Objective audiological diagnostics using novel acoustical and electrophysiological tests

Von der Fakultät für Mathematik und
Naturwissenschaften der
Carl von Ossietzky Universität Oldenburg

zur Erlangung des Grades und Titels eines Doktors
der Naturwissenschaften (Dr. rer. nat.)
angenommene Dissertation

Matthias Müller-Wehlau
geb. am 30. August 1971
in Varel (Oldb)

Erstreferent: Prof. Dr. Dr. Birger Kollmeier
Koreferent: Prof. Dr. Jesko Verhey

Tag der Disputation: 30.06.2010

Abstract

In this thesis different acoustical and electrophysiological approaches for the objective audiological diagnostic are investigated. The utilized methods involve higher stages of the audiometric pathway and therefore allow the assessment of the state of hearing up to neural levels. It was shown that a different method to measure the acoustic reflex elicitation in conjunction with a new robust detection algorithm allows a significantly reduced stimulus level and higher detection rates compared to the established method. The same method was used to correlate reflex thresholds with the loss of cochlear compression that results from sensorineural hearing loss thus offering an objective method to estimate the broadband hearing threshold. Yet another method connects objective measurements of amplitude modulation following responses (AMFR) with differences in modulation depths perception due to cochlear damage.

Kurzfassung

In dieser Arbeit werden verschiedene akustische und elektrophysiologische Methoden zur audiologischen Diagnostik untersucht. Die verwendeten Methoden beziehen höhere Stufen der auditorischen Verarbeitung mit ein und erlauben daher Aussagen über den Zustand des Gehörs bis zu einer neuronalen Ebene. Es wurde gezeigt, dass eine alternative Methode zur Messung des Stapediusreflexes in Verbindung mit einer neuen, robusten Auswertemethodik eine signifikante Reduzierung des notwendigen Stimuluspegels bei gleichzeitig erhöhter Detektionsrate erlaubt. Die gleiche Methode wurde verwendet um eine Beziehung zwischen der gemessenen Reflexschwelle und dem Kompressionsverlust als Folge einer sensorineuralen Schädigung herzustellen. Dieses Ergebnis erlaubt die Verwendung der Methode zur objektiven Abschätzung der breitband Ruhehörschwelle. Eine weitere Methode stellt eine Verbindung zwischen objektiven Messungen von Amplitudenmodulations-Folgepotentialen (Amplitude modulation following responses, AMFR) mit Unterschieden in der Modulationstiefen-wahrnehmung von Patienten mit cochleärer Schädigung her.

Contents

Chapter 1

General Introduction

Hearing is important to us in many ways. Its role in communication with each other makes it most important for our social life. It allows us to perceive our environment and thereby is an essential sense to realize dangers that are not in our direct field of vision. The auditory sense is even more important for children as a mean to acquire language that allows us to interact with other people. Impairment of hearing is therefore a serious handicap.

The perception of sound is a complex physiological process that can be separated in four different stages (see Figure 1.1). Any incident sound passes the outer and middle ear to the cochlea. The outer ear results in a spectral shaping that gives additional clues in localization of sound origins while the middle ear compensates for the impedance change between the outer ear and the fluid filled inner ear. Within the cochlea the frequency specific transformation of sound to nerve pulses takes place. This involves compressive processes that enable the large dynamic range of hearing. The brainstem is an early stage of auditory sound perception that is related to many subconscious mechanisms like acoustically elicited reflexes while the more vigilant processing of sound takes place in higher stages of the auditory cortex.

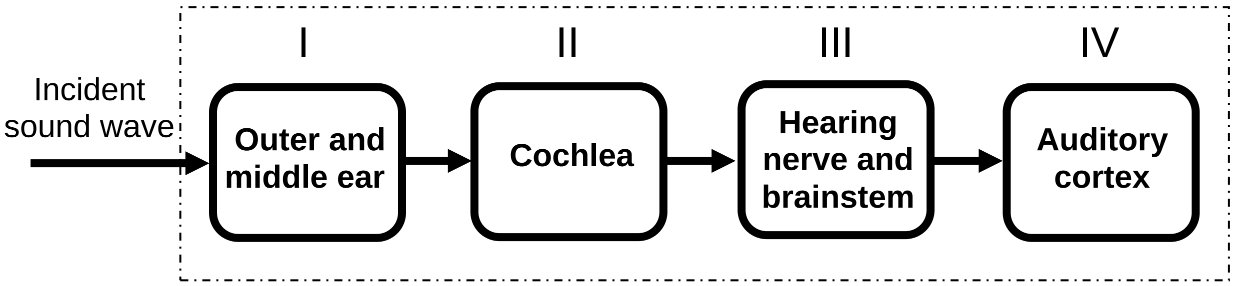

Figure 1.1: *Model of the different physiological stages of sound perception*

There are many psychoacoustical tests to qualify and quantify the state of hearing, most of which have in common that they rely on the cooperation and capability of the patient to perform the required tasks. A typical example and most commonly used is the determination of the hearing threshold by behavioral audiometry. However, the cooperation and capability is not always granted. Especially neonates and small children but also elderly patients might not be able to understand the task or to perform it in a reliable way. But also if the patient is physically and psychologically able to attend to these tests it might be necessary to determine the state of hearing by more objective means in order to rule out any intentional behavior. Hence, to allow for an accurate estimation of the status of the hearing apparatus tests have to be developed that address different stages of hearing and that do not rely on subjective assessments by either the test manager or the patient. The current thesis therefore aims at optimizing and validating such objective methods by connecting their respective results to those obtained with psychoacoustical audiological tests like behavioral audiograms and recruitment measurements.

Already, there are some objective methods for the screening of hearing function established. Exemplary for these is the measurement of otoacoustical emissions (OAE) that is based on the measurement of either spontaneous or evoked OAE that can normally be found in the healthy ear and that originate from the normal cochlear function. A miss or reduction of OAE can indicate a cochlear dysfunction. Unlike this method that is based on the peripheral function of the ear and that can therefore only give information on the functionality of the ear for the first two stages of hearing (compare Figure 1.1) it is desirable to have procedures available that depend on higher stages of the auditory response. One established technique used in the screening of hearing function that addresses higher auditory functions is the brainstem evoked response audiometry (BERA), i.e. the measurement of acoustically evoked brainstem potentials. Normal auditory function is thereby determined by the detection of potentials that are correlated with the stimulus presentation. Although both methods are well established as a tool for the hearing screening in neonates, their application does normally not go beyond the state to establish whether hearing is present or not. A failed test only indicates that further testing is required to determine if and to what degree there is a hearing disorder. Hence, the same problem as previously stated, i.e., how to quantify the hearing disorder in patients that are not capable or not willing to perform subjective psychoacoustical tests still exists.

So far no established method allows for a quantitative and precise prediction of the complete audiogram. There have been various studies that tried to establish a relationship between, e.g., OAEs and the audiogram (Harris & Probst 2002). However, most of the studies only allowed for a bivalent decision by separating patients with hearing loss from those with normal hearing. Some recent studies

(Boege & Janssen 2002; Mauermann 2004) tried to improve the prediction of the audiogram with means of the OAE but so far no method turned out to be advantageous compared to others.

One of the few established objective methods in the audiological examination that allows the quantification of hearing disorder is the so called impedance audiometry (Clemis 1984). This method has so far not been related to the audiogram but allows the measurement of the middle ear compliance, i.e. the receptivity of the middle ear to sound and has different useful applications:

1. Measurement of the absolute compliance as a function of pressure allows estimating the state of the middle ear (stage II in Figure 1.1) and gives indication in cases of a reduced mobility of the eardrum or the ossicular chain or a disruption of the ossicular chain.

2. It is possible to measure the change of the compliance caused by an acoustically elicited middle ear reflex known as acoustic or stapedius reflex. Characteristic parameters of the reflex like the reflex threshold, i.e. the acoustical sound level that is required to elicit the reflex, serve as indicators for disorders in higher stages of the auditory pathway (stage I to III in Figure 1.1).

The application of the established method to measure the acoustic reflex is restricted by the high stimulus levels that are required to elicit the reflex and measure the compliance change. A method to allow the detection of the reflex elicitation at lower stimulus levels has been described by Neumann et al. (Neumann et al. 1996). Since the method is expected to be more sensitive than the established method, it has been named low level acoustic reflex measurement (LLAR). The potential reflex detection at lower levels is advantageous in many ways since the established procedure is uncomfortable or might even be harmful in patients with previously impaired hearing or patients that suffered from a sudden hearing loss (cause by, e.g., ischemia or a noise trauma). To determine if the new method turns out to be beneficial compared to the established method and in order to evaluate the supplementation of a new analysis algorithm, measurements in a number of patients have been performed in chapter 2.

As mentioned above, the acoustic reflex originates in the brainstem (stage III in Figure 1.1). Measurements of the acoustic reflex elicitation are therefore influenced by the function of the middle ear and the cochlea (stages I and II in Figure 1.1). While the correct function of the middle ear can easily be assessed with tympanometric means, the influence of cochlear dysfunction, especially of the loss of the compressive properties on the reflex, has not been thoroughly investigated so far. This influence is investigated in chapter 3 and 4 using broad band stimuli that result in known excitation patterns on the basilar membrane of the cochlea. These excitation patterns are altered by the compressive properties of the basilar membrane. A loss of compression that is assumed to correspond with sensorineural hearing loss therefore results in a different excitation scheme and subsequently in a different reflex elicitation.

In chapter 3 a model of the different behavior of these stimuli on cochlear level is offered and discussed that accounts for the differences of the reflex thresholds. Because the measurements were performed with subjects with well defined hearing loss, the experiment was extended to subjects with a large variety of hearing losses in chapter 4. It was possible to relate parameters that have been derived from the reflex thresholds to the hearing losses with an accuracy that is equal to those of other experimental measures of the audiograms.

In chapter 5 a different relationship between the state of hearing up to the stage of the auditory cortex (stage IV in Figure 1.1) and another objective measure is investigated. Measurements of the amplitude modulation following responses (AMFR), i.e. potentials that are caused by the amplitude modulation of the evoking stimulus, were performed in dependance of the modulation depth in subjects with unilateral hearing loss. Depending on the modulation frequency of the stimulus the AMFR are though to originate from different stages of the auditory pathway. Low modulation frequencies of about 40 Hz are thereby connected with the higher auditory cortex while the responses to higher modulation frequencies are thought to originate in the brainstem (Pethe et al. 2001). Measurements of AMFR have therefore the potential to assess the state of hearing from the middle ear to the brainstem or the auditory cortex respectively.

In previous experiments it was found that the perception of modulation depth increases with the loss of cochlear compression (Moore et al. 1996), a finding that corresponds with the outcome of cochlear models (see chapter 5). In contrast to previous studies on the AMFR that investigated the influence of cochlear damage on the response amplitude for different stimulation levels (Ménard et al. 2008) the experiments in chapter 5 therefore concentrate on the dependancy of the responses on different modulation depth. This opens a new approach in the development of another objective means to assess hearing disorders. Finally, a brief summary of the findings and possible implications on further studies of the presented methods is given in chapter 6.

Chapter 2

Low level acoustic reflex (LLAR) audiometry: Feasibility and normative data

The low level acoustic reflex measurement (LLAR) (Neumann et al. 1996) is expected to be beneficial in the measurement of the acoustic reflex threshold (ART) compared to the commonly used measurement paradigm. Aim of the present study is to set the baseline of the LLAR method for clinical purposes and to provide normative data with a limited number of subjects. The measurements were done for frequencies of 500, 1000, 2000 and 4000 Hz in 41 subjects with normal hearing and within a pilot study using 10 subjects with mild to moderate hearing loss. The acoustic reflex thresholds (ARTs) measured with the LLAR were compared to results gained with a commercially available impedance audiometer.

The results show that lower detection thresholds can be achieved using the LLAR with a difference of the mean detection threshold of up to 7 dB. Since the stimulus used in the LLAR is much shorter compared to the conventional method, the perceived loudness difference between these methods is even larger. In addition to the increased sensitivity, the LLAR exhibits higher detection rates of the ART across all frequencies. The average detection rate of the LLAR is 16.9 % higher compared to the measurements done with the reference device. However, further methodological optimization is required since the measurement time for assessing the LLAR is still higher than the reference method in the commercially available device.

Introduction

The acoustic reflex (AR) is the contraction of the middle ear muscles in response to an intense auditory stimulus. It is believed that the acoustic reflex serves as an attenuator for low-frequency body noise (Simmons 1964; Katz 1977; Gelfand 1998). Nowadays it is routinely used in audiological diagnostics (Clemis 1984) and serves as an indicator of neural dysfunction along the reflex pathway. The AR is normally measured by means of the middle ear's impedance change due to the stiffening of the ossicular chain (Metz 1951; Lilly 1984). In commercially available electro-impedance testing equipment this is generally done by presenting two tones, i.e., a variable stimulus and a permanent low-frequency probe tone. The acoustical impedance can be directly derived from the resulting probe tone level recorded in the outer ear (Bennett 1984). Thereby, the impedance change corresponding to the presentation of the stimulus serves as an indicator for the presence of the AR.
In 1996 J. Neumann et al. described a new method to detect the acoustic reflex by means usually employed for the recording of otoacoustic emissions. Since AR can be detected by this method at considerably lower levels than for the classical AR measurement method, it has been named "low level acoustic reflex measurement (LLAR)". The method has been shown to reliably detect the AR already at levels as low as 65 dB SPL (Neumann et al. 1996). The use of low levels is supposed to be advantageous for practical applications because the high stimulation levels routinely used in ART measurement are uncomfortable or potentially even harmful to patients. They should therefore be avoided in audiological diagnostics if possible, especially for young patients, patients with high noise sensitivity and patients with a history of noise exposure. Also, a reliable AR detection at low levels for normal and moderately hearing-impaired listeners should bear the potential of reliably detecting the AR even for patients with a moderate to severe hearing loss where the conventional methods fails due to excessively high stimulation levels required. The aim of the current paper therefore is to set the baseline for clinical applications of the new LLAR method by providing normative data and by comparing its outcome with the conventional method within a group of 41 normal listeners. To assess the clinical feasibility, a pilot study with 10 subjects with a mild to moderate sensorineural hearing loss was performed. As opposed to the study of Neumann et al. (1996) study, a more robust

evaluation criterion of the LLAR was used by evaluating a phase criterion of the responses (see Figure 2.2 in the method section) that is supposed to be less susceptible to static nonlinear distortions of the measurement apparatus.

A first attempt of a clinical evaluation of the LLAR was performed by Baumann et al. (Baumann et al. 2006) with 20 hearing-impaired and 20 normal-hearing listeners. However, their measurement setup exhibited a potential flaw (i.e., a saturation hysteresis effect of the microphone preamplifier) which limits the validity of the reported results. Hence, the potential flaw in the measurement apparatus was avoided in this study, i.e., a microphone preamplifier was used that showed no saturation nonlinearity with a hysteresis in the time domain. The validity of the current apparatus was ascertained in pilot experiments prior to the current study which can therefore be considered as the first clinical application study of the LLAR method.

I. Experimental methods

a. Measurement paradigm and analysis method

The LLAR paradigm suggested by Neumann et al. (1996) uses two identical stimulus pulses separated by a small temporal gap to elicit and detect the reflex. The pulses can consist of pure tone sinusoids or broadband tone complexes whose presentation level is varied to determine the acoustic reflex threshold (Figure. 2.1 (a) and 2.1 (d)). The reflex is elicited and sustained by the first pulse of sufficient level thus resulting in a change of the middle ear’s impedance associated with the stiffening of the ossicular chain. A probe microphone placed in the occluded ear canal is used to measure the response to the two stimulus pulses. The measured response is comprised of the incident wave emitted by the probe’s receiver and the reflected wave running backwards from the tympanic membrane. The reflected wave portion depends on the acoustical properties of the middle ear so that a change in the middle ear's impedance directly affects the signal recorded by the probe microphone. The impedance change due to the acoustic reflex has a latency of 80 to 120 milliseconds (Wurzer et al. 1983; Sellari-Franceschini et al. 1986). The presented stimulus pulses are separated by a temporal gap whose length has been optimized with respect to that latency. Thus, the length of the first stimulus pulse (approx. 100 ms) in addition to the interstimulus gap of 50 ms is longer than the latency of the reflex. On the other hand, the interstimulus gap is shorter than the time it takes for the reflex to decay before the onset of the second tone pulse. This results in a maximized impedance change during the presentation of the stimulus. Therefore, the recorded responses to the two stimulus pulses differ if the acoustic reflex has been elicited by the first pulse. The difference in the responses can be expressed by simply subtracting one response from the other thus calculating the difference signal, in the following called 'residual signal'.

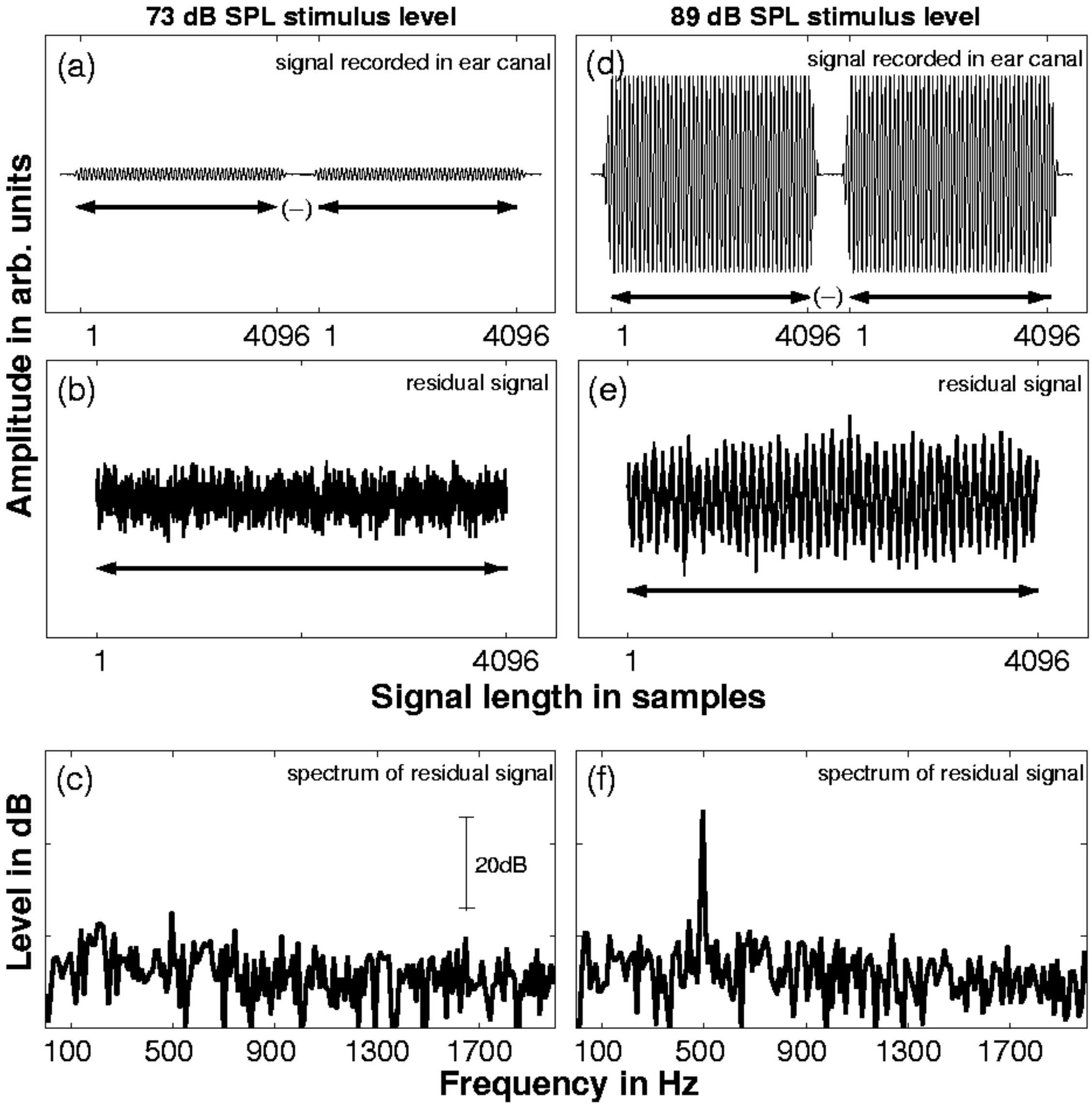

Figure 2.1: *Illustration of the LLAR method. Two identical stimulus pulses are delivered by the OAE probe used for the measurements (panel (a) and (d) respectively). The responses to the pulses were recorded by the probe's microphone and subtracted from each other in order to calculate the residual signal. If the presentation level does not elicit the reflex, the residual signal is mainly shaped by physiological noise or noise of the measurement system (panel (b)). Otherwise, the residual signal contains stimulus components (panel (e)). The presence of the components can easily be seen in the magnitude spectra (panel (c) and (f) respectively).*

In the case of an elicited reflex the spectrum of the residual signal shows the frequency components of the stimulus (Figure 2.1 (f)). Since the presence of these frequency components indicates the presence of an AR, the detection criterion of the reflex can therefore be based on an analysis of the residual signal. If the stimulus level is not sufficient to elicit the reflex, the recorded ear canal signals are almost equal for both pulses. In this case, the residual signal therefore is mainly composed of physiological noise and the noise of the measurement chain (Figure 2.1 (c)).
In order to exclude false-positive results due to random variation of the impedance during a single presentation, the method uses multiple presentations of the stimulus pair to determine the ART. By increasing the number n of repetitive measurements, the robustness towards artifacts caused by movements of the subjects can be increased at the expense of increasing the measurement time (Figure 2.2).

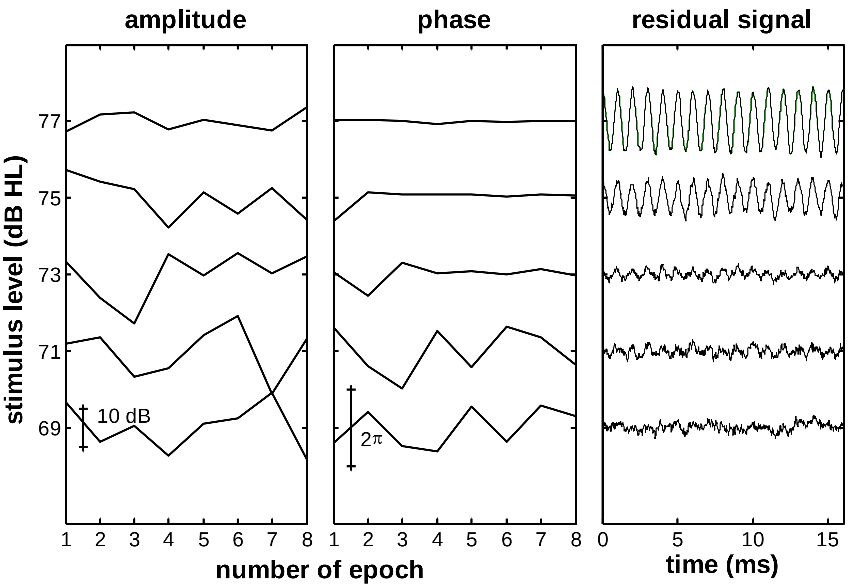

Figure 2.2: *Example of the development of phase and amplitude depending on the stimulus level. With increasing stimulus level the phase values (middle panel) of successive epochs stabilize very fast compared to the amplitude (left panel) of the residual signal (right panel).*

The criterion to determine the AR threshold is based on a coherence synchrony measure (CSM) (Valdes et al. 1997), a test of phase coherence similar to the Rayleigh test of circular uniformity (Mardia 1972). The phase coherence is determined on the basis of n successive measurements. The phase value of a selected frequency component in the residual signal is calculated for each presentation of the stimulus pair. The amplitudes of these frequency components are not considered. This results in n phase values whose coherence can be expressed by the vectorial mean of the n normalized phase vectors (Figure 2.3 (a) and (b)). The so called mean resultant length R can be computed from the phase values $\theta_i = \theta_1, ..., \theta_n$ of the selected frequency component by

$$R = \left| \frac{1}{n} \sum_{i=1}^{n} r_i \right|, \text{ with } r_i = \cos\theta_i + i \sin\theta_i$$

R can take values between 0 and 1, indicating the degree of phase coherence. If the reflex is systematically elicited by the stimulus, the reproducibility for n successive presentations and therefore the phase coherence is high, resulting in a value of R close to 1. A threshold value of $(R \geq 0.8)$ was found to allow a reliable detection of the elicited reflex with low false-positive occurrences. Since the value of the mean resultant length R does not depend on the number n of phase values used for its calculation, the same threshold detection value can be applied for the detection of the reflex regardless of the number of presentations used in the measurement.

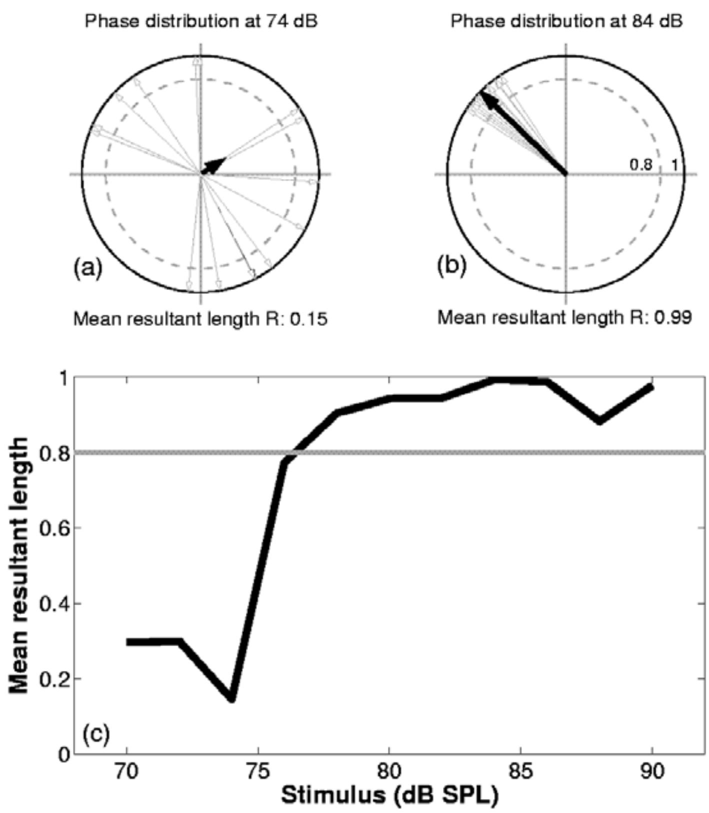

Figure 2.3: *Illustration of the phase coherence synchrony measure (CSM). The phase distribution of a selected frequency component is shown for 16 successive measurements at 74 (panel (a)) and 80 dB SPL (panel (b)), respectively. The alignment of the phase vectors at the higher stimulus level is almost identical for all measurements, indicating a high reproducibility and thus the presence of the AR. This phase coherence can be expressed by the value of the mean resultant length R, i.e. the vectorial means of the phase vectors. Panel (c) illustrates the development of R over increasing stimulus levels, showing a coherence jump at 75 dB SPL. The horizontal line at a value of R=0.8 indicates the empirically found threshold used to detect the presence of the AR.*

In this study the detection of the reflex was based on a repetition number of 8 successive presentations which was found to be a good compromise between robustness of the measurement towards artifacts and time effort (Müller-Wehlau et al. 2002). Additional artifact suppression was applied by rejecting all measurements with a residual signal amplitude at the evaluation frequency that was not within a 6 dB margin of all measurements at the respective stimulus level. This margin primarily serves to reject single presentations that are affected by singular epochs with high noise level.

b. Setup

The whole measurement was based on a PC and implemented in a customized program that controlled and varied the presentation level. The signals used for the stimulation were generated in advance and played back using a digital I/O-card (RME DIGI 96) in the host PC. The I/O-card was connected via an optical interface to a 24 bit DA/AD-converter (RME ADI 8 Pro). The analogous signal was delivered using an OAE-probe (Otodynamics ILO BT-Type) driven by a headphone buffer (Tucker-Davis Technologies HB6). The recorded signal was amplified by an external low-noise amplifier (Stanford Research SR560) and submitted to the AD-converter.
The microphone chain was calibrated according to Siegel (Siegel 2002) using a Bruel & Kjaer type 4192 microphone capsule as reference. An artificial ear for insert ear phone (Bruel & Kjaer Type 4157) and a broadband calibration signal (100-10000 Hz) were used to calibrate the output path including the probe speaker. The transfer function obtained by this calibration procedure was used to calculate a phase invariant overlap-add filter to correct the stimuli for the frequency response of the output system. No individual correction like an in-the-ear calibration was performed.
Since systematic distortions introduced by the measurement system can result in false-positive responses by the detection criterion, the artifact reliability was tested in different cavities as well as in subjects with no residual hearing. Measurements in cavities with volumes between 1 and 5 cc provided a test for the reliability of the procedure in a situation with low ambient noise and no physiological artifacts. The tests were done with different volumes of the cavities because the sound pressure at the plane of the microphone depends on the transfer function of the system. No elicited reflex was detected for measurements in any of the cavities for stimulation levels up to 105 dB SPL. To test the artifact reliability in a real ear canal,

corresponding measurements were done in subjects with no residual hearing but functional middle ear. Four experienced cochlear implant users (1 male, 3female, aged 51-67 years) participated in this experiment with the implant turned off for the duration of the measurement. The hearing threshold without the implant was higher than the maximal presentation level for the reflex measurement, so that no acoustical reflex could be expected for these subjects. As for the measurements in the cavities no reflex was found in these four subjects with presentation levels of maximal 101 dB SPL, demonstrating a high reliability under physiological conditions.

II. Experimental setup

a. Subjects

The evaluation of the LLAR was done with 51 subjects (32 male, 19 female) aged 16 to 64 years (average 30 years) with normal-hearing (41 subjects) or mild to moderate hearing loss (10 subjects). If no recent audiograms existed the pure tone thresholds for both ears were measured before the experiment. The middle ear function was tested by measuring a tympanogram with an impedance audiometer (Interacoustics AZ26). Subjects exhibiting only small compliance changes (< 0.3 ml) in the tympanograms were excluded from the experiment. The same impedance audiometer used for the audiological examination was utilized to obtain the reference reflex thresholds.

b. Stimuli

The stimuli consisted of two identical pulses containing pure tone sinusoids of 500, 1000, 2000 or 4000 Hz with a length of 4096 samples. The sampling frequency of the signals was 44.1 kHz resulting in a duration of the stimulus pulses of T=92.88 ms. The stimulus frequency was adjusted to fit exactly into the pulse length, i.e. the exact frequencies were chosen to be multiples of the fast Fourier transform (FFT) base frequency 1/T. Hanning-shape ramps of 20 samples length were added at the beginning and the end of the pulses to avoid onset effects. The two pulses were separated by a temporal gap of 2205 samples in order to account for the latency of the reflex. Successive presentations of the stimulus were set 1.15 s apart to allow the reflex to decay before subsequent stimulations. These settings were found to result in the largest residual signals.

c. Procedure

The measurement was set up inside a sound attenuated hearing booth where the subjects rested on a chair and where asked not to move for the duration of the experiment. The LLAR program was set to an automatic mode with the stimulus level starting at 80 dB SPL and subsequently decreasing or increasing depending on the reflex detection. After each reversal the level increment was reduced from 10 dB to 4 dB and finally to 2 dB. Depending on the direction of the level change, either the first or the last measured level at which the reflex was successfully detected after the final reversal was taken as the ART. The stimulus level was restricted to 101 dB SPL and no ART was recorded if the reflex could not be detected by three successive measurements at the maximal stimulus level. The phase coherence used for the detection of the acoustic reflex threshold was calculated from eight successive presentations of the stimulus. Since the number of measured stimulus levels varied for the different measurements, the time required for the experiment was not equal for all subjects. On average the measurement of both ears took approximately 12 minutes.

Before each measurement the fit of the OAE-probe was tested by presenting and recording a broadband signal in the sealed ear canals. The spectrum of the recorded signal was compared to a reference spectrum obtained with an artificial ear (Bruel & Kjaer type 4157) by the same procedure. The position of the probe in the subject's ear was adjusted to achieve a sufficient correspondence with the reference spectrum. The same procedure was repeated after the measurement and the correlation of the power spectra obtained before and after the measurement had to be at least 75 %.

Reference ARTs were obtained during the audiological examination using an impedance audiometer (Interacoustics AZ26) that is commercially available and well established in clinical diagnostics. To compare the thresholds gained by the LLAR and the established method the impedance audiometer was also set to an automatic mode. In this mode increasing stimulus levels were presented to the subjects and the acoustic reflex thresholds were determined by means of the absolute impedance change correlated with the stimulus presentation. The default detection threshold in this mode is given by a change of 3 % of the initial compliance value. The output level of the impedance audiometer was measured with the same artificial ear for insert ear phones (B&K Type 4157) used for the calibration of the LLAR setup to allow a direct comparison of the obtained ART values for the two procedures.

III. Results

The results of the evaluation for the normal hearing subjects are given in Figure 2.4 and 2.5. The results gained with the LLAR are referred to as ‘LLAR’ while the reference data measured with the conventional method are labelled ‘convAR’. Figure 2.5 displays a comparison of the detection rate of the acoustic reflex for the four test frequencies. The median response thresholds for the respective frequencies are shown in Figure 2.4. Statistically significant differences in the measured reflex thresholds (Wilcoxon rank test at $p < 0.01$) and the detection rates (two sample t-test at $p < 0.01$) are marked by one or two asterisks above the respective result bars. The data are based on the results of 41 subjects with 82 ears measured.

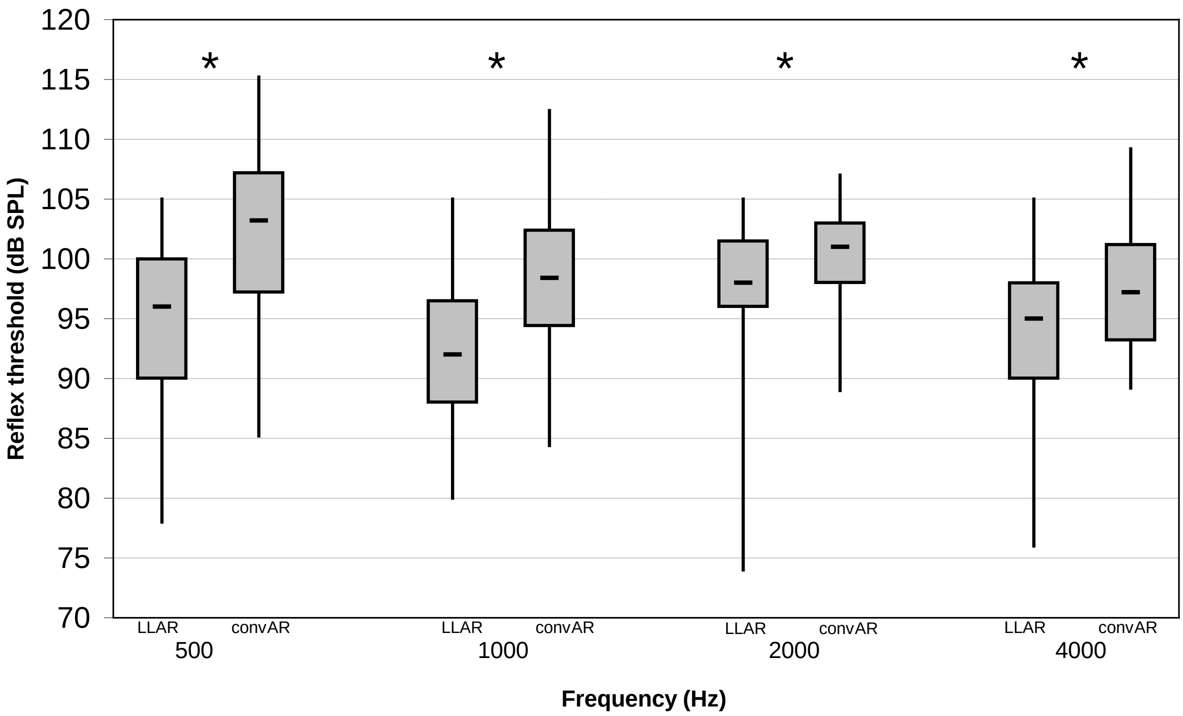

Figure 2.4: *Median acoustic reflex thresholds of the normal hearing subject group (N= 41) determined by the conventional method (convAR) and the LLAR. Bars indicate the interquartile range and the thin bar the total range of obtained thresholds for all subjects. Statistically significant differences of the acoustic reflex threshold (Wilcoxon rank test at p<0.01) between the two methods are indicated by the asterisk above the respective result bars.*

The detection rate of the LLAR method varies across frequency and is highest for the 1000 Hz stimulus (97.6 %) and lowest for 4000 Hz (80.5 %). The average detection rate is 88.7 %. This is clearly larger than the detection rates found with the established procedure (Method convAR) that range from 61.0 % (4000 Hz) to 81.7 % (1000 Hz) with an average of 75.9 %.

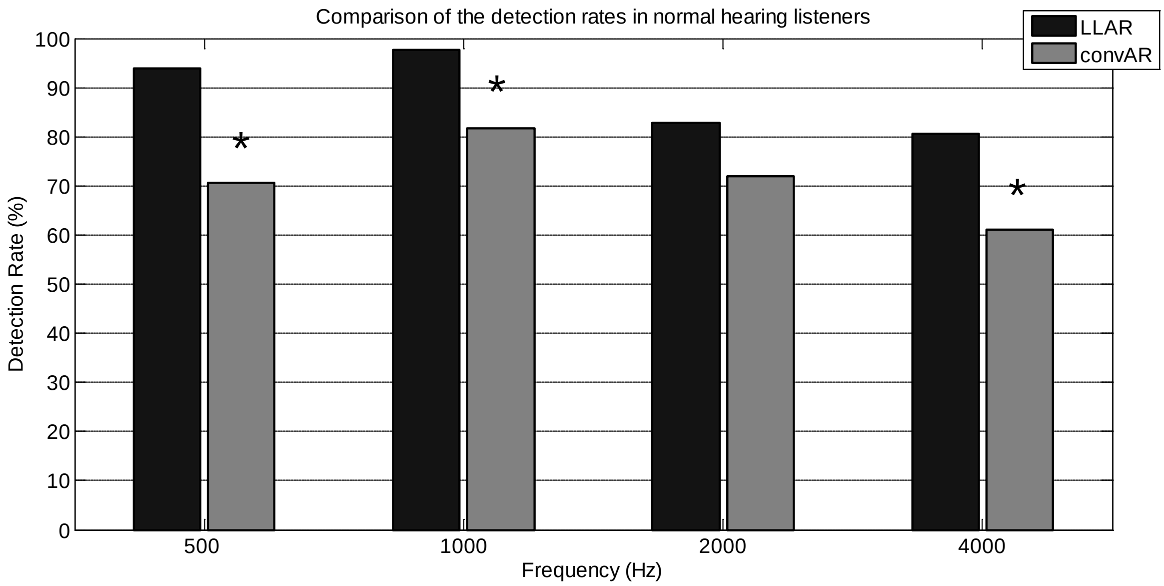

Figure 2.5: *Comparison of the detection rates of the two methods for 41 subjects. Significant differences (two sample t-test at p<0.01) of the rates are marked by the asterisk.*

The median response thresholds (Figure 2.4) determined with the LLAR range from 92 dB SPL (1000 Hz) to 98 dB SPL (2000 Hz). This is lower than the thresholds found with the conventional AR procedure with median differences amounting to 7.2 dB (500 Hz), 6.4 (1 kHz), 3 dB (2 kHz), and 2.2 dB (4 kHz), respectively.

A Wilcoxon rank sum test (Sachs 2002) reveals the significance of the differences ($p < 0.01$) between the mean ARTs measured with the LLAR and the conventional method for all test frequencies. On average the response threshold for the LLAR measurements were 4.7 dB lower than the ARTs obtained with the conventional method.

The results for the 10 subjects with mild to moderate hearing loss are shown in Figure 2.6 and 2.7. The detection rates for this subject group are generally lower compared to the rates found in all subjects. This is especially the case for the 4000 Hz stimulus with detection rates decreasing from 80.5 % to 45 % (LLAR) and 61.0 % to 30 % (convAR) respectively. The difference of the median response thresholds between the two methods amounts to 11.2 dB (500 Hz), 8.4 dB (1000 Hz), 2 dB (2 KHz), and 5.2 (4 kHz), respectively. However, due to the small number of ears where the ART could be detected with both methods the significance criterion could only be exceeded for the 500 Hz test frequency.

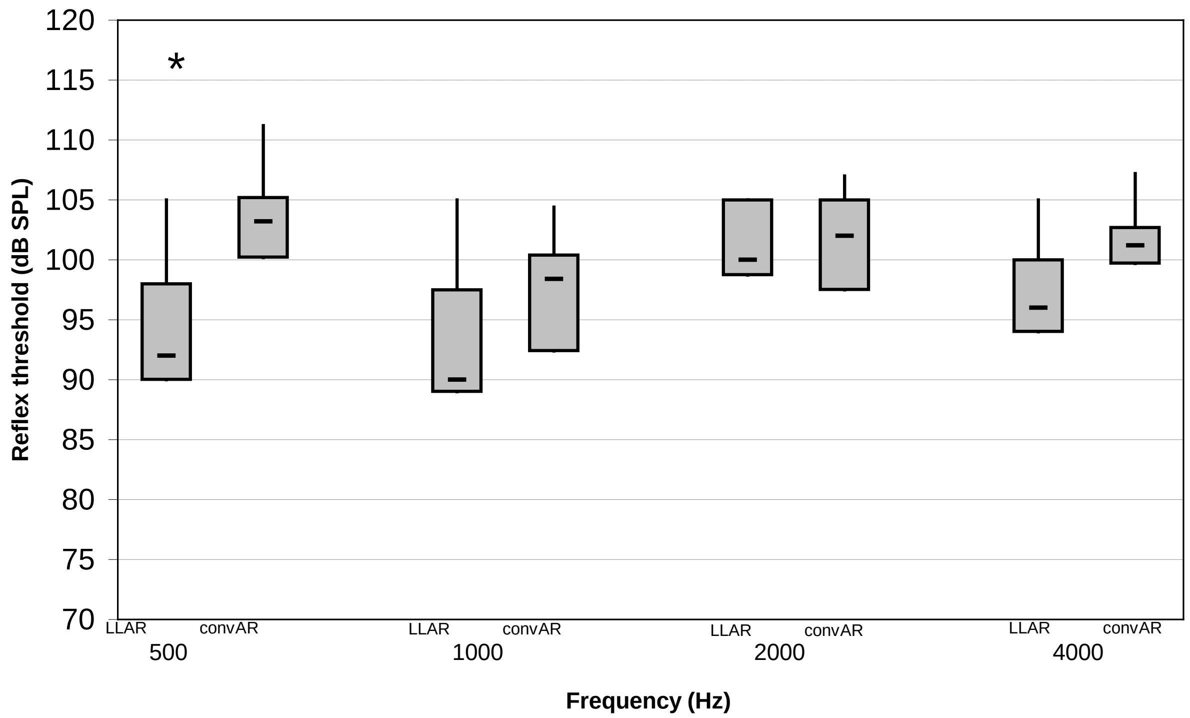

Figure 2.6: *Illustration of the median ARTs for the LLAR and the conventional method (convAR) for subjects with mild to moderate hearing loss (n=10). A significant difference between the two methods could only be found for the 500 Hz stimulus frequency.*

IV. Discussion

The results indicate that lower reflex thresholds can be obtained by the LLAR method compared to the ARTs measured with the conventional method. The ART difference of up to 7 dB or 11.2 dB (at 500 Hz), respectively, means a considerable reduction in the presentation level. Furthermore, the stimulus duration of less than 100 ms is much shorter than in the conventional method (600ms) which results in a loudness ratio between both stimuli corresponding to approx. 4 dB (Verhey & Kollmeier 1998). Hence, the subjects informally described the LLAR measurements to be much more comfortable than the conventional ART method. The detection rate (Figure 2.5) of the LLAR is higher for all frequencies compared to the detection rate achieved with the conventional method.

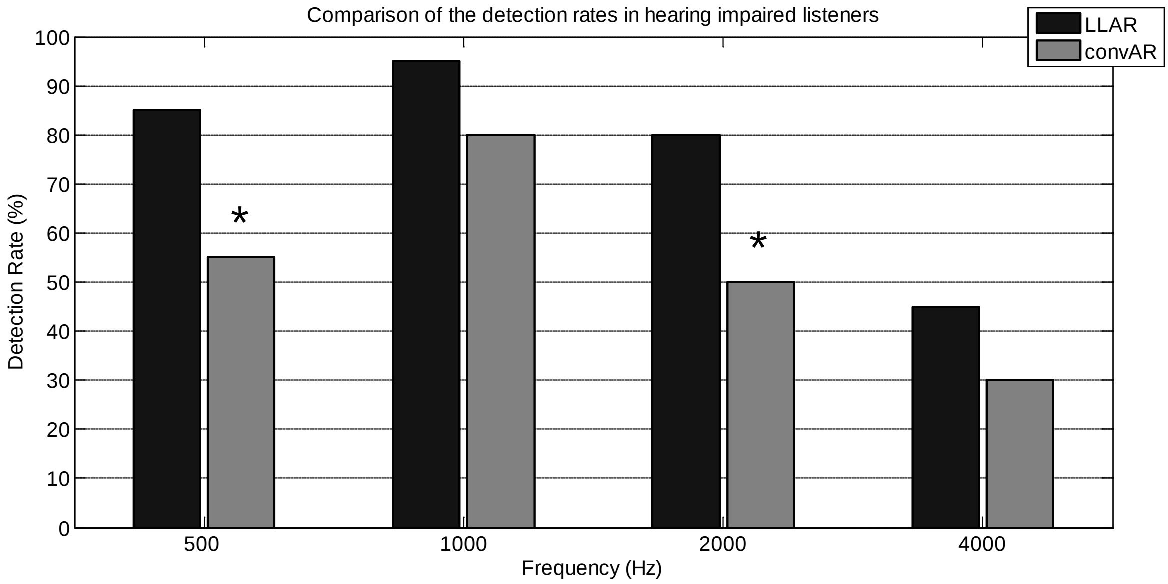

Figure 2.7: *Comparison of the detection rates of the two methods for 10 subjects with mild to moderate hearing loss. Measurement frequencies that show significant differences between the two methods are marked by the asterisk.*

In a similar investigation Baumann et al. (2006) compared the reflex thresholds obtained with the LLAR and the conventional AR method (using an Interacoustics AT235h) in normal-hearing and hearing-impaired listeners (n=20 ears in each subject group). In contrast to the present study the results by Baumann et al. show lower reference thresholds for the conventional method with normal-hearing listeners. This difference is due to the fact that the ARTs were not only automatically but visually determined by an experienced examiner. The LLAR thresholds and detection rates found by Baumann et al. were similar to the present study except for the 4000 Hz stimulus where a potential methodological problem existed (see below). Across all frequencies the acoustic reflex threshold determined by the LLAR method was 3.3 dB lower than the conventional ART. The results of the hearing-impaired subject group are comparable in both studies although the subject groups are too small and the variability in hearing loss is too large to obtain significant differences across methods.

For the 4000 Hz stimulus Baumann et al. (2006) obtained a LLAR threshold in all subjects which was much lower than in the present study. This difference is probably due to a potential technical flaw: Baumann et al. (2006) reported that their apparatus is susceptible to a hysteresis effect when overdriving the electret condenser microphone. Since the microphone is coupled to a measuring preamplifier with low input impedance such an overdrive might cause a depletion of the current in the probe microphone circuitry. This causes a systematic artifact that can result in a false detection of the reflex. In contrast, in the current study the problem has been accounted for by using a high-impedance microphone preamplifier. Also, the absence of false positive response detection was verified by testing the method in subjects fitted with cochlear implants.

The lower response thresholds obtained with the LLAR together with the shorter stimulation time shows the potential of the LLAR as a useful tool in patients with hyperacusis or in infants. The higher detection rate of the method additionally increases its value in the clinical diagnostics.

A restriction of the LLAR is given by the longer measurement and preparation time. On the average, determination of the reflex thresholds at four frequencies takes 6.5 minutes with the LLAR compared to the measurement time of less than 2 minutes using the conventional method. Additionally, more time is required to place the probe and execute the fitting test. The longer time to execute the test limits its feasibility in clinical application. However, the current procedure has not yet been optimized with respect to measurement time and the ratio between measurement accuracy and observation time. For example, the LLAR at a certain level is probed several times during the course of the adaptive tracking procedure in order to achieve a high reliability of ART estimation (see method section) while the conventional method uses a simple upward track of stimulus levels until the first significant response occurs. Hence, the LLAR procedure has a large potential to reduce the time effort if the same statistical uncertainty in threshold estimation would be implemented as for the conventional method. A second possibility to decrease the measurement time would be to use narrowband multifrequency-component stimuli instead of sinusoids in combination with a multifrequency detection algorithm. This would allow for several simultaneous observations in a certain frequency region and hence improve the observation statistics within a given amount of time or decrease the measurement time for a given statistical uncertainty of the observed threshold. A third possibility might be to apply a more efficient adaptive tracking procedure for a fast approximation of the reflex threshold.

V. Conclusions

Based on the group of 41 normal listeners and 10 mild-to-moderately hearing impaired listeners employed in this study the following conclusions can be drawn:

- The low level acoustic reflex audiometry (LLAR) yields significantly lower acoustic reflex thresholds and a higher acoustic reflex (AR) detection rate than the conventional measurement paradigm using a standard impedance audiometer.
- The LLAR procedure is subjectively more comfortable to patients due to a smaller perceived loudness of the stimuli.
- The measurement time of the experimental setup used with the LLAR is by a factor of three larger compared to the commercially available impedance audiometer. However a large potential exists to further cut down the time requirements in a clinically optimized procedure.
- A full clinical comparison of the LLAR method with the conventional ART method would be required using a large number of patients and the same rigourous statistical criteria for both methods (including a comparison of test and retest results).

Chapter 3

The effects of neural synchronization and peripheral compression on the acoustic-reflex threshold [a]

This study investigates the acoustic reflex threshold (ART) dependancy on stimulus phase utilizing low-level reflex audiometry (Neumann et al. 1996; Neumann 1997). The goal is to obtain optimal broadband stimuli for elicitation of the acoustic reflex and to obtain objective determinations of cochlear hearing loss. Three types of tone complexes with different phase characteristics were investigated: A stimulus that compensates for basilar-membrane dispersion thus causing a large overall neural synchrony (basilar membrane tone complex - BMTC), the temporally inversed stimulus (iBMTC) and random-phase tone complexes (rTC). The ARTs were measured in 8 normal-hearing and 7 hearing-impaired subjects. Five different conditions of peak amplitude and stimulus repetition rate were used for each stimulus type. The results of the present study suggest that the ART is influenced by at least two different factors: (a) the degree of synchrony of neural activity across frequency and (b) the fast-acting compression mechanism in the cochlea that is reduced in the case of a sensorineural hearing loss. The results allow a clear distinction of the two subject groups based on the different ART for the utilized types and conditions of the stimuli. These differences might be useful for objective recruitment detection in clinical diagnostics.

[a] This chapter is published as
Müller-Wehlau M., Mauermann M., Dau T. & Kollmeier B. 2005. The effects of neural synchronization and peripheral compression on the acoustic-reflex threshold. J. Acoustic. Soc. Am, 117, 3016-3027.

Parts of this study were presented at the 27th Midwinter Research Meeting of the Association for Research in Otolaryngology 2004 in Daytona Beach, Florida [Müller-Wehlau et al., abstract No. 913, p. 309].

Introduction

The acoustic reflex is a contraction of the middle ear muscles induced by an intense auditory stimulus. Stimulation on either the ipsi- or the contralateral side should result in bilateral muscle contraction in a normal system. Investigations indicate that the main purpose of the reflex is to serve as an attenuator for low frequency body noise (Simmons 1964; Katz 1977; Gelfand 1998). It is believed that, of the two middle-ear muscles in humans, only the stapedius muscle contracts in response to sound as an acoustic reflex (Borg 1973; Jerger & Northern 1980). The reflex elicitation is normally measured acoustically by means of the middle ear's impedance change due to the middle ear muscle contraction and hence the stiffening of the ossicular chain (Metz 1951; Lilly 1984). Detection of the reflex elicitation and assessment of its parameters are commonly used for clinical diagnostics of the hearing system. Deviations of the acoustic reflex threshold, for example, are used as an indicator for neural lesions affecting any portion of the reflex arc central to the cochlea (Clemis 1984). The pure-tone ART remains almost unaffected by sensorineural hearing loss up to 60 dB (Metz 1951; Kawase et al. 1997). Generally, the ART decreases with increasing bandwidth of the stimulus eliciting the reflex (Gorga et al. 1980) similarly to the effect of loudness summation in perception. In cases of severe sensorineural or conductive hearing loss, the ART often exceeds the maximal stimulus level of 100 dB HL applied by most impedance bridges. Lower detection thresholds would be preferable, e.g. to make ART measurements usable in subjects with an acute auditory damage.

The main goal of the current study is to find an optimal broadband stimulus for low-level elicitation of the ART. Therefore we adapted a stimulus that is optimized for the measurement of auditory brainstem responses (ABR). Dau et al. (2000) demonstrated a significant gain of wave-V amplitude of ABR compared to click stimuli by using a phase-optimized chirp stimulus (BMchirp) that compensates for basilar-membrane travel-time differences across frequency and thus results in a highly synchronized neural excitation. The gain of neural synchronization is reflected in higher stations of the neuronal pathway like the ventral cochlear nuclei (VCN) and the superior olivary complex (SO) where discharge timing is correlated with cochlear partition motion (Scherg & von Cramon 1985; Shore et al. 1987). A stimulus very similar to the chirp stimulus that was optimized for ABR measurements was tested here to reduce the ART. This seems reasonable since the afferent component of the neural pathway of the acoustic reflex can be assumed to follow almost the same path as the sources of ABR. The reflex arc comprises, among other stations, the auditory nerve (N. VIII), the VCN, and the medial nucleus of the SO, before it turns back via the facial nerve (N. VII) to the ear. Therefore, a larger excitation of certain nuclei involved in ABR measurements due to the use of phase-optimized stimulation may be accompanied by a reduction of the ART. The hypothesis tested in the present study was that the chirp stimulus suggested by Dau et al., or a variant of it, may represent an ideal stimulus also for ART measurement due to the increased synchrony of the neuronal excitation. In the following, we refer to this chirp stimulus as the BMchirp. Instead of using single BMchirps, specifically designed tone complexes were used in the present study. These basilar membrane tone complexes (BMTC) have essentially the same phase characteristics as the original BMchirps, but allow an easier analysis of the residual signal for reflex detection than the original chirps. In addition to the measurements using the BMTC stimuli corresponding measurements were done with the temporally inverted BMTC tone complexes (iBMTC). The expectation was that the gain due to neural synchronization using the BMTC stimuli would result in a low ART, while the excitation would be highly desynchronized using the iBMTC stimuli thus resulting in a much higher ART. As a reference, a set of noise-like stimuli was tested consisting of tone complexes with the same magnitude spectrum as the BMTC and iBMTC but with random phase components. Compared to the former stimuli these random-phase tone complexes (rTC) were expected to produce an ART that lies between those obtained with the BMTC and the iBMTC.

However, other aspects besides neural synchronization may also be important for ART determination. For example, effects of peripheral compression due to the different internal representations of the stimuli on the BM may play a role. Kubli et al. (Kubli et al. 2001) measured the acoustic reflex with positive and negative Schroeder phase tone complexes (Schroeder 1970). They explained the differences of ART for these two types of stimuli by the different internal representations at the output of cochlear filtering. The internally stronger modulated positive Schroeder phase stimuli (S+) are supposed to be more affected by fast-acting compression on the BM – thus resulting in increased ARTs - than the negative Schroeder phase stimuli (S-), which produce a flat internal envelope. In several psychoacoustical detection experiments

(Kohlrausch & Sander 1995; Summers & Leek 1998; Lentz & Leek 2001; Oxenham & Dau 2001; Oxenham & Dau 2004) the differences of internal representations produced by the Schroeder tone complexes with opposing phase have also been investigated. In these studies, modified Schroeder phase harmonic tone complexes with different phase curvature showed a different efficiency in masking according to their different temporal modulation within the local auditory filters. These different internal representations are presumably also affected by the compressive characteristics of the BM processing and result in perceptional differences (Carlyon & Datta 1997b; Summers & Leek 1998; Oxenham & Dau 2004). A further variable affecting the ART could be the influence of temporal integration of the stimulus. Although various studies have investigated factors that act as a trigger that elicit the acoustic reflex (Gorga et al. 1980; Kawase et al. 1997; Kawase et al. 1998) it is not entirely clear whether signal information is integrated within a certain time frame or whether the peak amplitude, power or loudness of the stimulus is appropriate to describe the internal threshold of ART elicitation. In order to test the role of temporal integration and peripheral compression in the current study the peak-to-rms ratio was varied within a stimulus time frame of about 100 ms. In addition, experiments were carried out in normal-hearing (NH) and hearing-impaired (HI) subjects to investigate the influence of the compressive mechanisms on the BM.

I. Measurement paradigms and data analysis

a. Low level reflex audiometry (LLAR)

To obtain improved ART measurements, i.e., low ART thresholds, we use a method suggested by Neumann et al. (1997), called low level acoustic reflex audiometry (LLAR). For tone-pulses, this method is more sensitive than the conventional paradigm (Tolsdorf et al. 2004). Also, the short stimulation time used in this method is more comfortable for the subjects than the stimulation used in the common method. This is especially important since the acoustical stimulation in this study was carried out with levels up to 103 dB SPL. The LLAR uses the same measurement paradigm and equipment as typically employed for the recording of otoacoustic emissions. In this method, rather than using two signals at different frequencies (the evoking stimulus and a continuous test tone – mostly at 226 Hz) as commonly used, a stimulus consisting of two identical short pulses is used to elicit and detect the reflex (see Figure 2.1 (a) and (d)). The technique is based on the following principles: If the reflex is elicited during the first stimulus pulse and holds, the eardrum impedance has changed during the presentation of the second pulse. This change of impedance causes a difference between the recorded time signal of the first and second pulse within the sealed ear canal. Since the change in impedance due to the acoustic reflex has a latency of some tens of milliseconds, the second tone pulse is presented after a sufficiently long time following the first, thus leading to a maximal difference of the measured ear canal response between these two pulses. The difference signal, or the residual of the ear canal signal, recorded during the presentation of the two tone pulses, is analyzed to indicate the elicitation of the acoustic reflex.

Without an impedance change of the eardrum, i.e. if the first stimulus pulse elicits no reflex, the recorded ear-canal signal is almost the same during both pulses (Figure 2.1 (b)). Thus the spectrum of the difference signal mainly reflects the physiological noise and the noise of the measurement system (Figure 2.1 (c)). In the case of an elicited reflex (Figure 2.1 (e)), the spectrum of the residual shows the frequency components of the stimulus signal (Figure 2.1 (f)). The existence of these frequency components indicates the elicited reflex.

A reliable detection of the stimulus component(s) within the residual signal is essential for the correct detection of the acoustic reflex. Further criteria are needed especially at higher stimulation levels (close to the limit of the experimental setup) to distinguish between difference components due to the acoustic reflex and physiological or system artifacts. The low level reflex measurement (Neumann 1997) utilized for this study was supplemented with a different threshold criterion (see below), since the original criterion used was shown not to be sufficiently reliable (Müller-Wehlau et al. 2002).

b. Analysis Methods and ART criterion

The analysis method originally suggested by Neumann et al. (1996) is based mainly on a signal-to-noise criterion for the frequency component(s) of the stimulus within the magnitude spectrum of the residual signal and a further rejection criterion to account for system distortion. However, at higher stimulus levels, this method sometimes indicated an ipsilateral acoustic reflex due to artifacts such as heartbeat, even in cochlea implant (CI) patients with complete hearing loss and the CI turned off (own unpublished data). In the current study the threshold criterion was based on a coherence synchrony measure (CSM), which is a highly accurate statistical indicator in signal detection (Valdes et al. 1997). The CSM takes the reproducibility of n repetitive measurements (in this study n = 16) as the criterion to detect the elicited reflex. The CSM is similar to the Rayleigh test of circular uniformity (Mardia 1972) and can be considered as a measure of phase coherence calculated only from the phase values of a selected frequency component from n successive measurements without considering the amplitude of the signal spectral component.

The threshold criterion is given by the mean resultant length R, i.e. the absolute value of the vectorial mean of the normalized phase vectors for a selected frequency component from n consecutive measurement intervals. This method takes into account that successive stimulations demonstrate fast stabilization of their phase values if the stimulus level is high enough to elicit the reflex, thus resulting in highly coherent phase values. This results in a small vectorial mean of the phase vectors, i.e., a small value of R (see Figure 2.3 (a)) if the phases from consecutive measurement intervals of the selected frequency component are randomly distributed. In contrast, similar phase values of consecutive residuals result in a value of R close to one (see Figure 2.3 (b)). The mean resultant length R can be computed from the phase values $\theta_i = \theta_1, \ldots, \theta_n$ of the selected frequency components by:

$$R = \left| \frac{1}{n} \sum_{i=1}^{n} r_i \right| \quad \text{with} \qquad r_i = \cos\theta_i + i \sin\theta_i$$

Depending on the phase coherence the mean resultant length can take values between 0 and 1. If the resultant length is higher than (an empirically found value) $R \geq 0.8$, the reflex is assumed to be elicited (see Figure 2.3). This value for R is higher than those commonly used for signal detection in noise by the Rayleigh test[1]. This higher R-value represents therefore a more conservative criterion for the reflex elicitation, and meets the fact that ambient factors give rise to small differences in the recorded microphone signal thus resulting in the presence of spectral components even if the reflex is not present.

[1] The critical value typically used for the detection of a sinusoid in noise for 16 repetitions $R_0(16,0.001)$ is 0.63 (Mardia, 1972). Here we use the more conservative empirically established reflex elicition threshold value of $R_0 = 0.8$.

Additional artifact suppression was used by rejecting all single measurements whose individual residual amplitude at the selected frequency component was not within a 6 dB margin of the median of all measurements at the respective stimulus level.
The statistical evaluation in the present study was based only on the analysis at one frequency (close to 1000 Hz). A detailed examination of the evaluation frequency by using broadband stimuli show that between 500 and 1500 Hz the reflex detection does not depend on the selected frequency component. Within this frequency band the change in middle ear impedance is relatively large resulting in a clear residual signal if the reflex is elicited. At lower frequencies the phase coherence is more affected by ambient low frequency noise, while there are broad frequency bands with a strongly reduced change in impedance at higher frequencies[2].

c. Stimuli

All stimuli consisted of two identical signal frames (see Figure 2.1) with frequency components between 100 and 8000 Hz and 4096 samples in length. Since the sampling frequency was 44.1 kHz, the duration T of a single stimulus frame was 92.88 ms. The frequency components were adjusted to the signal length, i.e. the exact frequencies were chosen to be multiples of the Fast-Fourier transform (FFT) base frequency, 1/T. ARTs were measured for three different types of stimuli. Since our data analysis requires that an appropriate frequency component is presented during the stimulation, all signals used in the experiments were chosen as tone complexes. Twenty samples of Hanning shaped ramps were added at the beginning and the end of each 4096 samples long stimulus plateau. Two stimulus frames were separated by a 50 ms gap to be used as a stimulus signal by the LLAR method. Presentations of this frame pair were 1.15 s apart to allow the reflex to decay before subsequent stimulations. In optimization measurements for the LLAR these settings were found to result in largest residual signals (own unpublished data).

1. Tone complexes compensating for cochlear delay across frequency

These stimuli, in the following referred to as the basilar membrane tone complexes (BMTC), were generated by adding frequency components with phases that hypothetically compensate for the BM travel-time differences between the different

---

[2] In some subjects at higher frequencies, the ART would have been detected even at lower levels while no reflex would have been detected in other subjects at these frequencies. Around 1000 Hz appears to be a frequency region of a reliable impedance change across all subjects

spectral components contained in the stimulus. The stimulus generation was based on the computation of the “approximate” chirp stimulus as defined in Dau et al. (2000) that was optimized for ABR recordings. According to Dau et al. (2000), the propagation time required for the calculation of the respective phase values was estimated using the cochlea model proposed by de Boer (Boer 1980) and the frequency-place transformation suggested by Greenwood (Greenwood 1990).

The phase of each frequency component of the tone complex was chosen as follows: The instantaneous phase, φ_{inst}, of the original BMchirp was calculated for the time $t = t_{fs}$ when the instantaneous frequency of the BMchirp equals the frequency f_s of the selected tone complex component. The starting phase, φ_0, for the frequency component at time t = 0 was computed such that this component has the phase φ_m at the time $t = t_{fs}$. By superimposing the components with a frequency spacing corresponding to the base frequency of the selected time frame, the respective time signal of a single chirp with flat spectral envelope is achieved (see Figure 3.1 (c) and (f)).

2. Temporally inverted tone complexes

The second class of stimuli was generated by temporally inverting the BMTC stimuli. In the following, these stimuli are referred to as the inverted basilar membrane tone complexes (iBMTC, see Figure 3.1 (b)). The expectation was that by inverting the BMTC stimulus the amount of neuronal excitation would be highly desynchronized thus leading to an increased ART.

3. Random-phase tone complexes

Corresponding measurements were also obtained with a third tone complex with identical magnitude spectrum but random phases of the components, referred to as the random tone complexes (rTC, Figure 3.1 (e)). The rTC stimulus for one measurement was generated with respect to one uniformly distributed random phase vector. To exclude incidental compression or synchronization effects due to this certain random phase vector, the measurements were carried out for three rTCs generated with different set of the random phases.

4. Number of chirp periods per frame - frequency spacing

The BMTC and iBMTC stimuli, comprising frequency components with spacing equal to the FFT base frequency, exhibit one chirp within the stimulating time frame. Doubling the frequency spacing gives rise to a time signal exhibiting two chirp periods within the time frame of about 100 ms. Further increase of the spacing by a factor N results in an increasing number of N "overlapping" chirps in the time domain. In the following, the number N of the chirps used in a certain stimulus is indicated by an index in the stimulus name (e.g. $BMTC_3$ for a BMTC-stimulus comprising three chirps per recording frame (see Fig 3.1 (a), (b) and (c)). The same notation is used for the rTC stimuli although the recurring structure in the time domain is not as clearly seen as for the chirp stimuli.

At a fixed rms-value, the number of chirp periods (N) and hence the peak-to-rms ratio was varied (compare Figure 3.1 (a), (d) and (e)) in order to investigate possible summation and compression effects within one stimulus frame. The duration of the original BMchirp for the frequency range used in the current study is 10.4 ms (Dau et al. 2000). We refer to this chirp length as the effective BMchirp duration. Using a maximum number of N=7 successive chirps within a stimulus frame of about 100 ms avoids a significant overlap of the chirps within the effective duration. Therefore, interactions of successive chirp periods in the same BM regions within the stimulation can be mostly excluded.

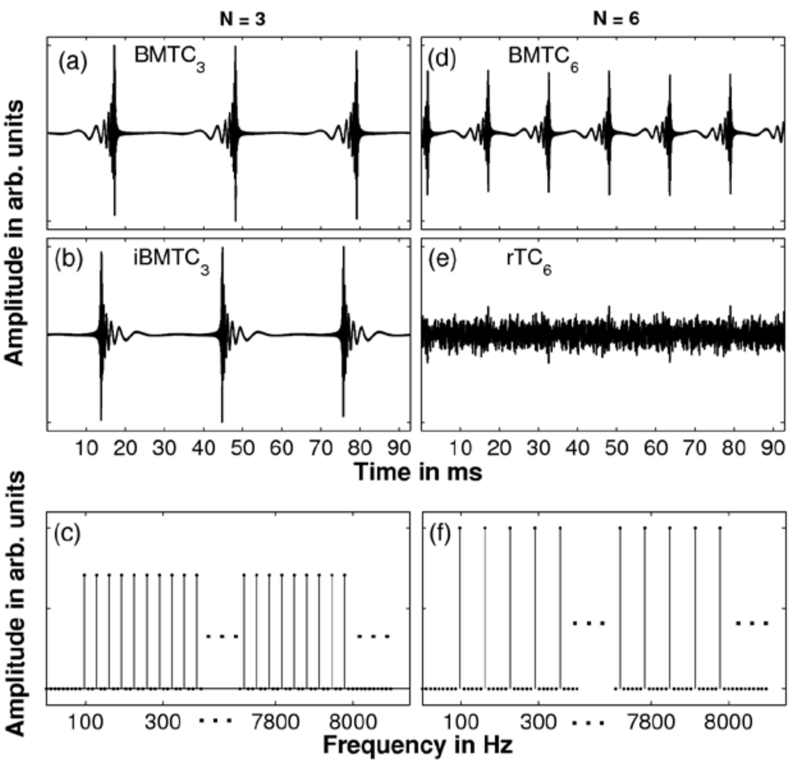

Figure 3.1:
Stimulus signals: $BMTC_3$ (a), $iBMTC_3$ (b), $BMTC_6$ (d) and rTC_6 (e). All signals are scaled to the same rms level and exhibit a flat spectral envelope with a varied number of contained frequency components. By adding frequency components that are separated by a multiple of the FFT base frequency apart, the number of chirp periods within the time frame is altered without changing the general temporal shape of the successive chirp. The amplitude spectra shown in the panels (c) and (f) correspond to the stimuli shown in the panels (a), (b), (d) and (e), respectively.

d. Detection of middle ear muscle reflex versus detection of medial olivocochlear efferent reflex

In general, we assume that the difference of the recorded signals during the two stimulation intervals is mainly due to a contraction of the middle ear muscle (MEM). In normal hearing subjects it is conceivable, that the residual signal is as well affected by the medial olivocochlear (MOC) efferent reflex. Thereby, the MOC reflex needs to cause a change of a stimulus frequency otoacoustic emission (SFOAE) that is elicited by the probe stimulus (Guinan et al. 2003). Analogous to the difference of the two stimulation intervals due to the MEM this would result in a residual signal. The residual signals in HI subjects should not be affected by the MOC anyway since no or only weak SFOAE can be expected for flat hearing losses of about 50 dB. Even in the NH subjects we expect no relevant effect of the MOC reflex on the residual signal since the stimuli used here are either noise- or chirp-like with a high sweeprate. Although these types of stimuli are appropriate to elicit the MOC reflex both are unlikely to generate a sufficiently stable SFOAE to allow the detection of the MOC reflex in the residual signal. This holds especially for the noise-like rTC signals. Guinan et al. (2003) described the detection of MOC/MEM reflexes based on the change of a SFOAE evoked by a continuous sinusoid. They pointed out that, for a residual signal dominated by the MOC reflex, a rotating phase (i.e. a long group delay) is expected, as known from SFOAE, while for a MEM dominated residual signal a short group delay can be assumed. An offline analysis of the phase characteristic of the residual signal was performed at the ART level to test for a relevant influence of the MOC on the residual signal and thus on the acoustic reflex detection. This was done for rTC and BMTC at N = 3 measurements in normal-hearing subjects. BMTC and rTC showed the lowest thresholds and for N = 3 the spacing of the frequency components is sufficiently close (approx. 30 Hz) to allow a reliable phase analysis across frequency.

II. Experimental methods

a. Subjects

Eight normal-hearing (NH) subjects (5 female, 3 male) aged between 23 and 32 (average 28 years) with hearing thresholds better than 15 dB HL and six hearing-impaired (HI) subjects (4 female, 2male) aged between 38 and 67 (average 54 years) with flat sensorineural hearing loss participated in this study (see Figure 3.2). The NH subject group had no known history of audiological diseases.

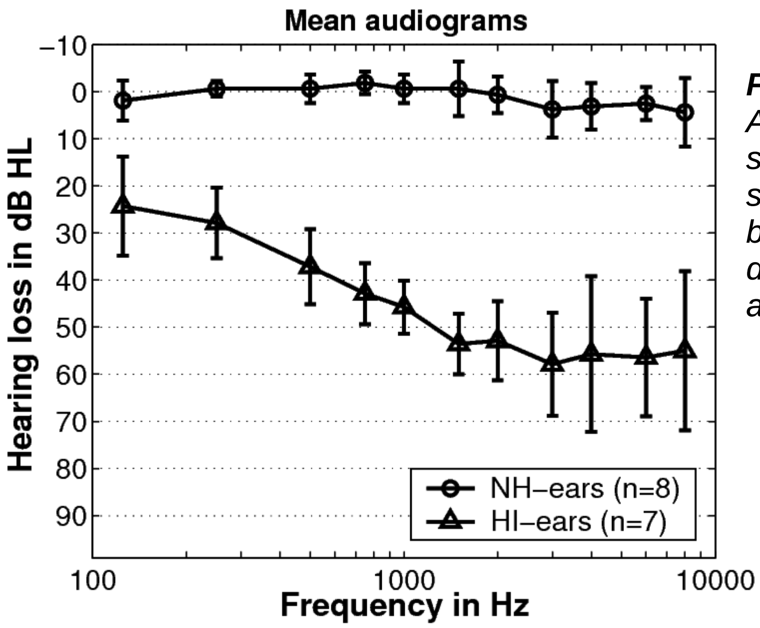

Figure 3.2:
Average hearing levels for NH subjects, (circles) and HI subjects (triangles). The error bars represent the standard deviation of the mean thresholds across subjects

The HI subjects were chosen under the assumption that the compressive non-linearity on the BM will be greatly reduced in these subjects. The ARTs in response to broadband stimulation can be expected to be elevated to some degree depending on the hearing loss. The members of the HI-subject group were restricted to subjects with a flat, moderate hearing loss of approximately 50 dB. The subject LP was measured on both sides so that for this group a total of seven measurements were performed.

An audiological examination was carried out on all subjects including reflex audiometry with a standard impedance audiometer (Grason-Stadler GSI33). The reflex threshold was ascertained by a well established method in order to make sure that the subjects showed ARTs below 100 dB HL. Subjects showing no conventionally measured ARTs within this range were excluded from further measurements since the experimental setup was limited to stimulus levels of 103 dB SPL. The limitation in sound levels was both due to technical reasons and the goal to restrict the exposure of the subjects to high level sound over the estimated measurement period of up to two hours for the full range of experiments conducted. Furthermore, subjects with tympanograms showing only small changes (<0.3 ml) in compliance were also excluded since the LLAR equipment provides no pressure equalization. No abnormally large changes in compliance (>2ml) have been observed within the subject groups.

b. Setup

The whole measurement was PC based and implemented in a customized program. The level of the signal was digitally controlled and varied on the PC. A digital I/O-card (RME DIGI 96) in the PC was used for the replay of the stimulus signal that was transmitted via an external DA/AD converter (RME ADI 8 DS) to a headphone buffer (TDT HB6) to drive the probe speaker (Otodynamics ILO BT-type OAE probe). The signal in the ear canal was recorded with an inserted probe microphone (Otodynamics ILO BT-type OAE probe) linked via a connection box that provided the required bias voltage. The microphone signal was amplified by an external low noise amplifier (Stanford Research SR560) and than directed to the AD converter. The microphone chain was calibrated according to Siegel (Siegel 2002) using a Bruel & Kjaer Type 4192 microphone capsule as reference. The output path including the probe's speakers was calibrated using an artificial ear for insert earphones (Bruel & Kjaer 4157) and a broadband (150-10000 Hz) calibration signal with flat temporal envelope. The transfer function obtained by this calibration procedure was used to calculate a phase invariant overlap-add filter to correct the stimuli for the frequency response of the output system. No individual correction or in-the-ear calibration was performed.

Before each measurement the fit of the OAE probe in the individual ear was tested online by presenting a broadband signal and recording with the OAE probe in the sealed ear canal. The spectrum of the recorded signal was displayed in comparison to a reference spectrum obtained in the artificial ear (Bruel & Kjaer 4157) with the same procedure. The fitting of the probe in the individual ear canal was altered to obtain a sufficient correspondence between the reference and the current spectrum.

c. Measurement

An automatic measurement mode was used to assert the reflex threshold starting at medium stimulus levels and subsequently increasing or decreasing the level depending on the reflex detection. After each reversal, the increment or decrement was reduced from 6 dB in the beginning down to 1 dB after the final reversal. Depending on the direction of the level change either the first or the last measured point where the reflex could successfully be detected after the final reversal, was taken as the acoustic reflex threshold. The automatic mode utilized a range of 50 to 103 dB SPL. No reflex threshold was recorded, if the reflex could not be detected for three successive measurements at the maximal stimulus level of 103 dB SPL. Since the resulting ARTs were expected to depend on the stimulus type, the starting levels of the automatic algorithm were different for the respective stimuli. All measurements took place inside a sound-attenuating hearing booth (IAC 1203) where the subjects rested in a chair and were allowed to read. Each stimulus was presented 16 times for each of the measured presentation levels. The measurement took approximately 20 minutes for each of the five stimuli. Therefore all measurements in one subject were performed in a single session of about two hours duration.

III. Results

The results were similar within each of the two subject groups, but differed significantly between the two groups ($p<0.005$)[3]. Mean data are shown in Figure 3.3.

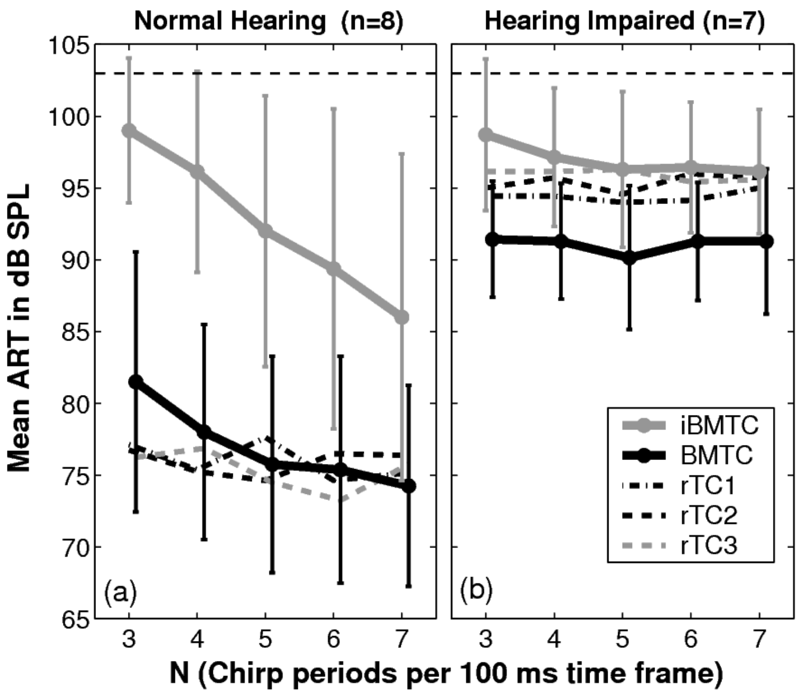

Figure 3.3:
Mean acoustic reflex thresholds (ART) for NH (Panel (a)) and HI-listeners (Panel (b)). The dashed horizontal line at 103 dB SPL indicates the maximal applied stimulus level. The error bars indicate the inter-individual standard deviation of the respective ART measurement. For the reason of clarity, no error bars are given for the three rTC-type stimuli.

[3] The comparison of the iBMTC/BMTC difference for both subject groups was done using the Wilcoxon, Mann and Whitney U-test for independent samples ($U=3.5 < 6 = U_{8;7;.005}$).

a. ARTs in normal-hearing subjects

The NH subjects all exhibit significantly (see Table 3.1) lower ARTs for the BMTC stimuli compared to the iBMTC stimuli. The acoustic reflex thresholds of these two stimuli show a clear dependancy on the number of chirps, N, within the stimulus time frame.

N=3 $t_{(7;0.05;2)}$=2.36	BMTC	iBMTC	rTC1	rTC2	rTC3	N=7 $t_{(7;0.05;2)}$=2.36
rTC_3	**2.95**	**14.02**	0.42	0.36		rTC3
rTC_2	2.08	**9.53**	0.15		0.43	rTC2
rTC_1	**3.34**	**7.94**		0.63	0.42	rTC1
iBMTC	**7.74**		**6.26**	**4.77**	**5.79**	iBMTC
BMTC		**6.07**	0.88	1.13	1.43	BMTC

Table 3.1: *Test for significance of the stimulus dependent ART differences for the NH subjects using the two-sided t-test for paired values (degree of freedom FG=7, α=0.05) for the two test stimulus conditions N=3 and N=7. The significance threshold was t(7;0.05;2)= 2.36. The values of the t-statistic are given for the mutual comparison of the different stimuli at N=3 (upper left part of the table) and N=7 (lower right side of the table). Statistically significant differences that correspond to t-values exceeding the criterion are given in bold numbers.*

Paired samples t-tests reveal the significant decrease of the ARTs with increasing N for both stimuli[4]. This is the case for the BMTC stimuli, where mean thresholds decrease from 81.5 to 74.3 dB SPL and more pronounced for the iBMTC stimuli with mean thresholds dropping from 98.6 to 86 dB SPL thus resulting in a convergence that can be generally observed in the NH group. Surprisingly, the ARTs for the rTC stimuli are equal or even lower than those obtained for the BMTC signals. Two-sided paired samples t-tests show significantly lower ARTs in response to the rTC stimuli for N=3 chirp periods within the time frame for rTC_1 and rTC_3, but no significant difference between any rTC stimulus and BMTC for N=7 (see Table 3.1). It can also be observed that the rTC stimulus type does not show a dependancy on N with the mean thresholds nearly constant around 76 dB SPL.[5] As expected, all three stimuli of the rTC type with different random phase vectors lead to the same ART.

[4] The single sided paired samples t-test revealed significant ART differences for both stimuli under all conditions except for the ARTs in response to $BMTC_6$ compared to $BMTC_7$.

[5] Paired samples t-tests reveal no significant differences between N=3 and N=7 for any of the rTC-type stimuli.

The characteristics of the ARTs for the different stimulus types were similar among all NH subjects, although the absolute ART level values for the same stimuli varied between the subjects. In some cases differences of the ART for the respective stimuli between two NH subjects were up to 15 dB. This difference was also observed for acoustic reflex thresholds measured at 500 and 1000 Hz with a standard procedure (GSI 33 impedance audiometer). If the thresholds in response to the BMTC stimuli were elevated it was not always possible to assert the threshold for the iBMTC signals due to the limitation of the presentation levels. This was the case for three of the eight NH subjects. In cases where the iBMTC threshold could not be determined, the ART was assumed to be 1 dB higher than the maximal tested stimulation level of 103 dB for statistical analysis. Therefore, the mean values of the iBMTC thresholds, as shown in Figure 3.3, are most likely underestimated to some extent. This holds especially for stimuli comprising a low number of chirps within the stimulating time frame where the resulting thresholds were particularly high for this stimulus type.
Due to the differences in the absolute ART levels the inter-individual standard deviation seen in Figure 3.3 for the BMTC and iBMTC thresholds are quite large. Nevertheless, the key properties exhibited by this subject group, i.e. (i) the large difference between the ARTs for the BMTC and iBMTC stimuli, (ii) the dependancy of these ARTs on the frequency spacing and (iii) the low thresholds resulting from the rTC stimuli, are the same for all subjects of the NH group.

b. ARTs in hearing-impaired subjects

The ARTs for the BMTC stimuli are also significantly lower for the HI subjects (right panel of Figure 3.3) than the ARTs obtained by stimulation with iBMTCs (see Table 3.2). However, the threshold differences between these stimuli are distinctly smaller[3] than for the NH subjects, and range from 8 dB for N=3 to 5 dB for N=7. Second, in contrast to the NH subjects, no significant difference of the mean ARTs can be found as a function of N, neither for the BMTC nor the iBMTC stimulus[6]. The

[6] A paired sample t-test between the thresholds in response to iBMTC3/iBMTC7 and BMTC3/BMTC7 revealed no significant difference between these ART pairs. Therefore a systematic dependancy of the ARTs on N can be rejected for these stimuli in the HI subject group. However, a complete pair comparison reveal single deviations from a constant threshold across N. The ART for iBMTC3 for example are significantly higher compared to iBMTC4,5 and 6. For the BMTC stimuli, the ART in response to BMTC5 was significantly lower compared to BMTC6 and 7.

mean difference of ART between N=3 and N=7 for iBMTC stimuli in the HI group is only 2.5 dB (98.6 dB for N=3, and 96.1 dB for N=7) compared to 12.6 dB in NH subjects. The mean ART in the HI subjects for the BMTC stimuli are nearly independent of N (about 91 dB SPL) while the NH subject group showed a significant[3] decrease of 7.2 dB with increasing N.

N=3 $t_{(6;0.05;2)}$=2.45	BMTC	iBMTC	rTC1	rTC2	rTC3	N=7 $t_{(6;0.05;2)}$=2.45
rTC3	**2.98**	1.35	2.40	0.97		rTC3
rTC2	2.01	2.26	0.46		0.24	rTC2
rTC1	**2.47**	**2.84**		0.72	0.66	rTC1
iBMTC	**8.70**		1.49	0.33	0.62	iBMTC
BMTC		**4.25**	**3.57**	**3.15**	**3.54**	BMTC

Table 3.2: *Test for significance of the ART differences for the HI-listeners. The significance threshold in this case was t(6;0.05;2)=2.45. Again, the results for N=3 and N=7 are shown in the upper left or lower right part of the table respectively. As for the NH-listeners, the difference between iBMTC and BMTC is significant. In contrast to the NH-subject group, the BMTC stimuli were significantly different from the rTC stimuli types, even for N=7.*

Even though the BMTC thresholds found in the HI subjects were elevated compared to the NH subjects it was, with one exception, possible to assert all ARTs for the iBMTC stimuli in this subject group. As for the NH subjects, the three rTC stimuli led to essentially the same ART, independent of the frequency spacing and the random vector used for the generation. However, the BMTC thresholds found for the HI were lower than those found for the rTC stimuli, in contrast to the results of the NH group.

For one subject (LP) of the HI group, the pure-tone hearing thresholds for the right ear were about 15 dB lower than for the left ear. A difference of the ARTs for the respective signals can be observed between the two sides, with slightly elevated thresholds for all stimuli on the worse side compared to the thresholds measured in the better ear (compare Figure 3.5 (a) with (b)). It can also be observed that the threshold difference between the BMTC and the iBMTC becomes smaller and the dependancy on N less pronounced especially of the iBMTC on the worse ear.

Basic ART characteristics for all subjects are summarized in Table 3.3 as the ART T of rTC stimuli (for N=3), the difference D1 between the ART from rTC and iBMTC stimuli (for N=3), the slope of the iBMTC thresholds with increasing N (D2) and the decrease G of ARTs for iBMTC from N= 3 to N=7 (for illustration see also Figure 3.6).

NH subjects					HI subjects				
Subject	*D1 (dB)*	*D2 (dB)*	*G (dB)*	*T (dB)*	Subject	*D1 (dB)*	*D2 (dB)*	*G (dB)*	*T (dB)*
JN	23	-4	16	68	FR	0	4	2	91
MM	34	-7	32	67	BU	2	13	-1	100
OM*	26	-4	12	78	FD	1	5	-3	92
SA	21	1	14	73	FW*	10	-2	7	94
JJ*	18	-4	-	86	WW	-1	8	2	97
KA*	18	-11	16	86	LP (better ear)	8	2	7	94
BS	16	-1	14	82	LP (worse ear)	4	2	4	99
LA	22	-9	10	74					

Table 3.3: *Comparison of the individual difference D between ARTs for rTC and iBMTC stimuli and the difference G of the ARTs for iBMTC stimuli between iBMTC$_3$ and iBMTC$_7$ (see. Figure 3.6). The ART T of the rTC stimuli for each subject were calculated with respect to the mean ART of the three rTC type stimuli. No ART for the iBMTC at N=3 could be obtained for the subjects indicated by the asterisk (*). In these cases the ART for the iBMTC$_3$ stimulus are approximated from the slope of the remaining iBMTC thresholds. This was not possible for subject JJ, where only the iBMTC$_7$ threshold could be measured. The D1 value for this subject is estimated from the difference between the mean rTC thresholds and an assumed iBMTC threshold of 104 dB SPL.*

c. Detection of middle ear muscle reflex versus detection of medial olivo-cochlear efferent reflex

In order to exclude possible effects of the MOC on the acoustic reflex detection, the phase characteristics of the residual signal across frequency were investigated. All normal-hearing subjects exhibited a constant phase across frequency at threshold levels, indicating that the residual signals are clearly dominated by the MEM contraction (Guinan et al. 2003). This corresponds to the findings of Guinan et al (2003) who discovered that for elicitor levels of 65 dB SPL or higher, the residual signal is either MEM dominated or a mixture of MEM and MOC.

Furthermore, to exclude the possible influence of spontaneous otoacoustic emission (SOAE) that might be triggered by the stimulus and thereby obscure the ART, we conducted an offline examination of the residual signal at several frequencies between 500 and 1500 Hz using the analysis method mentioned above. This examination did not show the frequency specificity that could be expected if the residual signal was caused by SOAE. All frequencies within certain bands were equally appropriate to detect the reflex, indicating that the residual signal was caused by the impedance change resulting from the MEM contraction.

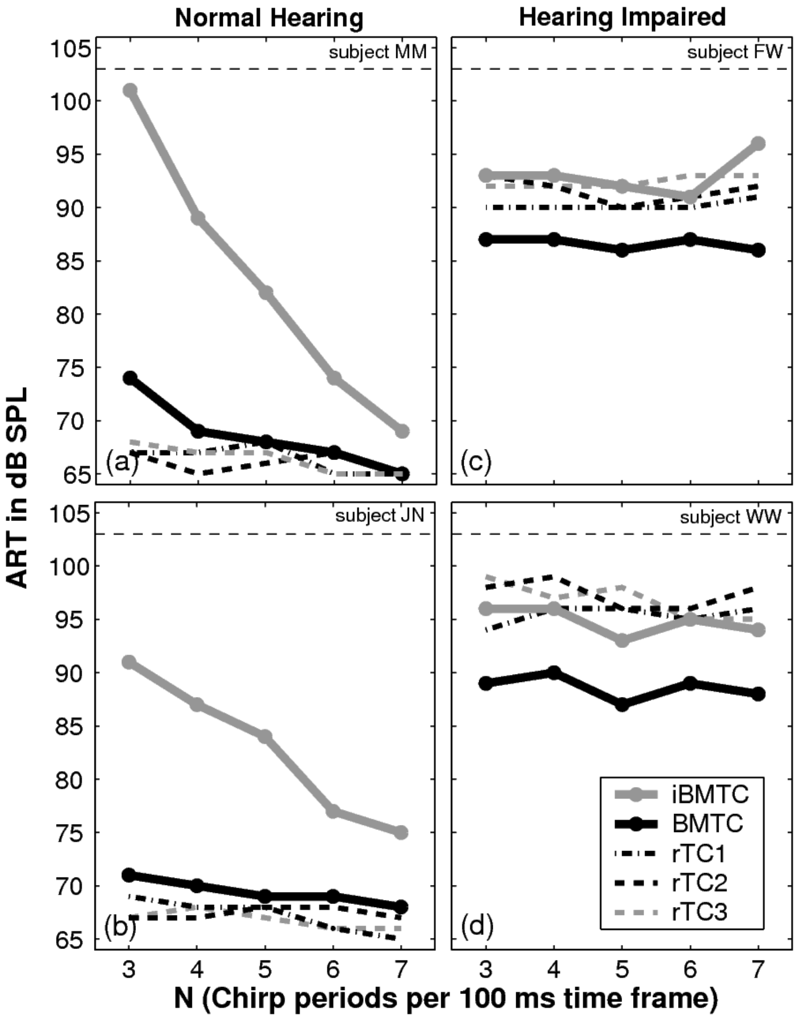

Figure 3.4: *Examples of ART measured for two NH (panels (a) and (b)) and two HI subjects (panels (c) and (d))*

IV. Discussion

a. Mechanisms affecting the acoustic reflex thresholds

The idea behind the generation of the stimuli used in the present study was based on the hypothesis that the reflex threshold is related to the amount of synchronized neural excitation produced by the respective activating stimulus. The experimental results found in the current study partially support this hypothesis. The data also suggest that peripheral compression strongly influences the results for the different stimuli. In all HI subjects, the “optimized” BMTC produced the lowest ARTs (see Figure 3.4 (c) and (d)). The ARTs obtained with the noise-like rTC stimuli decreased with decreasing hearing loss (Fig 3.5 (b) and (a)) and obtained values slightly below those for the BMTC stimuli (Fig 3.4 (a) and (b)) in the NH subjects. This effect and several of the other key observations in the data are discussed in the following. A detailed modeling of the effects was beyond the scope of the study. However, it is attempted to at least qualitatively explain the results based on the different aspects associated with cochlear processing.

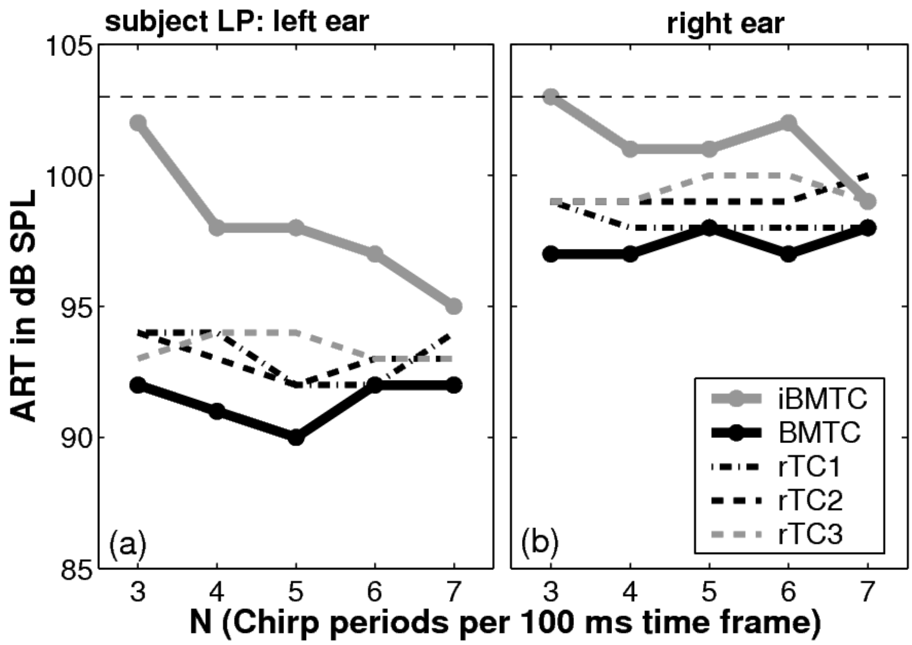

Figure 3.5:
Examples of the ART characteristic in dependance of the hearing loss. Subject LP showed a general difference in hearing thresholds of about 15 dB between the left (a) and right ear (b). Accordingly, the ART characteristics are different for both ears with the better ear (b) showing attributes that can also be found in NH-listeners. This indicates sufficient sensitivity to utilize this method as an indicator for the loss of BM compression that is associated with OHC damage.

1. Excitation characteristics of the different stimuli

The BMTC were designed to compensate for BM dispersion. Ideally, these stimuli produce a maximum amount of excitation across frequency at a particular point in time. In a non-ideal case, e.g. if the sweep rate of the chirp does not exactly compensate the delay line characteristic of the cochlea, still a relatively broadband synchronized excitation can be expected that moves in apical or basal direction. The summation of excitation for the BMTC across all frequency bands as a function of time results in a peaky, i.e. temporally highly modulated “spectral summation response”, with the maximum at the time when each auditory filter reaches its maximal excitation. The BMTC are trains of up-chirps with the instantaneous frequency of each single chirp moving from low to high frequencies. A relatively flat temporal response (slowly increasing and decreasing in time) in each single (local) auditory filter can be expected for up-chirps since the stimulus phase curvature has the same sign as the curvature of the phase transfer function of the BM, at least at medium to high frequencies (Smith et al. 1986; Oxenham & Dau 2001; Shera 2001; Oxenham & Dau 2004). The temporally inversed iBMTC are trains of down-chirps. A relatively narrowband BM excitation can be expected at each point in time for a single chirp that moves apically in time, similar to the excitation of a click but moving slower in apical direction. The spectral summation across frequency will result in a flat response as a function of time (only shaped by the spectral sensitivity of the cochlea and the frequency characteristic of ear canal and middle-ear). In contrast to the stimulation with BMTC, not all filters contribute simultaneously; instead, only a few adjacent filters will contribute significantly to the “spectral summation response” at each point in time. From the perspective of the individual auditory filters, a relatively peaky, temporally more modulated response can be expected at the output, since the phase curvature of the down-chirps has the opposite sign as the curvature of (most of) the cochlear phase transfer functions (Oxenham & Dau 2001). Finally, the rTC stimuli are tone complexes with random phases. These noise-like stimuli are expected to produce a spectrally flat response during the whole stimulation period.

2. Spectral summation and temporal integration

Overall, the acoustic reflex elicitation seems related to the overall spectrally summed cochlear (neural) excitation within a certain time window[7]. The observation that the ARTs in response to $BMTC_3$ and $BMTC_6$ in hearing impaired subjects are at the same rms level allows a rough estimation of the minimal integration time constant, assuming that nonlinear effects are strongly reduced or absent in the HI subjects. The spectrally summed excitation for $BMTC_6$ comprises two smaller peaks for every peak in the $BMTC_3$ output signal. In order to obtain the same reflex threshold for $BMTC_3$ and $BMTC_6$ (as seen in the HI subjects), the temporally integrated activity or excitation must be the same for the two stimuli. This would be achieved by an integration time window of at least 30 ms, sufficient to include a full chirp of the $BMTC_3$ stimulus and at least two peaks of the spectrally summed cochlear excitation related to two consecutive chirps of the $BMTC_6$ stimulus. However, it is not clear what the criterion for reflex elicitation is. A simple energy summation cannot explain the

[7] This might be some kind of leaky integrator. However this is subject to a more detailed modeling and will not be discussed here.

ART differences between BMTC and iBMTC stimuli. Instead the differences could possibly be explained by assuming a peak integrator that sums up only contributions of the spectral summation response that exceed an internal threshold. The peaks in the spectral summation response of the BMTCs due to their higher synchronized excitation on the BM exceed this internal threshold at lower stimulus levels than the iBMTC and rTC with their flat temporal envelope of the spectral summation response. However, since the relative amount of excitation that is cut off by the internal threshold increases with decreasing stimulus amplitudes, and since the stimulus amplitude decreases with increasing N while keeping the rms level constant, this model would lead to the prediction of slightly increasing ARTs with N. Thus, for a more detailed model further aspects of processing have to be taken into account.

3. The influence of neural synchronization on the acoustic reflex

Nevertheless, it is reasonable to assume that the “gain” obtained with the BMTCs in the HI subjects, reflected in their lower ARTs relative to iBMTC and rTC stimulation (Figure 3.3 (b)), can be mainly ascribed to the higher neural synchronization. Similar to the explanations for the higher responses in ABR and MEG measurements using BM chirps (Rupp et al. 2002; Dau 2003) this can be explained by the higher peakiness of the spectral summation response as a function of time. Although derived from a passive BM model, BMTC or BM chirps have so far only been tested in NH subjects (e.g. Dau, 2003). It is not clear whether the improvement obtained with the BM chirp in NH subjects can be expected to hold for HI subjects. A broadening of the BM filters, i.e. a loss of tuning of the BM filters in the HI subjects, may cause a reduction in BM travel time and thus a change of the neural synchronization effect by the stimuli. In turn, it might be that the greater differences between the ARTs for BMTC and iBMTC stimuli, as observed in the NH subjects compared to the HI group (compare Figure 3.3 (a) and 3.3 (b)), might reflect the better suitability of the stimuli for compensating the travel-time differences in the healthy cochlea.

4. The influence of cochlear compression on acoustic reflex thresholds

However, with increasing hearing loss the ARTs for the rTC stimuli show a stronger reduction than for the BMTC/iBMTC stimuli. This observation can hardly be explained by a change of the dispersive properties of the BM. Timing effects should not strongly affect these noise-like rTC stimuli, whereas the gain of the spectrally summed activity for the other stimuli is probably strongly influenced by the fast-acting compression in the peripheral auditory system. As is known, e.g. from models of loudness, it is generally assumed that the input from a broadband stimulus to each auditory filter is compressed separately before being summed up across frequencies. Thus, a broadband BM excitation will lead to a higher overall output in comparison to a narrow band excitation. Zwicker and Fastl (Zwicker & Fastl 1999) describe spectral loudness-summation of up to 20 dB in NH subjects for broadband noises centered at 4 kHz while nearly no loudness summation was found in HI subjects. Thus, the difference of loudness summation between NH and HI subjects is in the order of the gain observed here for the ARTs from the noise like rTC stimuli in NH subjects in comparison to HI subjects. Although BMTC, iBMTC and rTC show the same long-term spectrum, they possess different BM excitations in time. The iBMTC is assumed to produce a high local excitation at each point in time and therefore obtain less gain (maybe nearly no gain) from a fast acting compressive nonlinearity in comparison to the broadband excitation caused by BMTC or rTC. In each auditory filter, the iBMTCs are expected to produce the peakiest response in time, the BMTCs are assumed to show only a slightly modulated temporal excitation and the excitation of the rTCs in each local filter will be almost flat in time as well. Assuming an almost instantaneous compression this will lead to a further gain of the rTC from nonlinear compression in comparison to BMTC and especially iBMTC, since a series of instantaneously compressed low-amplitude excitations will result in a higher integrated output than the respective excitation with only a few higher peaks.

Another observation, the decrease of the ARTs for BMTC and iBMTC with N that can be observed in the NH subject group, can also not be associated with a change in neural synchronization since the phase characteristics for the single chirps are kept constant with increasing N[8]. Similar to the decrease in the absolute rTC thresholds, this observation might also be explained by the effects of peripheral compression. Both BMTC and iBMTC produce a temporally defined excitation in each local BM filter. Assuming a static power law compression in the local cochlear filters, the sum

[8] This is different from the characteristic known for Schroeder phase tone complexes. An increase of the repetition rate, i.e., of the fundamental frequency f_0 in Schroeder phase tone complexes means by definition a change in sweeprate or phase curvature as well. This is not the case for the BMTC and iBMTC. An increase of f_0 results simply in an increasing number of consecutive chirps within the stimulus duration. Thus, for the BMTC/iBMTC the phase characteristic of each chirp is kept almost constant as long as $1/f_0$ does not exceed an “effective chirp duration” of about 10 ms. For higher f_0 the chirps are shifted into one another.

of the compressed output for three excitations with a given amplitude resulting from a $BMTC_3$ elicitor would be smaller than that of six excitations evoked by a $BMTC_6$ stimulus at the same overall rms level[9]. Furthermore, the decrease of ARTs with N might be related to an interaction of successive stimuli on the BM. Especially for the narrowband excitation of the iBMTC, slowly moving along the cochlear partition, it can be assumed that, for higher N, the excitation of the preceding chirp is still moving towards the apex while the excitation of the current chirp is starting at the base of the cochlea. In the case of a compressive cochlear nonlinearity the output for lower-level inputs to many filters will exceed the output from a single filter with a respectively higher input and thus result in lower ARTs. This effect would be more pronounced for the iBMTCs than for the BMTCs, since the iBMTCs are expected to produce a narrowband excitation slowly moving from the base to the apex in contrast to a synchronized (already) broadband BM excitation from the BMTC. A presumed reduction in travel time on the BM for the damaged cochlear might result in a reduced effect in the HI subject group, leading to no or only a slight dependancy on N for these subjects.

Overall, assuming a different gain of neural synchronization for the different stimuli in combination with a major effect of a fast-acting cochlear nonlinearity (in NH subjects) on the observed effects of ART for the different stimuli gives the qualitatively most consistent view on the data. Most HI subjects with severe hearing loss have a strongly reduced compression. In these subjects (see Figure 3.4 (c) and (d)) the observed effects are dominated by the gain of neural synchronization. There is no ART decrease with increasing N and the ART from the rTC stimuli are similar or slightly below the iBMTC stimuli. The peakier overall excitation of the BMTC might be used by a mechanism based on a peak integrator to obtain lower ARTs. With decreasing hearing loss and increasing influence of a nonlinear compression, the ARTs of the rTC stimuli are shifted towards the ARTs of the BMTC stimuli, which are also reduced (see Fig 3.5 (b)), and even the decrease of the ARTs with increasing N becomes observable for the iBMTC stimuli (see Figure 3.5 (a), Figure 3.4 (b) and (a)). Thus, besides the absolute ARTs the differences between the ARTs for different stimuli might be used to improve the value of ART measurements as a

[9] For example with an amplitude reduced by a factor of 0.71. Thus, a reduction of approximately 2 dB from N=3 to N=6 could be expected for an exponent of 0.3 while no effect can be expected for the HI subjects assuming negligible compression and therefore an exponent close to 1.

screening tool in clinical diagnostics. For example, the difference G for ART from iBMTC stimuli at N=3 and N=6 or the differences D1 and D2 between the ARTs of iBMTC, BMTC and rTC might be useful to indicate a loss of compression.

b. Prediction of hearing status and clinical applications

Besides the absolute thresholds like the threshold T for the rTC (see Figure 3.6 and Table 3.3), other characteristics of the ART allow for a clear distinction between NH and HI subjects, such as (1) the decrease for ART especially for iBMTC, but also for BMTC, stimulation in NH subjects with increasing N (indicated by G - see Figure 3.6 and Table 3.3), while no dependancy was found for the HI subjects, and (2) larger ART differences between diverse stimuli types. Thus, appropriate criteria to distinguish between NH and HI subjects may be given by the ART differences D1 and D2 (see Figure 3.6 and Table 3.3). D1 is the difference between a rTC_3 and the $iBMTC_3$ stimulus, which shows a significant reduction from 22.3 dB in NH subjects compared to 3.5 dB in the HI subjects[10]. The difference D2 between rTC_3 and $BMTC_3$ is negative for most NH subjects and is positive for most HI subjects – probably closely related to an increasing loss of compression. Additionally, the difference G between ARTs from iBMTC stimuli for N=3 and N=7 allow a clear distinction between NH and HI subjects (see Figure 3.6 and Table 3.3). A high sensitivity of the ART differences, e.g., D1, with respect to hearing loss and loss of compression may be indicated by the results from subject LP (see Figure 3.5). This subject showed an almost parallel shift of hearing thresholds across frequency of about 15 dB between the two ears that is clearly reflected in different values of T, D1, D2 and G (see Table 3.3). Therefore, the additional consideration of ART differences for different stimuli beside the evaluation of absolute thresholds may allow a more reliable prediction of hearing impairment than using absolute ARTs alone. Overall, based on the data from this limited group of subjects the differences of D1, D2, G or T in NH and HI subjects for the specially designed stimuli in this study may offer the opportunity to utilize the measurement of ARTs for the objective prediction of hearing loss and recruitment or for hearing aid fitting in young or uncooperative patients.

Earlier studies showed that a close relationship of the mean ART and the uncomfortable level (UCL) might exist. However, the prediction of the UCL based on

[10] The comparison of the iBMTC/mean(rTC) difference for both subject groups using the Willcoxon, Mann and Whitney U-test for independent samples demonstrates a significant reduction of this difference in the HI listeners ($p < 0.001$: $U=0 < 2=U_{8;7;0.001}$).

the ART measurement will be inaccurate because of the high inter-subject variability (Margolis & Popelka 1975; Kawase et al. 1997; Olsen 1999a; Olsen et al. 1999b; Olsen et al. 1999c). As opposed to these studies where loudness and ART were compared directly, the present results suggest a comparison of the differences of ARTs for appropriate stimuli (e.g. BMTC, rTC vs. iBMTC) that are differently affected by cochlear compression. Thus, the large inter-subject variability might be reduced if the ART differences for special stimuli are considered, rather than the absolute thresholds alone. Based on this limited group of subjects, the derived measures D1, D2, G and the ART T for the rTC stimuli give at least a set of highly significant screening indicators (compare Table 3.2) to distinguish between NH and HI subjects (see Table 3.3). Further studies will have to investigate if a classification of the individual hearing loss or even a quantitative prediction can be obtained by combining the different indicators in a larger group of subjects with different shapes and types of hearing loss. Another point of interest is to find stimuli with similar properties but higher frequency specificity than the ones used here.

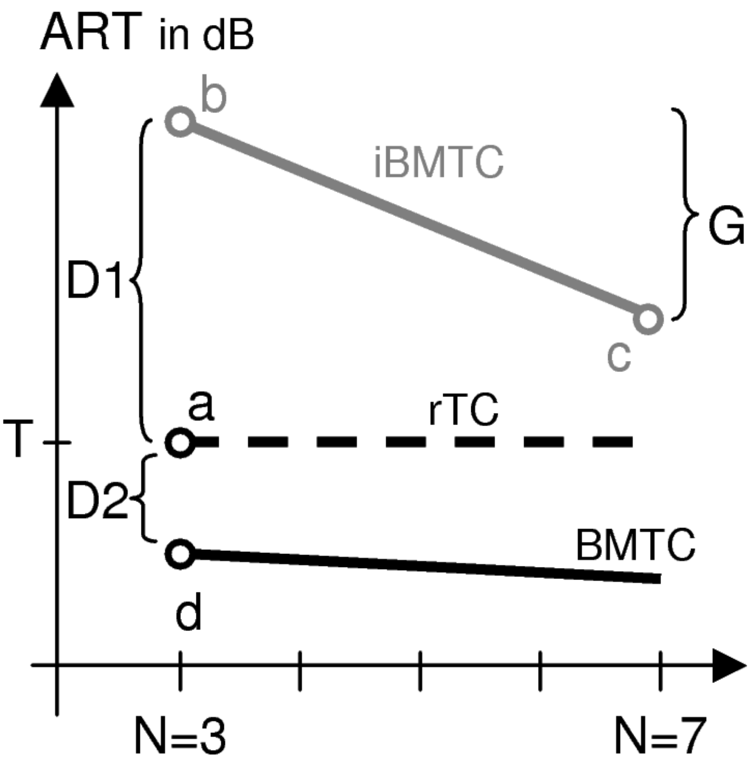

Figure 3.6:
Illustration of ART characteristics T, D1, D2, G as given in Table 3.3 for all subjects obtained from ART measurements at only four different stimulus conditions (a,b,c,d). T is the ART for a rTC stimulus at N=3 given by measurement point a. D1 (b-a) is given by the ART difference for a rTC and the iBMTC stimulus at N=3 and D2 (d-a) as the difference for a rTC and the BMTC respectively. Finally G (b-c) gives the ART difference for iBMTC stimuli at N=3 and N=7.

V. Summary and outlook

- A clear effect of neural synchronization on acoustic reflex threshold (using the low-level-reflex audiometry according to Neumann et al. (1996)) can be observed when comparing results obtained from BMTC and iBMTC stimuli. Therefore, the acoustic reflex threshold is strongly affected by the phase properties of the stimulus and thus by the dispersive characteristics of the cochlea. The results suggest that the ART depends on the amount of synchronized neural excitation integrated across frequency.
- The large differences between the different stimuli used here (BMTC, iBMTC and rTC stimuli) as well as the large difference between normal and hearing-impaired subjects can qualitatively be explained by assuming a compressive nonlinearity as typically found in BM input-output functions of normally functioning cochleae. However, in order to obtain a more quantitative understanding of the cochlear mechanisms that contribute to elicitation of the ART, modeling work is needed in future studies.
- Besides the absolute ART values, there are several other indicators of hearing-loss in our (limited) group of subjects like the differences (D1 and D2) of the acoustic-reflex thresholds for rTC_3 and $iBMTC_3$ or $BMTC_3$ stimuli, respectively. The clear distinctions between the two subject groups by the derived measures D1, D2 and G in combination with absolute ART may improve the use of acoustic reflex threshold measurements as an objective predictor of a loss of cochlear compression. Further studies are required to validate these measures as a clinical tool.
- The online-analysis method might be improved in future studies by incorporating a multi- frequency evaluation. This might be useful to reduce the total number of consecutive stimulus presentations and consequently in measurement time without a decrease in statistical significance. Furthermore, this approach can provide additional artifact suppression with regard to the MOC efferent reflex by considering the change in group delay across frequencies. However, utilizing more than one frequency for the evaluation corresponds with an increase of the number, n, of phase values as long as all used frequencies are equally appropriate. Therefore, no relevant difference in the detection threshold, i.e., in the sensitivity of the method can be expected.

Acknowledgements

This study was supported by Deutsche Forschungsgemeinschaft, DFG Ko 942/11-3. We want to thank Jesko Verhey for fruitful discussions about compression. We gratefully acknowledge the two anonymous reviewers for their valuable comments on the manuscript.

Chapter 4

Investigation of the correlation of acoustic reflex thresholds and cochlear damage using the low level acoustic reflex audiometry

This study investigates the effect of the loss of compression due to sensorineural hearing loss on the acoustic reflex thresholds. The reflex thresholds were determined for stimuli that have identical spectral composure but differ in their temporal shape and are thereby thought to cause different excitation patterns on the level of the basilar membrane (Müller-Wehlau et al. 2005). Resulting acoustic reflex thresholds were previously observed in normal hearing and hearing impaired subjects and the differences could be explained by the influence of cochlear compression (Müller-Wehlau et al. 2005). The aim of this study is to further investigate whether these results can be generalized for different degrees of hearing losses and if ART differences are correlated with extend or characteristic of the cochlear damage. 28 subjects of different age and extend of sensorineural hearing loss with a total of 41 ears were measured. The hearing losses were compared to three different parameters derived from the respective acoustic reflex thresholds. The results show a high correlation of these parameters with the hearing loss thus allowing the prediction of individual broadband hearing threshold with an accuracy of 14 dB. Nonetheless, no significant dependancy on the spectral characteristic could be found.

Introduction

The acoustic reflex threshold (ART), i.e. the contraction of middle ear muscles in response to an intense acoustical stimulus, is normally used in screening of otoneurologic patients (Clemis 1984) in clinical diagnostics and serves as an indicator of neural dysfunction along the reflex pathway. Measurements of the ART with broad band stimuli that are designed to result in different basilar membrane (BM) excitation patterns revealed characteristic differences of the ARTs caused by these stimuli between normal hearing and hearing impaired listeners (Müller-Wehlau et al. 2005). These differences can be explained by the influence of the compressive properties of the ear and the loss of compression due to cochlear damage. The aim of this study is to investigate whether these results can be generalized for different degrees of hearing losses and if these ART differences are correlated with the extend or characteristic of the cochlear damage. The measurements were done using the low level reflex audiometry (LLAR) method introduced by Neumann et al. (1996). This method allows a robust measurement of the reflex threshold with high accuracy.

I. Experimental methods

a. Measurement paradigm and analysis method

The LLAR paradigm suggested by Neumann et al. (1996) uses two identical stimulus pulses separated by a small temporal gap to elicit and detect the reflex. The pulses can consist of pure tone sinusoids or broad band tone complexes whose presentation level is varied to determine the acoustic reflex threshold (Figure 2.1 (a) and 2.1 (d)). The reflex is elicited and abided by the first pulse of sufficient level thus resulting in a change of the middle ear’s impedance associated with the stiffening of the ossicular chain. A probe microphone placed in the ear canal is used to measure the response to the two stimulus pulses. The measured response is comprised of the incident wave emitted by the probe’s receiver and the reflected wave running backwards from the tympanic membrane. Since the reflected wave portion depends on the acoustical properties of the middle ear, the change in the middle ear's impedance directly affects the signal recorded by the probe microphone. The presented stimulus pulses are separated by a temporal gap whose length has been optimized with respect to the latency of the impedance change of 80 to 120 ms (Wurzer et al. 1983; Sellari-Franceschini et al. 1986). Therefore, the effect of the impedance change on the recorded signal in the ear channel is maximized during the presentation of the stimulus with the result that the recorded responses to the two stimulus pulses differ if the acoustic reflex has been elicited by the first pulse. The difference in the responses can by expressed by simply subtracting one response from the other thus calculating the residual called difference signal.

In the case of an elicited reflex the spectrum of the residual shows the frequency components of the stimulus (Figure 2.1 (f)). Since the presence of these frequency components indicates the elicited reflex it can therefore be detected by analyzing the residual. If the stimulus level is not sufficient to elicit the reflex, the recorded ear canal signals are almost equal for both pulses. The residual therefore mainly reflects the physiological noise and the noise of the measurement chain (Figure 2.1 (c)).

In order to exclude false-positive results due to random variation of the impedance during a single presentation, the method uses multiple presentations of the stimulus pair to determine the ART. By increasing the number n of repetitive measurements the robustness towards artifacts caused by movements of the subjects can be increased at the expense of measurement time.

The criterion to determine the AR threshold is based on a coherence synchrony measure (CSM) (Valdes et al. 1997), a test of phase coherence similar to the Rayleigh test of circular uniformity (Mardia 1972). The phase coherence is determined on the basis of n successive measurements. The phase value of a selected frequency component in the residual is calculated for each presentation of the stimulus pair. The amplitudes of these frequency components are not considered. This results in n phase values whose coherence can be expressed by the vectorial mean of the n normalized phase vectors (Figure 2.3 (a) and (b)). The so called mean resultant length R can be computed from the phase values $\theta_i = \theta_1,...,\theta_n$ of the selected frequency component by

$$R = \left| \frac{1}{n} \sum_{i=1}^{n} r_i \right|, \text{ with } r_i = \cos\theta_i + i \sin\theta_i$$

R can take values between 0 and 1, indicating the degree of phase coherence. If the reflex is systematically elicited by the stimulus, the reproducibility for n successive presentations and therefore the phase coherence is high, resulting in a value of R close to 1. An empirically found threshold value of R ($R \geq 0.8$) was used to determine whether the reflex was elicited or not (Müller-Wehlau et al. 2005). Since the value of the mean resultant length R does not depend on the number n of phase values used for its calculation, the same threshold detection value can be applied for the detection of the reflex. In this study a repetition number of 16 was used.

Since the impedance change caused by the stiffening of the ossicular chain in the middle ear depends on the frequency, not all spectral components present in broad band signals are equally appropriate for the detection of the acoustic reflex. A detailed examination of the residuals of broad band stimuli showed that in case of the elicited reflex the frequency range between 500 and 1500 Hz is clearly found in all subjects. A spectral component close to 1000 Hz was therefore used to calculate the mean resultant length R in the experiments with broad band stimuli. In case of the experiments with sinusoidal stimuli the evaluation frequency was equal to the stimulation frequency.

An additional artifact suppression was applied by rejecting all measurements whose residual amplitude at the evaluation frequency was not within a 6 dB margin of all measurements at the respective stimulus level.

b. Setup

The whole measurement was based on a PC and implemented in a customized program that controlled and varied the presentation level. The signals used for the stimulation were generated in advance and played back using a digital I/O-card (RME DIGI 96) in the host PC. The I/O-card was connected via an optical interface to a 24 bit DA/AD-converter (RME ADI 8 Pro). The analogous signal was delivered using an OAE-probe (Otodynamics ILO BT-Type) driven by a headphone buffer (Tucker-Davis Technologies HB6). The recorded signal was amplified by an external low-noise amplifier (Stanford Research SR560) and submitted to the AD-converter.

The microphone chain was calibrated according to Siegel (Siegel 2002) using a Bruel & Kjaer type 4192 microphone capsule as reference. An artificial ear for insert ear phone (Bruel & Kjaer Type 4157) and a broadband calibration signal (100-10000 Hz) were used to calibrate the output path including the probe speaker. The transfer function obtained by this calibration procedure was used to calculate a phase invariant overlap-add filter to correct the stimuli for the frequency response of the output system. No individual correction like an in-the-ear calibration was performed.

Since systematic distortions introduced by the measurement system can result in false-positive responses by the detection criterion, the artifact reliability was tested in different cavities as well as in subjects with no residual hearing. Measurements in cavities with volumes between 1 and 5 cc provided a test for the reliability of the procedure in a situation with low ambient noise and no physiological artifacts. The tests were done with different volumes of the cavities because the sound pressure at the plane of the microphone depends on the transfer function of the system. No elicited reflex was detected for measurements in any of the cavities for stimulation levels up to 105 dB SPL. To test the artifact reliability in a real ear canal corresponding measurements were done in subjects with no residual hearing but functional middle ear. Four experienced cochlear implant users (1 male, 3female, aged 51-67 years) participated in this experiment with the implant turned off for the duration of the measurement. The hearing threshold without the implant was higher than the maximal presentation level for the reflex measurement, so that no acoustical reflex can be expected for these subjects. As for the measurements in the cavities no reflex was found in these four subjects with presentation levels of maximal 101 dB SPL, demonstrating a high reliability under physiological conditions.

II. Experimental setup

In Müller-Wehlau et al. it could be shown that the ARTs in response to different broadband stimuli that cause different excitation patterns on the basilar membrane are influenced by cochlear damage (Müller-Wehlau et al. 2004). Three different types of tone complexes with identical magnitude spectra but different phases of their respective components were used in this experiment. The original idea behind the measurements was to use stimuli that effect the temporal excitation on the basilar membrane. This was done by generating chirp-like stimuli type that were designed to compensate for the BM travel time and therefore result in a temporal synchronization of the overall excitation pattern. Acoustic reflex response thresholds for this basilar membrane tone complex (BMTC) called stimulus were expected to be low. The second class of stimuli was generated by temporally inverting the BMTC stimuli. In contrast to the BMTC stimuli the inverted basilar membrane tone complex (iBMTC) result in a highly desynchronised excitation pattern on the BM, i.e. the frequencies contained in the tone complex reach their characteristic place on the BM successively. Therefore the iBMTC stimuli were expected to result in high ARTs. The third type of stimuli used for this experiment was generated from tone complexes with identical magnitude spectra as the former two but random phases of their components. This results in random phase tone complexes (rTC) with noise-like time signals (Figure 3.1). No special properties in terms of the synchronization of the excitation were attributed to this stimulus type and the resulting ARTs were therefore expected to be between those of BMTC and iBMTC stimuli.

An important parameter in the design of these tone complexes was the frequency spacing of their components. Doubling of the frequency spacing, i.e. by omitting every second component in the tone complex, leads to a doubling of the number of chirps present in the time frame of given length. Generally, an increase of the frequency spacing by a factor N results in N equidistant chirps in the time domain. Since the parameter N, i.e. the frequency spacing as multiples of the FFT base frequency, was found to influence the measured ARTs it was systematically varied between N=3 and N=7.

Initial measurements were done in normal-hearing and hearing-impaired listeners with equal hearing loss and the obtained ARTs were compared across these subject groups. It was found that the ARTs in response to different stimulus types differed between the two subject groups. Three characteristics (see Figure 3.6) were found whose values changed characteristically (Müller-Wehlau et al. 2005):

1. The absolute response threshold T of the rTC–stimuli. These were found to be much higher in the hearing-impaired listeners.

2. The difference D1 between the ARTs in response to the rTC_3 and the $iBMTC_3$ stimulus. Since the ARTs in response of the iBMTC stimuli were found to depend on the frequency spacing N and generally decrease with increasing frequency spacing this difference is largest for N=3. In normal-hearing listeners D1 was significantly larger than in the hearing-impaired subject group.

3. The gradient G of the ARTs in response to the iBMTC stimuli. In normal-hearing listeners the ARTs for these stimuli decrease strongly with increasing N. In hearing-impaired listeners this decrease was significantly smaller.

The aim of this supplemental study is to investigate whether these observations can be generalized for different characteristics of cochlear damage and if a prediction of cochlear damage based on the evaluation of the investigated parameters is possible.

a. Subjects

28 subjects (9 male, 19 female) aged 15 to 71 years (average 46 years) participated in this study with a total of 41 ears measured. The subjects exhibited different hearing thresholds ranging from normal hearing to moderate and severe hearing loss (Figure 4.1). Hearing levels were measured with a standard audiometer (Siemens Unity SD100). The hearing impairment of those subjects with elevated hearing thresholds were diagnosed as being of cochlear origin based on the findings for the absolute hearing thresholds, the conductive hearing levels and the tympanograms. Normal acoustic reflex thresholds in response to small band stimuli were ascertained by a well established method with an impedance audiometer (either Grason-Stadler GSI33 or Interacoustics AZ 26).

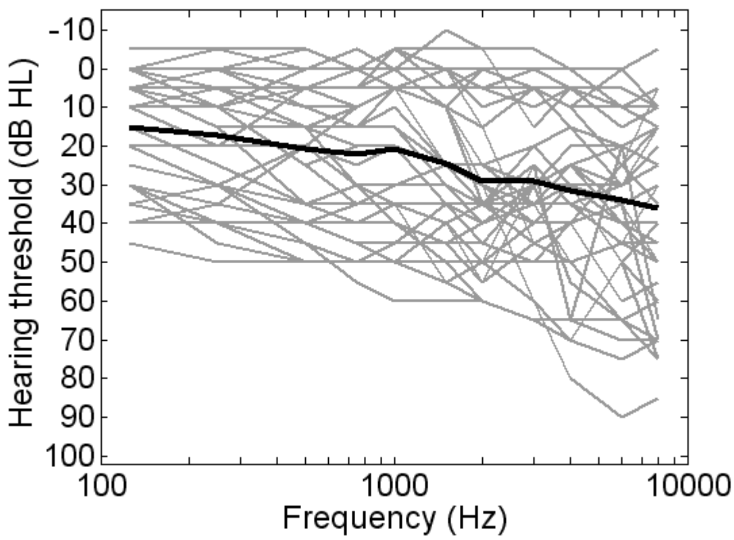

Figure 4.1: *Individual (grey lines) and mean (black line) audiograms of the participants. A wide variety of hearing thresholds were chosen in order to generalize the results.*

b. Stimuli

The stimuli consisted of two identical signal pulses of 4096 samples length that are separated by a gap of 2210 samples. The pulses were flanked by Hanning-shape ramps of 20 samples and successive presentations of the stimulus were set 1.15 s apart. The stimulus pulses consisted of tone complexes with frequency components between 100 and 8000 Hz. As carried out above, three different types of tone complexes with equal magnitude spectra but different phases of the contained frequency components were used (Müller-Wehlau et al. 2005).

1. BMTC

These tone complexes were generated by adding frequency components with phases that are calculated to compensate for the BM travel-time differences across frequency, so that a temporal synchronization of the BM excitation is achieved. The calculation was done according the BM chirp stimulus introduced by Dau et al. (2000) for recordings of auditory brainstem responses and was based on the cochlear model proposed by de Boer (1980) and the frequency place transformation suggested by Greenwood (1990).

The starting phase ρ_0 of a component with frequency f_s contained in the tone complex is calculated from the phase ρ_{inst} the original BM chirp has at the time t_{fs} when the phase's instantaneous frequency is equal to the frequency f_s. By superimposing components with a frequency spacing corresponding to the FFT base frequency results in a time signal exhibiting a single BM chirp with flat spectral envelope.

In normal-hearing subjects a dependancy of the evoked ARTs on the frequency spacing N was observed for the BMTC stimuli. The stimuli were therefore generated for N=3 and N=7, i.e. the stimulus pulses therefore exhibited 3 or 7 chirps within the 4096 samples frame. In the following this is indicated by an index to the stimulus name, e.g. $BMTC_3$ indicates the BMTC stimulus with N=3. Exemplary signal frames and magnitude spectra are shown in Figure 3.1 (a), (d) and (c), (f) respectively.

2. iBMTC

This stimulus type was generated by calculating the components' phases according to the BMTC stimulus and subsequent inverting the obtained stimulus in the time domain. Since a strong influence of the frequency spacing N on the measured AR response thresholds was observed in normal-hearing listeners (Müller-Wehlau et al. 2005) two sets of stimuli were generated with N=3 and N=7.

3. rTC

The third type of stimulus used for this experiment was generated from tone complexes with identical magnitude spectrum as BMTC and iBMTC but random phases of its components. This random-phase tone-complex was generated using one uniformly distributed random phase vector so that the same frequencies contained in rTC_3 and in rTC_7 stimuli have equal phase values. Although this stimulus type proofed to be mostly independent of the frequency spacing N of its components in normal-hearing and hearing-impaired listeners, stimuli were generated with N=3 and N=7.

The six stimuli (3 types, each with N=3 and N=7) were calibrated with respect to their rms-values with the effect that the absolute amplitudes of the chirp signals at a given presentation level decrease with increasing N (Figure 3.1 (a) and (d)). Since the rTC stimuli retain their noise-like time signal independent of the frequency spacing N, the absolute amplitude of this signal type remains almost unaffected of N.

The detection of the elicited reflex at a given stimulus level was done for n = 16 presentations of the stimulus with an evaluation frequency component close to 1 kHz.

c. Measurement

The subjects were seated on a chair within a sound attenuated hearing booth. The subjects were asked to relax and remain quiet for the duration of the measurement (approx. 20 minutes per ear). The same automatic procedure described in chapter 2 to find the acoustic reflex threshold level with the LLAR method was used in this experiment. The starting level of the automatic mode was set to 90 dB SPL for all stimuli and the level increment applied after each reversal was 6, 2 and 1 dB. The fit of the OAE-probe before and after the measurement was tested with the same procedure explained in chapter 2.

III. Results

An illustration of the three characteristics introduced above is shown in panel (a) of Figure 4.2. The results for the 41 ears are given in panels (b) (parameter T), (c) (parameter G) and (d) (parameter D1). The data are plotted versus the mean hearing loss calculated from the individual hearing thresholds at 500, 1000, 2000 and 4000 Hz. Note that it was not in all cases possible to obtain the ART for the $iBMTC_3$ due to the limitation of the presentation level. Therefore only 38 data points are shown for the parameters G and D1 that depend on the $iBMTC_3$ reflex threshold. All three characteristics show a clear correlation with the mean hearing loss with the parameter T increasing and the parameters G and D1 decreasing with the hearing loss.

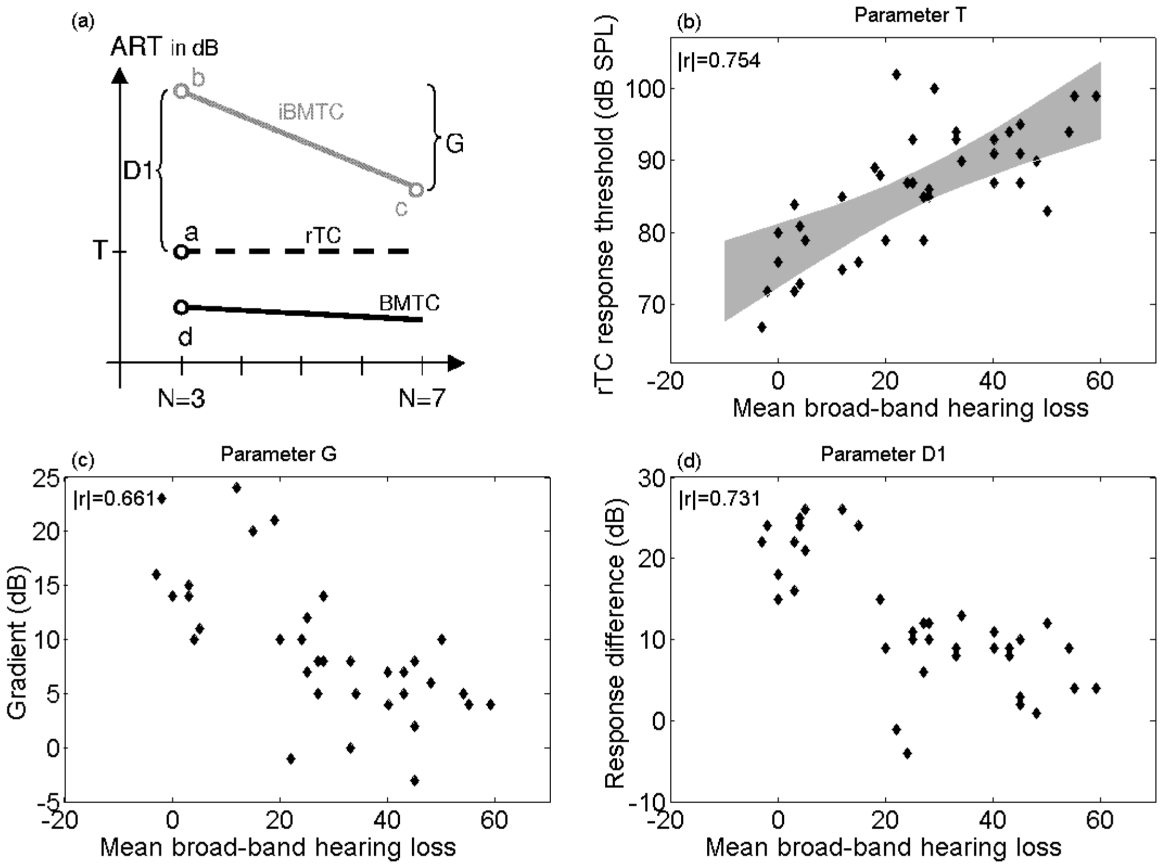

Figure 4.2: *Illustration of the characteristic parameters investigated for their correlation with cochlear damage (panel (a)). The results are shown for the parameter T (absolute rTC threshold, panel (b)), G (gradient of the iBMTC threshold across N, panel (c)) and D1 (difference between iBMTC$_3$ and rTC$_3$ threshold, panel (d)). All three parameters are clearly correlated with the mean hearing loss calculated from the individual hearing thresholds at 500, 1000, 2000 and 4000 Hz.*

A test for linear correlation reveals that the correlation of all three parameters is significant at 1 % probability. The correlation coefficients r are given in the upper left hand side of the plots in Figure 4.2 and the 95 % confidential interval is marked in Figure 4.2 (b) for the parameter T. The best correlation is found for this parameter with |r|=0.754. More meaningful and easier relatable to the given data is the prediction accuracy that is calculated by an iterative prediction of the hearing loss of one data point based on a linear correlation model of the remaining data points. Using this method, the deviation of the predicted to the actual hearing threshold can be calculated for all subjects and all parameters. The results of this calculation are shown in Figure 4.3. As it can be expected, the mean value of the prediction is close to 0 but the standard deviation of the prediction differs between the three parameters.

The parameters D1 (13.6 dB) and T (14.4 dB) have almost equal prediction accuracy while the standard deviation for parameter G is clearly larger (20.5 dB).

However, plotting of these parameters according to the mean broadband hearing loss is arbitrary since it cannot be assumed that all frequencies contribute equally to the acoustic reflex threshold. In order to investigate an influence of the characteristic of the hearing loss, the prediction accuracy of the three parameters was also calculated for mean hearing loss in the low frequency region between 125 and 1000 Hz (designated MHL_L in Figure 4.3) and for the high-frequency hearing loss between 1500 and 8000 Hz (MHL_H in Figure 4.3). Visual comparison of the results show a slightly higher prediction accuracy for high frequency hearing loss than for the low frequency hearing loss with parameter T (Figure 4.3 (a)). For parameter G, the prediction accuracy of the high frequency hearing loss is lower compared to prediction of the low frequency hearing loss. This might hint to some kind of frequency dependance. However, a two sample t test revealed no significant dependancy of either of the parameters on the region of the hearing loss at 1% probability.

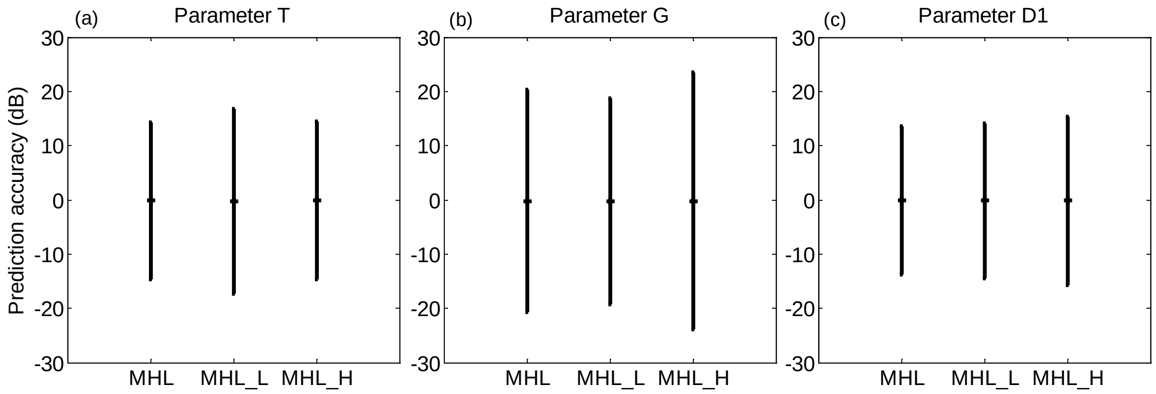

Figure 4.3: *Calculation of the prediction accuracy of parameter T (panel (a)), G (panel (b)) and D1 (panel (c)). The method was used to predict the mean broadband hearing loss (MHL) or the hearing loss in the low frequency (MHL_L) or high-frequency (MHL_H) region. The accuracy is higher for parameters T and D1 compared to parameter G. No significant dependancy on the frequency region of the hearing loss could be found for any of the parameters.*

IV. Discussion

The ARTs resulting from the signals used in this study are differently affected by the loss of peripheral compression due to cochlear damage. Although the stimuli posses equal power spectra, they exhibit completely different excitation patterns on the basilar membrane. The broad band excitation caused by the noise-like rTC-stimulus has a flat temporal envelope and will therefore receive the highest gain from fast-acting compression since its excitation energy is spread in time. Down-chirps like the iBMTC are believed to produce a high excitation at each point in time with strongly modulated excitation patterns within the auditory filter (Smith et al. 1986; Oxenham & Dau 2001; Shera 2001; Oxenham & Dau 2004). Therefore these stimuli will gain less benefit from peripheral compression than the rTC or the BMTC that produce a less modulated temporal excitation. The influence of the fast-acting compression on different excitation patterns can also be responsible for the observed decrease of ARTs from BMTC and iBMTC stimuli with increasing N. The totalized output from a compressive mechanism will increase with the number of excitations if the overall energy of the excitation remains constant. Therefore, the output in response to an $iBMTC_6$ stimulus will be higher compared to an $iBMTC_3$ stimulus thus resulting in a lower ART (Müller-Wehlau et al. 2005). Furthermore, the decrease of ARTs with N might be related to an interaction of successive stimulations due to the propagation time on the BM. This effect would be more pronounced for the iBMTC since they produce a narrowband excitation slowly moving from the base to the apex of the BM and are therefore more susceptible to interaction with subsequent stimulations. A presumed reduction in travel time on the BM due to a broadening of auditory filters in the damaged cochlea might be responsible for the observed reduction of the ART decrease in HI subjects.

Another factor influencing the resulting ARTs of these stimuli might be given by the effect of neural synchronization. Especially the resultant ART difference of iBMTC and BMTC stimuli observed in HI listeners can be largely ascribed to this effect since the influence of cochlear compression will be diminished in the damaged ear. It is not clear to what extend the influence of neural synchronization on the resulting ART is comparable in normal-hearing and hearing-impaired listeners. The larger ART difference between BMTC and iBMTC stimuli found in the normal-hearing listeners might reflect the better suitability of the stimuli for compensating the BM travel times in the healthy ear. However, effects like the decreasing iBMTC thresholds with increasing N and the different absolute rTC thresholds found in normal-hearing and hearing-impaired listeners cannot be ascribed to the influence of neural synchronization.

Recapitulating, the different ART thresholds found in hearing-impaired and normal-hearing listeners can be described by the parameters T, G and D1. According to the considerations above, they therefore reflect the influence of cochlear damage on the ARTs of the utilized stimuli. All three parameters are significantly correlated with the hearing loss (Figure 4.2). Since the exact relation of any of the parameters and the hearing loss of the subjects is unknown, a linear correlation was assumed. This linear connection is debatable since a saturation effect can be expected when the whole cochlear shows a complete loss of peripheral compression. A changing slope of the data points corresponding to hearing losses above 40 dB can be observed for the parameter G and D1 (Figure 4.2 (c) and (d)). Nonetheless, assuming a linear correlation is sufficient to prove the correlation of the chosen parameters with the hearing loss.

However, even for the best correlated parameter (rTC response threshold T) the inter-individual variance of the reflex thresholds across the subjects derogates a prediction of the individual hearing loss. For the parameter T, the 95 % confidential interval along the abscissa ranges between 10.7 and 34.6 dB (Figure 4.2 (b)), i.e. that a given measured rTC response threshold is associated with the respective range in hearing loss.

Plotting the dependance of the parameters against the mean hearing loss calculated from frequencies of 500, 1000, 2000 and 4000 Hz (Figure 4.3) implies that these frequencies contribute equally to the acoustic reflex threshold. It is common knowledge that the reflex can easily be evoked at low frequencies (Katz 1977) and it is therefore believed that the purpose of the reflex is to attenuate low-frequency body noise in order to improve the signal to noise ratio of ambient sounds (Simmons 1964). One could therefore expect that the low-frequency range of broadband stimuli has a stronger influence on the resulting reflex thresholds than higher frequencies. In this case subjects with profound high-frequency hearing loss would achieve better, i.e. lower, ARTs than the mean hearing loss calculated over a broad frequency range would suggest. In this case the response thresholds to the rTC stimuli could be expected to be relatively low despite severe hearing losses in the upper frequency regions.

The hypothesis is not supported by the results plotted in Figure 4.3 where the prediction accuracy has been plotted for different characteristics of hearing loss. For the parameters T the highest degree of accuracy was found when the results were used to predict the high frequency hearing loss. This indicates that, contrary to the expectations, the high-frequency regime of the cochlear is decisive for the resulting ART. The same observation is found for the parameter D1 although the effect is not as clearly seen as for the rTC thresholds. The prediction accuracy for the parameter G is higher for the low frequency hearing loss. This could hint towards a frequency dependance of the calculated parameter but the difference in prediction accuracy is not significant at a probability level of 1 %.

V. Summary and outlook

- The applied stimuli exhibit different resulting acoustic reflex thresholds in normal hearing and hearing impaired listeners. These differences can be ascribed to the excitation patterns of the stimuli on the basilar membrane that are influenced by the different properties of the healthy or the damaged ear.
- The ART differences between the two subject groups can be described by a number of correlated parameters that can be extracted from the acoustic reflex thresholds. These parameters are significantly correlated with hearing loss.
- The inter-individual variance of the results hampers the prediction of the hearing threshold based on individual results.
- A more detailed study of the frequency dependance found for the stimuli might improve the understanding of the acoustic reflex.

Acknowledgements

This study was supported by Deutsche Forschungsgemeinschaft, DFG Ko 942/11-3. I would like to thank Manfred Mauermann for many fruitful discussions and Anita Gorges for her relentless support.

Chapter 5

Does recruitment change the dependancy on modulation depth in Amplitude Modulation Following Responses (AMFR)? – A case study using five subjects with asymmetric hearing loss

The effect of sensorineural hearing loss on modulation processing was studied using amplitude modulation follow response (AMFR). Recordings from five subjects with asymmetric hearing loss with a difference in hearing thresholds across sides of between 20 and 65 dB were obtained using carrier frequencies of 500 and 4000 Hz and a modulation frequency of 80 Hz. Responses were registered for modulation depths between 5 and 85 % in order to investigate the response growth. The stimulus levels in both ears were adjusted to equal perceived loudness using a loudness matching experiment prior to the AMFR recording. The presentation levels on the better ear were within the range of compressive basilar membrane behavior.

At 500 Hz larger responses were found by stimulating the worse ear compared to the better ear stimulation. In one subject where a reliable recording at 4 kHz was possible, similar results were found for this stimulus. The results are consistent with the assumption that cochlear mechanics is less compressive in ears with cochlear hearing loss. They also agree with psychoacoustical findings of a higher perceived modulation depth due to cochlear hearing loss. Hence, the results from this limited number of subjects point towards the potential use of the AMFR as an objective indicator of loudness recruitment. However, its usage is hampered by the variance of the responses across the subjects and by the necessity to set the appropriate stimulation levels at both ears.

Introduction

The detection of cochlear damage in non-cooperative patients like infants requires diagnostic tools that are independent of the behavioral response of those subjects. Hearing loss due to cochlear damage usually results from damage of the outer hair cells and is frequently accompanied by loudness recruitment, i.e. a stronger increase of perceived loudness with increasing stimulus level (Fowler 1936). There is strong indication that recruitment is directly connected to a loss of fast-acting compression on the basilar membrane (Moore et al. 1996; Carlyon & Datta 1997a; Robles & Ruggero 2001) leading to a more linear response characteristic. This loss of compression influences dynamic aspects of sounds in a way that fluctuations of the excitation on the basilar membrane (BM) are magnified. Figure 5.1 shows the output of a cochlear simulation (Duifhuis et al. 2003) using amplitude modulated sinusoids with a carrier frequency of 500 Hz and a modulation frequency of 80 Hz. In panel (A) the fluctuation of the excitation as calculated from the Hilbert envelope of the BM displacement at the characteristic place is plotted over the simulation time. The simulation was executed with a non-linear (solid lines) and a linear BM setting (dashed line) with stimulus modulation depths of 0, 15, 50 and 85 % (marked in different shades), respectively. In all cases the model stimulus level remained constant at 65 dB SPL. Panel (B) shows the difference between maxima and minima of the Hilbert envelope of the displacement against the modulation depth. It can be seen that the resulting fluctuation for a given modulation depth is larger in the linear case compared to the non-linear BM setting. This enhancement of the fluctuation has also perceptual consequences. Moore et al. (1996) have shown that subjects with unilateral hearing loss match a given modulation depth in the worse ear by a greater modulation depth in the normal ear. In other words, the perception of modulation depth is more distinct in the presence of recruitment.

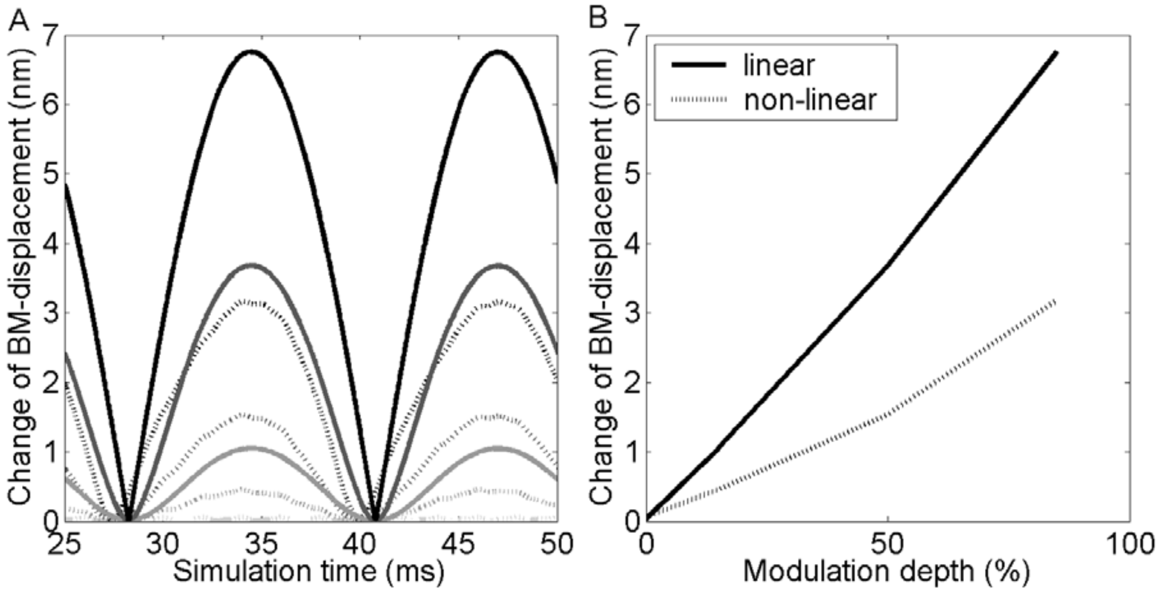

Figure 5.1: *Output of a cochlear simulation (Duifhuis et al. 2003) with amplitude modulated sinusoids. Panel (A) shows the fluctuation of the basilar membrane (BM) displacement at the characteristic place. The simulation was done with a linear BM setting, approximating a damaged cochlea (solid lines), and with a non-linear BM setting (dashed lines) to reproduce normal BM behavior. The different shades of the lines mark the four different modulation depths (0, 15, 50 and 85 %) that were used for the simulation. Panel (B) shows the magnitude of the displacement fluctuation in dependance of the modulation depth for the linear (solid line) and the non-linear (dashed line) case. It can be seen that the fluctuation for the linear cochlea is clearly larger than for the non-linear BM setting.*

The aim of this study is to verify these differences in the perception of modulation depth by an objective method and to investigate their potential use for an objective assessment of cochlear damage. Since the decisive parameter of the above experiments is the amplitude modulation of the stimulus, a possible objective method that can be used to quantify the individual´s response to amplitude modulations is the amplitude modulation following response (AMFR).

The AMFR is a special case of the auditory steady-state response (ASSR) which is obtained by measuring the EEG response evoked by a repeating stimulus that is successively presented, so that the responses to the single stimuli overlap and thereby generate a periodic potential. The spectrum of this potential mainly consists of components correlated to the temporal envelope of the stimulus. Hence, it sustains phase and amplitude over time. In principle every acoustical signal with an appropriate temporal structure or stimulus repetition rate can evoke steady state potentials. However, the sinusoidally amplitude modulated waves used for the AMFR have the advantage that their spectra only consist of three lines: one at the carrier frequency and two lines set apart by the modulation frequency above and below the carrier frequency. The excitation energy is therefore concentrated on a small region of the cochlea, hence permitting frequency specific hearing tests (Lins et al. 1996; Herdman et al. 2002; Mühler 2004). AMFR can be recorded for a wide range of modulation frequencies but it is commonly assumed that the choice of modulation frequency determines the origin of the evoked potential (Kuwada et al. 1985; John & Picton 2000; Pethe et al. 2001). Potentials evoked by modulation frequencies around 40 Hz are believed to originate from a cortical source and yield high potentials but decrease in amplitude during sleep (Kuwada et al. 1985; Linden et al. 1985; Jerger et al. 1986; John et al. 1998).

The AMFR to stimuli for higher modulation frequencies are by a factor of 4 lower in amplitude than the low frequency responses but are independent of the vigilance of the subjects and can also be recorded in infants (Kuwada et al. 1985; John et al. 1998). In practice, the potentials of the so called “middle latency AMFR” measured at 40 Hz yield the largest potentials while the 80 Hz responses, designated as “brainstem AMFR”, are almost equally stable but independent on the vigilance of the subjects (Pethe et al. 2002). The normal approach to develop an objective hearing test is to determine the AMFR detection level for a fixed modulation depth. By using the multiple auditory steady state response (MASTER), i.e. by presenting multiple carrier frequencies each modulated with its unique modulation frequency, it is possible to screen the hearing for four frequencies within reasonable expenditure of time (John et al. 1998; John et al. 2001). Depending on the measurement time and the individual noise level of the subjects the hearing threshold can typically be approximated to 10 – 20 dB (Lux et al. 2003; Mühler 2004). Using suprathreshold carrier levels, on the other hand, Kuwada et al. (1985) have shown that AMFR amplitudes for normal hearing listeners increase monotonously with increasing modulation depth. It is unclear, however, if a similar increase is found in listeners with a cochlear hearing loss and if this increase relates to the recruitment phenomenon. The current study therefore investigates the dependancy of the AMFR on the modulation depth at a fixed stimulus level for subjects with different hearing loss and therefore different loudness perception between left and right ear. Since the amplitude of the ASSR response was found to be directly correlated with the perceived loudness (Ménard et al. 2008), the different loudness percept was compensated by different presentation levels of the stimuli. The aim was to ascertain that the intra-individual difference in loudness perception is reflected in a stronger increase of AMFR amplitudes as a function of modulation depth. In order to be independent of changes in the subjects’ vigilance state during the AMFR recording, the measurements were performed at a modulation frequency of 80 Hz.

I. Experimental methods

a. Subjects

In order to investigate the intra-individual difference of the AMFR amplitudes only subjects with asymmetric hearing loss were asked to participate in this study. Only subjects were chosen with a hearing loss smaller or equal than 25 dB on one ear at the tested frequencies 500 Hz and 4 kHz and a hearing loss which is at least 25 dB larger on the other ear (see Table 5.1). In all cases the pure tone thresholds and uncomfortable levels (UCL) of all subjects were screened using a Siemens Unity SD100 clinical audiometer. In cases in which the reason of the hearing loss remained unclear, an additional tympanometric examination was done to exclude conductive hearing loss originating from the middle ear. Due to this demands five subjects (all female, aged between 18 and 67 years, average 50 years) could be found to participate in the experiments.

b. Stimuli

The stimuli were amplitude modulated sinusoids specified by:

$$A(t) = \frac{1}{(1+M/100)}\left(\sin(2\pi f_c t) * \left(1 + \frac{M}{100} * \cos(2\pi f_m t)\right)\right)$$

where M is the modulation depth (between 0 and 100 %) and f_c and f_m were the carrier and modulation frequency, respectively. The fraction on the left side normalizes the peak amplitude to one. The stimuli were digitally generated with a sampling frequency of 48 kHz and had a length of 1250 ms (60000 samples). Two different carrier frequencies (500 and 4000 Hz) and five different modulation depths (5, 25, 45, 65 and 85 %) were applied so that 10 different stimulus conditions were used for the experiment. The modulation frequency was 72.8 Hz and 80.8 Hz for the 500 Hz and 4000 Hz stimulus, respectively. Since the presentation of the stimuli was carried out separately, the difference in modulation frequency had no physiological or technical relevance, but only served as an identifier for the data analysis. Carrier and modulation frequencies were chosen such that an integer number of cycles fitted in the stimulus frame. This allowed for a continuous presentation of the stimuli without acoustical artifacts at the joints.

All stimuli were calibrated to the same rms value. The same presentation level was set for the five stimuli of the same carrier frequency. The presentation level of the stimulus during the measurement was at least 16 dB above the individual hearing threshold to ensure that the ear can respond to the full amplitude range of the most modulated stimulus signal. In order to avoid air conductive cross hearing, the non-stimulated ear was occluded by a foam tip. Due to the high differences of the presentation level bone conducting crosstalk to the contralateral ear cannot be ruled out in the individual cases (see Table 5.1) when stimulating the worse ear. However, since the interaural attenuation can be assumed to exceed 60 dB, the resulting stimulus levels on the contralateral side are too small to contribute to the measured response potentials.

	Hearing threshold (dB)				Presentation level (dB SPL)				Slope of the loudness function at presentation level (cu/dB)			
	500 Hz		4000 Hz		500 Hz		4000 Hz		500 Hz		4000 Hz	
	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right	Left	Right
S1	77	10	55	-5	90	55	88.5	63	0.92	0.25	0.74	0.28
S2	5	50	0	65	66	86	56	89.5	0.53	1.05	0.51	0.82
S3	15	40	25	80	55	65	54.5	--	0.46	0.70	0.42	--
S4	10	40	5	40	44.5	82	56.5	73.5	0.43	0.63	0.37	0.64
S5	0	45	35	65	50	80	57	86.5	./.	./.	./.	./.

Table 5.1: *Hearing thresholds (left columns), presentation levels for the AMFR recordings (middle columns) and slope of the loudness function (right columns) for the subjects S1-S5. Loudness scaling did not yield valid results for subject 5. Presentation levels were mainly determined by the adaptive loudness equalization procedure in this subject.*

c. Apparatus

The stimuli were generated in real time on a PC and replayed by an I/O card (RME DIGI 96 PAD). The I/O card was connected via an optic fiber to a 24-bit external AD/DA converter (RME ADI-8 PRO) whose analog output was then conveyed to a programmable attenuator (Tucker-Davis Technology (TDT) PA5) and a headphone buffer (TDT HB7). The signals were presented by an Etymotic-Research ER2 insert earphone built into an electromagnetically shielded box. The whole output path was calibrated using an artificial ear for insert earphones (Bruel & Kjaer Type 4157).

Stimulus levels and the replay sequence were controlled by a Matlab based software (Soundmex 2006).

Scalp potentials were recorded differentially between the vertex and the mastoids using electrodes attached to an EEG cap. An additional ground electrode was placed on the forehead. The potentials were amplified by an EEG amplifier (Neuroscan SynAmp) and recorded on a separate PC. A trigger line from the stimulus PC to the recording PC permitted the correct mapping of the recorded potentials. All measurements took place inside a sound-attenuating and electrically shielded listening booth (IAC 1205).

d. AMFR recording

The recording was done with ten stimulus conditions composed of two different carrier frequencies and five modulation depths[1] (see stimuli section). Each stimulus condition was presented between 800 and 1000 times depending on the noise level of the recording. These 800 to 1000 presentations for each stimulus condition were divided into eight subsets containing 100 to 125 presentations. Eight runs were formed containing one subset of each stimulus condition with a randomized sequence of the conditions within each run. Prior and after each subset there was an additional presentation of the same stimulus condition but with a different trigger word. Thus, only eight of the ten subsets in each run were analyzed. These additional presentations were excluded from the subsequent averaging in order to avoid onset effects. During the measurement the subjects rested on a couch inside a hearing booth. In order to reduce background noise levels of the recorded scalp potentials they were encouraged to relax and fall asleep.

[1] Preliminary measurements with a modulation frequency of 40 Hz have shown a strong interaction of the resulting vigilance dependent potentials for stimuli whose carrier frequencies were up to three octaves apart when different modulation depths were measured simultaneously in a multi-carrier experiment design (own unpublished data). For measurements with a modulation frequency of 80 Hz this interaction was substantially smaller. Nonetheless this observation is somewhat at odds with studies of the multiple auditory steady state response (MASTER) method where different carrier frequencies are presented simultaneously thereby saving measurement time (John et al. 1998; John et al. 2001). In these studies no significant interaction was found for high modulation frequencies when the carrier frequencies were more than half an octave apart. The difference might be explained by the fact that John et al. used the same modulation depth (100 %) for all stimuli while we randomly mixed stimuli with completely different modulation depth. Especially with modulation frequencies of 40 Hz the resulting perceptual differences due to different modulation depths result in a strong interaction across frequency bands. Thereby the potentials of the less modulated carriers were substantially attenuated. For higher modulation frequencies this effect is less distinct but nonetheless noticeable. We therefore decided to present the different stimuli separately.

An artifact rejection threshold of 100 μV was applied to the recordings prior to the averaging. All presentations with the same trigger words were averaged across the eight runs and band pass filtered between 10 and 150 Hz using a second order butterworth filter. The latter was not required for the data analysis but only served to enhance visualization of the AMFR. The AMFR was analyzed by calculating the spectrum of the averaged recording and determining the amplitude of the spectra at the respective modulation frequency.

The presence of a valid response was confirmed by power spectrum analysis using the F test. This was done by calculating the ratio of the power at the modulation frequency and the average power of 23 neighboring frequency bins between 72 and 90.4 Hz (Zurek 1992; Dobie & Wilson 1996; Sachs 2002) and testing this ratio for statistical significance.

The stimulus level for the AMFR was determined in two steps:

1. The results of the loudness scaling served as a first indicator for the stimulus level on the worse ear. All stimuli were presented to the subject’s worse ear with a level corresponding to 20 cu (perceived as ‘soft’, see below). The subjects had then the opportunity to assess the level and decide whether or not it is comfortable for the duration of the AMFR measurement. If the level was too high (or in rare occasions perceived as being too quiet) the level was adjusted according to the response given by the subjects. Most subjects asked for a reduction of the stimulus level between 4 and 6 dB.
2. The presentation level on the better ear was determined as the level of equal loudness as the presentation level on the worse ear. This level was found by a loudness matching experiment done during the first session (see below).

The AMFR-experiment was split into four sessions (two for each ear) measured on different days with four runs of the stimulus presentation measured in each session, starting with the worse ear in the first session. The loudness matching was performed twice after the first AMFR session. In the first measurement the subjects were asked to familiarize themselves with the procedure while the result of the second measurement was used to determine the presentation level of the subsequent AMFR measurements. The total measurement time was up to 7.5 hours per subject.

e. Loudness scaling and matching procedure

Since the subjects exhibited different loudness perception between both ears and since the loudness was found to be directly correlated with the response amplitude of the ASSR-measurement (Ménard et al. 2008), the perceptual difference was equalized by different presentation levels on both ears thus achieving an equal degree of excitation on the basilar membrane. For that, the subjects performed a loudness scaling of narrow band noise to verify the presence of recruitment (Allen et al. 1990; Brand & Hohmann 2002) using the ACALOS procedure of Brand and Hohmann (2002). The subjects were asked to categorize the presented third octave band wide low-noise-noise, i.e. low-fluctuation noise (centered at 500 and 4000 Hz) into one of 11 given categories ranging between 'inaudible' and 'too loud'. The length of the presented test signal was one second. From the responses the automatic adaptive algorithm estimated the loudness function, i.e. the perceived loudness in categorical units (cu) over the stimulus level. The running estimate was also used to set the stimulus levels in an optimal way in order to achieve an unbiased estimate of the categorical loudness function within a short measurement time (see Brand & Hohmann, 2002).

For loudness matching, subjects were asked to match a given loudness of an unmodulated test signal (500 or 4000 Hz sinusoid) on one ear ('reference side') by adjusting the level of a subsequent corresponding signal on the other ear ('test side'). In successive runs the reference side could either be the worse or the better ear. If the worse ear was chosen, the fixed reference level was given by the stimulus level chosen for the AMFR measurement. Otherwise, if the better ear was chosen, the reference level was calculated from the loudness scaling (level corresponding to 20 cu). The starting level on the test side was chosen randomly between 0 and 85 dB SPL, regardless of the test ear. Presentation always started on the reference side and the subject could arbitrarily change sides either by keyboard or by touching the corresponding field on a graphical user interface shown on a monitor. Fading in and out was done by applying Hanning-shape ramps of 20 ms length to the respective signals. The subjects could change the presentation level on the test side in three different steps of 5, 2 and 1 dB marked by different sized symbols on the user interface. If the subjects achieved a level of equal loudness between reference and test side they continued to the next condition by pushing a corresponding field on the screen until the measurement was finished. The four stimulus conditions (two frequencies and two reference sides) were completely randomized and presented twice. The presentation level of the better ear for the AMFR-measurement was determined by calculating the mean level of equal loudness to the fixed level on the worse ear. The runs with the better ear as the reference side were used as an additional control condition of the results.

II. Results

a. Loudness scaling

Hearing thresholds, presentation levels and the slopes of the loudness function at the respective presentation level are listed in Table 5.1. Subject S5 was not able to judge the categorical loudness in a reliable way. Hence, the adaptive loudness scaling procedure did not yield usable results. All other subjects exhibited larger slopes of the loudness function on the ear with the higher hearing threshold, indicating a higher degree of recruitment on the worse ear. Nonetheless, no correlation was found between the hearing loss and neither the presentation level nor the slope of the subjective loudness function. The variation of the loudness function across subjects is also not correlated with the variation of the amplitudes of the potentials measured in the respective ear.

b. AMFR for 500 Hz carrier frequency

Measurement results for the 500 Hz stimulus of the subjects (S1 to S4) are presented in Figure 5.2. The panels on the left side show the growth function of the response amplitude over the modulation depth. Responses to stimulation on the worse and the better ear are indicated by the solid and the dashed line, respectively. The electrode side is given by the left or right pointing triangles used as line markers. Potentials that differ significantly from the background noise (as estimated from the adjacent frequency bins (F-Test with P=0.05; (Zurek 1992))) are denoted by black symbols while potentials that do not meet the significance threshold are shaded in grey. On the right panels each marker represents a pair of response amplitudes for a given modulation depth with different presentation sides, with the potential evoked by presenting the stimulus on the worse ear (‘worse ear potential’) plotted on the ordinate. The potential corresponding to the highest degree of modulation is marked by a filled symbol. If one of the potentials was not significant the symbols were drawn in grey while points composed of two not significant potentials were omitted. The dotted diagonal line indicates equal potential for both ears. In cases of comparable potentials between worse and better ear stimulation at low modulation depth, data points above the diagonal line for higher modulated stimuli indicate the stronger increase of the worse ear potentials. This stronger increase of the worse ear potentials can clearly be seen in subjects S1 (Figure 5.2, first row), S3 (third row), S4 (forth row) and S5 (fifth row). This result is consistent with the assumption that hearing loss accompanied by the loss of cochlear compression leads to an extension of the fluctuations of basilar membrane excitation due to the amplitude modulation of the stimulus. The slope of the growth function does not remain constant across the range of modulation depths. In many cases saturation effects can be observed especially for the better ear potentials (e.g. Figure 5.2, forth and fifth row). This effect is less distinct for the worse ear potential so that highest difference in response amplitudes can frequently be observed for the points with the highest modulation depth.

Subject S2 (Figure 5.2, second row) exhibits much higher worse ear potentials only on the right electrode while the left electrode only yields very low potentials in case of the worse ear stimulation. Differences in the measured potentials between the electrodes can also be observed to a smaller extent in other subjects (e.g., subject S1, Figure 5.2, first row). Since this observation was consistent across the different measurement sessions the subjects participated in and since these measurements were interspersed with other subjects’ sessions a technical reason for this observation can be ruled out. Hence, the potential difference of the ipsi- and contralateral electrode is most probably due to large individual differences in subject S2´s equivalent dipole orientation across stimulation conditions that will be discussed below.

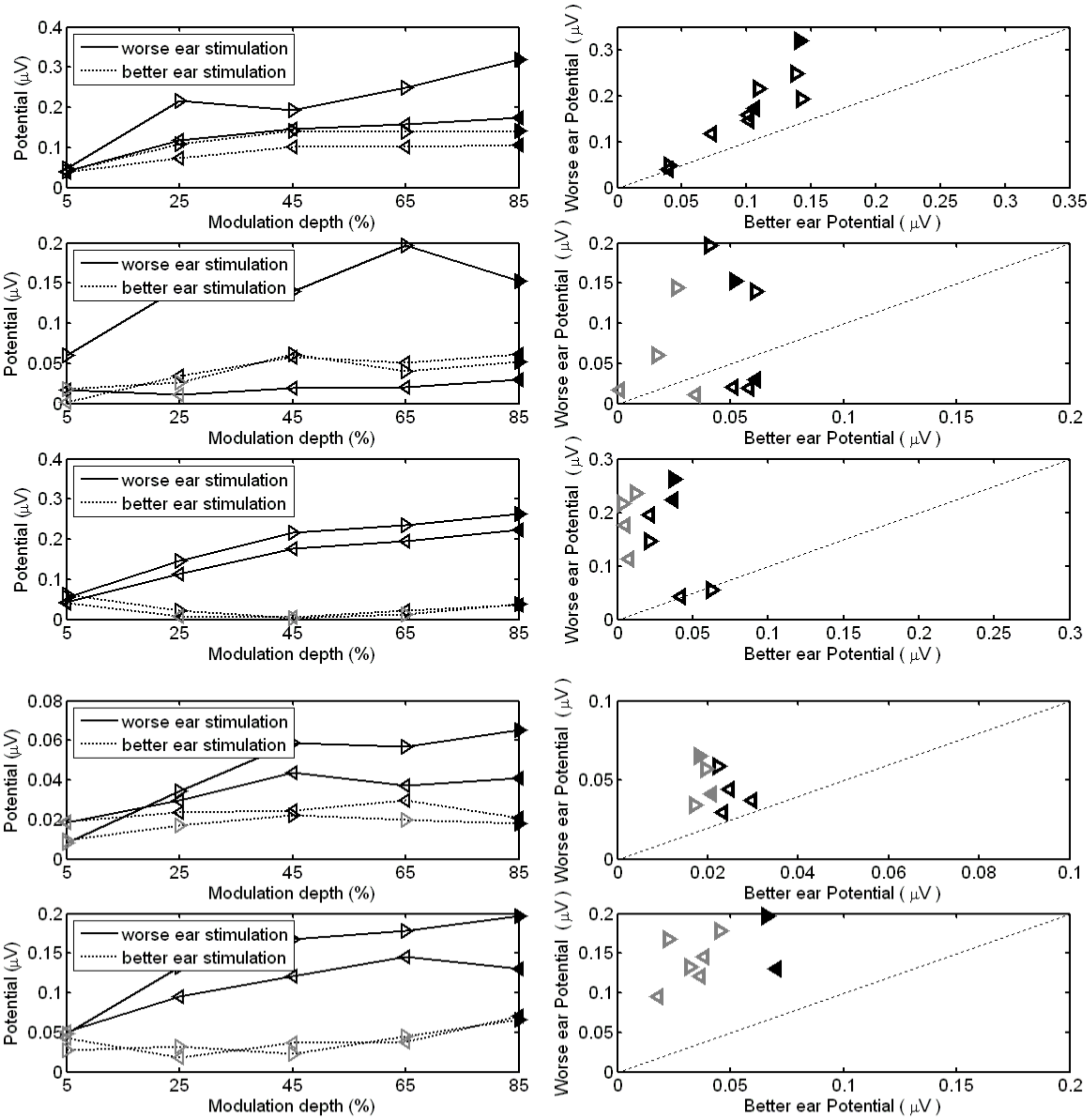

***Figure 5.2:** Results of the AMFR measurements for subjects S1 (first row) to S5 (fifth row). The carrier frequency was 500 Hz. The left panels shows the AMFR growth function, i.e. the potentials plotted across the modulation depth. Stimulation on the worse ear is marked by the solid lines while the dashed lines indicate presentation of the stimulus to the better ear. Potentials were measured with two electrodes placed on the left and right mastoid, marked by the left and right pointing symbols. Points that do not meet the significance threshold (F-Test with P=0.05) are shaded in grey. The right panel shows the ratio of corresponding worse ear and better ear potential. Points where one of the two potentials is not significant are marked by grey symbols while points were omitted if both responses were not significant. The dotted diagonal line indicates equal potentials on both ears. Points above the line therefore show higher potentials on the worse ear.*

In case of subject S2 (second row) the measured potential on the right (ipsilateral) electrode is by a magnitude higher than that of the contralateral electrode. The stronger increase of the worse ear potentials can only be observed on the right electrode.

The results for the 500 Hz stimulus are summed up in Figure 5.3 where the ratio of the worse ear potential and the better ear potential for the 85 % modulation depth is plotted for all subjects. Comparison of the ratio of worse ear amplitude to better ear amplitude with the hearing loss (compare Figure 5.3 with Table 5.1) reveals no correlation. However, most of the ratio values are around two to three which is largely consistent with the amount of compression in the healthy cochlea in relation to a potential compression loss in the damaged cochlea.

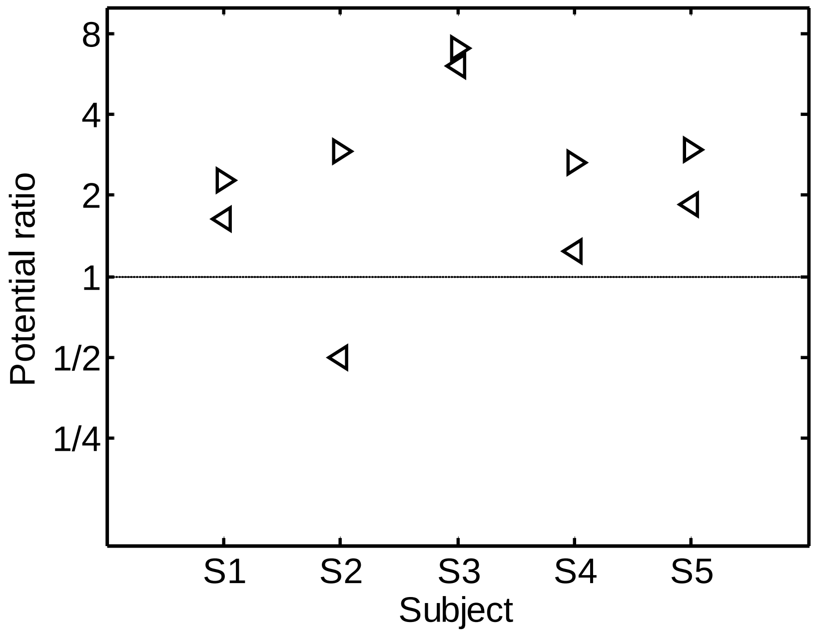

Figure 5.3: *Ratio of the corresponding worse ear and better ear potentials at the highest modulation depth for the 500 Hz carrier frequency for subjects S1-S5. The dotted line indicates equal potentials on both sides, i.e. no influence of the loss of cochlear compression on the AMFR. All subjects demonstrate higher worse ear responses on at least one electrode.*

c. AMFR for 4000 Hz carrier frequency

The measurements for the 4000 Hz carrier frequency were only done with three of the five subjects since no level of equal perceived loudness could be achieved on the worse ear of subjects S3 and S5 at this frequency. The results for the remaining subjects show distinct inter-individual variation. Significant responses could only be found in one of the three subjects (left panel of Figure 5.4) while the responses for the other subjects were by a magnitude lower (right panel of Figure 5.4). Therefore, a stronger increase of the worse ear response can only be seen in subject S1. One reason might be that the 4000 Hz carrier is perceived as being more uncomfortable than the 500 Hz carrier and that therefore the presentation levels are too low to evoke reliable responses in all subjects. Much longer acquisition times would be required to achieve significant responses for this carrier frequency. Unfortunately, such acquisition times are not practical for patients in a clinical setting.

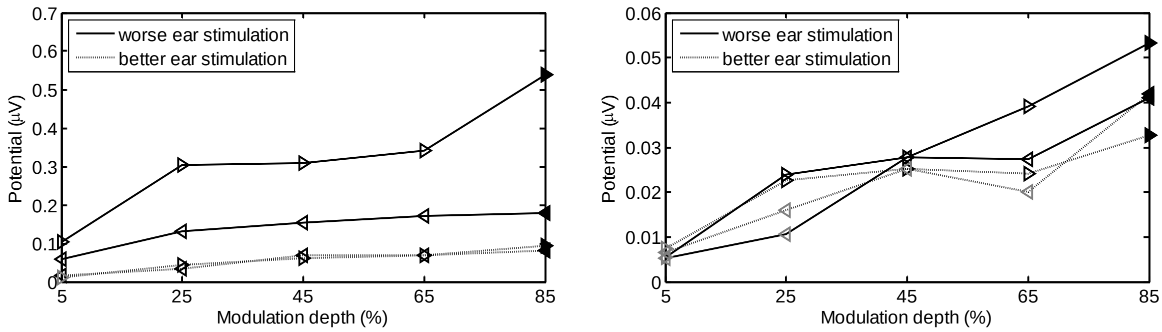

Figure 5.4: *AMFR growth functions of the 4000 Hz measurement for subjects S1 (left panel) and S4 (right panel). Subject S1 demonstrates higher worse ear potentials and a stronger increase of the potentials across the modulation depth. No increased absolute value and no stronger increase of the potential were found for the worse ear potentials of subject S4.*

III. Discussion

The general finding from most subjects is that the evoked AMFR for a given modulation depth is larger for the worse ear than for the better ear if carrier levels are adjusted to equal loudness at both ears. One crucial aspect of the experiments described here is the carrier level adjustment performed in order to (partially) compensate for the hearing loss in both ears by yielding the same perceived loudness. This was done analogous to the investigations by Moore et al. (1996) who also employed subjects with asymmetric hearing loss. The justification for the loudness adjustment is the assumption that equal loudness levels correspond with equal excitation on the basilar membrane and that the equalization therefore represents an adequate compensation for the loss of BM excitation due to the hearing loss. We followed this paradigm to ensure the compatibility with the previous psychophysical experiments by Moore et al (1996).

The results for the 500 Hz stimulus (Figure 5.2) show higher worse ear potentials in all subjects on at least one of the measurement electrodes, i.e. an increase of the response to amplitude modulation is already observed on the level of the brainstem. These results are consistent with the psychophysical results from (Moore et al. 1996).

In addition to verifying the psychophysical results, the aim of measuring the growth functions over the modulation depth rather than the response to a single stimulus with fixed modulation depth was to investigate if systematic differences between the normal and the worse ear occur and if these differences might be used to predict the state of hearing. The results show that the slope of the growth function does not remain constant across the modulation depth. The strongest increase in growth functions can normally be found between 5 and 25 % modulation depth and increase is smaller for higher modulation depths. The better ear potentials frequently show a saturation effect with nearly constant responses for increasing modulation depth. However, since this saturation cannot be observed throughout all subjects and the worse ear potential generally continues to increase with modulation depth, the maximal difference between better ear and worse ear potential can almost always be found for the highest modulation depth. Our assumption that the presence of cochlear damage gives rise to an increase of the AMFR can therefore be probed for the highest modulation depth alone and does not necessarily need a detailed growth function.

Despite the fact that all subjects exhibited similar hearing thresholds on the better ear (see Table 5.1) and that similar presented levels were chosen for the stimuli, a strong inter-individual variation of the recorded better ear responses can be observed (see subjects S1 and S4 (Figure 5.2, first and forth row)) . This is also the case for the worse ear potentials where response amplitudes are not related to the individual hearing loss and the absolute applied stimulus level. Differences in the recorded potentials for different subjects have also been observed in other studies (Kuwada et al. 1985) indicating that the potentials and noise levels are strongly influenced by the individual electrical properties of the scalp. Therefore a comparison of the responses is only reasonable within subjects across both ears.

Different amplitudes in the responses measured on the two electrodes could be observed in most subjects. Since these response differences were larger than the standard deviation of the amplitudes calculated from neighboring frequency bins, they cannot be explained by the underlying noise. In case of subject S2 (see Figure 5.2, second row) the response measured on one electrode was even by an order of magnitude smaller than the simultaneously measured response on the contralateral electrode. The smaller response neither occurred always on the same side nor is it correlated with the side of the stimulus presentation. The measurements were done in at least two different sessions, normally separated by some days. The measured responses are consistent across the different sessions so that technical reasons for the potential differences of the electrodes can be excluded. The most likely explanation is that the measured responses originate from dipole sources whose orientation results in different potentials measured at the electrodes. To obtain information about the actual source potential a dipole analysis based on a multi channel AMFR (either in EEG or MEG) would by necessary. Tracing of the dipole source amplitudes could also lower the across-subject variability of the results.

It was not possible to obtain significant responses in three of the five subjects for the 4000 Hz stimulus. In one of these subjects (S3) that exhibited the largest hearing loss at 4 kHz, no attempt to record the AMFR at this frequency was performed since the required stimulus level exceeded the maximum output level of the technical setup. For the other subjects, the maximum presentation level for these stimuli was restricted in order to prevent uncomfortable stimulus levels and to meet the constraints of the useable span of compressive BM behavior in which the measurement was set. An increase of the signal-to-noise ratio without major increase of the measurement effort might be achieved in future work by recording multi-channel AMFR. This technique also facilitates the assessment of the response differences across electrodes (see above).

The usability of the AMFR growth function as an objective measure of recruitment is hampered by the fact that the amplitude of the response and thereby the slope of the growth function depends on the level of the evoking stimulus. Based on the AMFR response to a given stimulus alone it is therefore impossible to derive any conclusions about the individual patients hearing status. In subjects with asymmetric or unilateral hearing loss, however, a comparison of the responses across both ears is possible but requires a non-objective procedure like a loudness-matching in order to adjust presentation levels. Even for subjects with unilateral hearing loss the variability of the results across the subjects impedes the usage as a recruitment detector. Multi-channel AMFR with subsequent dipole source analysis might help to exclude the influence of the dipole source orientation and thereby to reduce some of the inter-individual variance. Again, however, this might not suffice to allow the assessment of hearing damage based on the measurement result alone.

IV. Summary and outlook

- In most cases from our limited set of subjects with asymmetric hearing impairment presentation of an acoustical stimulus to the worse ear results in a clear increase of the AMFR potentials compared to presentation of a stimulus with equal loudness to the better ear. This observation corresponds with the assumption that the loss of cochlear compression leads to an increase of the BM fluctuations due to the modulation of the evoking stimulus. This increase can therefore be confirmed at brainstem level and is consistent with psychophysical findings (Moore et al. 1996).
- For the purposes of verifying the dependance of AMFR on modulation depth it is sufficient to record the respective responses at the extreme values (i.e. 5 % and 85 % modulation depth). No additional information seems to be gained from the intermediate values, i.e. by recording the complete growth function of the AMFR potential over the modulation depth.
- Differences in the potentials simultaneously measured with two electrodes placed at the mastoids suggest a strong orientation effect of the underlying current dipole sources on the recorded AMFR. In order to investigate the source potential unbiased by the orientation a multi-channel AMFR might be favourable. This might also improve the signal-to-noise ratio for the 4000 Hz stimulus.
- The direct usability of suprathreshold AMFR recordings as an objective recruitment indicator is hampered by the variance of the responses across the subjects and by the necessity to set the appropriate stimulation levels at both ears. If the presentation level is set accordingly (e.g. by a loudness balancing technique or similar), a direct comparison between both ears is possible in subjects with asymmetric or unilateral hearing loss.
- In future measurements 40 Hz modulation frequency could be used to investigate whether an increased response to amplitude modulation can also be demonstrated at a higher stage of the auditory pathway.

Acknowledgements

This study was supported by Deutsche Forschungsgemeinschaft, DFG HO1697/3-1. We thank A. Gorges for technical support, H. Riedel for sharing his EEG knowledge and the members of the Medical Physics group for numerous discussions.

Chapter 6

Summary and outlook

The optimal method for the objective prediction and quantification of hearing has still to be found. Within this thesis, the measurement of the acoustic reflex as one of the few established methods used in the audiological examination was improved by providing a new analysis algorithm to the low level acoustic reflex (LLAR) measurement. This analysis method has been tested and normative data were collected showing the potential benefit in terms of detection rate and detection threshold of the acoustic reflex. It could be shown that the detection of the acoustic reflex was possible at stimulus levels up to 7 dB below the stimulus level required with the established method. At the same time, the detection levels were significantly higher thus indicating that the LLAR proves to be a reliable and sensitive measure of the acoustic reflex and could therefore turn out to be a valuable tool in diagnostics. Several extensions of the work are conceivable to further improve the LLAR method. In particular improvements of the adaptive tracking procedure would potentially decrease the required time effort. This would be advantageous for the clinical application of the method. Another conceivable line of investigation could be the use narrowband multifrequency-component stimuli instead of sinusoids in combination with a multifrequency detection algorithm. This would allow for several simultaneous observations in a certain frequency region and hence improve the observation statistics within a given amount of time or decrease the measurement time for a given statistical uncertainty of the observed threshold.

An application of the LLAR method as a possible objective measure of cochlear damage has been demonstrated in chapter 3 and further investigated in chapter 4 thus opening a new line of investigations of objective methods to validate and quantify the state of hearing. The measurements were performed with broad band stimuli that have identical spectral energy distribution but differ in the phase relation of their components. The results of chapter 3 show that the acoustic reflex is strongly affected by these phase properties and that the acoustic reflex therefore shows a clear effect of neural synchronization. In normal hearing listeners, acoustic reflex thresholds (ART) in response to signals that cause a high neural synchronization of the excitation pattern are much lower compared to the ARTs measured with the temporally inverted signals. This suggests that the amount of synchronized neural excitation is important to elicit the reflex.

The measurements with the normal hearing subjects were repeated with hearing impaired listeners. Comparison of the results show a large difference of the ARTs in response to the different stimuli compared to the results from normal hearing listeners. This finding was consistent with the assumption of a compressive nonlinearity as typically found in basilar membrane input-output functions of normally functioning cochleae. This compressive nonlinearity is reduced in the damaged cochlea thus offering a qualitative explanation of the difference between the subject groups. In order to quantify these differences characteristic measures have been derived from the relation of the ARTs in response to the different stimuli. These measures allowed a clear distinction between the subject groups and have been hypothesized to serve as an objective predictor of the loss of cochlear compression. This assumption was investigated in chapter 4 with 28 subjects that exhibited different hearing thresholds ranging from normal hearing to moderate and severe hearing loss. A high degree of correlation could be shown between the hearing threshold and the measures derived in chapter 3. The method can therefore serve as an objective predictor e.g. in the screening of hearing function. However, the inter-individual variance of the results hampers the prediction accuracy of the hearing threshold based on individual results but allows distinguishing between different severities of broad band hearing losses.

In order to investigate the frequency dependance of the acoustic reflex, the results were related to the type of hearing loss of the subjects. Since the acoustic reflex is known to be easily evoked at low frequencies (Katz 1977) it could be assumed that the hearing in the low frequencies is more important to the reflex elicitation than the higher frequencies. In terms of the experiments performed in chapter 4 this would mean that the parameters that were found to be influenced by the hearing loss are more correlated with the low frequency hearing loss than with the high frequency hearing loss. The results in chapter 4 show, that especially the the correlation of the ARTs in response to random-phased-broadband stimuli does not depend on the spectral shape of the hearing threshold thus contradicting this assumption. This finding indicates that the mid to high-frequency regime of the cochlea is also important for the resulting ART. The results of these studies could provide the base for several further investigations in the future. The usage of broadband stimuli and the established effect of neural synchronization on the reflex threshold could lead to further improvements of the LLAR method by investigating means to further reduce the required stimulus level in order to elicit and detect the acoustic reflex threshold. The multi spectral phase analysis used for the study could be utilized to distinguish between the acoustic reflex and the medial olivocochlear (MOC) efferent reflex thus providing additional artifact suppression.

Taken together, the established relation between cochlear damage and the measures derived from the ARTs provide a promising objective prediction of the state of hearing. Further investigations should concentrate on the frequency dependance of the ARTs not only to improve the prediction accuracy but also in order to better understand the physiology of the acoustic reflex.

A more detailed approach on the neural level to the influence of cochlear damage on objective measures was investigated in chapter 5. The experiments established a relationship between the recruitment phenomenon that is common in the presence of cochlear damage and the growth function of amplitude modulation following responses (AMFR) for different modulation depths of the evoking stimuli. Because of the large inter-individual variance that is found in the AMFR, the measurements had to be performed in subjects with asymmetrical hearing loss. The layout of the study therefore hampers generalizations of the results and the large inter-individual variance found in the results makes it unlikely that the method could be utilized as an objective predictor of recruitment. Nevertheless, the relationship between recruitment and the level of the AMFR potential for a given modulation depth supports the physiological model and thereby confirms our understanding of the hearing process.

Pilot measurements with a modulation frequency of 40 Hz have shown a strong interaction of the resulting potentials for stimuli whose carrier frequencies were up to three octaves apart when different modulation depths were measured simultaneously in a multi-carrier experiment design. AMFR potentials in response to a stimulus modulation frequency as low as 40 Hz are believed to originate from higher stages of the auditory pathway and are therefore expected to be vigilance dependent (Kuwada et al. 1985; John et al. 1998). For measurements with a modulation frequency of 80 Hz this interaction was substantially smaller. The observed interaction is somewhat at odds with studies of the multiple auditory steady state response (MASTER) method where different carrier frequencies are presented simultaneously thereby saving measurement time (John et al. 1998; John et al. 2001). In these studies no significant interaction was found for high modulation frequencies when the carrier frequencies were more than half an octave apart. In chapter 5 it was hypothesized that the discrepancy can be explained by the fact that John et al. used the same modulation depth (100 %) for all stimuli while the measurements in chapter 5 were performed with randomly mixed stimuli with completely different modulation depths. The resulting perceptual differences due to different modulation depths could therefore account for the strong interaction across frequency bands. Further investigations should establish and quantify these interactions in order to relate the perceptual dimension to measurable quantities and thereby help our understanding of the hearing.

In conclusion the aim of the thesis was to investigate objective measures of the state of hearing that address higher stages of the auditory pathway. The two approaches, the reflex audiometry and the AMFR measurements, were found to be influenced by hearing disorders on cochlear level and were related to established perceptual measures. Also the utilized methods cannot be directly used in clinical applications the results open new avenues of research. The prediction of hearing thresholds by means of the reflex audiometry turned out to be comparable to other methods that are already used in clinical screening but include neural stages of the auditory pathway. The application of the AMFR measurements are challenging because of the large inter-individual variance of the responses but the results can serve as an experimental confirmation of the auditory model.

References

Allen, J. B., J. L. Hall and P. S. Jeng (1990). "Loudness growth in 1/2 octave bands (LGOB) - A procedure for the assessment of loudness." J. Acoust. Soc. Am **88**: 745-753.

Baumann, U., K. Vudjam and M. Müller-Wehlau (2006). Clinical Investigations of the Low Level Acoustic Reflex - Caveats and Results. 28th International Congress of Audiology, Insbruck.

Bennett, M. (1984). Impedance Concepts Relating to the Acoustic Reflex. The acoustic reflex. S. Silman, Academic Press, Inc.**:** 36-59.

Boege, P. and T. Janssen (2002). "Pure-tone threshold estimation from extrapolated distortion product otoacoustic emission I/O-functions in normal and cochlear hearing loss ears." J. Acoust. Soc. Am **111**(4): 1810-8.

Boer, E. d. (1980). "Auditory physics. Physical principles in hearing theory I." Phys. Rep. **62**: 87-174.

Borg, E. (1973). "On the neural organization of the acoustic middle ear reflex. A physiological and anatomical study." Brain Research **49**: 101-123.

Brand, T. and V. Hohmann (2002). "An adaptive procedure for categorical loudness scaling." J. Acoust. Soc. Am **112**(4): 1597-1604.

Carlyon, R. P. and A. J. Datta (1997a). "Excitation produced by Schroeder-phase complexes: evidence for fast acting compression in the auditory system." J. Acoustic. Soc. Am. **101**: 3636-3647.

Carlyon, R. P. and A. J. Datta (1997b). "Masking period patterns of Schroeder-phase complexes: Effects of level, number of components, and phase of flanking components." J. Acoustic. Soc. Am **101**(6): 3648-3657.

Clemis, J. D. (1984). "Acoustic reflex testing in otoneurology." Otolaryngol Head Neck Surg **92**: 141-144.

Dau, T. (2003). "The importance of cochlear processing for the formation of auditory brainstem and frequency following responses." J. Acoustic. Soc. Am **113**(2): 936-950.

Dau, T., O. Wegner, V. Mellert and B. Kollmeier (2000). "Auditory brainstem responses with optimized chirp signals compensating basilar-membrane dispersion." J. Acoustic. Soc. Am. **107**: 1530-1540.

Dobie, R. A. and M. J. Wilson (1996). "A comparison of t test, Ftest, and coherence methods of detecting steady-state auditory evoked potentials, distortion-product otoacoustic emissions, or other sinusoids." J. Acoust. Soc. Am **100**(4): 2236-2246.

Duifhuis, H., J. M. Kruseman and P. W. J. v. Hengel (2003). An Improved Cochlea Model with a General User Interface. The Biophysics of the Cochlea; from Molecules to Models. A. W. Gummer. Singapore, World Scientific**:** 376-382.

Fowler, E. P. (1936). "A method for the early detection of otosclerosis." Arch. Otolaryngol. **24**: 731-741.

Gelfand, S. A. (1998). Hearing - An Introduction to Psychological and Physiological Acoustics. New York, Marcel Dekker,Inc.

Gorga, M. P., D. J. Lilly and R. V. Lenth (1980). "Effect of signal bandwidth upon threshold of the acoustic reflex and upon loudness." Audiology **19**: 277-292.

Greenwood, D. D. (1990). "A cochlear frequency position function for several species - 29 years later." J. Acoustic. Soc. Am. **87**: 2592-2605.

Guinan, J. J. J., C. B. Bradford, W. Lilaonitkul and V. Aharonson (2003). "Medial olivocochlear efferent reflex in humans: otoacoustic emission (OAE) measurement issues and the advantage of stimulus frequency OAEs." J. Assoc. Res. Otolaryng **4**: 521-540.

Harris, F. P. and R. Probst (2002). Otoacoustic Emissions and Audiometric Outcomes. Otoacoustic Emissions - Clinical Applications. M. S. Robinette and T. J. Glattke. New York, Stuttgart**:** 416-438.

Herdman, A. T., T. W. Picton and D. R. Stapells (2002). "Place specificity of multiple auditory steady state responses." J. Acoust. Soc. Am **112**: 1569-1582.

Jerger, J., R. Chmiel, J. D. J. Frost and N. Coker (1986). "Effekt of sleep on the auditory steady state potential." Ear Hear **7**: 240-245.

Jerger, J. and J. L. Northern (1980). Clinical Impedance Audiometry. Stuttgart, New York, George Thieme Verlag.

John, M. S., A. Dimitrijevic, P. van Roon and T. W. Picton (2001). "Multiple auditory steady-state responses to AM and FM stimuli." Audiol Neurootol **6**(1): 12-27.

John, M. S., O. G. Lins, B. L. Boucher and T. W. Picton (1998). "Multiple auditory steady-state responses (MASTER): stimulus and recording parameters." Audiology **37**(2): 59-82.

John, M. S. and T. W. Picton (2000). "Human auditory steady-state responses to amplitude-modulated tones: phase and latency measurements." Hear Res **141**(1-2): 57-79.

Katz, J. (1977). Handbook of Clinical Audiology. Philadelphia, Lippincott Williams & Wilkins.

Kawase, T., H. Hidaka, K. Ikeda, S. Hashimoto and T. Takasaka (1998). "Acoustic reflex thresholds and loudness in patients with unilateral hearing losses." Eur. Arch. Otorhinolaryngol **255**: 7-11.

Kawase, T., H. Hidaka and T. Takasaka (1997). "Frequency summation observed in the human acoustic reflex." Hearing Research **108**: 37-45.

Kohlrausch, A. and A. Sander (1995). "Phase effects in masking related to dispersion in the inner ear II. Masking period patterns of short targets." J. Acoustic. Soc. Am **97**: 1817-1829.

Kubli, L., L. Dreisbach, M. Leek and J. Lentz (2001). Acoustic reflexes to schroeder-phase harmonic complexes in normal-hearing and hearing-impaired individuals. ARO.

Kuwada, S., R. Batra and V. L. Maher (1985). "Scalp potentials of normal and hearing-impaired subjects in response to sinusoidally amplitude-modulated tones." Hear. Research **21**: 179-192.

Lentz, J. J. and M. R. Leek (2001). "Psychophysical estimates of cochlear phase response: masking by harmonic complexes." J. Assoc. Res. Otolaryng **02**: 408-422.

Lilly, D. J. (1984). Evaluation of the response time of acoustic-immittance instruments. The acoustic reflex. S. Silman, Academic Press, Inc.**:** 102-135.

Linden, R. D., K. B. Campbell, G. Hamel and T. W. Picton (1985). "Human auditory steady state evoked potentials during sleep." Ear Hear **6**: 167-174.

Lins, O. G., T. W. Picton, B. L. Boucher, A. Durieux-Smith, S. Champagne, L. Moran, M. Perez-Abalo and G. Savio (1996). "Frequency-specific audiometry using steady-state responses " Ear Hear **17**: 81-96.

Lux, L., J. Pethe, R. Mühler and H. von Specht (2003). "Bestimmung der Hörschwelle durch die Registrierung von Amplitude Modulation Following Responses (AMFR) bei multifrequenter Stimulation." Z. Audiol. **42**: 18-124.

Mardia, K. V. (1972). Statistics of directional Data. London, New York, Academic Press.

Margolis, R. H. and G. R. Popelka (1975). "Loudness and the acoustic Reflex." J. Acoustic. Soc. Am. **58**: 1330-1332.

Mauermann, M. (2004). Fine Structure in Distortion Product Otoacoustic Emissions and Auditory Perception. Oldenburg, Carl-von-Ossietzky Universität.

Ménard, M., S. Gallégo, C. Berger-Vachon, L. Collet and H. Thai-Van (2008). "Relationship between loudness growth function and auditory steady-state response in normal hearing subjects." Hear Res **235**: 105-113.

Metz, O. (1951). "Studies on the contraction of the tympanic nuscles as indicated by changes in the impedance of the ear." Acta Oto-Laryngologica **39**: 397-405.

Moore, C. J. B., M. Wojtczak and D. A. Vickers (1996). "Effect of loudness recruitment on the perception of amplitude modulation." J. Acoust. Soc. Am **100**: 481-489.

Mühler, R. (2004). "Auditory Steady-State Response - An der Schwelle zur klinischen Nutzung?" HNO **52**: 779-782.

Müller-Wehlau, M., M. Mauermann, T. Dau and B. Kollmeier (2004). Acoustic reflex thresholds obtained with chirp stimuli compensating for cochlear dispersion. Midwinter Meeting of the Assoc Res Otolaryngol, Daytone Beach, FL, USA.

Müller-Wehlau, M., M. Mauermann, T. Dau and B. Kollmeier (2005). " The effects of neural synchronization and peripheral compression on the acoustic-reflex threshold." J. Acoustic. Soc. Am **117**(5): 3016-3027.

Müller-Wehlau, M., M. Mauermann and B. Kollmeier (2002). Auswertealgorithmen zur Niedrigpegel-Reflexaudiometrie [Evaluation algorithmen for the low level reflex audiometry]. Fortschritte der Akustik - DAGA 2002**:** 52-53.

Neumann, J. (1997). Recording Techniques, Theory and Audiological Application of Otoacoustic Emissions. Oldenburg, bis, Oldenburg.

Neumann, J., S. Uppenkamp and B. Kollmeier (1996). "Detection of the acoustic reflex below 80dB HL." Audiology and Neurootology **1**: 359-369.

Olsen, S. Ø. (1999a). "The relationship between the uncomfortable loudness level and the acoustic reflex threshold for pure tones in normally-hearing and impaired listeners -- a meta-analysis." Audiology **38**: 61-68.

Olsen, S. Ø., A. N. Rassmussen, L. H. Nielsen and B. V. Borgkvist (1999b). "The acoustic reflex threshold: not predictive for loudness perception in normally-hearing subjects." Audiology **38**: 303-307.

Olsen, S. Ø., A. N. Rassmussen, L. H. Nielsen and B. V. Borgkvist (1999c). "The relationship between the acoustic reflex threshold and levels of loudness categories in hearing-impaired listeners." Audiology **38**(308-311).

Oxenham, A. and T. Dau (2001). "Phase effects in masking in normal-hearing and hearing-impaired listeners." J. Acoustic. Soc. Am. **110**: 3169-3177.

Oxenham, A. and T. Dau (2004). "Masker phase effects in normal-hearing and hearing-impaired listeners: Evidence for peripheral compression at low signal frequencies." J. Acoustic. Soc. Am **116**(4): 2248-2257.

Pethe, J., R. Mühler and H. Von Specht (2001). "Zur Abhängigkeit der AMFR von der Vigilanz." HNO **49**: 188-193.

Pethe, J., R. Mühler and H. Von Specht (2002). "Amplitude Modulation Following Response (AMFR) in der audiologischen Diagnostik." HNO **50**: 1045-1052.

Robles, L. and A. Ruggero (2001). "Mechanics of the Mammalian Cochlea." Physiol Rev **81**(3): 1305-52.

Rupp, A., S. Uppenkamp, A. Gutschalk, R. Beucker, R. D. Patterson, T. Dau and M. Scherg (2002). "The representation of peripheral neural activity in the middle-latency evoked field of primary auditory cortex in humans(1)." Hear. Res. **174**: 19-31.

Sachs, L. (2002). Angewandte Statistik [Applied statistics]. Berlin / Heidelberg / New York, Springer.

Scherg, M. and D. von Cramon (1985). "A new interpretation of the generators of BAEP waves I-V: Results of a spatio-temporal dipole model." Electroencephalogr Clin Neurophysiol **62**(4): 290-299.

Schroeder, M. R. (1970). "Synthesis of low-peak-factor and binary sequences with low autocorrelation." IEEE trans. inf. theory **IT 16**: 85-95.

Sellari-Franceschini, S., P. Bruschini, L. Pardini and S. Berrettini (1986). "Quantification of the parameters of the acoustic reflex in normal ears." Audiology **25**: 165-175.

Shera, C. A. (2001). "Frequency glides in click responses of the basilar membrane and auditory nerve: Their scaling behavior and origin in traveling-wave dispersion." J. Acoustic. Soc. Am. **109**(5): 2023-2034.

Shore, S. E., B. M. Clopton and Y. N. Au (1987). "Unit response in ventral cochlear nucleus reflect cochlear coding of rapid frequency sweeps." J. Acoustic. Soc. Am. **82**: 471-478.

Siegel, J. H. (2002). Calibrating otoacoustic emission probes. Otoacoustic Emissions - Clinical Applications. M. S. Robinette and T.J.Glattke. New York, Stuttgart, Thieme Verlag**:** 416-441.

Simmons, F. B. (1964). "Perceptual theories of middle ear muscle function." Ann Otol Rhinol Laryngol **73**: 724-739.

Smith, B. K., U. K. Sieben, A. Kohlrausch and M. R. Schroeder (1986). "Phase effects in masking related to dispersion in the inner ear." J. Acoustic. Soc. Am. **80**(6): 1631-1637.

Soundmex (2006). SoundMex - The Professional Audio Tool for MATLAB®, HörTech gGmbH.

Summers, V. and M. R. Leek (1998). "Masking of tones and speech by Schroeder-phase harmonic complexes in normally hearing and hearing impaired listeners." Hear. Res. **118**: 139-150.

Tolsdorf, B., A. Münscher, H. Maier, K. Plotz, M. Müller-Wehlau, M. Mauermann, U. Baumann and R. Leuwer (2004). Clinical evaluation of low level acoustic reflex audiometry. ARO, Daytona.
827

Valdes, J. L., M. C. Perez-Abalo, V. Martin, G. Savio, C. Sierra, E. Rodriguez and O. Lins (1997). "Comparison of Statistical Indicators for the Automatic Detection of 80 Hz Auditory Steady State Respondes." Ear & Hearing **18**(5): 420-429.

Verhey, J. and B. Kollmeier (1998). Temporal aspects of loudness summation. . Psychophysics, Physiology and Models of Hearing. T. Dau, V. Hohmann and B. Kollmeier. Singapore, World Scientific**:** 97-100.

Wurzer, H., M. Chucholowski and K. Schorn (1983). "Stapedius reflex. 2. Latency periods of the stapedial reflex." Laryngol Rhinol Otol (Stuttg) **62**(7).

Zurek, P. (1992). "Detectability of transient and sinusoidal otoacoustic emissions." Ear & Hearing **13**(5): 307-310.

Zwicker, E. and H. Fastl (1999). Psychoacoustics: Facts and Models. Berlin, Springer.

Erklärung

Hiermit erkläre ich, dass ich die Arbeit selbständig verfasst und nur die angegebenen Quellen und Hilfsmittel verwendet habe.

Oldenburg, den 01. März 2010 Matthias Müller-Wehlau

Danksagung

Ich möchte mich an dieser Stelle bei all denen bedanken, die mich bei der Anfertigung der Dissertation unterstützt haben und diese dadurch erst ermöglicht haben:

Mein besonderer Dank gilt Herrn Prof. Dr. Dr. Birger Kollmeier, der nicht nur den Rahmen für diese Arbeit geschaffen hat, sondern der bei Fragen, Sorgen und Nöten immer Platz in seinem engen Terminkalender geschaffen hat und der mich auch in der Zeit nach meinem Weggang von der Uni immer ermuntert und unterstützt hat, diese Arbeit zu beenden - Vielen Dank, Birger.

Prof. Dr. Jesko Verhey danke ich für die freundliche Übernahme des Koreferats und darüber hinaus für viele erhellende Diskussionen nicht nur zu psychoakustischen Themen.

Dr. Manfred (Mani) Mauermann danke ich für die geduldige Einarbeitung in das Thema Stapediusreflex während meiner Diplomarbeit, für seinen unermüdlichen Einsatzes, die sehr guten Zusammenarbeit während der Doktorarbeit, für die Unterstützung bei den Studien für die Kapitel 2, 3 und 4 sowie für manch privates Gespräch.

PD Dr. Volker Hohmann möchte ich besonders für seine Unterstützung bei den Studien für das fünfte Kapitel danken. Speziell die vielen Diskussionen der Ergebnisse und ihrer Interpretation waren von unschätzbarem Wert.

Dr. Helmut Riedel ist das wandelnde elektrophysiologische Lexikon der Arbeitsgruppe und hat dieses Wissen immer bereitwillig weiter gegeben. Dafür und für die vielen Anregungen und Denkanstöße vielen Dank.

Prof. Dr. Torsten Dau danke ich für seine Unterstützung und erklärenden Worte bei den Studien für die Kapitel 3 und 4. Außerdem haben die mitreißend gehaltenen Seminare viel dazu beigetragen, mein Interesse für die Thematik zu wecken.

Dr. Daniel Berg und Dr. Thomas Wittkopp danke ich für ihre Unterstützung bei der Programmierung des Mess-Moduls für die Messung des Stapedius-Reflexes und für ihre Hilfe bei den Problemen, Fragen, Veränderungswünschen und Abstürzen, die beim Betrieb der Software auftauchten.

Für ihre Unterstützung bei der Durchführung aller Messungen, ihre Präsenz bei technischen Problemen und für die Bereitstellung vieler kohlenhydrathaltiger Lebensretter möchte ich Anita Gorges danken.

Mein Dank gilt auch PD Dr. Roland Mühler für lehrreiche Diskussionen zur Elektrophysiologie.

Diskussionen mit Dr. Thomas Brand zu praktischen Aspekten der Lautheits-skalierung haben mir sehr weiter geholfen - Vielen Dank.

Vielen Dank generell an alle Mitglieder der Arbeitsgruppe medizinische Physik für die unkomplizierte, konstruktive und freundschaftliche Zusammenarbeit, das gute "Betriebsklima" und so manches entspannende Volleyball-Match.

Besonders bedanken möchte ich mich bei meiner Familie und bei Janet Neerken für die Unterstützung und ausdauernde Motivierung während der Anfertigung der Arbeit.

Lebenslauf

Persönliche Angaben

Name:	Matthias Müller-Wehlau
E-Mail:	wehlau@uni-oldenburg.de
Geburtsdatum/-ort	30.08.1971 in Varel

Schulische Ausbildung

08/1978 - 06/1982	Grundschule in Varel
08/1982 - 06/1984	Orientierungsstufe in Obenstrohe
08/1984 - 06/1992	Lothar-Meyer Gymnasium in Varel Abitur in den Fächern Mathematik, Physik, Deutsch und Gemeinschaftskunde (Abschlussnote 2.4)

Hochschulausbildung

10/1994 - 09/1996	Grundstudium im Studiengang Diplomphysik an der Carl von Ossietzky Universität Oldenburg.
09/1996 - 04/2002	Hauptstudium mit Schwerpunkt Spektroskopie und medizinische Physik. Nebenfach Informatik im Bereich „Entwicklung integrierter Systeme“
02/1998 - 03/1999	Auslandsstudium an der Victoria University of Wellington, Neuseeland. Erwerb des Bachelor of Science with Honours (2nd division)
01/2001 - 04/2002	Diplomarbeit bei Prof. Dr. Dr. Kollmeier. Thema der Arbeit „Physikalische Eigenschaften des Stapediusreflexes“ Abschluss: Diplomphysiker mit der Note - gut -
Seit 04/2002	Promotionsstudiengang an der Carl-von-Ossietzky Universität Oldenburg mit thematischen Schwerpunkt der cochlearen und neuronalen Reizverarbeitung im menschlichen Ohr.

Berufsausbildung, praktische Tätigkeiten

07/1992 - 06/1994	Soldat auf Zeit in der technischen Instandsetzung, Laufbahn der Reserveoffiziere. Ausbildungstechnische Befähigungsnachweise als Kfz-Panzerschlosser, Instandsetzungs- und Sicherungszugführer. Ausgeschieden als Fähnrich d. R. mit späterer Beförderung zum Leutnant d. R.
11/2000 - 03/2006	Freiberufliche Tätigkeit für das Hörzentrum Oldenburg mit den Schwerpunkten Planung, Aufbau und Kalibrierung akustischer Messungen sowie der Rechner- und Netzwerkadministration.
seit 11/2006	Angestellter bei der Siemens Audiologischen Technik in Erlangen als Forschungsaudiologe in der Abteilung für audiologische Grundlagenforschung

Praktika

Juli/Oktober 1997	Sommerschule am Hahn-Meitner-Institut, Berlin Thema: Entwicklung heterogener Dünnschicht-Solarzellen