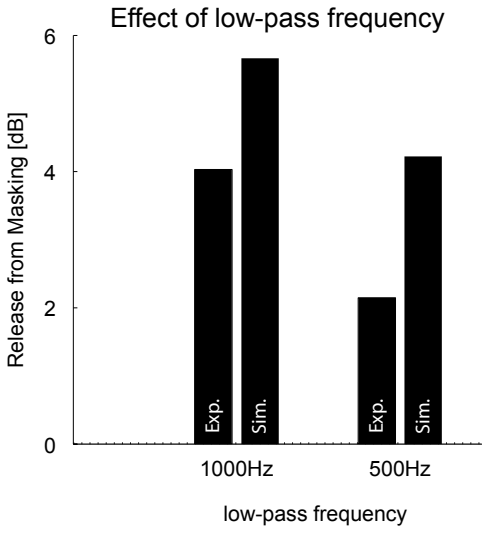

Figure 3.6: Effect of Low-Pass Frequency. The comparison of the release from masking in humans determined from the experimental (Exp.) and simulated data (Sim.) is shown for two different low-pass cutoff frequencies.

3.3 Azimuthal Sound Localization and the MNTB

In the last part of the current thesis, I investigated the importance of MNTB-mediated inhibition on behaviorally determined sound source localization. I therefore compared the MRA of 5 animals before and after lesioning of the MNTB with KA. KA is shown to lead to a very fast cell apoptosis within minutes (Simonian et al., 1996) without affecting or damaging passing fibers existing in the MNTB (Masterton et al., 1979). Four animals received bilateral injections, one animal was only injected monolaterally. Three additional animals were injected with physiological NaCl, serving as control group. Data recorded before the surgery were already presented in the first result part of the thesis. Histological verifications after completed data recording verified different lesioning extents, thus we grouped animals with similar lesioning extent together. Fig. 3.7 gives an overview of the different groups, thus the different lesioning extents found in this study.

#	Solution	Effect
3	Saline	None
1	Kainic Acid	MNTB unilateral
2	Kainic Acid	MNTB partially
2	Kainic Acid	MNTB + MSO

Figure 3.7: Listing of the different Lesioning Effects. This table shows the different lesioning effects after KA or NaCl injection. Three animals were injected with NaCl, five animals were injected with KA. The first column depicts the number of animals, the second column depicts the injected solution and the last column depicts the extent of the lesion after histological verification.

Results will be presented according to this grouping. Each section will start with the results of the histological verifications and afterwards relate them to the observed localization precision.

'None' An exemplary histological picture of one control animal is shown in Fig. 3.8A. These individual data indicate that the injection of NaCl lead to no damage within the MNTB. Furthermore, the number of cells within each MNTB for each animals lead to a very similar number (not shown here). Thus, we calculated the mean cell number for the left and right MNTB of all three control animals (see Fig. 3.8B). This number will serve as a control for the subsequent analysis of the lesioning extent. A rough estimate of the rostro-caudal extent of all MNTBs was 1.5mm, being nicely within the range of 1.41 $\pm$0.11mm measured by Gleich et al. (2001), further indicating a normal appearance of the MNTBs after the injection protocol.

The localization performance of each control animal is depicted in Fig. 3.9. The localization performance before surgery is opposed to the localization performance analyzed in the early window after surgery (panel A, C and E) and to the localization performance analyzed in the late window after surgery (panel B, D, and F). The MRA for each analyzing window is depicted in the graph. Only one of the three animals showed a slight impairment in the localization ability after the surgery (compare panel A and B). The other two showed no obvious impairment in the localization ability after the surgery. Furthermore, each point of the psychometric function, tested for significant differences with a chi-square test, revealed a highly significant difference ($p<0.01$) in the performance before and after surgery (see Fig. 3.9A). All other differences found between the performance before and after the surgery where only significant different ($p<0.05$). I assume that these significant differences reflect the normal variances in the performance of a behaving animal.

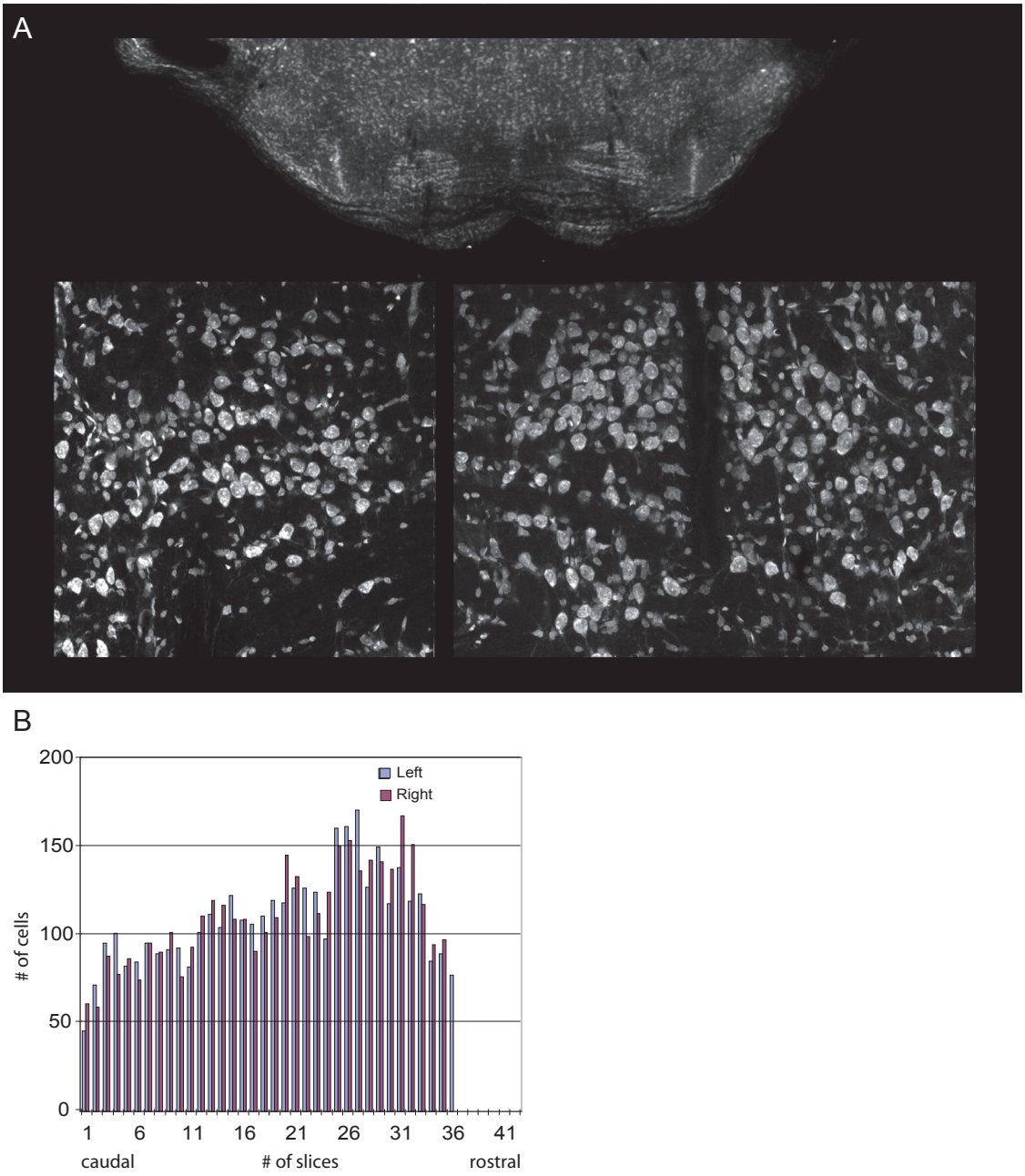

Figure 3.8: Histological Verification of the Lesion (Control Animals). Panel A shows an exemplary brain slice of one control animal with additional magnifications of the left and right MNTB. This picture indicates no obvious damage of the MNTB. Number of cells per brain slice are plotted as a mean over three animals, serving as control condition, see panel B.

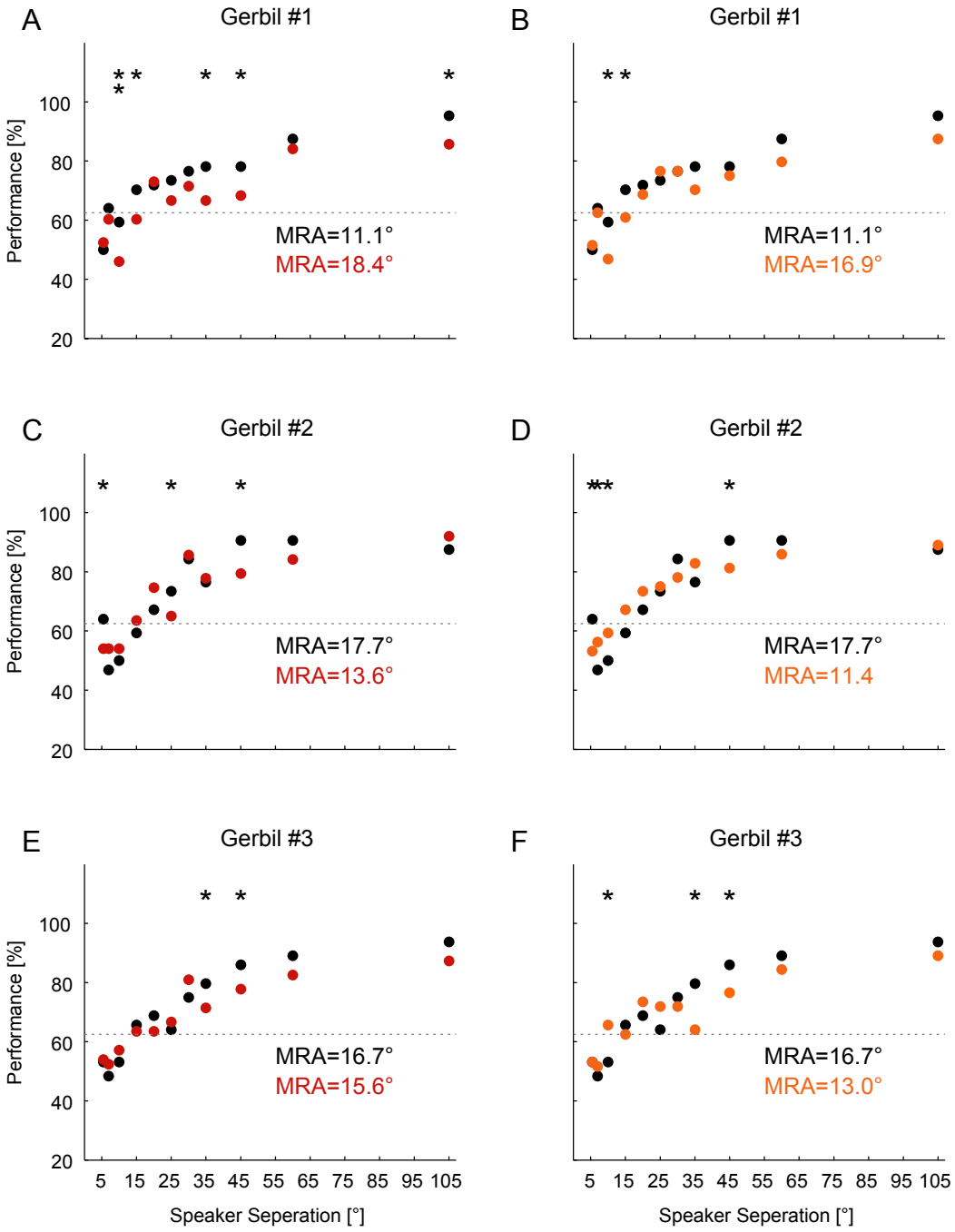

Figure 3.9: Azimuthal Sound Localization Before and After Saline Injection. Panel A-F show the localization ability for 3 control animals at speaker separations ranging from 5.5° to 105°. The gray dashed line indicates the significance level of 62.5 % ($p<0.05$, two-tailed binomial test in a 2-AFC with 64 trials per point). Panel A, C and E show the comparison of the localization performance before (black dots) and early after the injection (red dots). Panel B, D and F show again the localization performance before injection (black dots) but now compared to localization performance late after the injection (orange dots).

'MNTB unilateral' An exemplary histological picture of the unilaterally injected animal is shown in Fig. 3.10A. The picture verifies a damage of the right (injected) MNTB in this animal. Additionally, the comparison of the mean control cell numbers with those of the unilaterally injected animal, showes lower cell numbers in the right MNTB but not the left one (Fig. 3.10B). However, KA injection did not lead to a complete lesion of the MNTB. Thus, it is very likely that there is still MNTB-mediated inhibition from the right MNTB to the MSO.
The localization performance of the unilaterally injected animal is depicted in Fig. 3.11. The localization performance before surgery is opposed to the localization performance analyzed in the early window after surgery (panel A) and to the localization performance analyzed in the late window after surgery (panel B). The MRA for each analyzing window is depicted in the graph. Even though the animal received a unilateral lesion of the right MNTB, resulting in partial damage, the localization performance in both early and late window is improved (compare MRA before and after injection). Furthermore, a chi-square test revealed two highly significant differences ($p<0.01$) in the performance before and after surgery (see Fig. 3.11A and B). In both cases, the localization performance after surgery is better than the localization performance before surgery. Thus, even though the animal had lost a considerable amount of MNTB cells on one side, the ability to localize low-frequency sounds seems not to be influenced, at least in this animal.

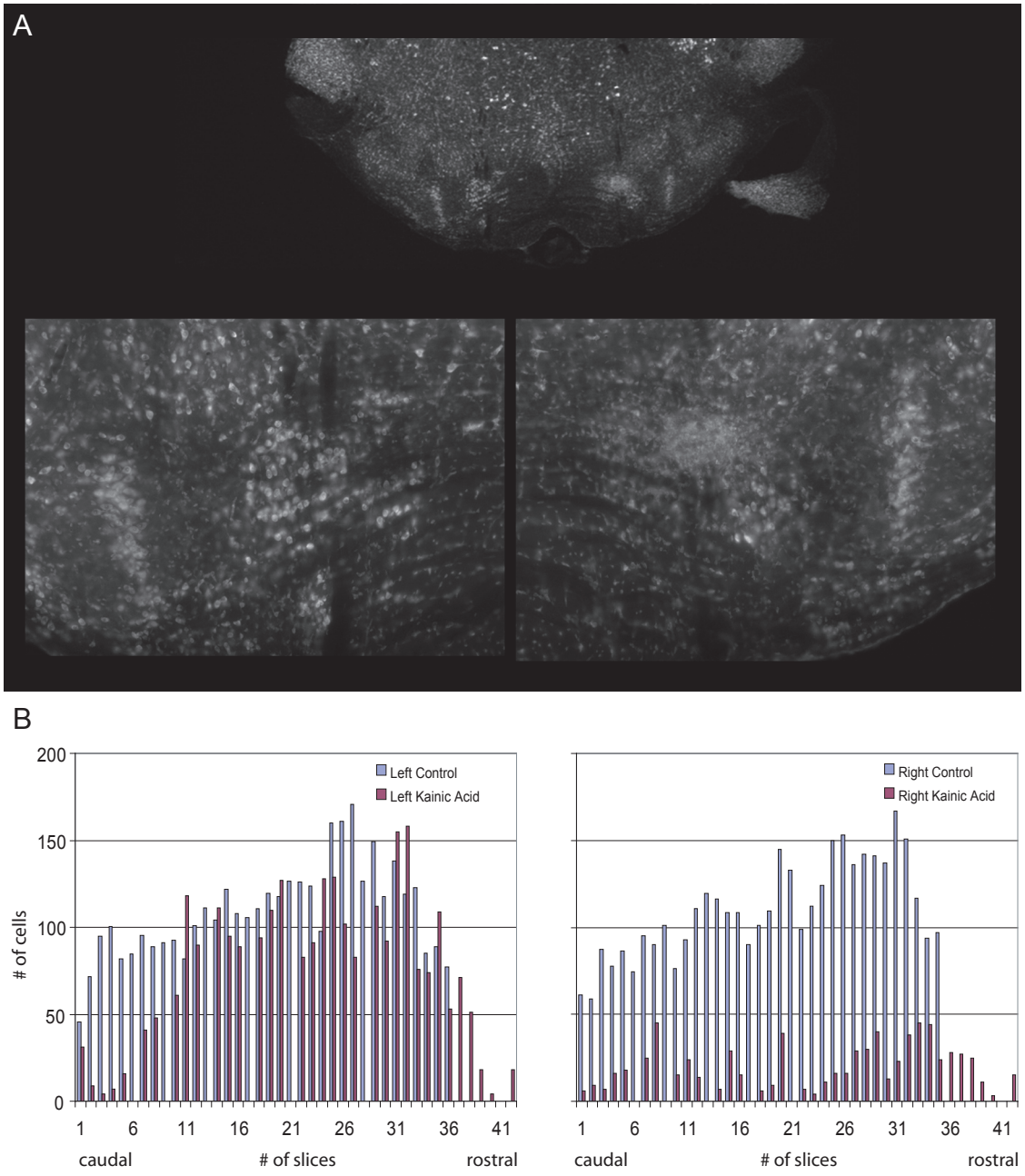

Figure 3.10: Histological Verification of the Lesion (Unilateral Injected Animal). Panel A shows an exemplary brain slice of the unilaterally injected animal with additional magnifications of the left and right MNTB. This picture indicates a damage of the right but not the left MNTB. Cell numbers plotted as a comparison between the control animals and the unilateral injected animal also reveal the partial damage of the right MNTB, see panel B.

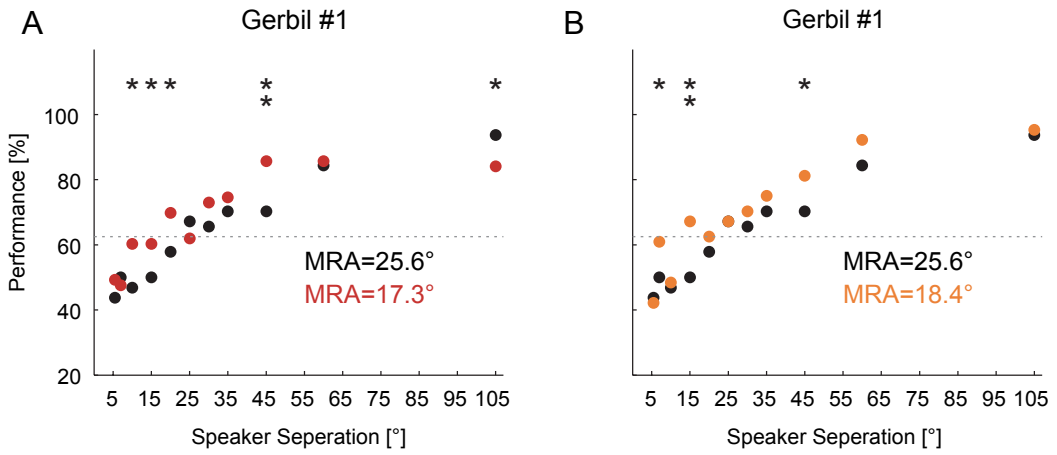

Figure 3.11: Azimuthal Sound Localization Before and After Unilateral KA Injection. Panel A and B show the localization ability of the unilaterally injected animal at speaker separations ranging from 5.5° to 105°. The gray dashed line indicates the significance level of 62.5 % ($p<0.05$, two-tailed binomial test in a 2-AFC with 64 trials per point). Panel A shows the comparison of the localization performance before (black dots) and early after the injection (red dots). Panel B shows again the localization performance before injection (black dots) but now compared to the localization performance late after the injection (orange dots).

'MNTB partially' An exemplary histological picture of one bilaterally injected animal is shown in Fig. 3.12A. The picture verifies a damage of both MNTBs in this animal. Additionally, the comparison of the mean control cell numbers with those of bilaterally injected animal, shows lower cell numbers in both MNTBs. However, KA injection did not lead to a complete lesion of both MNTBs. Similar results are found for the second bilaterally injected animal (not shown). Thus, it is very likely that in both animals MNTB-mediated inhibition from the right and left MNTB to the MSO is still present.

The localization performance of the two bilaterally injected animal is depicted in Fig. 3.13. The localization performance before surgery is opposed to the localization performance analyzed in the early window after surgery (panel A and C) and to the localization performance analyzed in the late window after surgery (panel B and D). The MRA for each analyzing window is depicted in the graph. Both animals showed an impairment in the localization performance immediately after the surgery, compare the MRA of both animals in Fig. 3.13A and C. Furthermore, a chi-square test revealed two highly significant differences ($p<0.01$) for animal 1

and four highly significant differences ($p<0.01$) for animal 2 in the performance before and early after surgery (see Fig. 3.11A and C). In the control animals I only found one point of the psychometric function being highly significantly different. However, the comparison of the localization performance before and late after the surgery showed no longer an impairment of the localization ability. The MRA of both animals recovered nearly to the same value as before injection. Furthermore, I only found one point of the psychometric function (panel D) to be highly significantly different. I still found points of the psychometric function analyzed in the late window to be significantly different from the performance before surgery, however this seems to be a normal variance in behavior and seems not to be due to the lesion (compare control animals). Thus, it seems that the localization ability of low-frequency sounds is impaired after a partial lesion of both MNTBs, however this impairment recovers during the time of data recording.

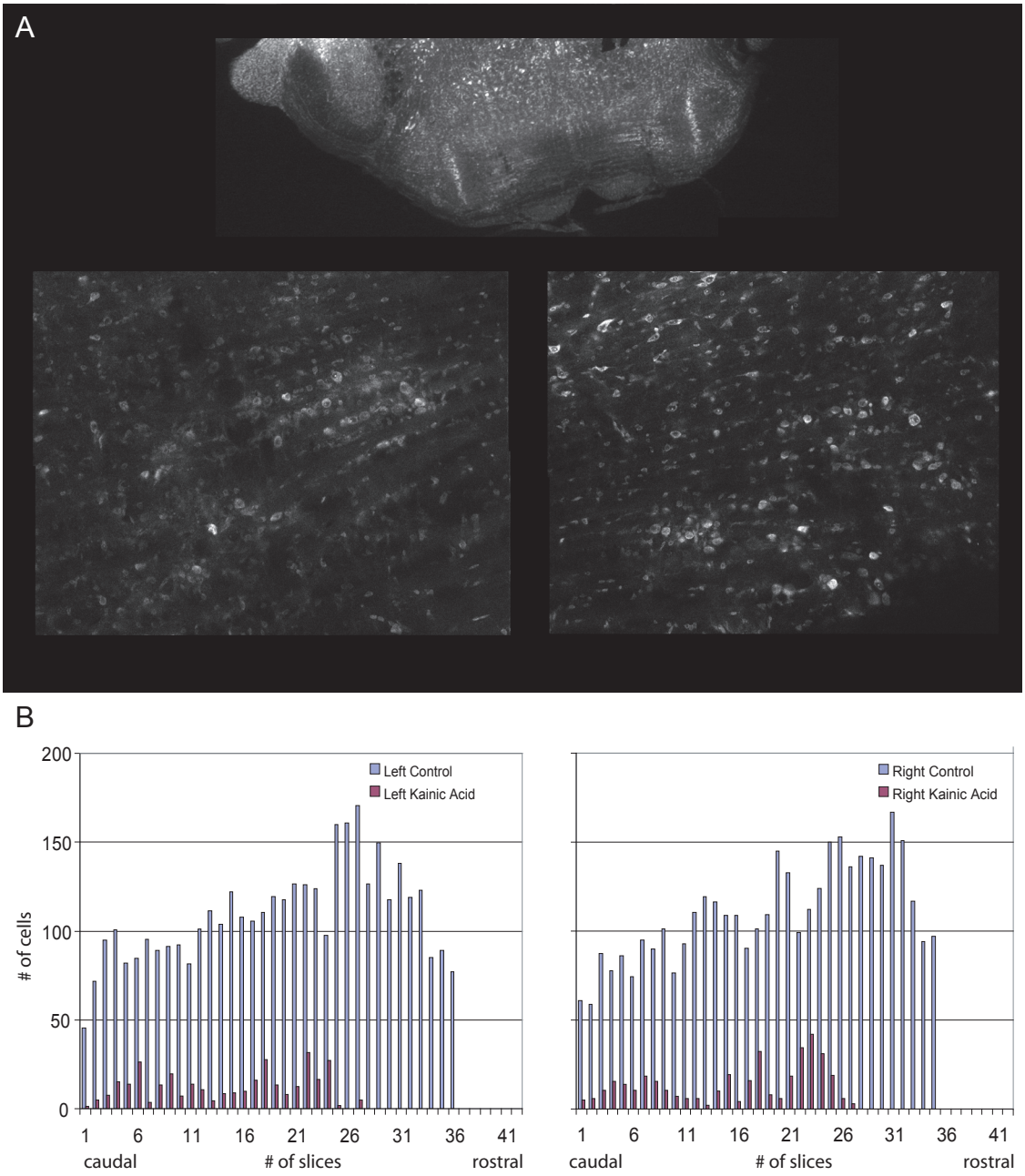

Figure 3.12: Histological Verification of the Lesion (Bilaterally Injected Animals). Panel A shows an exemplary brain slice of one bilaterally injected animal with additional magnifications of the left and right MNTB. This picture indicates a damage of both left and right MNTB. Cell numbers plotted as a comparison between the control animals and the bilateral injected animal also reveal the partial damage of both MNTBs, see panel B.

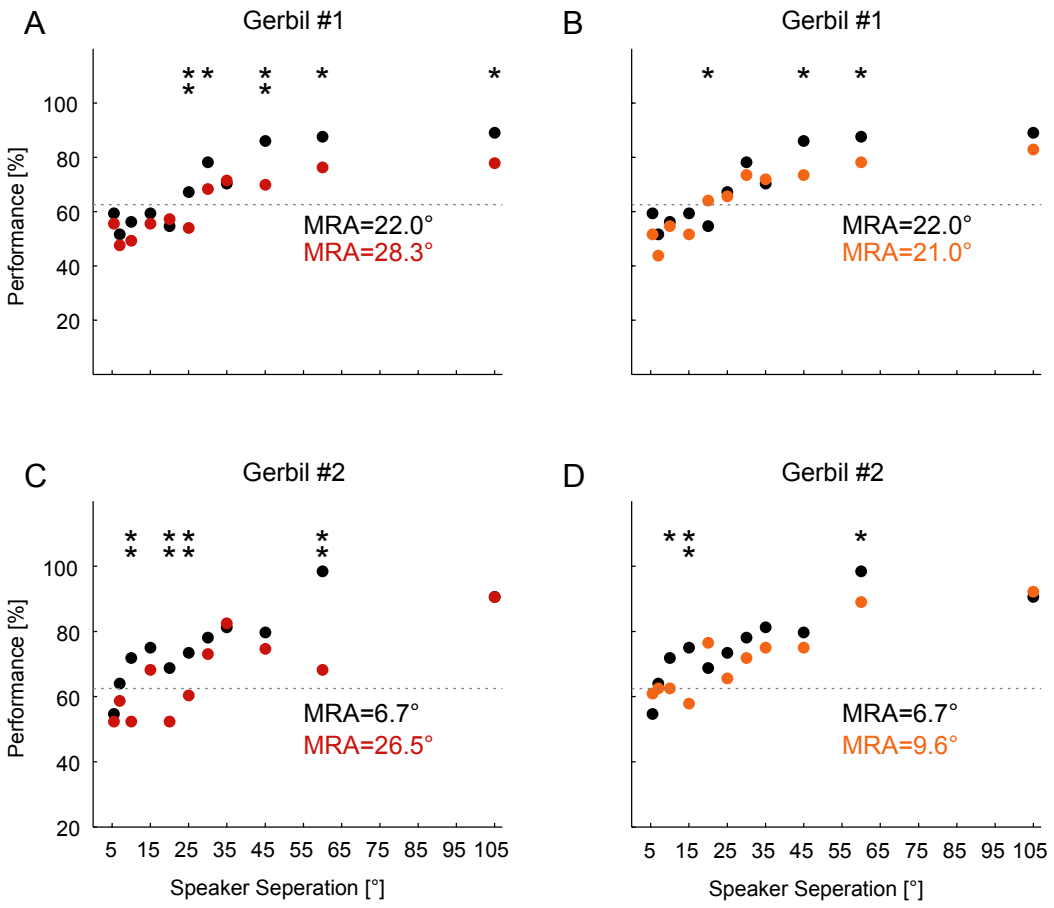

Figure 3.13: Azimuthal Sound Localization Before and After Bilateral KA Injection. Panel A-D show the localization ability of two bilaterally injected animals at speaker separations ranging from 5.5° to 105°. The gray dashed line indicates the significance level of 62.5 % ($p<0.05$, two-tailed binomial test in a 2-AFC with 64 trials per point). Panel A and C show the comparison of the localization performance before (black dots) and early after the injection (red dots) for each animal. Panel B and D show again the localization performance before injection (black dots), but now compared to localization performance late after the injection (orange dots) for each animal.

'MNTB + MSO' An exemplary histological picture of one bilaterally injected animal of the last group is shown in Fig. 3.14A. The picture verifies a damage of both MNTBs in this animal. Additionally, the comparison of the mean control cell numbers with those of bilaterally injected animal, shows lower cell numbers in both MNTBs (panel B). However, KA injection did not lead to a complete lesion of both MNTBs. Unfortunately, I also found the MSO to be damaged by the KA injection (see little arrows in Fig. 3.14A). Similar results are found for the second

bilaterally injected animal (not shown), meaning both animals exhibit a partial MNTB lesion with an additional damage of the ITD detection unit, the MSO. The localization performance of the two bilaterally injected animal is depicted in Fig. 3.15. The localization performance before surgery is opposed to the localization performance analyzed in the early window after surgery (panel A and C) and to the localization performance analyzed in the late window after surgery (panel B and C). The MRA for each analyzing window is depicted in the graph. Both animals showed a complete inability to localize low-frequency sounds immediately after the injection (Fig. 3.15A and C). This is visible in the localization performance of both animals which dropped to 50% at all speaker seperation. Furthermore, none of the animals was able to recover from this inability to localize a sound (see Fig. 3.15B and D). Both the MRA and the point-by point analysis of both time windows reveled the inability to localize sounds. This presumable loss of ITD computation and therefore the complete inability to localize sounds is consistent with the MSO damage in both animals.

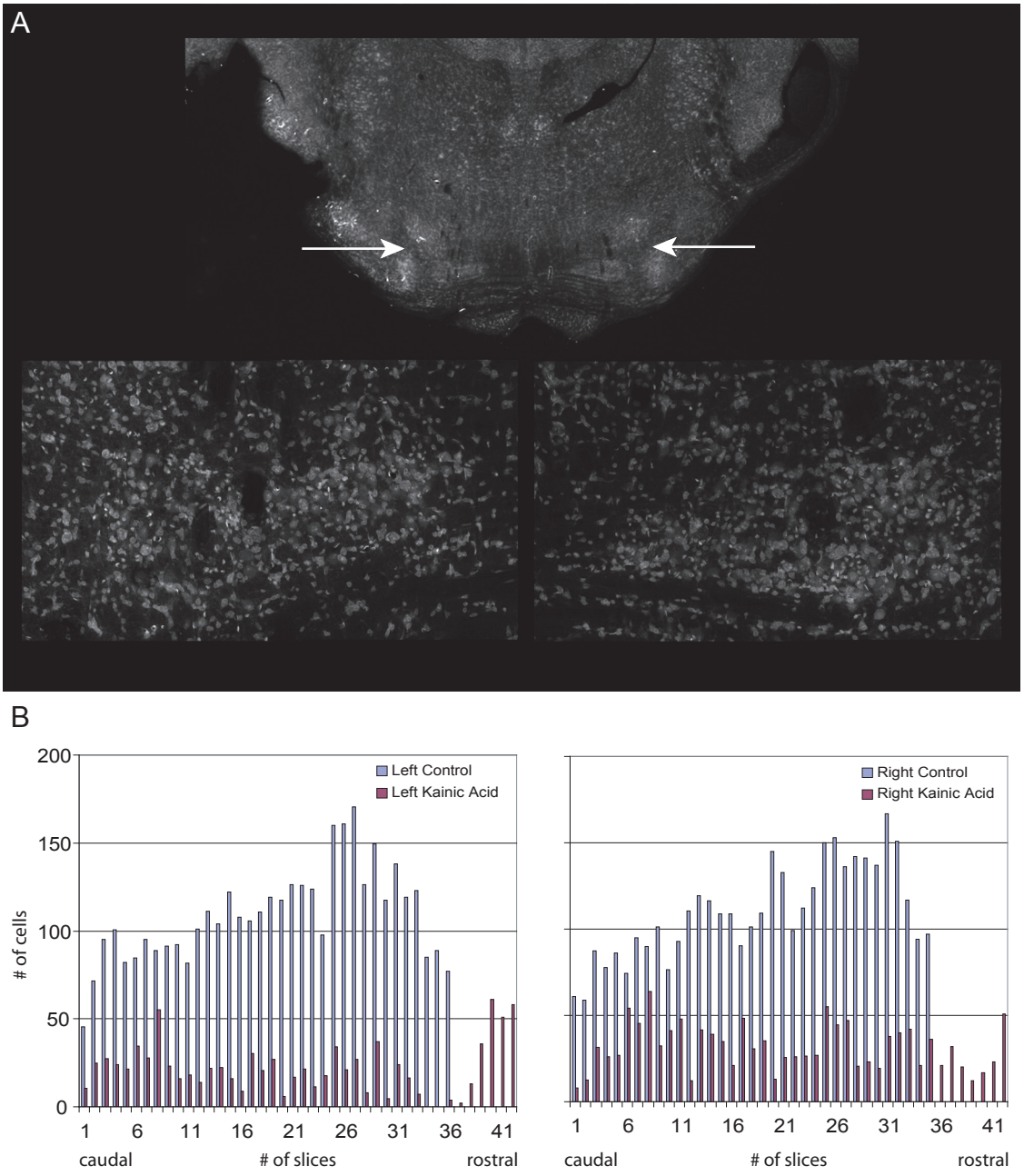

Figure 3.14: Histological Verification of the Lesion (Bilaterally Injected Animals). Panel A shows an exemplary brain slice of one bilaterally injected animal with additional magnifications of the left and right MNTBs. This picture indicates a damage of both left and right MNTB. Additionally to the partial lesion of both MNTBs, I also found the MSO to be damaged. Cell numbers plotted as a comparison between the control animals and the bilaterally injected animal also reveal the partial damage of both MNTBs, see panel B.

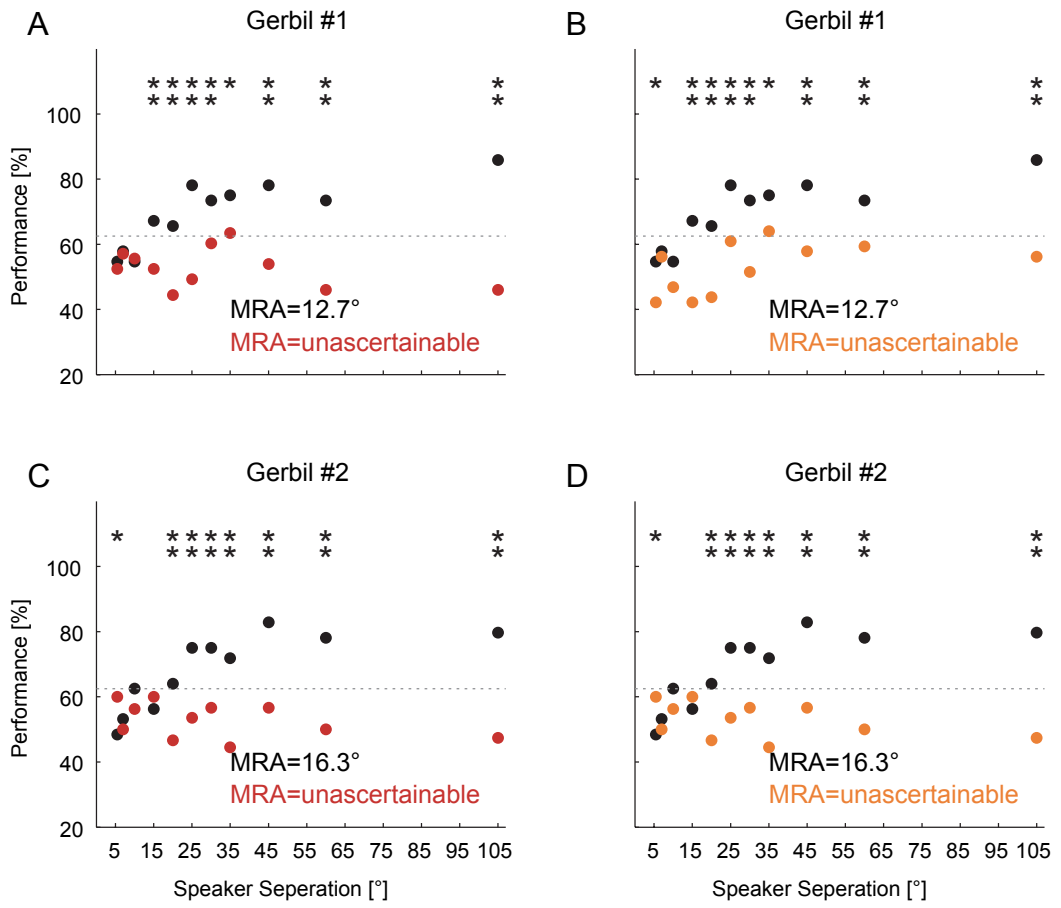

Figure 3.15: Azimuthal Sound Localization Before and After Bilateral KA Injection. Panel A-D show the localization ability of two bilaterally injected animals at speaker separations ranging from 5.5° to 105°. The gray dashed line indicates the significance level of 62.5 % ($p<0.05$, two-tailed binomial test in a 2-AFC with 64 trials per point). Panel A and C show the comparison of the localization performance before (black dots) and early after the injection (red dots) for each animal. Panel B and D show again the localization performance before injection (black dots), but now compared to localization performance late after the injection (orange dots) for each animal.

A short overview and summary of the results obtained in this part of the thesis is given in Fig. 3.16. It shows the mean MRA as bargraphs for each group before and twice after the surgery (early and late analyzing window). These results show that neither surgery nor medical treatment had an effect on low-frequency sound localization (see panel A). Furthermore, these data indicate that a unilateral lesion of the MNTB seems to have no effect on the localization ability, see panel B. However, as this interpretation is only based on one animal, the results have to be

handled with care and more animals are needed to draw a conclusive statement. The analysis of the MRAs of two animals with partial-bilateral MNTB lesion show that they exhibit an impaired localization ability of low-frequency sounds. Both animals revealed a considerably increased MRA directly after the surgery. However, this localization impairment does not seem to be a long-lasting effect, as the MRA decreased to its initial value at the end of data recording (see panel C). The last group contained animals that were histologically shown to have an additional lesion of the MSO. As expected, these animals lost their ability to localize low-frequency sounds completely. The performance dropped to 50% at each tested speaker seperation and no MRA for neither early after or late after the surgery could be determined (see panel D).

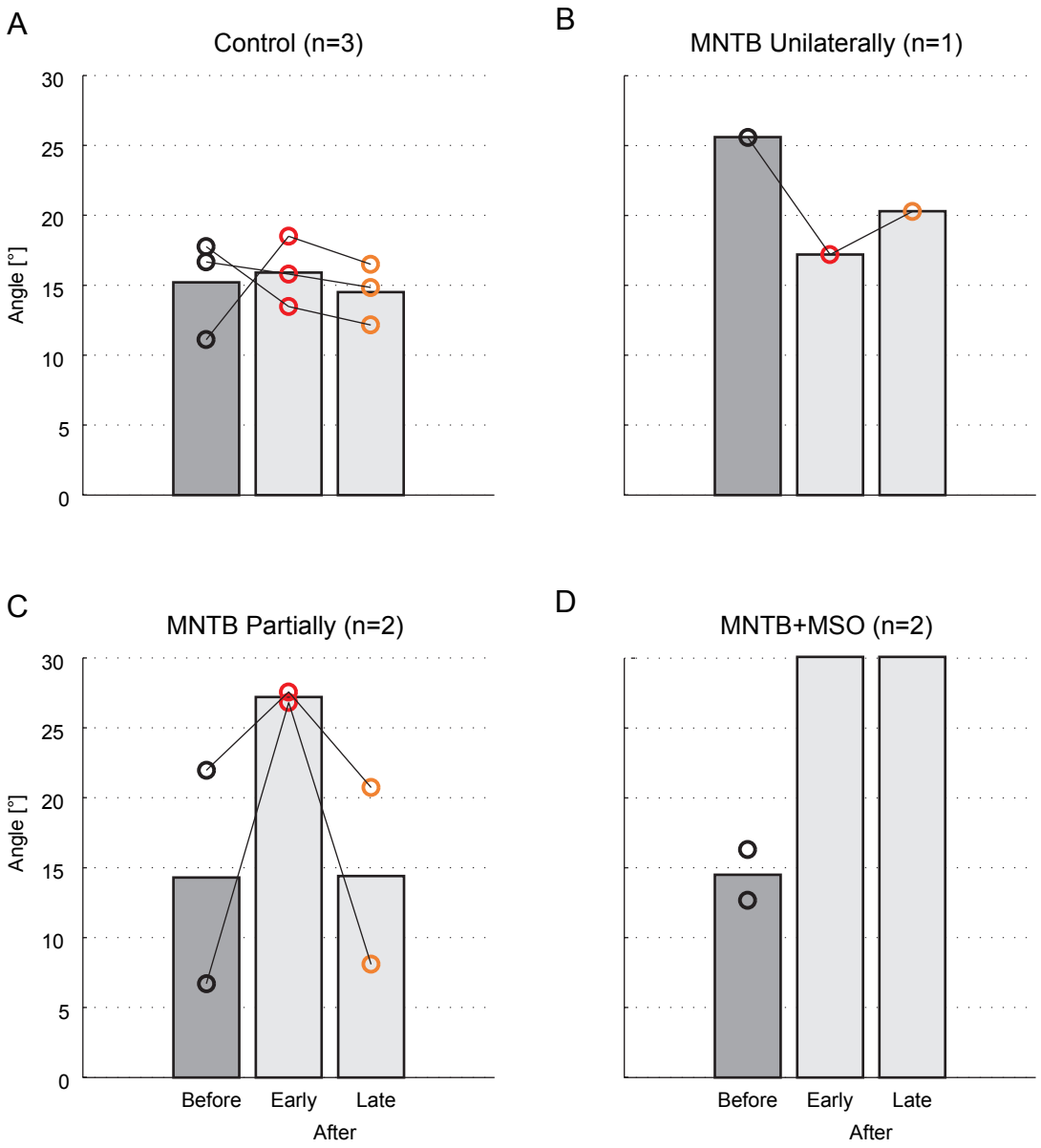

Figure 3.16: Mean MRA Before and After Injection for all Animals. Panel A-D show the mean MRAs for all injected animals as bargraphs. The mean MRA before the surgery is depicted in dark gray. The mean MRA analyzed at two time windows after the surgery is depicted in light gray. The circles indicate the individual MRA for each animal at the corresponding analyzing time.

4 Discussion

The present thesis investigates one of the fundamental functions of the auditory system: the localization of low-frequency sounds in the azimuthal plane by detecting ITDs. Therefore, three different behavioral experiments were conducted using the Mongolian Gerbil to examine the processing of low-frequency spatial cues.
The thesis initially revises the azimuthal sound localization ability of gerbils in an elementary experimental approach. That is, the localization of a signal without any interfering sounds. This is followed by a second set of experiments with an elaborated approach, using a more naturalistic representation of the environment. Here, the gerbils had to detect a signal in presence of two different interfering maskers. As there were no data available for humans using a comparable approach, these experiments were also conducted in humans. The last set of experiments dealt with the underlying neuronal mechanisms of ITD detection.

Azimuthal Sound Localization

The azimuthal sound localization ability of gerbils was investigated by determining the smallest azimuthal separation of two sound sources located left and right off midline which the animal can still correctly distinguish, i.e. the MRA. For all 15 gerbils tested in this first set of experiments, the MRAs ranged from 6° to 26° with a mean MRA of 16.1°. The use of ILDs as binaural cue could be excluded as the presented stimulus in the current experiment consisted only of frequencies up to 1.2 kHz. Due to the wave length of the stimulus, ITDs are most likely the major binaural cue underlying the performance in this task, approving the conversion of the determined MRA into an ITD sensitivity for gerbils. There are two possibilities to estimate ITDs for a given angle and experimental animal. That is, ITDs can either be derived from a formula, comprising of three parameters: the sound veloc-

ity, head size and localization angle (e.g. Kuhn, 1977). However, one disadvantage of a theoretical estimation is the possibility of variations from the real value as mathematical calculations only represent an approximation of the real value. It is more precise to experimentally measure the time it takes for the sound to travel from one ear to the other. Therefore, we used the ITDs published by Maki and Furukawa (2005). Based on those measurements, our gerbils were able to discriminate sound sources as either left or right with ITDs of about ±11 to ±30 μs (MRA from 6° to 26°). On average they needed an ITD of about ±21 μs (corresponding to the mean MRA of 16.1°) to correctly determine the sound source position as either left or right.

Azimuthal Sound Localization in Gerbils Revisited. So far, there have been three other studies investigating the azimuthal sound localization ability in gerbils in a comparable approach (Heffner and Heffner, 1988a; Maier and Klump, 2006; Maier et al., 2008). All of them investigated the localization ability in a 2-AFC paradigm with food as a positive reinforcement and used rather short stimuli, between 100-125 ms. Such rather short stimuli are important to investigate the localization ability in a so-called open-loop manner, meaning that the stimulus presentation terminates before the animal was able to execute any head movements to get feedback about the direction of a sound. A study by Ehret and Dreyer (1984) showed that the localization ability of mice increased with increasing stimulus length (indicating the change from an open-loop to a closed-loop localization). Accordingly, only studies conducted under open-loop requirements will provide evidence for the limits of the sound localization ability. Although, all studies used comparable paradigms and procedures (e.g. training paradigm and stimulus length), the results are highly diverse.

STUDY 1. The mean MRA determined in the first study by Heffner and Heffner (1988a) is 27°. This is approximately 10° worse than the results obtained in the present study. In regard of the tested stimulus, a 100 ms white noise burst, this difference is surprising. White noise contains all frequencies and therefore provides both binaural cues (ILDs and ITDs), i.e. there is more information available for the subjects to localize the sound, most probably improving the localization ability. However, Heffner and Heffner used a very conservative criterion to determine the localization threshold (=MRA). The applied threshold at a performance of 75%

and at least 100 trials per speaker seperation would correspond to an exceptionally high significance level. Thus, the authors most likely underestimated the lower limit of the localization ability in gerbils. Nevertheless, further comparisons regarding the ITD sensitivity are still not feasible, as these animals were tested with a broad band signal, allowing the use of ILDs as additional cue.

STUDY 2+3. Two further studies (Maier and Klump, 2006; Maier et al., 2008) investigated the localization ability of gerbils with a wide variety of stimulus types (pure tones and band-pass noise of different frequencies). This comparison will focus on the localization ability determined with a 300 Hz-wide band-pass noise centered at 0.5 kHz. Thus, the animals had only access to ITDs as binaural cue to localize the signal. The mean MRAs determined in both studies are very similar (25.8° and 26.5°) but again about 10° worse than the results obtained in the present study. However, one major drawback of both studies is the number of speaker separations used to determine the localization threshold. In the study by Maier and Klump conducted in 2006, the MRA of 25.8° was based on only three different speaker separations, namely: 10°, 30° and 90°. Such a small number of points, especially around the estimated MRA has impacts on the fitting routing used to determine the MRA, leading to deviations from the actual threshold. In the second study conducted in the same lab, the MRA is based on five different speaker separations (12°, 36°, 60°, 90° and 120°). However, similar to the first study, the number of recorded points around the estimated threshold is very low (12° and 36°). In contrast, the localization thresholds determined in the present study are based on eleven different speaker separations (5.5°, 7°, 10°, 15°, 20°, 25°, 30°, 35°, 45°, 60° and 105°). Moreover, the distribution of speaker separations around the estimated threshold is very narrow, suggesting that the determined mean MRA of 16.1° in the present study is closer to the actual limit of low-frequency sound localization ability of gerbils.

UNPUBLISHED DATA FROM OUR OWN LAB. The mean MRA of 16.1° is also supported by additional experiments performed in our lab. In these experiments, gerbils were trained in a 6-AFC paradigm with varying speaker separations, forcing the gerbils to determine the actual sound source positions instead of a left vs. right discrimination. The localization ability determined in the 6-AFC paradigm ranged between 15° and 19° depending on the stimulus and thus, is comparable to the

mean MRA determined in the present thesis.

EXCLUSION OF USING NON-SPATIAL CUES. Both the stimulus generation and presentation were highly controlled in the present experimental paradigm. The generation and/or the presentation of the stimulus are always a weak point of an auditory task. That means, one has to be able to exclude non-spatial cues, i.e. different loudspeaker properties, that could be used by the subjects to perform the task on. Therefore, the presented localization signal was generated new for every conducted trial. Additionally, the spectral envelope and the overall sound pressure level was roved by ±6 dB. As a last step before presenting the localization signal to the gerbils, similar transmission properties for each loudspeaker were guaranteed (for details see 'Material&Methods', section stimulus). Therefore, one can exclude that the animals relied on any other cues but the speakers' spatial separation to localize the presented signal.

Azimuthal Sound Localization in other Mammals. This section focuses on the localization ability of gerbils in comparison to other mammals, particularly focusing on other small rodent species. A comparison with highly specialized animals, especially cave-dwelling rodents (like naked mole rats: Heffner and Heffner, 1993; blind mole rats: Heffner and Heffner, 1992) is excluded, as it was shown that they have very poor localization abilities. The comparison is restricted to albino rats (Kavanagh and Kelly, 1986) and wild Norway rats (Heffner and Heffner, 1985b) as very popular laboratory animals for every type of research, kangaroo rats (Heffner and Masterton, 1980) and chinchillas (Heffner et al., 1994) as examples of animals with a comparable low-frequency hearing sensitivity as gerbils and finally the grasshopper mouse as an example of a very small rodent (Heffner and Heffner, 1988b). In all studies, the localization ability was tested with very brief stimuli (only up to 150 ms), and all animals had to localize the sounds in an open-loop manner. However, the frequency range of the used stimuli differed from that used in our study. Most animals were tested with broad-band stimuli, except for the chinchillas. They were tested with a 500 Hz low-pass noise. The animals were either tested with a conditioned avoidance procedure (grasshopper mouse, chinchilla, Norway rat) or a 2-AFC paradigm (kangaroo rat, albino rat) similar to the present one. MRAs for the aforementioned rodents are between 12° and 23°. Details of the individual MRAs and the used stimuli are summarized in Fig. 4.1. As apparent

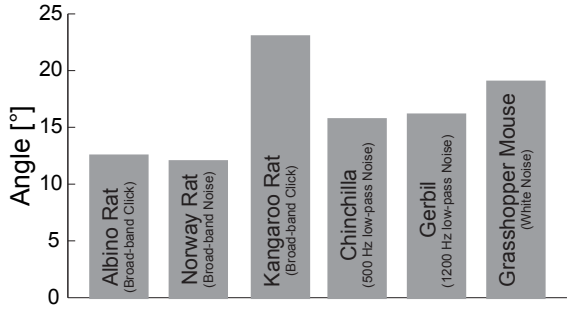

Figure 4.1: Localization Ability of Different Small Rodents. This diagram shows the localization ability of five different rodents, including the localization ability of gerbils measured in the present study. The comparison is limited to rodents with a comparable head size. The stimuli used to determine the localization ability is indicated in brackets.

from this figure, the localization ability of gerbils is comparable to that obtained in other rodents. Whether this also reflects a similar ITD sensitivity will be discussed in the following.

CHINCHILLA. The localization ability of chinchillas is with 15.7° very similar to that found in gerbils. As the chinchillas were tested with a 500 Hz low-pass filtered noise, there were presumably only ITDs as binaural cue available. Thus, the chinchilla is less sensitive to ITDs, as the chinchillas' head diameter (52 mm) is approximately twice as large as that of the gerbil (Koka et al., 2008).

RAT. The localization ability of albino and wild Norway rats is with 12.5° and 12° slightly better than that found in gerbils. As rats have a somewhat larger head diameter (approximately 35 mm) compared to gerbils, the improved localization ability would (if determined with a low-frequency signal) correspond to a similar ITD sensitivity. However, data from a recently published study showed that rats are incapable of using ITDs (Wesolek et al., 2010), suggesting that the good localization ability of both albino and Norway rats is exclusively due to the use of ILDs.

GRASSHOPPER MOUSE. The grasshopper mouse is a comparatively small rodent, with a head diameter of 24 mm. In terms of the hearing range, this animal exhibits a good high-frequency sensitivity with its best sensitivity at 8 kHz (Heffner and Heffner, 1985a), degrading gradually up to 64 kHz. The sensitivity for frequencies lower than 8 kHz decreases even faster. Even though the ITD sensitivity can not be determined from the present data as the MRA of 19° was measured with a broad-band signal, these animals presumably are, similar to rats, not able to process ITDs due to their very poor low-frequency sensitivity.

KANGAROO RAT. Kangaroo rats are slightly smaller than gerbils but also have a very pronounced low-frequency hearing sensitivity down to 250 Hz (Heffner and Masterton, 1980). As in gerbils, this is thought to be a result of the enlarge-

ment of the middle ear cavity. However, a conclusions about the ITD sensitivity limit can not be drawn from the study by Heffner and Masterton as these authors did not determine a lower limit of the low-frequency sound localization. In this study the ability to localize sounds was only determined for a broad-band stimulus (clicks). Due to a MRA of 23°, the authors state that the kangaroo rat is a very poor localizer. However, a closer look on the threshold criterion used to determine the MRA, showed that this is, with a significance level of $p=10^{-11}$, rather conservative (two-tailed binomial test for a 2-AFC on the basis of 200 trials). If one would determine the MRA with the more commonly used significance level of $p<0.05$, it would be around 10° for the kangaroo rat (derived from Fig. 7A in Heffner and Masterton, 1980), suggesting that the kangaroo rat is a similar good localizer compared to the gerbil, at least for broad-band signals. Whether this holds also true for low-frequency sounds remains to be determined. Nevertheless, the study by Heffner and Masterton demonstrated that the animals are able to determine the position of a low-frequency sounds (<1kHz) as either left or right at fixed positions of ±30°, suggesting that the animals are able to process ITDs. This is also supported by ITD-sensitive neurons in the IC and MSO (Stillman, 1971; Crow et al., 1978).

In summary, the gerbils' ability to localize sounds is similar or even better (compare chinchilla) to that of other rodents with a similar head size. This is true despite the fact that most other animals were tested with broad-band signal. Again, it has to be emphasized here that a clear conclusion whether this also leads to similar ITD sensitivity could only be clarified for the chinchilla. The use of broad-band signals precluded the translation of the MRA into an ITD sensitivity for all other animals.

Azimuthal Sound Localization in Humans. As this part compares two species with considerably different sized heads, one has to compare the localization ability in terms of ITD sensitivity and not MRA. The same ITD sensitivity would lead to different MRA for experimental subjects with different sized heads. Thus, the MRA can not be used to specify the resolution of the auditory system. A study by Mills (1958) showed that humans are able to localize pure tone sounds, presented in the frontal hemisphere, with an accuracy of about 1° to 3° (depending on the stimulus frequency). That means, human listeners are able to discriminate ITDs with an accuracy of about ±10 to ±20 μs. As already depicted above, ITD sen-

sitivity in gerbils is ±21 μs, signifying that the ITD sensitivity of gerbils is quite comparable to that found in humans. Therefore, the neural processing of binaural spatial cues in gerbils seems to be similarly effective as in humans. This study is the first to prove that the gerbil exhibits an ITD sensitivity equivalent to humans.
Azimuthal Sound Localization - The Conclusion. In summary, the results of the first set of experiments showed that the gerbil has an exquisite ITD sensitivity. Due to the stimulus generation, the possibility of using cues other than ITDs can be excluded. The gerbils' ITD sensitivity is even better than that of other small rodents with comparable low-frequency hearing capabilities (i.e. chinchilla). Finally, the results show that the gerbil is similarly sensitive to ITDs as humans. Thus, additionally to its audiogram (Ryan, 1976), matching that of humans, the ITD sensitivity - as a basic property of auditory-spatial processing - strengthens the validity of gerbils as an animal model for human auditory research.

Release from Masking

However, the localization of sounds in an entirely anechoic room with a signal being presented without any maskers is of course not what animals have to deal with in real environment. Background noise decreases the possibility to detect a target, i.e. potential predators, prey or mating partners. The ability of humans to focus on and follow a communication is likewise impaired in a noisy environment. Several factors have been shown experimentally to improve the detection ability in noise. The most-investigated factor is probably the spatial arrangement of signal and masker, showing that the spatial separation of signal and masker increases the detection ability compared to co-located signal and masker.
Another experiment in this thesis investigated detection thresholds for a signal embedded in two different masker conditions. The two masker conditions were presented over six spatially distributed loudspeakers. The masker presentation was either correlated or uncorrelated at the six loudspeakers. This experiment was conducted both in gerbils and humans. The results showed that the detection thresholds depend on the masker condition. The release from masking for both gerbils and humans was determined using the uncorrelated masker condition as reference. The results exhibit strong deviations of the release from masking for the

two subjects, i.e. a negative release from masking for gerbils and a positive release from masking for humans.

Release from Masking in other Studies. Several studies compared the release from masking in dependency of the spatial arrangement in humans and animals: studies conducted in birds showed that it is very similar to that of humans. This was both investigated for non-naturalistic stimuli (birds: Dent et al., 1997; humans: Saberi et al., 1991), and naturalistic stimuli (birds: Dent et al., 2009; humans: Best et al., 2005). Furthermore, spatial unmasking in ferrets was also shown to be comparable to those of birds and humans (Hine et al., 1994). Moreover, spatial unmasking was also demonstrated in mice (Ison and Agrawal, 1998), frogs (Schwartz and Gerhardt, 1989) and bats (Sumer et al., 2009).

Studies determining BMLDs (manipulation of the spatial arrangement under head-phones) in animals are, due to the experimental approach of wearing head-phones, rare. Studies conducted in cats and rabbits revealed that these animals are able to benefit from spatially separated masker and signal for their detection thresholds (Wakeford and Robinson, 1974; Early et al., 2001). As in humans, both spatial unmasking in free-field but also BMLDs are thought to improve target detection (e.g. potential mating partners) in a noisy environment, like frog chorus (Bee, 2008). The amount of unmasking, however, was slightly smaller than that found for humans. This comparison indicates that animals and humans can similarly benefit from spatially distributed masker and signal (both presented in free-field and under head-phones) in detection tasks.

Release from Masking in Gerbils and Humans. Contrary to the results in the just mentioned studies there are strong deviations in the release from masking in gerbils and humans in the present study, i.e. gerbils show a negative release from masking of -7.6 dB, whereas humans show a positive release from masking of +4 dB. These differences are remarkable as the first experiment of this thesis lead to the assumption that the gerbil is a well-suited animal model to study auditory spatial processing. This raises the question whether the deviations originate from differences in the central neural processing and thus show the limits of gerbils as an animal model to study underlying circuitries. Another possible explanation for the deviations between gerbils and humans is the difference in the paradigm used in the present experiment compared to the paradigm of classical spatial unmasking

or BMLD experiments.

FREE-FIELD VS. HEAD-PHONE EXPERIMENTS. The release from masking in the present study was investigated under free-field conditions. In contrast to head-phone experiments, any manipulation to the stimulus presented in a free-field approach leads to changes in the overall sound field. In our experiment, the change from the uncorrelated to the correlated masker condition leads to an overall masker level increase from 60 dB SPL to 68 dB SPL at the position of the subject's head. The reason is uncorrelated noise increases the sound level by 3 dB through a doubling of the number of speakers emitting the noise, whereas correlated noise increases by 6 dB per doubling of the number of speakers. Thus, irrespective of the correlation degree of the noise at the six speakers, lowered detection thresholds are expected for the uncorrelated masker condition due to the lower sound level. Indeed, this was found for gerbils. The gerbils' masked thresholds were 7.6 dB higher in the correlated masker condition than in the uncorrelated masker condition, thus, quantitatively reflecting the difference in the overall masker sound level. In humans, however, detection thresholds for the correlated masker condition are 4 dB lower than those for the uncorrelated masker condition. Thus, humans show a lower detection threshold for the masker condition that has a higher overall masker level.

SIMULATING THE PSYCHOPHYSICAL DATA. To understand the pattern of detection thresholds across gerbils and humans in the different masker conditions, a numerical model of binaural processing was created. This model was qualitatively able to correctly predict the observed differences. The inspection of the binaural display of the masker-only and signal template offered valuable cues to understand the deviations in the detection thresholds. In general, the binaural displays of gerbils and humans indicated that the task of detecting a signal superimposed on the maskers might be easier for humans than for gerbils due to a bigger head. Thus, larger ITDs seems to be responsible for the improved overall detection performance in humans. Moreover, the inspection of the binaural displays showed that the difference in the auditory filter bandwidth of gerbils and humans is a second potential factor leading to the observed pattern of detection thresholds. In summary, this model could show that the differences in the psychophysical performance between gerbils and humans in a binaural detection task can be explained to a large extent

based exclusively on the differences in the inputs to their binaural processor: the smaller head size (smaller ITDs) and the broader auditory filters deteriorate the salience of signal-related features in the binaural display. To check whether the head size and specifically the ratio of head size and sound wavelength contributes to the observed pattern of results, the human psychophysical study was repeated and the low-pass cutoff was lowered to 500 Hz, i.e., the ratio of head size and wavelength was changed. In qualitative agreement with the above analysis, the release from masking decreased from about 4 to about 2 dB which corroborates the validity of the simulation approach (see Fig. 3.5, page 60). Further runs of the simulation (data not shown) indicated that head size and auditory filter bandwidth contributed in a different way to the observed pattern of detection thresholds. That is, head size is mainly responsible for the observed difference in the overall performance, whereas both head size and auditory filter bandwidth account for the differential effect of the masker conditions.

Release from Masking - The Conclusion. Overall, the second set of experiments suggests that the neural processing of low-frequency spatial cues for both gerbils and humans is similarly effective. Deviations in the release from masking between gerbils and humans presumably arise from the difference in the inputs to their binaural processor, i.e. differences in the head-size and the auditory filter bandwidth. Consequentially, this leads to a difference in the internal representation of the two masker conditions and thus results in differences in the detection thresholds, even though the neural processing is similarly effective in gerbils and humans.

So far, results of this thesis showed that the central neural processing of low-frequency spatial cues, i.e. ITDs, in a basic (experiment 1: "Azimuthal Sound Localization“) but also in a complex spatial auditory tasks (experiment 2: "Release from Masking“) is similarly effective in gerbils and humans. This shows that the gerbil is a suitable animal model for investigating circuitries underlying the processing of ITDs but also for auditory research in general. Several psychophysical studies conducted in gerbils further strengthen this hypothesis: for one, the temporal resolution of gerbils, measured in a gap detection task, is similar to that in humans (gerbils: 2ms, Wagner et al., 2003; humans: 2-4ms, e.g. Penner, 1977). Moreover, a recently published study showed that gerbils are a suitable animal model even

for more complex spatial auditory settings (Wolf et al., 2010). The authors investigated the localization dominance as an important part of the precedence effect in gerbils. The precedence effect is the suppression of spatial information in echoes to enhance the localization ability of sounds in reverberant environments. Gerbils exhibit a localization dominance comparable to that of humans. Thus, psychophysical studies justify the use of gerbils as an animal model to study basic auditory functions but also more sophisticated auditory phenomena found in humans.

ITD Processing

One of the important goals of auditory research is to understand the neural circuitry underlying the perceptual performance. Therefore, two different approaches were used in this thesis to investigate the neural circuitry of ITD processing, particularly the importance of the inhibition for this process. It is assumed that inhibition to the MSO plays a major role in the encoding of low-frequency spatial cues, i.e. ITDs, in mammals (Brand et al., 2002; Seidl and Grothe, 2005; Pecka et al., 2008; for reviews of this topic see: Grothe, 2003; Palmer, 2004).

ITD Processing and Inhibition. Although the model of ITD processing as proposed by Jeffress incorporates no inhibitory inputs, the ITD detection unit of both birds (NL) and mammals (MSO) possess inhibitory inputs (Lachica et al., 1994; Kuwabara and Zook, 1992). It was shown that there is a functional difference of the inhibition to the NL and MSO. In birds, inhibition to the NL originates from the superior olivary nucleus (von Bartheld et al., 1989; Lachica et al., 1994) and is provided by gamma-amino-butyric acid (GABA) whereas inhibition to the MSO is provided by glycine. It is shown that glycine exhibits very fast kinetics compared to those of GABA (Gingrich et al., 1995; Legendre, 2001; Magnusson et al., 2005). Additionally, the superior olivary nucleus does not preserve the temporal pattern of a signal as it does not exhibit phase-locking behavior (Yang et al., 1999). In contrast, the MNTB, as the major source of inhibition to MSO (Grothe and Sanes, 1993) exhibits a very fast and precise transmission and thus is able to preserve timing. A last but also striking difference between birds and mammals is the demonstrated refinement of inhibitory inputs in gerbils. This process is dependent on normal acoustic experience during a critical period (Kapfer et al., 2002). The

maturation process of the inhibitory inputs depends on a direct adjustment with the spatial information present in the outer world. After the maturation process, the inhibitory inputs are mainly located at the soma of the MSO neurons.
Studies examining the function of the GABAergic inputs to the NL suggested that it sharpens coincidence detection and thus presumably improves ITD detection (Funabiki et al., 1998). Furthermore, it was shown that inhibition acts as a gain control within the avian ITD detection circuitry (Peña et al., 1996; Yang et al., 1999; Dasika et al., 2005), by preserving the ITD sensitivity even at high sound pressure levels (for a review of this topic see Nishino and Ohmori, 2009).
A similar mechanism can not be excluded in mammals. However, the above mentioned differences of the inhibition to the MSO and moreover recent experimental studies give rise to the assumption that inhibition in mammals is even more important for tuning the ITD sensitivity (Brand et al., 2002; Seidl and Grothe, 2005 for review see: Grothe, 2003; Grothe et al., 2010). MSO neurons with intact inhibition, but also ITD-sensitive neurons in the IC, fire maximally at an ITD that the animal never experiences, resulting in firing rate changes that are largest for biologically relevant ITDs (Stillman, 1971; McAlpine et al., 2001; Brand et al., 2002). Thus, it is assumed that ITDs in mammals are represented by a change in firing rate, rather than the peak activity. However, blocking inhibition to MSO neurons pharmacologically results in a shift of the peak activity towards 0 ITD, suggesting that inhibition is responsible for the ITD tuning in mammals (Brand et al., 2002). A just recently published study by Pecka et al. (2008) confirmed this importance and further demonstrated that the temporal dynamics, i.e. the precise timing, of the inhibition seems to be crucial for the neural ITD representation in mammals. A similar importance of inhibition for the ITD representation in birds could not be confirmed (Dasika et al., 2005).
Concerning mammals, the hypothesis states that lacking inhibitory inputs to only one MSO lead to localization impairments only for sounds presented in one hemifield. The reason is that each of the two MSOs displays inversely tuned channels, i.e. left MSO neurons are tuned to the right hemifield and right MSO neurons are tuned to the left hemifield. Thus, lacking inhibitory inputs to the left MSO would lead to localization impairments for sounds presented in the right azimuthal hemifield. In contrast, animals without bilateral inhibition show a deterioration in

their ability to localize sounds in the complete azimuthal space. However, effects of altered (due to noise-rearing) or even non-existing inhibitory inputs to the MSO for the localization ability could not be shown yet. Therefore, two experiments were conducted in this thesis: One experiment (subpart of experiment 2: "Release from Masking") examined the effects of noise-rearing. Another experiment ("Azimuthal Sound Localization and the MNTB") also investigated the importance of inhibitory inputs and directly probed the significance of MNTB-mediated inhibition by lesioning the MNTB. However, this experiment was methodologically highly demanding as a lesion restricted to the MNTB was very difficult to achieve. The following part will discuss the effects on the localization ability after both altering and eliminating of the MNTB-mediated inhibition to the MSO in regard to the hypothesis.

EFFECT OF NOISE-REARING ON ITD PROCESSING. In a first experimental paradigm, the detection ability of a signal in two different masker conditions of noise-reared and control gerbils was investigated. Noise-rearing, analogous to cochlea ablations but more specific, disrupts the maturation of inhibitory inputs in gerbils (Kapfer et al., 2002). This was shown to have impacts on the neural ITD representation in a similar manner as blocking inhibition does. The hypothesis of these studies was that animals deprived of normal acoustic experience should show an impaired low-frequency localization ability. However, our results revealed no difference in the determined localization ability between noise-reared and control gerbils. Thus, even in a highly challenging situation, noise-reared gerbils seem to have no impaired localization and detection ability. These results are in contrast to assumptions drawn from anatomical and *in-vivo* studies. However, our findings are in accordance with another psychophysical study conducted by Maier and colleagues (2008). These authors did, similar to this study, not find any differences in the localization ability of noise-reared and control gerbils.

There are two possible explanations for the non-existence of a localization impairment after depriving gerbils of normal acoustic experience. First, gerbils are able to build up a compensatory mechanism. Compensatory mechanisms after altering spectral or binaural cues were found in other animals and also humans (ferrets: Kacelnik et al., 2006; owls: Knudsen et al., 1984; humans: Wanrooij and Opstal, 2005; Kumpik et al., 2010). However, the more likely explanation for the deviating results of electrophysiological studies and psychophysical measurements is

the time discrepancy between noise-rearing and data recording. Compared to the required time of behavioral training and data recording (up to several months) after noise exposure, the electrophysiological experiments are conducted very early after noise exposure. It is possible that the maturation process of the inhibitory synapses is not completely disrupted by noise-rearing but shifted to a later period in time. That means, effects of noise-rearing would be shadowed by the time of training and are supposedly diminished by the time psychoacoustical data can be recorded. Thus, the absence of differences between noise-reared and control gerbils in this experimental paradigm is presumably due to the time discrepancies between psychoacoustical and electrophysiological data recording. To exclude that compensatory mechanisms are responsible for a similarly good localization performance of noise-reared and control gerbils and to further strengthen the hypothesis of a time-shifted maturation process, it would be necessary to determine whether ITD functions change over time in an *in-vivo* approach.

EFFECTS OF PARTIALLY LESIONED MNTBs ON ITD PROCESSING. To further investigate the role of MNTB-mediated inhibition, a second experimental paradigm was performed. It determined the localization ability before and after lesioning the MNTB. Complete lesioning of the MNTB will cause an entire loss of inhibition from the MNTB. However, as already depicted, setting the lesion was methodologically highly demanding. Nevertheless, it was possible to partially lesion the MNTB bilaterally in two animals. Furthermore, it was possible to partially lesion the MNTB unilaterally in one animal. The unilaterally lesioned animal did not show any localization impairment after the surgery. This is in contrast to the hypothesis that animals with a unilaterally lacking inhibition to the MSO show localization impairments for sounds presented in the contralateral hemifield. However, the non-existence of a localization impairment can be attributed the incomplete MNTB lesion. Moreover, as we only found one animal with an unilateral lesion these results need to be handled with care. Further experiments are needed to determine effects of an unilaterally lesioned MNTB. In contrast to the just presented animal, the localization ability of the two bilaterally lesioned animals was considerably impaired after the surgery. Thus, it seems that at least a bilateral partial removal of inhibition has influences on the low-frequency sound localization, i.e. the processing of ITDs. This effect can be attributed to the MNTB-mediated inhibition and not to

a damage of fibers passing the MNTB as it was shown that a local injection of KA does not affect fibers passing through the MNTB (Masterton and Diamond, 1967; Rooney et al., 1991). Thus, these two animals, exhibiting partial lesion of both MNTBs, support the importance of MNTB-mediated inhibition for low-frequency sound localization. However, two drawbacks of this study are both the incomplete lesions of the MNTB and the fact that the localization impairment of the two animals was not permanent. The animals exhibiting partial lesion of both MNTBs, were able to completely recover from the localization impairment. As the animals achieved more training during data recording after the lesion, this recovery is presumably due to the fact that the animals learn to localize with the altered though not completely abandoned neuronal representations of ITDs. This is also supported by a study showing that stimulus specific behavioral training could lead to adaptive changes in auditory localization responses within a few days (Kacelnik et al., 2006). As the two bilaterally lesioned animals were able to recover and one further animal exhibiting a unilateral lesion of the MNTB did not show any localization impairment, the role of MNTB-mediated inhibition could not be clarified conclusively.

ITD Processing - The Conclusion. Nevertheless, especially the results obtained from the two animals with a partial bilateral lesion further strengthen the hypothesis that the MNTB-mediated inhibition to the MSO is more than a gain control as suggested in birds, where this gain control (preserves ITD sensitivity at high sound levels) is most important for sound levels above 90 dB SPL (Nishino and Ohmori, 2009). The stimuli used in the present study were considerable lower than 90 dB SPL. If inhibition in mammals also acted as a pure gain control as shown for birds, a removal of inhibition to the MSO would not cause a localization impairment due to the use of a low stimulus sound level. This supports the hypothesis, drawn by earlier studies, that inhibition in mammals is mostly important to establish an accurate ITD tuning and is therefore important for low-frequency sound localization. These preliminary results indicate that the experimental inactivation of the MNTB is a step in the right direction. However, further investigations should study the effect of inhibition not by irreversibly destroying the MNTB, but rather by reversibly deactivating the MNTB. A possible approach for the future would be the expression of light-sensitive opsin genes in the desired brain region. The activity of infected cells can then be controlled by

light and moreover acts on a physiological relevant time-scale (Boyden et al., 2005; Zhang et al., 2007). With this approach, it might be possible to study the influence of inhibition on a day-by-day basis by activating and inactivating of one or both MNTBs.

5 Concluding Remarks

This study further strengthens the applicability of gerbils to study auditory spatial processing, in particular in the low-frequency regime up to approximately 1500 Hz. Additionally to the long-known fact that gerbils and humans exhibit a similar developed low-frequency hearing threshold up to 8 kHz (Ryan, 1976), several studies in the past already suggested the suitability of gerbils to study different aspects of human hearing. Gerbils, similar to humans (Smith et al., 2005), are able to perceptually segregate size and structure information present in vowels (Schebesch et al., 2009) and they also exhibit localization dominance (Wolf et al., 2010). Furthermore, the temporal resolution of the gerbils' auditory system, examined in a gap detection test, is comparable to that found for humans (Wagner et al., 2003). However, ITD sensitivity determined in previous studies was two- to threefold higher than that of humans (Heffner and Heffner, 1988a; Maier and Klump, 2006; Maier et al., 2008), suggesting a worse temporal processing of gerbils. The present study could behaviorally indicate that the neural processing of low-frequency spatial cues, i.e. the processing of ITDs is similarly effective in gerbils and humans. This is true for both a rather basic but also more sophisticated experimental approach. However, the role of MNTB-mediated inhibition for this process could not be clarified conclusively. It is assumed to play the key role in the ITD processing circuitry. The present results strengthen this hypothesis by providing evidence that a partial lesion of both MNTBs lead to an impaired localization ability. However, as this effect was not permanent, the role of MNTB-mediated inhibition for the behaviorally determined localization ability could not be verified conclusively.
In summary, this study has strong implications for the future as it not only proved that the gerbil is an ideal animal model to study ITD processing and its underlying neuronal circuitry in mammals, but, that the gerbil can also serve as an animal model for further auditory research related to spatial hearing.

Bibliography

Algazi VR, Avendano C, Duda RO (2001) Elevation localization and head-related transfer function analysis at low frequencies. *J Acoust Soc Am* 109:1110–1122.

Barnes W, Magoun H, Ranson S (1943) The ascending auditory pathway in the brain stem of the monkey. *J Comp Neurol* 79:129–152.

Beckius GE, Batra R, Oliver DL (1999) Axons from anteroventral cochlear nucleus that terminate in medial superior olive of cat: observations related to delay lines. *J Neurosci* 19:3146–3161.

Bee M (2008) Finding a mate at a cocktail party: Spatial release from masking improves acoustic mate recognition in grey treefrogs. *Anim Behav.* 75:1781–1791.

Bernstein L (2001) Auditory processing of interaural timing information: new insights. *J Neurosci.Res.* 66:1035–1046.

Bernstein L, Trahiotis C (1996) On the use of the normalized correlation as an index of interaural envelope correlation. *J Acoust.Soc.Am* 100:1754–1763.

Best V, Ozmeral E, Gallun FJ, Sen K, Shinn-Cunningham BG (2005) Spatial unmasking of birdsong in human listeners: energetic and informational factors. *J Acoust Soc Am* 118:3766–3773.

Blauert J (1997) *Spatial Hearing: The psychophysics of Human Sound Localization* Cambridge, MA: MIT Press.

Boudreau JC, Tsuchitani C (1968) Binaural interaction in the cat superior olive s segment. *J Neurophysiol* 31h:442–454.

Boyden ES, Zhang F, Bamberg E, Nagel G, Deisseroth K (2005) Millisecond-timescale, genetically targeted optical control of neural activity. *Nat Neurosci* 8:1263–1268.

Brand A, Behrend O, Marquardt T, McAlpine D, Grothe B (2002) Precise inhibition is essential for microsecond interaural time difference coding. *Nature* 417:543–547.

Bronkhorst A (2000) The cocktail party phenomenon: A review of research on speech intelligibility in multiple-talker conditions. *Acustica* 86:117–128.

Brungart DS, Rabinowitz WM (1999) Auditory localization of nearby sources. head-related transfer functions. *J Acoust Soc Am* 106:1465–1479.

Brunso-Bechtold JK, Thompson GC, Masterton RB (1981) Hrp study of the organization of auditory afferents ascending to central nucleus of inferior colliculus in cat. *J Comp Neurol* 197:705–722.

Caird D, Klinke R (1983) Processing of binaural stimuli by cat superior olivary complex neurons. *Exp Brain Res* 52:385–399.

Cant NB, Casseday JH (1986) Projections from the anteroventral cochlear nucleus to the lateral and medial superior olivary nuclei. *J Comp Neurol* 247:457–476.

Cant N, Hyson R (1992) Projections from the lateral nucleus of the trapezoid body to the medial superior olivary nucleus in the gerbil. *Hear.Res.* 58:26–34.

Cant NB, Benson CG (2003) Parallel auditory pathways: projection patterns of the different neuronal populations in the dorsal and ventral cochlear nuclei. *Brain Res Bull* 60:457–474.

Carr CE, Konishi M (1988) Axonal delay lines for time measurement in the owl's brainstem. *Proc Natl Acad Sci U S A* 85:8311–8315.

Carr CE, Konishi M (1990) A circuit for detection of interaural time differences in the brain stem of the barn owl. *J Neurosci* 10:3227–3246.

Cherry E (1953) Some experiments on the recognition of speech, with one and with two ears. *J.Acoust.Soc.Am.* 25:975–979.

Crow G, Rupert AL, Moushegian G (1978) Phase locking in monaural and binaural medullary neurons: implications for binaural phenomena. *J Acoust Soc Am* 64:493–501.

Dasika VK, White JA, Carney LH, Colburn HS (2005) Effects of inhibitory feedback in a network model of avian brain stem. *J Neurophysiol* 94:400–414.

Dau T, Puschel D, Kohlrausch A (1996) A quantitative model of the "effective" signal processing in the auditory system. i. model structure. *J.Acoust.Soc.Am.* 99:3615–3622.

Dent ML, McClaine EM, Best V, Ozmeral E, Narayan R, Gallun FJ, Sen K, Shinn-Cunningham BG (2009) Spatial unmasking of birdsong in zebra finches (taeniopygia guttata) and budgerigars (melopsittacus undulatus). *J Comp Psychol* 123:357–367.

Dent M, Larsen O, Dooling R (1997) Free-field binaural unmasking in budgerigars (melopsittacus undulatus). *Behav.Neurosci.* 111:590–598.

Early S, Mason C, Zheng L, Evilsizer M, Idrobo F, Harrison J, Carney L (2001) Studies of binaural detection in the rabbit (oryctolagus cuniculus) with pavlovian conditioning. *Behav.Neurosci.* 115:650–660.

Ebata M (2003) Spatial unmasking and attention related to the cocktail party problem. *J. Acoust. Sc. And Tech.* 24:208–219.

Ehret G, Dreyer A (1984) Localization of tones and noise in the horizontal plane by unrestrained house mice (mus musculus). *J Exp.Biol.* 109:163–174.

Feddersen W, Sandel T, Teas D, Jeffress L (1957) Localization of high-frequency tones. *J Acoust.Soc.Am* 29:988–991.

Friauf E, Ostwald J (1988) Divergent projections of physiologically characterized rat ventral cochlear nucleus neurons as shown by intra-axonal injection of horseradish peroxidase. *Exp Brain Res* 73:263–284.

Funabiki K, Koyano K, Ohmori H (1998) The role of gabaergic inputs for coincidence detection in the neurones of nucleus laminaris of the chick. *J Physiol* 508 (Pt 3):851–869.

Gardner MB, Gardner RS (1973) Problem of localization in the median plane: effect of pinnae cavity occlusion. *J Acoust Soc Am* 53:400–408.

Gingrich KJ, Roberts WA, Kass RS (1995) Dependence of the gabaa receptor gating kinetics on the alpha-subunit isoform: implications for structure-function relations and synaptic transmission. *J Physiol* 489 (Pt 2):529–543.

Glasberg B, Moore B (1994) Growth-of-masking functions for several types of maskers. *J Acoust.Soc.Am* 96:134–144.

Gleich O, Hamann I, Kittel M, Klump G, Strutz J (2007) Forward masking in gerbils: the effect of age. *Hear.Res.* 223:122–128.

Glendenning KK, Baker BN, Hutson KA, Masterton RB (1992) Acoustic chiasm v: inhibition and excitation in the ipsilateral and contralateral projections of lso. *J Comp Neurol* 319:100–122.

Goldberg J, Brown P (1969) Response of binaural neurons of dog superior olivary complex to dichotic tonal stimuli: some physiological mechanisms of sound localization. *J.Neurophysiol.* 32:613–636.

Good MD, Gilkey RH (1996) Sound localization in noise: the effect of signal-to-noise ratio. *J Acoust Soc Am* 99:1108–1117.

Grothe B (2003) New roles for synaptic inhibition in sound localization. *Nat.Rev.Neurosci.* 4:540–550.

Grothe B, Park TJ (1998) Sensitivity to interaural time differences in the medial superior olive of a small mammal, the mexican free-tailed bat. *J Neurosci* 18:6608–6622.

Grothe B, Sanes D (1993) Bilateral inhibition by glycinergic afferents in the medial superior olive. *J Neurophysiol.* 69:1192–1196.

Grothe B, Pecka M, McAlpine D (2010) Mechanisms of sound localization in mammals. *Physiol Rev* 90:983–1012.

Hafter ER, Dye RH, Wenzel EM, Knecht K (1990) The combination of interaural time and intensity in the lateralization of high-frequency complex signals. *J Acoust Soc Am* 87:1702–1708.

Hamann I, Gleich O, Klump G, Kittel M, Strutz J (2004) Age-dependent changes of gap detection in the mongolian gerbil (meriones unguiculatus). *J.Assoc.Res.Otolaryngol.* 5:49–57.

Heffner HE, Heffner RS (1985a) Hearing in two cricetid rodents: wood rat (neotoma floridana) and grasshopper mouse (onychomys leucogaster). *J Comp Psychol* 99:275–288.

Heffner H, Heffner R (1985b) Sound localization in wild norway rats (rattus norvegicus). *Hear.Res.* 19:151–155.

Heffner H, Masterton B (1980) Hearing in glires: Domestic rabbit, cotton rat, feral house mouse, and kangaroo rat. *J Acoust.Soc.Am* 68:1584–1599.

Heffner RS (1997) Comparative study of sound localization and its anatomical correlates in mammals. *Acta Otolaryngol Suppl* 532:46–53.

Heffner R, Heffner H (1988a) Sound localization and use of binaural cues by the gerbil (meriones unguiculatus). *Behav.Neurosci.* 102:422–428.

Heffner R, Heffner H (1988b) Sound localization in a predatory rodent, the northern grasshopper mouse (onychomys leucogaster). *J Comp Psychol.* 102:66–71.

Heffner R, Heffner H (1992) Hearing and sound localization in blind mole rats (spalax ehrenbergi). *Hear.Res.* 62:206–216.

Heffner R, Heffner H (1993) Degenerate hearing and sound localization in naked mole rats (heterocephalus glaber), with an overview of central auditory structures. *J Comp Neurol.* 331:418–433.

Heffner R, Heffner H, Kearns D, Vogel J, Koay G (1994) Sound localization in chinchillas. i: Left/right discriminations. *Hear.Res.* 80:247–257.

Heffner R, Koay G, Heffner H (2001) Audiograms of five species of rodents: implications for the evolution of hearing and the perception of pitch. *Hear.Res.* 157:138–152.

Henkel CK, Spangler KM (1983) Organization of the efferent projections of the medial superior olivary nucleus in the cat as revealed by hrp and autoradiographic tracing methods. *J Comp Neurol* 221:416–428.

Henning G (1974) Detectability of interaural delay in high-frequency complex waveforms. *J Acoust.Soc.Am* 55:84–90.

Hine J, Martin R, Moore D (1994) Free-field binaural unmasking in ferrets. *Behav.Neurosci.* 108:196–205.

Hirsh I (1948) The influence of interaural phase on interaural summation and inhibition. *J Acoust.Soc.Am* 20:536–544.

Holt M, Schusterman R (2007) Spatial release from masking of aerial tones in pinnipeds. *J.Acoust.Soc.Am.* 121:1219–1225.

Ison J, Agrawal P (1998) The effect of spatial separation of signal and noise on masking in the free field as a function of signal frequency and age in the mouse. *J.Acoust.Soc.Am.* 104:1689–1695.

Jeffress L (1948) A place theory of sound localization. *J.Comp Physiol Psychol.* 41:35–39.

Joris PX, Carney LH, Smith PH, Yin TC (1994) Enhancement of neural synchronization in the anteroventral cochlear nucleus. i. responses to tones at the characteristic frequency. *J Neurophysiol* 71:1022–1036.

Joris PX, Smith PH, Yin TC (1994) Enhancement of neural synchronization in the anteroventral cochlear nucleus. ii. responses in the tuning curve tail. *J Neurophysiol* 71:1037–1051.

Joris PX, Yin TC (1995) Envelope coding in the lateral superior olive. i. sensitivity to interaural time differences. *J Neurophysiol* 73:1043–1062.

Kacelnik O, Nodal F, Parsons C, King A (2006) Training-induced plasticity of auditory localization in adult mammals. *PLoS.Biol.* 4:e71–.

Kapfer C, Seidl A, Schweizer H, Grothe B (2002) Experience-dependent refinement of inhibitory inputs to auditory coincidence-detector neurons. *Nat.Neurosci.* 5:247–253.

Kavanagh G, Kelly J (1986) Midline and lateral field sound localization in the albino rat (rattus norvegicus). *Behav.Neurosci.* 100:200–205.

King AJ, Schnupp JW, Doubell TP (2001) The shape of ears to come: dynamic coding of auditory space. *Trends Cogn Sci* 5:261–270.

Klumpp G, Eady H (1956) Some measurements of interaural time difference thresholds. *J.Acoust.Soc.Am.* 28:859–860.

Knudsen EI, Knudsen PF, Esterly SD (1984) A critical period for the recovery of sound localization accuracy following monaural occlusion in the barn owl. *J Neurosci* 4:1012–1020.

Koka K, Jones H, Lupo J, Tollin D (2008) The acoustical cues to sound location in the adult chinchilla: Measurements of directional transfer functions (dtfs). Midwinter Research Meeting of the ARO 2008.

Kuhn G (1977) Model for the interaural time differences in the azimuthal plane. *J.Acoust.Soc.Am.* 62:157–167.

Kumpik DP, Kacelnik O, King AJ (2010) Adaptive reweighting of auditory localization cues in response to chronic unilateral earplugging in humans. *J Neurosci* 30:4883–4894.

Kuwabara N, DiCaprio RA, Zook JM (1991) Afferents to the medial nucleus of the trapezoid body and their collateral projections. *J Comp Neurol* 314:684–706.

Kuwabara N, Zook JM (1992) Projections to the medial superior olive from the medial and lateral nuclei of the trapezoid body in rodents and bats. *J Comp Neurol* 324:522–538.

Lachica EA, Rübsamen R, Rubel EW (1994) Gabaergic terminals in nucleus magnocellularis and laminaris originate from the superior olivary nucleus. *J Comp Neurol* 348:403–418.

Lay DM (1972) The anatomy, physiology, functional significance and evolution of specialized hearing organs of gerbilline rodents. *J Morphol* 138:41–120.

Legendre P (2001) The glycinergic inhibitory synapse. *Cell Mol Life Sci* 58:760–793.

Licklider J (1948) The influence of interaural phase relations upon masking of speech by white noise. *J Acoust.Soc.Am* 20:150–159.

Lorente de No R (1933) Anatomy of the eighth nerve. iii: General plan of structure of the primary cochlear nuclei. *Laryngoscope* 43:327–349.

Loskota W, Lomax P, Verity M (1974) *A Stereotaxic Atlas of the Mongolian Gerbil Brain (Meriones Unguiculatus)* Ann Arbor Science, Ann Arbor, Michigan.

Magnusson AK, Kapfer C, Grothe B, Koch U (2005) Maturation of glycinergic inhibition in the gerbil medial superior olive after hearing onset. *J Physiol* 568:497–512.

Maier J, Kindermann T, Grothe B, Klump G (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 J, Klump G (2006) Resolution in azimuth sound localization in the mongolian gerbil (meriones unguiculatus). *J.Acoust.Soc.Am.* 119:1029–1036.

Maki K, Furukawa S (2005) Acoustical cues for sound localization by the mongolian gerbil, meriones unguiculatus. *J.Acoust.Soc.Am.* 118:872–886.

Masterton B, Diamond I (1967) Medial superior olive and sound localization. *Science* 155:1696–1697.

Masterton RB, Glendenning KK, Hutson KA (1979) Preservation of trapezoid body fibers after biochemical ablation of superior olives with kainic acid. *Brain Res* 173:156–159.

May BJ (2000) Role of the dorsal cochlear nucleus in the sound localization behavior of cats. *Hear Res* 148:74–87.

McAlpine D, Jiang D, Palmer A (2001) A neural code for low-frequency sound localization in mammals. *Nat.Neurosci.* 4:396–401.

McFadden D, Pasanen E (1976) Lateralization of high frequencies based on interaural time differences. *J Acoust.Soc.Am* 59:634–639.

Middlebrooks JC (1992) Narrow-band sound localization related to external ear acoustics. *J Acoust Soc Am* 92:2607–2624.

Mills A (1958) On the minimum audible angle. *J.Acoust.Soc.Am.* 30:237–246.

Nishino E, Ohmori H (2009) The modulation by intensity of the processing of interaural timing cues for localizing sounds. *Mol.Neurobiol.* 40:157–165.

Oliver DL, Beckius GE, Shneiderman A (1995) Axonal projections from the lateral and medial superior olive to the inferior colliculus of the cat: a study using electron microscopic autoradiography. *J Comp Neurol* 360:17–32.

Osen K (1969) Cytoarchitecture of the cochlear nuclei in the cat. *J Comp Neurol.* 136:453–484.

Overholt EM, Rubel EW, Hyson RL (1992) A circuit for coding interaural time differences in the chick brainstem. *J Neurosci* 12:1698–1708.

Oxenham A, Moore B (1994) Modeling the additivity of nonsimultaneous masking. *Hear.Res.* 80:105–118.

Palmer AR, Russell IJ (1986) Phase-locking in the cochlear nerve of the guinea-pig and its relation to the receptor potential of inner hair-cells. *Hear Res* 24:1–15.

Palmer A (2004) Reassessing mechanisms of low-frequency sound localisation. *Curr.Opin.Neurobiol.* 14:457–460.

Parks TN, Rubel EW (1975) Organization and development of brain stem auditory nuclei of the chicken: organization of projections from n. magnocellularis to n. laminaris. *J Comp Neurol* 164:435–448.

Peña JL, Viete S, Albeck Y, Konishi M (1996) Tolerance to sound intensity of binaural coincidence detection in the nucleus laminaris of the owl. *J Neurosci* 16:7046–7054.

Pecka M, Brand A, Behrend O, Grothe B (2008) Interaural time difference processing in the mammalian medial superior olive: the role of glycinergic inhibition. *J Neurosci.* 28:6914–6925.

Pecka M, Zahn T, Saunier-Rebori B, Siveke I, Felmy F, Wiegrebe L, Klug A, Pollak G, Grothe B (2007) Inhibiting the inhibition: a neuronal network for sound localization in reverberant environments. *J.Neurosci.* 27:1782–1790.

Penner MJ (1977) Detection of temporal gaps in noise as a measure of the decay of auditory sensation. *J Acoust Soc Am* 61:552–557.

Perkins RE (1973) An electron microscopic study of synaptic organization in the medial superior olive of normal and experimental chinchillas. *J Comp Neurol* 148:387–415.

Plassmann W, Peetz W, Schmidt M (1987) The cochlea in gerbilline rodents. *Brain Behav Evol* 30:82–101.

Refinetti R (2006) Variability of diurnality in laboratory rodents. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 192:701–714.

Rooney BJ, Kavanagh GL, Kelly JB (1991) Kainic acid lesions of the superior olivary complex: a horseradish peroxidase study of surviving brain-stem projections. *J Neurosci Methods* 39:65–75.

Rose JE, Galambos R, Hughes JR (1959) Microelectrode studies of the cochlear nuclei of the cat. *Bull Johns Hopkins Hosp* 104:211–251.

Ryan A (1976) Hearing sensitivity of the mongolian gerbil, meriones unguiculatis. *J Acoust.Soc.Am* 59:1222–1226.

Saberi K, Dostal L, Sadralodabai T, Bull V, Perrott DR (1991) Free-field release from masking. *J Acoust Soc Am* 90:1355–1370.

Schebesch G, Lingner A, Firzlaff U, Wiegrebe L, Grothe B (2009) Perception and neural representation of size-variant human vowels in the mongolian gerbil (meriones unguiculatus). *Hear.Res.* 261:1–8.

Schuller G, Radtke-Schuller S, Betz M (1986) A stereotaxic method for small animals using experimentally determined reference profiles. *J.Neurosci.Methods* 18:339–350.

Schwartz JJ, Gerhardt HC (1989) Spatially mediated release from auditory masking in an anuran amphibian. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 166:37–41.

Seidl A, Grothe B (2005) Development of sound localization mechanisms in the mongolian gerbil is shaped by early acoustic experience. *J.Neurophysiol.* 94:1028–1036.

Shinn-Cunningham BG, Santarelli S, Kopco N (2000) Tori of confusion: binaural localization cues for sources within reach of a listener. *J Acoust Soc Am* 107:1627–1636.

Shneiderman A, Henkel CK (1985) Evidence of collateral axonal projections to the superior olivary complex. *Hear Res* 19:199–205.

Simonian N, Getz R, Leveque J, Konradi C, Coyle J (1996) Kainic acid induces apoptosis in neurons. *Neuroscience* 75:1047–1055.

Sinnott J, Mosqueda S (2003) Effects of aging on speech sound discrimination in the mongolian gerbil. *Ear Hear.* 24:30–37.

Siveke I, Ewert S, Grothe B, Wiegrebe L (2008) Psychophysical and physiological evidence for fast binaural processing. *J Neurosci.* 28:2043–2052.

Smith DRR, Patterson RD, Turner R, Kawahara H, Irino T (2005) The processing and perception of size information in speech sounds. *J Acoust Soc Am* 117:305–318.

Smith PH, Joris PX, Carney LH, Yin TC (1991) Projections of physiologically characterized globular bushy cell axons from the cochlear nucleus of the cat. *J Comp Neurol* 304:387–407.

Smith P, Joris P, Yin T (1993) Projections of physiologically characterized spherical bushy cell axons from the cochlear nucleus of the cat: evidence for delay lines to the medial superior olive. *J Comp Neurol.* 331:245–260.

Spirou GA, Berrebi AS (1996) Organization of ventrolateral periolivary cells of the cat superior olive as revealed by pep-19 immunocytochemistry and nissl stain. *J Comp Neurol* 368:100–120.

Stern RM, Slocum JE, Phillips MS (1983) Interaural time and amplitude discrimination in noise. *J Acoust Soc Am* 73:1714–1722.

Stevens S, Newman E (1936) The localization of actual sources of sound. *Am J Psychol.* 48:297–306.

Stillman RD (1971) Characteristic delay neurons in the inferior colliculus of the kangaroo rat. *Exp Neurol* 32:404–412.

Stotler W (1953) An experimental study of the cells and connections of the superior olivary complex of the cat. *J Comp Neurol.* 98:401–431.

Strutt J (1907) On our perception on sound direction. *Philosophical Magazine* 13:214–232.

Sullivan WE, Konishi M (1986) Neural map of interaural phase difference in the owl's brainstem. *Proc Natl Acad Sci U S A* 83:8400–8404.

Sumer S, Denzinger A, Schnitzler H (2009) Spatial unmasking in the echolocating big brown bat, eptesicus fuscus. *J.Comp Physiol A Neuroethol.Sens.Neural Behav.Physiol* 195:463–472.

Taschenberger H, von Gersdorff H (2000) Fine-tuning an auditory synapse for speed and fidelity: developmental changes in presynaptic waveform, epsc kinetics, and synaptic plasticity. *J Neurosci* 20:9162–9173.

Thompson SP (1882) On the function of the two ears in the perception of space. *Philosophical Magazine Series 5* 13:406–416.

Tollin DJ, Yin TCT (2005) Interaural phase and level difference sensitivity in low-frequency neurons in the lateral superior olive. *J Neurosci* 25:10648–10657.

Tollin D (2003) The lateral superior olive: a functional role in sound source localization. *Neuroscientist.* 9:127–143.

Tsuchitani C, Boudreau JC (1969) Stimulus level of dichotically presented tones and cat superior olive s-segment cell dcharge. *J Acoust Soc Am* 46:979–988.

von Bartheld CS, Code RA, Rubel EW (1989) Gabaergic neurons in brainstem auditory nuclei of the chick: distribution, morphology, and connectivity. *J Comp Neurol* 287:470–483.

von Gersdorff H, Borst JGG (2002) Short-term plasticity at the calyx of held. *Nat Rev Neurosci* 3:53–64.

Wagner E, Klump G, Hamann I (2003) Gap detection in mongolian gerbils (meriones unguiculatus). *Hear.Res.* 176:11–16.

Wakeford O, Robinson D (1974) Detection of binaurally masked tones by the cat. *J.Acoust.Soc.Am.* 56:952–956.

Wanrooij MMV, Opstal AJV (2005) Relearning sound localization with a new ear. *J Neurosci* 25:5413–5424.

Wesolek CM, Koay G, Heffner RS, Heffner HE (2010) Laboratory rats (rattus norvegicus) do not use binaural phase differences to localize sound. *Hear Res* 265:54–62.

Withington-Wray D, Binns K, Dhanjal S, Brickley S, Keating M (1990) The maturation of the superior collicular map of auditory space in the guinea pig is disrupted by developmental auditory deprivation. *Eur.J.Neurosci.* 2:693–703.

Wolf M, Schuchmann M, Wiegrebe L (2010) Localization dominance and the effect of frequency in the mongolian gerbil, meriones unguiculatus. *J Comp Physiol A Neuroethol Sens Neural Behav Physiol* 196:463–470.

Wu SH, Kelly JB (1993) Response of neurons in the lateral superior olive and medial nucleus of the trapezoid body to repetitive stimulation: intracellular and extracellular recordings from mouse brain slice. *Hear Res* 68:189–201.

Yang L, Monsivais P, Rubel EW (1999) The superior olivary nucleus and its influence on nucleus laminaris: a source of inhibitory feedback for coincidence detection in the avian auditory brainstem. *J Neurosci* 19:2313–2325.

Yin TC, Chan JC (1990) Interaural time sensitivity in medial superior olive of cat. *J Neurophysiol* 64:465–488.

Zhang F, Aravanis AM, Adamantidis A, de Lecea L, Deisseroth K (2007) Circuit-breakers: optical technologies for probing neural signals and systems. *Nat Rev Neurosci* 8:577–581.

Contributions to the Manuscript

Section 2.3: Azimuthal Sound Localization and the MNTB

Michael Pecka performed the surgery and lesion of the MNTB, Ludwig Feldmann counted the cells for the histological verification of the lesion.

Acknowledgment

Zuallererst möchte ich mich bei Prof. Benedikt Grothe für die Überlassung dieser Doktorarbeit und für die Unterstützung während der gesamten Zeit dieser Arbeit bedanken. Ein großer Dank geht an Lutz Wiegrebe, der in den letzten fünf Jahren immer ein offenes Ohr für mich hatte und mir bei Fragen und Problemen zur Seite stand und von dem ich viel lernen konnte.
Michael Pecka möchte ich für viele wissenschaftliche Gespräche und für die gute Zusammenarbeit während der Doktorarbeit danken.
Bei der gesamten Neurobiologie Truppe möchte ich mich für das gute Arbeitsklima, aber auch für einige super Rafting-, Ski- und Wiesn-Ausflüge bedanken. Es hat Spaß gemacht hier zu abreiten.
Im speziellen möchte ich mich noch bei Sven Schörnich bedanken, ohne ihn hätte so manch kleineres aber auch größeres Computer- oder technisches Problem Auswirkungen auf die Weiterarbeit gehabt. Dieter Leippert, Monika Holik und Sabrina Schenk sei gedankt für die gute Pflege und Versorgung meiner Gerbils und natürlich auch für die gute Zeit und die lustigen Gespräche, arbeiten im Keller hat Spaß gemacht.
Sabine Heitzer möchte ich für eine großartige Freundschaft danken: Auf das verspätete Bio-Studium!
Ein ganz großer Dank geht an Daria Genzel für die MatLab Starthilfen zu Beginn meiner Doktorarbeit, aber auch für wissenschaftliche Gespräche, Mittagspausen und nicht zuletzt dafür, dass sie eine sehr, sehr gute Freundin geworden ist! Ein spezieller Dank geht natürlich noch an meine Familie! Vielen Dank für die Unterstützung während der Doktorarbeit aber auch während meines gesamten Studiums.
Und nicht zuletzt: Danke Jochen!!! Danke, für die Unterstützung; danke, für das ertragen so mancher Launen und danke dafür, dass du immer da warst wenn ich dich brauchte!

Curriculum Vitæ

Andrea Lingner
Friedrich-Berber-Weg 18
81739 München
+49 177 3140482
lingner@bio.lmu.de
14.04.1982

EDUCATION

09/1988 – 07/1992	Elementary School in Munich
09/1992 – 07/2001	Secondary School in Munich
07/2001	Abitur

UNIVERSITARY EDUCATION

10/2001 – 09/2005	Studies of Biology at the LMU Munich
10/2005 – 12/2006	Diploma thesis "Auditory object normalisation in the Mongolian Gerbil"
01/2007 – present	PhD-Thesis "The Processing of Low-Frequency Spatial Cues – A Behavioral Approach –"

MAIN CONFERENCE PARTICIPATIONS

Sept 2007	Bernstein Symposium on Object Localization "Effect of Correlated and Uncorrelated Masking Noise on the Azimuthal Sound Localization Ability in the Mongolian Gerbil"

Febr 2008	ARO 31 MidWinter Research Meeting "Azimuthal Sound Localization and Spatial Unmasking in the Mongolian Gerbil“
March 2009	32th Göttingen Neurobiology Conference "Effects of Bilateral Lesioning of the Medial Nucleus of the Trapezoid Body on Behavioral Sensitivity to Interaural Time Differences “

PUBLICATIONS

Schebesch G., Lingner A., Firzlaff, U., Wiegrebe L., Grothe B.
"Perception and neural representation of size-variant human vowels in the Mongolian gerbil (Meriones unguiculatus)."
Hear Res. 2010 Mar; 261(1-2): 1-8.

Lesica N., Lingner A., Grothe B.
"Population coding of interaural time differences in gerbils and barn owls.“
J Neurosci. 2010 Sept; 30(35): 11696-11702.

Ehrenwörtliche Erklärung

Hiermit versichere ich, Andrea Lingner, dass die hier vorliegende Arbeit von mir selbständig und nur unter Verwednung der angegeben Hilfsmittel verfasst wurde.

München, den 28.09.2010

Andrea Lingner