Diagnostics of the cochlear amplifier by means of distortion product otoacoustic emissions

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Contents

List of Symbols

A/D	Analog-to-digital
ALU	Arithmetic logic unit
AN	Auditory nerve
API	Application programming interface
c	Sound velocity [m/s]
CA	Cochlear amplifier
CAS	Contralateral acoustic stimulation
CLS	Categorical loudness scaling
CN	Cochlear nucleus
Codec	Coder/Decoder
CU	Categorical unit
D/A	Digital-to-analog
dB	Decibel
DFG	Deutsche Forschungsgemeinschaft
DLL	Dynamically linked library
DMA	Dynamic memory access
DPOAE	Distortion product otoacoustic emission
DRAM	Dynamic RAM
DSP	Digital signal processor
eCL	Estimated compression loss
eHL	Estimated hearing loss
ECV	Ear canal equivalent volume
ϕ	Phase
f	Frequency [Hz]
FFT	Fast Fourier Transformation
GUI	Graphical user interface
HL	Hearing level
IAS	Ipsilateral acoustic stimulation
IHC	Inner hair cell
I/O	Input/Output
IVN	Inferior vestibular nerve
k	Compression of I/O function (= 1/slope)
λ	Wave length [m]
l	Length [m]

L	Sound pressure level [dB SPL]
L_N	Loudness level [phon]
LOC	Lateral olivocochlear
MFLOPS	Million floating point operations per second
m	DPOAE adaptation magnitude [dB]
mho	Compliance unit [$= \Omega^{-1}$]
MIPS	Million instructions per second
MOC	Medial olivocochlear
N	Loudness [sone] or [CU]
N_{buffer}	Number of samples per buffer
NIHL	Noise-induced hearing loss
NIOSH	National Institute for Occupational Safety and Health
ω	Angular frequency [Hz]
OHC	Outer hair cell
p	Sound pressure [Pa]
PCMCIA	Personal Computer Memory Card International Association
PTA	Pure-tone audiometry
PTS	Permanent threshold shift
r	Correlation coefficient
RAM	Random access memory
RETSPL	Reference-equivalent sound pressure level
s	Slope of I/O function
SFOAE	Stimulus-frequency otoacoustic emission
SOAE	Spontaneous otoacoustic emission
SL	Sensation level
SNR	Signal-to-noise ratio
SPL	Sound pressure level
SRAM	Static RAM
τ	Time constant for one-exponential fitting [s]
t	Time [s]
T	Temperature [^{o}C]
TDR	Total dynamic range
TEOAE	Transiently evoked otoacoustic emission
THD	Total harmonic distortion
TTS	Temporary threshold shift
UNHS	Universal newborn hearing screening
VAF	Variance accounted for

Abstract

This dissertation addresses improvements in diagnostics of the cochlear amplifier by means of distortion product otoacoustic emissions (DPOAEs) and the applicability of DPOAEs in diverse clinical fields. In the first instance, the possibility to use DPOAEs as a means of objective hearing aid fitting was further investigated. Therefore, DPOAE and categorical loudness scaling (CLS) input/output (I/O) functions were recorded in hearing-impaired subjects. By comparison to reference data from normal hearing subjects, level-dependent gain functions were derived from the respective I/O functions. Similar results could be achieved for CLS and normalized DPOAE data suggesting that DPOAEs might be suitable to serve as an indicator for loudness growth and hence might be capable of delivering objective hearing aid fitting parameters.

Moreover, the clinical applicability of using DPOAE threshold estimation (Boege and Janssen, 2002) in neonates and the possibility of using DPOAE I/O function properties to differentiate between sound conductive (e.g., due to amniotic fluid in the tympanic cavity) and sensorineural (e.g., due to outer hair cell (OHC) dysfunction) hearing loss was investigated. Therefore, DPOAE I/O functions were compared in neonates measured briefly after and one month after birth, and in normal hearing and hearing-impaired adults with sensorineural hearing loss. DPOAE threshold estimation was found to be applicable under newborn hearing screening conditions. A possible method for detecting sound conductive hearing loss was developed on the basis of a simple model.

Furthermore, the quantification of efferent medial olivocochlear (MOC) reflex strength by means of DPOAEs could be improved. Based on findings with ipsilateral DPOAE adaptation in guinea-pigs (Maison and Liberman, 2000), a novel stimulus paradigm for measuring MOC reflex strength in humans was developed. Similar to the results from Maison and Liberman, a large change in DPOAE level due to contralateral acoustic stimulation could be found when varying primary tone levels within a large range. In contrast, ipsilateral DPOAE adaptation yielded mainly small effects in humans. In general, MOC reflex strength, as quantified by means of contralateral DPOAE suppression, was found to be largest in dips of the DPOAE fine structure.

Based on results from Maison and Liberman (2000), which suggested a relationship between MOC reflex strength and noise vulnerability in guinea-pigs, the developed method of quantifying MOC reflex strength was applied in noise-exposed subjects in order to study its applicability to evaluate individual susceptibility to noise overexposure in humans. Moreover, the impact of noise of different intensity and duration on hearing capability

and specifically on OHC operability was investigated. Therefore, in two subject samples, i.e. discotheque attendants and factory workers employed in the metal-working industry, pure-tone thresholds, DPOAE fine structure, and contralateral DPOAE suppression was measured. A significant impact on pure-tone thresholds and DPOAE levels could be observed in both groups. However, no clear correlation between MOC reflex strength and change in either pure-tone threshold or DPOAE level after noise exposure could be found.

Finally, it was investigated whether age-related hearing loss is more due to peripheral (i.e., deterioration of the cochlear amplifier) or central (i.e., deterioration of the MOC feedback loop) causes. Therefore, pure-tone threshold and DPOAE fine structure as well as contralateral DPOAE suppression was measured in otologically normal subjects with varying age. A significant shift in DPOAE level and threshold could be found with increasing age suggesting a deterioration of the cochlear amplifier. In contrast, no clear deterioration of MOC reflex strength could be found.

1 Introduction

1.1 Motivation

Hearing is one of the most important human senses and is necessary for communicating with other people, for orientation in the world around us, and for enjoying pleasures of life such as listening to music. However, for a lot of people normal hearing sensations are not self-evident. In Germany, more than 10 million people suffer from hearing loss. This issue affects persons of all ages but proportions increase with increasing age. Every third person between 60 and 70 years and every second person above 70 years is subject to hearing damage (Fördergemeinschaft Gutes Hören, 2005). Hearing disorders may occur, besides diseases and a natural aging process, mainly due to the impact of recreational and occupational noise exposure which gains in significance in a modern society. A lot of people suffer from traffic noise or from noise exposure at the workplace with occupational noise being the second most self-reported occupational injury (Plinske *et al.*, 2002). Beyond that, people voluntarily expose themselves to noise during their leisure time, including amplified music in discotheques or concerts, which is a popular leisure-time occupation especially for adolescents. Hence, hearing damage already starts to emerge at a steadily decreasing age. In Germany, about every fourth adolescent is reported to be subject to hearing damage (Struwe *et al.*, 1996). Therefore, besides prevention and education programs, the early detection of noise-induced hearing loss is most important. Also, a quantification of individual susceptibility to noise exposure could be beneficial in advising people concerning their choice of profession, their choice of leisure-time activities, and for increasing their awareness towards protecting the ear from acoustic overexposure.

Moreover, about 1 to 6 out of 1000 newborns are born with a congenital hearing defect (Bachmann and Arvedson, 1998). Especially for newborns, a proper and early treatment of a hearing defect is important for speech, language, and cognitive development. In general, hearing defects may result in a reduced ability to communicate and hence may yield negative psychosocial consequences. Therefore, it is important to improve objective diagnostic methods in neonatal hearing screening to reliably detect hearing disorders at an early stage.

In adults, deterioration in hearing capability is usually a sneaking process which may last over years or decades. The treatment of hearing disorders is up to now only partially possible. Hearing aids may help to restore lost sensitivity of the cochlear amplifier but do not allow for compensating lost discriminative power of the cochlear amplifier. Furthermore, hearing aid adjustment is only possible in cooperative and mentally sane subjects and hence complicates applicability in young children or elder persons, who may have problems with behavioral psychoacoustic diagnostic methods. Objective hearing aid adjustment methods could increase the area of applicability of hearing aids and improve therapeutical success.

The cooperation in several projects sponsored by Deutsche Forschungsgemeinschaft (DFG) was the basis for this dissertation. The work was conducted with support of the laboratory of experimental audiology at Klinikum rechts der Isar (Technische Universität München). Within this framework, a measurement system, based on a commercial clinical measurement device, was developed, which allowed for conducting several audiologic testing methods, i.e. pure-tone threshold determination, categorical loudness scaling, and the recording of distortion product otoacoustic emissions (DPOAEs). The main aim was to develop methods for improving diagnostics of the cochlear amplifier by means of DPOAEs and to investigate the clinical applicability of the developed methods. This included improvements in objective hearing aid fitting, neonatal hearing screening, and quantification of the efferent medial olivocochlear reflex strength, which has been suggested to be a measure for protection from acoustic overexposure (Maison and Liberman, 2000). Moreover, the impact of noise of different intensity and duration on the cochlear amplifier and on overall hearing and the quantification of individual susceptibility to noise overexposure was investigated. Finally, age-related hearing loss was examined in order to improve knowledge about its primary sources and to answer the question if age-related hearing loss is more due to peripheral or central causes.

1.2 Outline

Principles of hearing and hearing testing: In this chapter the most important psychoacoustic and physiologic principles are explained. The functioning of the hearing process is laid down in some more detail in order to give background information about the ear's physiology and pathophysiology. Furthermore, the hearing testing methods, which were applied in the presented studies, are explained. This includes pure-tone audiometry, impedance audiometry, and otoacoustic emissions. The generation, evaluation, and current clinical applications of DPOAEs are explained in some more detail, since DPOAEs were the main focus of the presented studies (see Chapter 2).

Instrumentation and methods: The measurement system, which was developed on the basis of a clinical measurement device, is presented. This includes the commercial hardware and the developed firm- and software. The graphical user interfaces show the parameter options for each of the implemented measurement techniques, which include pure-tone threshold determination, categorical loudness scaling, and different DPOAE recording methods (see Chapter 3).

Implications for objective hearing aid fitting by means of DPOAEs: This chapter deals with the applicability of DPOAEs as an objective means for hearing aid adjustment. In this study, starting from data of normal hearing subjects from Müller (2002) and Oswald (2005), the relationship between DPOAEs and categorical loudness and the capability of DPOAEs to recreate loudness growth was investigated in hearing-impaired subjects. The gain functions, which can be used for objective hearing aid fitting, were calculated from DPOAE and loudness growth functions and were compared for the group of cochlear hearing loss subjects (see Chapter 4).

Differentiation between middle ear and cochlear hearing loss by means of DPOAEs: Universal newborn hearing screening (UNHS) is important in identifying hearing loss in newborns. In UNHS, mainly otoacoustic emissions and brainstem evoked potentials are used to identify normal or impaired hearing. The result is given as a "pass"/"fail" decision. In this chapter the applicability of DPOAEs to quantify hearing loss in newborns was investigated by applying the method of Boege and Janssen (2002), which was found to be suitable to quantify hearing loss in adults. Moreover, an objective DPOAE-based method was developed in order to differentiate between sound conductive (i.e., middle ear) and sensorineural (i.e., cochlear) hearing loss. Sound conductive hearing loss is known to occur frequently in newborns directly after birth due to remnants of amniotic fluid residing in the tympanic cavity. Therefore, measurements were conducted in newborns immediately after birth, about one month after birth, and for comparison in normal hearing and hearing-impaired adults (see Chapter 5).

Improvements in quantifying efferent reflex strength by means of DPOAEs: Efferent medial olivocochlear (MOC) reflex strength is supposed to alter the motility of outer hair cells (OHCs) and hence to adjust the operability of the cochlear amplifier. Current methods of measuring MOC reflex strength include ipsilateral DPOAE adaptation and contralateral DPOAE suppression. However, in previous studies both methods yielded small effects in humans. Maison and Liberman (2000) found in guinea-pigs much larger effects for ipsilateral DPOAE adaptation when measuring within a wide range of primary tone level combinations. In this chapter, the method of Maison and Liberman (2000) was similarly investigated in humans for contralateral DPOAE suppression and ipsilateral DPOAE adaptation in order to examine if this new method allows for a better quantification of efferent MOC reflex strength also in humans (see Chapter 6).

Further efforts to predict individual vulnerability to noise overexposure: In two studies the impact of noise of different intensity and duration on the cochlear amplifier and on overall hearing capability was examined by means of DPOAE and pure-tone threshold measurements. Moreover, the capability of efferent MOC reflex strength to quantify vulnerability to noise overexposure was investigated. For quantifying efferent MOC reflex strength, the DPOAE-based method proposed in Chapter 6 was applied. The first study was conducted in subjects exposed to three hours of high-level discotheque music, whereas the second study was conducted in factory workers exposed to mid-level occupational noise for one workday and for control in office workers with no major noise exposure (see Chapter 7).

Further efforts to determine the causes for age-related hearing loss: In order to determine whether age-related hearing loss occurs more due to peripheral or central causes, age-related changes in overall hearing capability, cochlear amplifier functionality, and efferent MOC reflex strength were investigated in otologically normal subjects of different age. Therefore, pure-tone threshold and DPOAE measurements were conducted. Contralateral DPOAE suppression, as proposed in Chapter 6, was used to quantify efferent MOC reflex strength. (see Chapter 8).

Conclusions and outlook: Besides a recapitulation of the main results of the dissertation, further steps towards improvement of diagnostics of the cochlear amplifier by means of DPOAEs are given with respect to the examined problems (see Chapter 9).

2 Principles of hearing and hearing testing

2.1 Physics and psychoacoustics

The human ear receives and processes sound waves, which are mechanical longitudinal waves that propagate from a sound source, an oscillating body, in solids, liquids or gas via pressure variations. For the human ear, mainly the propagation via air is of importance. At the sound source, the air is compressed and expanded alternately. These pressure variations propagate with sound velocity c, which amounts for air to 331.6 m/s at $T = 0^o$C. The sound velocity in gases is strongly dependent on pressure, density, and temperature. The sound pressure p that occurs due to the compression and expansion of the medium is superimposed on the static equilibrium pressure and shows in the easiest case of a pure tone a sinusoidal dependency on time and space. The amplitude of the oscillation influences the perception of loudness. The spatial distance between two adjacent points with equal sound pressure is denoted as wave length λ. The tone pitch is characterized by the frequency f. Wave length λ, frequency f, and sound velocity c are associated as shown in Eq. 2.1.

$$c = \lambda \cdot f \tag{2.1}$$

The human hearing organ is capable of perceiving sounds within a frequency range from about 20 to 20000 Hz while being able to separate about 640 pitches within this range. Frequency differences as small as 0.7 % can be discriminated (Zwicker and Fastl, 1998). Whether a sound can be perceived depends both on frequency and amplitude. The minimal sound pressure that is necessary to elicit a hearing perception constitutes the hearing threshold (see Fig. 2.1). Human hearing is most sensitive between 2 and 5 kHz, which is the most important frequency region for perceiving speech. The human ear is able to detect a minimal sound pressure of 10^{-5} Pa at 4 kHz and is as well able to treat even sound pressures of up to about 200 Pa. At this point, the threshold of pain begins and the hearing organ gets overstrained. However, the limit of damage risk is lower, but depends on individual vulnerability and exposure time.

In order to better describe the huge dynamic range of human hearing, the sound pressure level L is introduced, which is defined as the actual sound pressure p_x related to the reference sound pressure $p_0 = 2 \cdot 10^{-5}$ Pa according to Eq. 2.2.

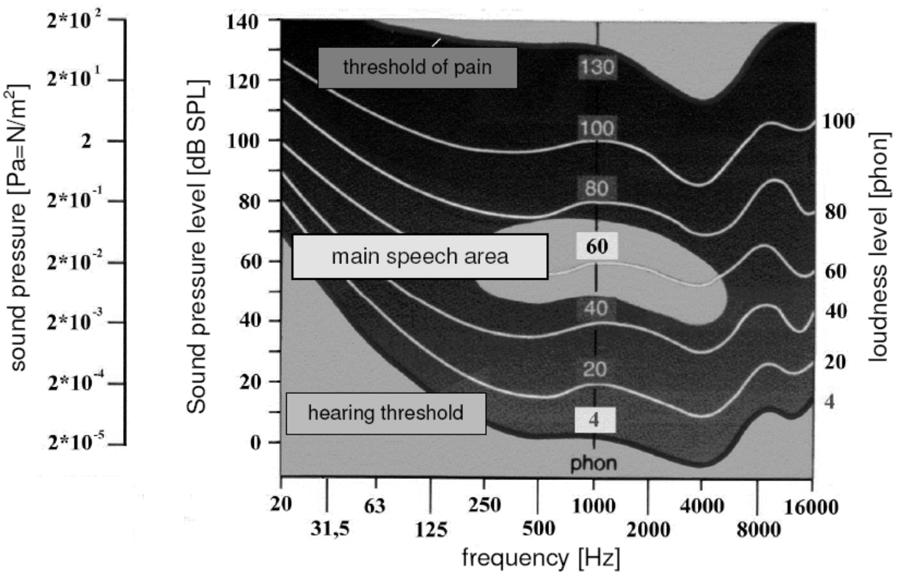

Figure 2.1: Hearing area of the human ear (adopted from Spornitz, 1996)

$$L = 20 \cdot \log \frac{p_x}{p_0} \tag{2.2}$$

The sound pressure level L is as the logarithm of a relative measure dimensionless and therefore without unit. However, to indicate the logarithmic operation and the chosen reference value, the unit dB SPL (= sound pressure level) is appended to the numeric value. If the given sound pressure level is related to the average hearing threshold of a reference group of normal hearing subjects, the unit dB HL (= hearing level) is used. If it is related to an individual subjects' hearing threshold, the unit dB SL (= sensation level) is appended. The sound pressure level is a physically measurable parameter and does not directly reflect the physiological frequency-dependent perception of loudness in the human ear.

An overview of the level and frequency range perceptible by the human ear is shown in Fig. 2.1, which presents the hearing area according to Robinson and Dadson (1956). This area is confined on the one hand for low levels by the hearing threshold and on the other hand for high levels by the threshold of pain. More curves of equal loudness level, the so-called isophones, are depicted in between. They show for a certain frequency and for an average normal hearing subject, which sound pressure level is necessary to elicit the same perception of loudness as a sound pressure level of a 1-kHz-tone. The loudness level L_N is dimensionless, but is marked with the unit phon. Since the human ear exhibits the largest dynamic range at 1 kHz, loudness levels are referenced to this frequency. Therefore, by definition, the phon scale at 1 kHz is equal to the dB SPL scale. It is important to note that the relation between sound pressure level and loudness level is strongly frequency-dependent. An overview of some exemplary sounds and their respective loudness level is given in Tab. 2.1.

Sound example	Whisper	Speech	Traffic noise	Disco music
Loudness level [phon]	10-40	50-75	70-90	100-125

Table 2.1: Loudness level of different sounds in phon (adopted from Spornitz, 1996)

The hearing threshold of a normal hearing subject is at about 4 phon and the threshold of pain at about 130 phon. The resolution of different loudness levels of the human ear is dependent on the type, the duration, the frequency, and the level of the sound but amounts to about 1 phon. This means that very small relative differences in loudness levels can be resolved. The absolute resolution of loudness levels, however, is much smaller.

The loudness level L_N is useful to demonstrate the frequency-dependent perception of loudness, but not to demonstrate the relative change in the perception of loudness at different sound pressure levels for a specific frequency. Therefore, the measure of loudness N is introduced, which is as the loudness level dimensionless, but is usually given with the unit sone. The loudness in sone indicates how many times a specific sound is perceived louder (values > 1) or more quiet (values < 1) in comparison to a 1-kHz-tone of 40 dB SPL, which by definition corresponds to 1 sone. The shape of the loudness curve according to Zwicker (1958) and Fletcher and Munson (1933) is shown for 1 kHz and for normal hearing subjects in Fig. 2.2.

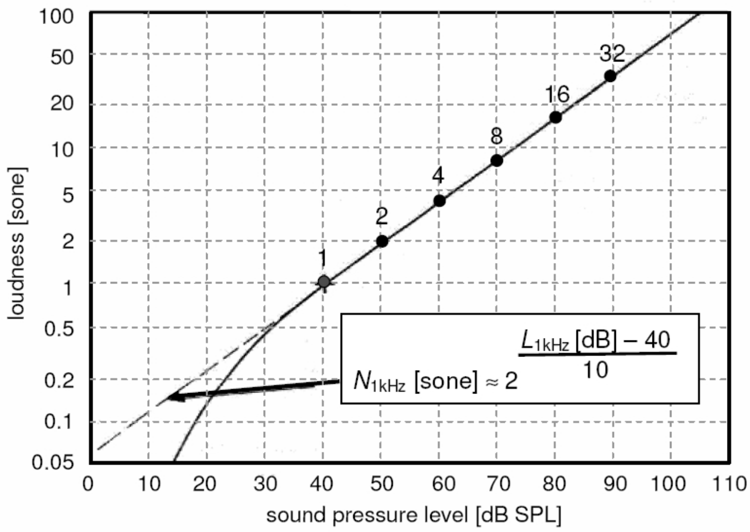

Figure 2.2: Function between loudness and sound pressure level for normal hearing subjects at 1 kHz (adopted from Zwicker and Fastl, 1998)

The loudness curve was derived from experimental data and was smoothed to fit the data. Thus, it is an approximation to the individual loudness function of each individual. The loudness in sone is displayed preferably in a logarithmic scale and can be approximated by a straight line (see equation in Fig. 2.2) when plotted above the logarithmic measure of sound pressure level. For sound pressure levels below 40 dB SPL, there is some deviation from this line. For sound pressure levels above 40 dB SPL, one can assume that an increase in 10 dB SPL is associated with a doubling of loudness.

Please note, that in clinical practice other measures for estimating loudness are commonly used, i.e. principally the method of categorical loudness scaling (CLS). The hereby derived measure of loudness is not given in sone but in CU (= categorical units). This method is explained in more detail in Sec. 2.3.

2.2 Physiology and pathophysiology

In Fig. 2.3, the human hearing organ is displayed. It is constituted of three parts, the outer ear, the middle ear, and the inner ear. The function of the outer ear is to channel the energy of the sound waves via the auricle and to transmit the collected energy via the auditory canal to the ear drum. For adults, the slightly s-shaped auditory canal exhibits a length of about 15 to 30 mm. The outer ear canal acts like an open pipe and hence amplifies frequencies around the resonant frequency at $\frac{\lambda}{4}$, which is dependent on ear canal length at around 4 kHz. Thus, the ear canal is responsible for the ear's high sensitivity as well as the ear's high susceptibility to damage in this frequency range. The ear drum distinguishes the outer ear canal from the tympanic cavity of the middle ear and consists of an oval membrane which is placed angular in the auditory canal. On the inner side of the ear drum, the membrane is adnated to the malleus, one of the ossicles. The sound pressure variations put the ear drum into oscillation.

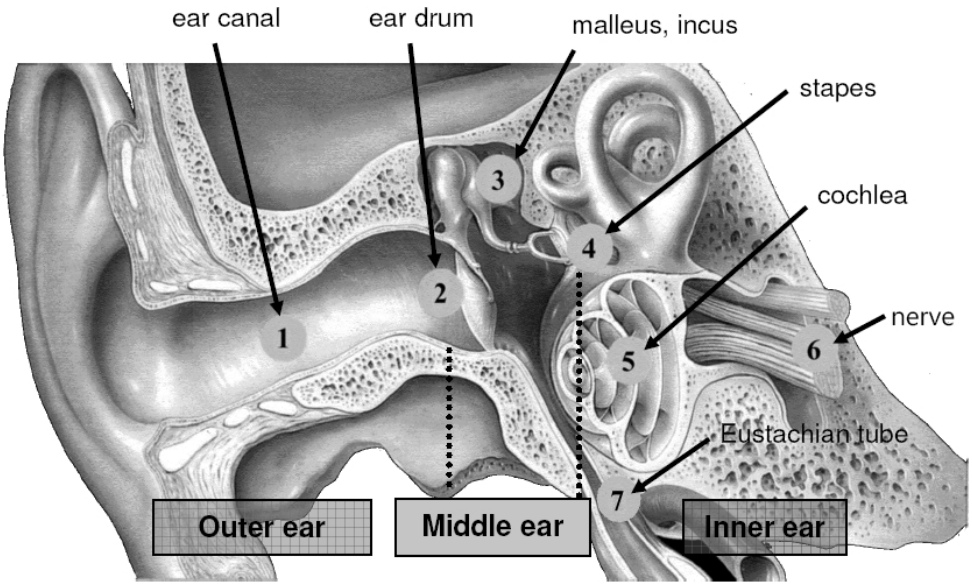

Figure 2.3: Anatomy of the ear (adopted from Apotheken Umschau, 1999)

In the middle ear, the pressure variations are transmitted via the ossicles malleus ('hammer'), incus ('anvil'), and stapes ('stirrup') onto the oval window, a membrane covering the cochlea at the point of the attachment of the stapes footplate. The ossicles form a mechanical set of levers whose role is to match the different acoustic impedances of the outer ear (air) and the inner ear (liquid). This guarantees a low-loss sound transmission.

The difference in the surface area between ear drum and oval window further causes an increase in force exerted on the oval window. Moreover, the middle ear provides for pressure compensation via the Eustachian tube that is connected to the nasopharynx. Pressure compensation is important to ensure an optimal adjustment of the ear drum tension to the ambient pressure which amounts dependent on altitude and meteorological conditions to about 960 to 1050 Pa. Thus, the ambient pressure is much larger than sound pressure variations processed by the auditory system which range typically from about 100 μPa to 100 Pa (see Sec. 2.1).

Middle ear disorders, which result in sound conductive hearing loss and thus reduce energy transmitted to the inner ear, may include a stiffening of the chain of ossicles, fixation of the stapes (e.g., due to otosclerosis), fluid in the middle ear (e.g., tympanic effusion due to secretory otitis media), scarring or perforation of the tympanic membrane, or Eustachian tube dysfunction. Common reasons for middle ear disorders may include genetic disposition, inflammatory or degenerative processes, noise trauma (e.g., concussion from an explosion or a blow to the ear), or violent injuries (e.g., temporal bone fracture).

In order to understand the physiological implications of several kinds of pathological changes which can occur in sound conduction in the middle ear, it is helpful to consider some of the basic properties of a vibrating mechanical system, of which the middle ear ossicles are an example. In general, a vibrating system includes three elements: mass, stiffness and friction. The corresponding three types of forces which act on the system are: 1) an inertia force given by the product of the mass and its acceleration; 2) a stiffness force proportional to the deflection of the spring from its resting position; 3) a frictional or damping force which dissipates energy in the form of heat when movement occurs. When such a system is subjected to a sinusoidal driving force of constant magnitude, the resulting amplitude of vibration is maximal at the resonant frequency. The resonant frequency of the middle ear is at about 1 kHz. If the stiffness of the system is increased with the mass and friction remaining unchanged (e.g., Eustachian tube dysfunction), the resulting amplitude is reduced for frequencies below the resonant frequency. Conversely, if the stiffness of the original system is not changed but the mass is increased (e.g., tympanic effusion), the response amplitude is little changed for frequencies below the resonant frequency but is reduced for frequencies above resonance.

After the sound has been transmitted via the middle ear to the oval window, the sound pressure waves reach the inner ear which is enclosed by the temporal bone. The inner ear is the actual acoustic transducer. Here the sound signals are converted from mechanical oscillations to nerve impulses which are relayed via the auditory nerve to the auditory cortex where the effective auditory perception eventually evolves. For a better understanding of the transformation of the physical stimulus to a neural signal, the functionality of the inner ear and especially the organ of Corti, which is located within the cochlea, shall be explained in the following. A sectional view of the cochlea can be seen in Fig. 2.4.

The cochlea consists of a single bony tube which spirals in two and a half turns around a middle core containing the auditory nerve. In each turn, the bony tube is divided into three separate compartments by the membranous tissues. The three spirals, called scalae,

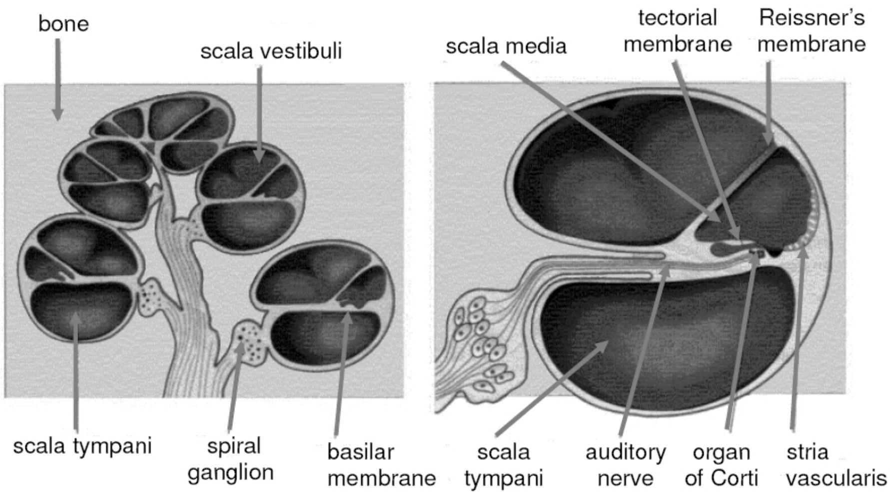

Figure 2.4: Sectional view of the cochlea (adopted from Spornitz, 1996)

are filled with liquid and stretch from the base, i.e. the oval window, to the apex, i.e. the helicotrema. At the helicotrema, scala vestibuli and scala tympani join. These two compartments are filled with perilymph high in sodium ions (Na^+), whereas the scala media is filled with endolymph high in potassium ions (K^+). Endolymph is produced in the stria vascularis.

Perilymph and endolymph have unique ionic compositions suited to their functions in regulating electrochemical impulses of hair cells. The electric potential of endolymph is about 80 to 90 mV more positive than the perilymph potential. An important feature of the endolymphatic space is that it is completely bounded by tissues and there are no ducts or open connections between perilymph and endolymph. Scala vestibuli and scala tympani contain perilymph with slightly different chemical composition. However, these two compartments are not independent of each other. There is considerable cross-communication across the spongy spiral ligament in all turns of the cochlea, so that substances present in the scala tympani will rapidly diffuse into the scala vestibuli and vice versa.

The scala vestibuli extends from the oval window to the helicotrema and is separated from the scala media by Reissner's membrane which functions as a diffusion barrier. The scala tympani extends from the helicotrema to the round window and is separated from the scala media by the basilar membrane, which is a part of the organ of Corti, the actual hearing organ. The fluid within the cochlea is sealed off, so that the oscillation of the stapes due to the incoming sound wave is directly transformed into an oscillation of the incompressible perilymphatic liquid. This consequently results in an oscillation of the membrane at the round window, which closes off the scala tympani at the base. The round window is crucial in providing pressure relief within the cochlea. Since the walls of the scala media are not stiff but give in to the wavelike volume shift of the perilymph in the surrounding chambers, a traveling wave spreads across the basilar membrane. This is shown in Fig. 2.5.

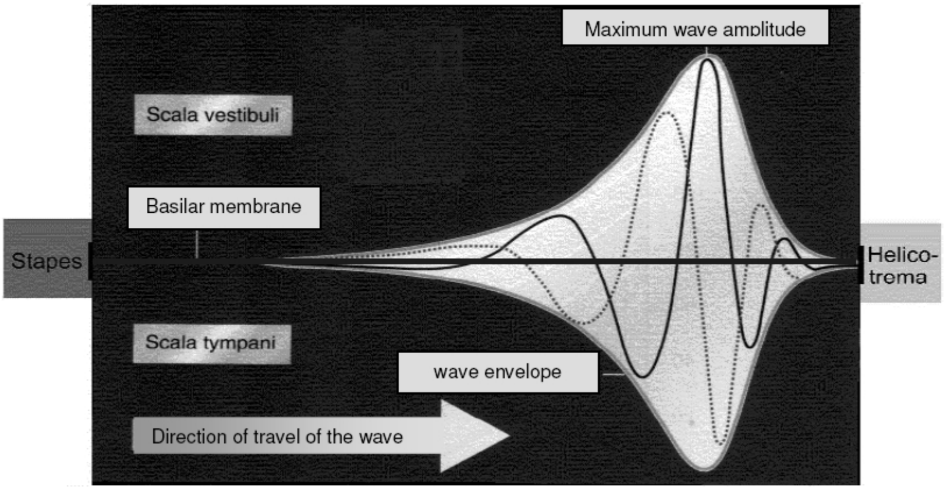

Figure 2.5: Spread of a traveling wave on the basilar membrane (adopted from Spornitz, 1996)

The traveling wave is characterized by an envelope that exhibits, in contrast to a standing wave, no locally stationary wave nodes or antinodes, whereas in steady state the wave envelope is constant. A traveling wave can be described as a function of time t and place x as shown in Eq. 2.3.

$$y(x,t) = A(x,t)sin(kx - \omega t + \phi) \tag{2.3}$$

with $A(x,t)$: amplitude envelope of the wave, k: wave number, ϕ: phase of the wave

In the course of the cochlea, the wave length of the traveling wave decreases while its amplitude increases to a maximum so as to ebbing away swiftly afterward. The place of maximum basilar membrane deflection depends on the frequency of the sound wave. Each frequency is mapped to a specific place on the basilar membrane where the maximum of the traveling wave occurs. This characteristic function of the basilar membrane is denoted as the place-frequency mapping which is illustrated in Fig. 2.6.

The frequency dispersion results from the varying width and stiffness along the basilar membrane. The basilar membrane is tapered and it is thinnest (ca. 0.1 mm) at the base and widest (ca. 0.5 mm) at the apex. Also, the basilar membrane is more than a thousand-fold stiffer at the base compared to the apex. Thus, the higher the frequency, the more basal the maximum of the traveling wave.

Due to the oscillation within the endolymphatic chamber, the basilar membrane is deflected towards the tectorial membrane. Both membranes are part of the actual hearing organ, the organ of Corti, which is shown in Fig. 2.7. The hair cells are located along the basilar membrane and can be differentiated between inner hair cells (IHCs) standing in one row, and outer hair cells (OHCs) standing in three parallel rows. IHCs and OHCs are both anatomically and functionally distinct types. Each hair cell features a tuft of about

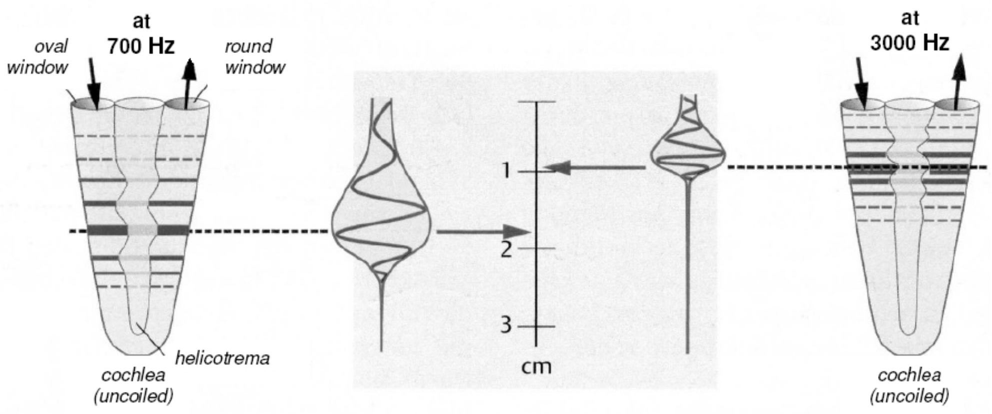

Figure 2.6: Place-frequency mapping within the cochlea (adopted from Silbernagl and Despopoulos, 2001)

100 small sensory hairs, the stereocilia, protruding from the apical surface of the cell and connected via the tip-links. Only the stereocilia of the OHCs are in close contact with the tectorial membrane.

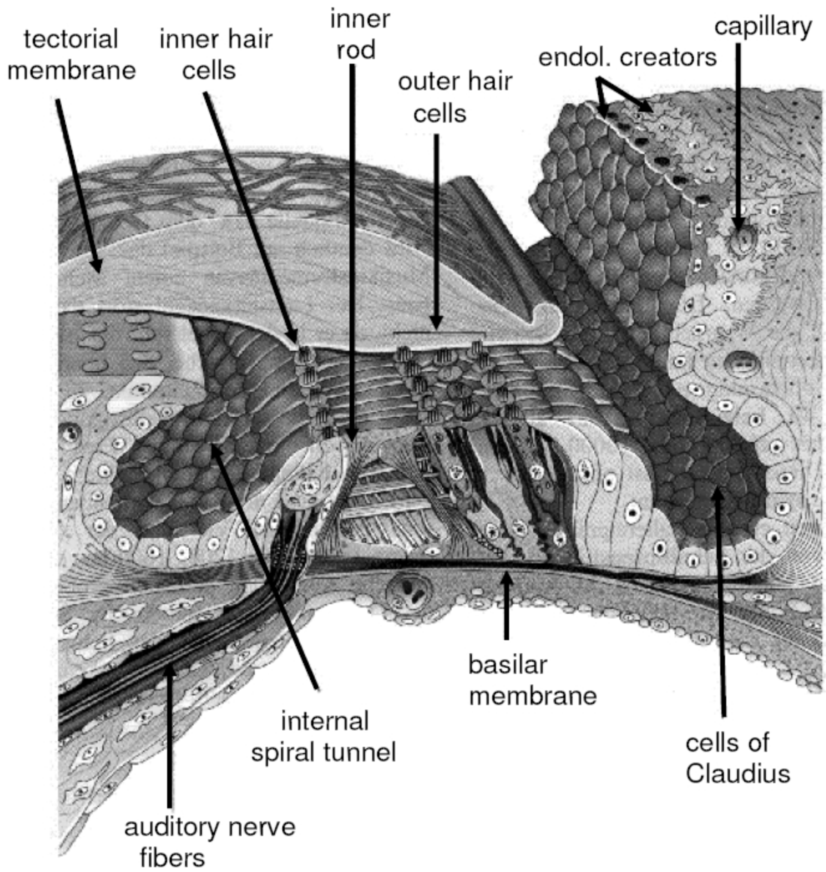

Figure 2.7: Organ of Corti (adopted from Spornitz, 1996)

A relative movement of the basilar membrane against the tectorial membrane yields a deflection of the IHC's stereocilia, which opens mechanically gated ion channels that allow any small, positively charged ions (primarily potassium and calcium) to enter the cell. The influx of positive ions from the endolymph in the scala media depolarizes the cell, resulting in a receptor potential. This receptor potential opens voltage gated calcium channels. Calcium ions then enter the cell and trigger the release of neurotransmitters at the basal end of the cell. The neurotransmitters diffuse across the narrow space between the hair cell and a nerve terminal, where they then bind to receptors and thus trigger action potentials in the nerve (Sewell, 1996). In this way, the mechanical sound signal is converted into an electrical nerve signal which is then relayed via the auditory nerve to the auditory cortex. The repolarization in the hair cell occurs due to the very low concentration of positive ions in the perilymph in the scala tympani. The electrochemical gradient makes the positive ions flow through channels to the perilymph.

In contrast to the IHCs, which are responsible for transforming sound vibrations in the fluids of the cochlea into electrical nerve impulses, the OHCs are supposed to mechanically amplify basilar membrane motion (e.g., Rhode, 1971). The receptor potential within the OHC triggers active vibrations of the cell body. This so-called somatic electromotility consists of oscillations of the cell's length, which occur at the frequency of the incoming sound and in a stable phase relation. This means that OHCs are capable of periodically exerting alternate contractions and relaxations. The motor protein prestin has been identified to be the main force behind somatic electromotility and it is highly expressed in OHCs, whereas it is not expressed in the nonmotile IHCs (Zheng *et al.*, 2000; Dallos and Fakler, 2002).

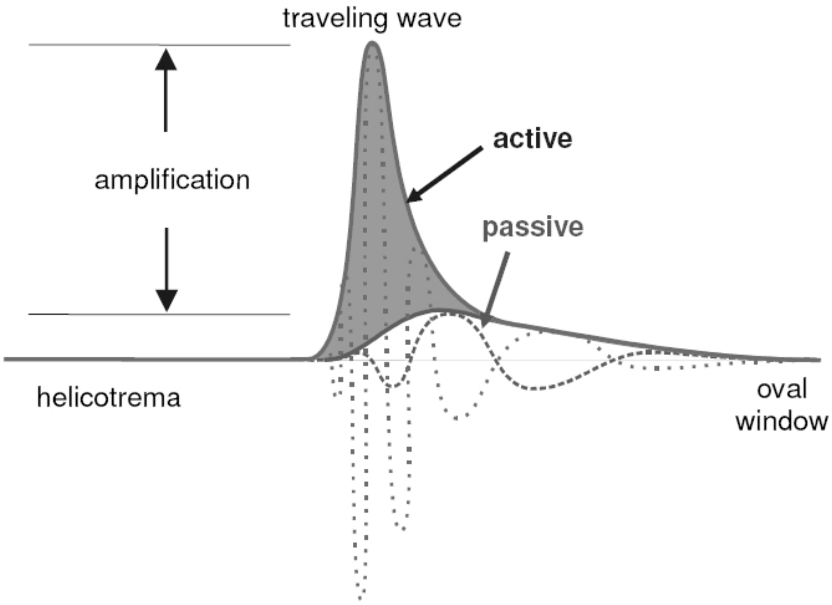

Figure 2.8: Active outer hair cell amplification of the traveling wave (adopted from Janssen, 2000)

The passive deflection of the basilar membrane is very small at low sound pressure levels and amounts at normal speech volume to about a tenth of a nanometer, which is in the order of magnitude of the diameter of an atom, being too small to enervate enough IHCs. Therefore, an additional mechanical amplification is necessary. The OHCs enforce a frequency-selective, nonlinear, active amplification of the traveling wave (Davis, 1983; Dallos, 1992) and by that increase the adequate stimulation of IHCs at low sound pressure levels (see Fig. 2.8). This results in a nonlinear, compressive mechanical response of the basilar membrane (Rhode, 1971; Johnstone *et al.*, 1986; Ruggero *et al.*, 1997). At higher sound pressure levels above about 60 dB SPL, the amplification process of OHCs reaches saturation and IHCs are stimulated mainly due to the by now sufficiently large passive deflection of the basilar membrane. This level-dependent amplification is referred to as cochlear dynamic compression.

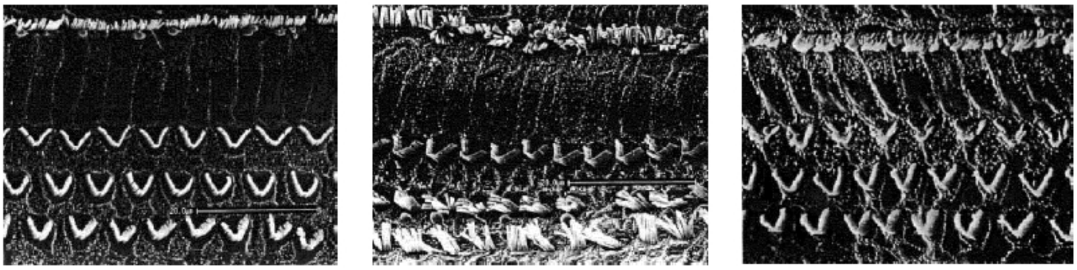

Figure 2.9: Pictures of healthy and damaged guinea-pig hair cells. Left panel: healthy hair cells. Middle panel: hair cells after noise trauma. Right panel: hair cells after long-time noise exposure (Hess, 2000)

Cochlear disorders, which result in sensory hearing loss and thus in reduced or altered cochlear processes may include genetic disposition, diseases (e.g., meningitis), degenerative processes (e.g., presbycusis), ototoxic drugs (e.g., salicylate, cis-platinum), sudden hearing loss, anoxia (e.g., birth trauma), noise trauma (e.g., explosion) or long-time noise exposure (e.g., traffic or factory noise), and physical trauma (e.g., temporal bone fracture).

OHCs are supposed to be the most vulnerable part of the cochlea, especially with respect to mechanical overstrain due to hazardous noise exposure (Zhang and Zwislocki, 1995; Linss *et al.*, 2005). Thus, sensory hearing loss is supposed to result commonly in a failure of OHC amplification (see Fig. 2.9) and with that in a loss of sensitivity, frequency-selectivity, and compression, i.e. reduced cochlear dynamics (Liberman and Dodds, 1984). As a consequence of OHC damage, the compressive, nonlinear characteristic of the basilar membrane becomes linear. The loss of sensitivity and compression is normally associated with normal or near-normal hearing at higher sound pressure levels but strongly reduced hearing at lower sound pressure levels, resulting in increased hearing thresholds. This phenomenon is described as recruitment. Damage to IHCs, in contrast, results in a hearing loss independent of sound pressure level (see Fig. 2.10). Noise-induced damage to hair cells might be initially temporary, recovering within about 48 hours due to restoration mechanisms provided by the inner ear (Schneider *et al.*, 2002). With accumulating hazardous noise exposure, a temporary disturbance in functionality of the cochlear amplifier may, however, result eventually in permanent hearing damage.

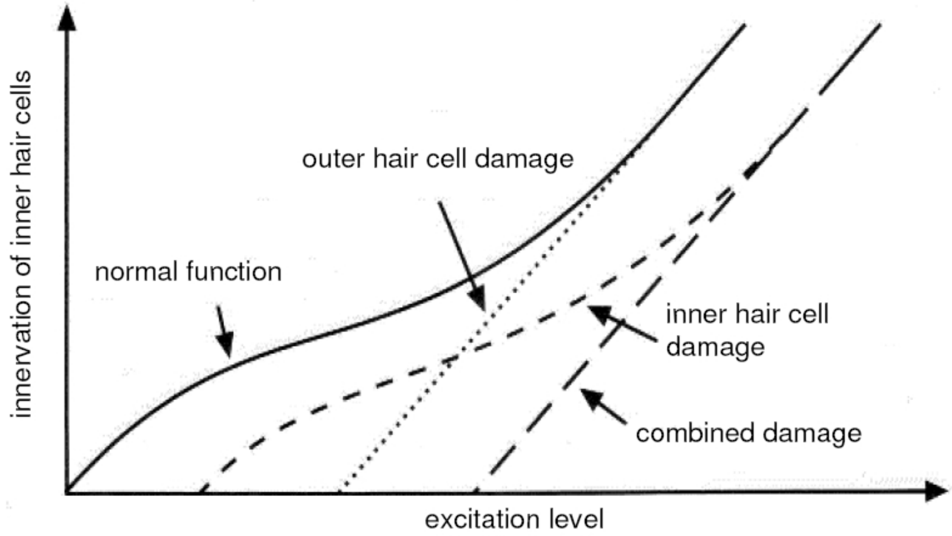

Figure 2.10: Change in innervation of IHCs due to damage of hair cells (adopted from Kollmeier, 1997)

Besides lesions in hair cells, which are supposed to be the most common reasons for hearing dysfunction, a damage of the battery of the cochlear amplifier, the stria vascularis, can be crucial in reducing the effectiveness of cochlear functionality. Atrophy of the stria vascularis results in a decline of the endocochlear potential and with that in a reduced operability of the cochlear amplifier which is voltage starved reducing its gain. The decline in endocochlear potential is supposed to affect transmission of the nerve impulses even more than the amplification process since IHC activity is affected in two ways: a low endocochlear potential causes the cochlear amplifier gain to decrease because of lowered drive to the OHCs, which causes a lower peak amplitude in the physical input to the IHC at low sound levels. In addition, the voltage across the IHC transduction channel is also decreased (Gates *et al.*, 2002).

Retrocochlear lesions, which result in neural hearing loss and thus in reduced or altered neural transmission may include genetic diposition, diseases (e.g., measles), auditory neuropathy, acoustic neuroma, or physical trauma. These neural defects shall not be explained here in more detail.

The neural connections of hair cells differ substantially. IHCs possess about 95 % of all afferent auditory nerve fibers, whereas most efferent auditory nerve fibers terminate at OHCs. Nerve fiber innervation is much denser for IHCs than for OHCs. A single IHC is innervated by numerous nerve fibers, whereas a single nerve fiber innervates many OHCs. IHC nerve fibers are also very heavily myelinated, which is in contrast to the unmyelinated OHC nerve fibers. The main consequence of a myelin sheath is an increase in the speed at which impulses propagate along the myelinated fiber and a myelinated sheath also provides a mechanism for regrowth of peripheral fibers.

The afferent nerve fibers make up the auditory nerve which relays the incoming sound signals as nerve impulses to the auditory cortex. The afferent nerve fibers start from the IHCs and are split and switched several times on their way to the auditory cortex, including also several efferent feedback loops. The basic upward pathway shall be outlined briefly in the following. The first split of the auditory nerve fibers results in one pathway proceeding to the Nucleus cochlearis dorsalis, and the other to the Nucleus cochlearis anterior. The latter path further continues to the ipsilateral and contralateral superior olivary complex and its Nucleus lateralis and Nucleus medialis. The medial nucleus is supposed to be responsible for a localization of sound sources. Signals then further proceed via the Colliculus inferior to the auditory cortex, the actual place of hearing.

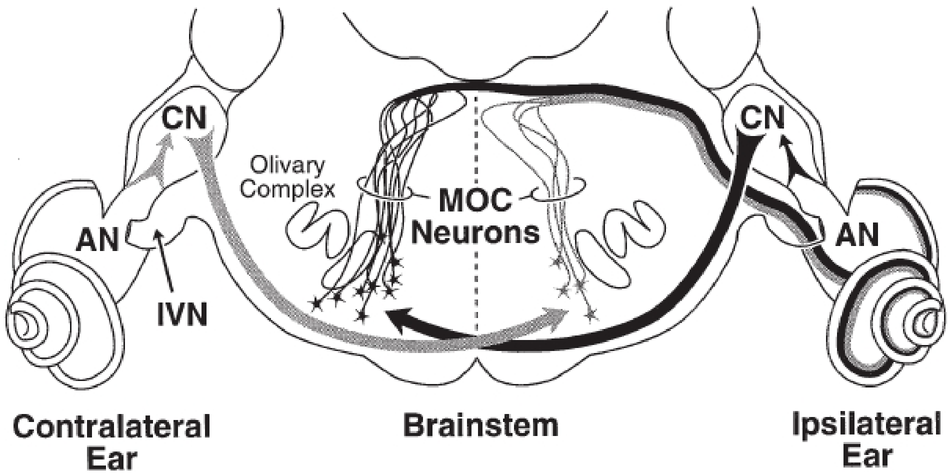

Figure 2.11: Neuronal circuitry underlying the medial olivocochlear reflex in mammals (AN: auditory nerve; CN: cochlear nucleus; IVN: inferior vestibular nerve) (Liberman and Guinan, 1998)

The efferent hearing system has been strongly investigated lately. However, its functional significance is still ambiguous and controversially discussed. There are two major efferent subsystems, which differ with respect to their peripheral targets. On the one hand there is the lateral olivocochlear (LOC) bundle, which projects from the lateral nucleus of the superior olivary complex onto the IHCs. Its function is widely unknown and shall not be discussed here. On the other hand, there is the medial olivocochlear (MOC) bundle. There is evidence that OHC amplification is directly influenced by the efferent MOC system, i.e. it seems to be capable of fine-tuning the gain of OHC amplification by adjusting the operating point of OHCs. The efferent nerve fibers of the MOC system emanate from the medial nuclei of the superior olivary complex and are comprised mostly of fibers that almost exclusively synapse on the base of the OHCs (Mountain, 1980; Guinan *et al.*, 1984; Brownell *et al.*, 1985; Guinan, 1996). Figure 2.11 shows a schematic of the MOC system. The plot shows an ipsilateral and a contralateral cochlea and the respective auditory nerve (AN) and cochlear nucleus (CN). The MOC fibers exit the brainstem via the inferior vestibular nerve (IVN). The MOC bundle consists of two fiber pathways both projecting onto the ipsilateral OHCs: the crossed (solid lines and arrows in Fig. 2.11) and the uncrossed (shaded lines and arrows in Fig. 2.11) feedback loop. The crossed MOC fibers are stimulated ipsilaterally, while the uncrossed fibers are stimulated contralaterally (Liberman *et al.*, 1996). Maximal excitation is supposed to occur for binaural noise. The ipsilaterally responsive loop was found in animals to be stronger than the contralaterally responsive loop. The thresholds for activation can be rather low setting off at about 10 to 20 dB SL. Sound frequencies most strongly affected by the MOC pathway are supposed to be in the mid- to high-frequency regions. This frequency specificity mimics the density of MOC terminals along the cochlear spiral: efferent terminals are quite rare in apical (low-frequency) regions (Liberman and Guinan, 1998). There is extensive neurophysiological literature which demonstrates that the MOC system attenuates the cochlear response to sound by reducing the gain of the cochlear amplifier (Galambos, 1956; Wiederhold, 1970; Murugasu and Russell, 1996). However, its functionality and its role in the hearing system is still not known. Current assumptions concerning the physiological function of the MOC neurons include the improvement of detection of transient low-level stimuli in the presence of background noise (Winslow and Sachs, 1987; Liberman and Guinan, 1998; Kirk and Smith, 2003; Kumar and Vanaja, 2004) or the protection from acoustic overexposure (Cody and Johnstone, 1982; Reiter and Liberman, 1995; Maison and Liberman, 2000, Luebke and Foster, 2002).

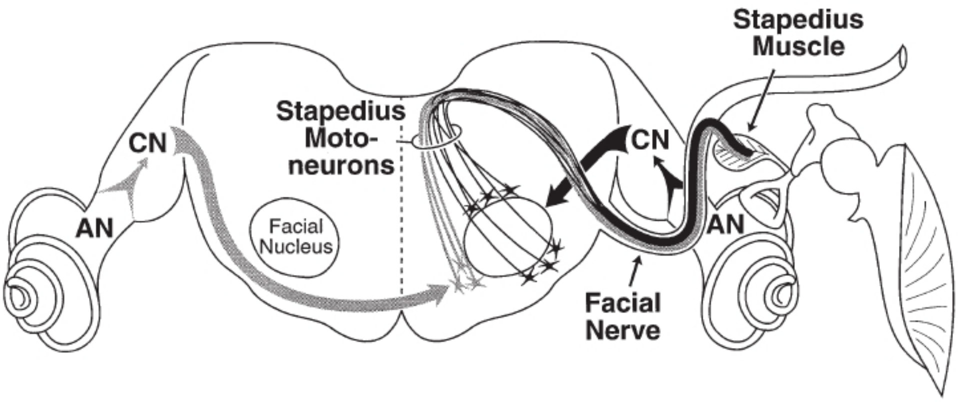

Figure 2.12: Neuronal circuitry underlying the stapedius reflex (AN: auditory nerve; CN: cochlear nucleus) (Liberman and Guinan, 1998)

Another efferent reflex is the stapedius reflex (see Fig. 2.12). The stapedius muscle is enervated by motoneurons, which originate in the brainstem around the ipsilateral facial motor nucleus and exit with the facial nerve. These motoneurons form the effector arm of a sound-evoked feedback pathway. Activation of the stapedius muscle pulls on the head of the stapes, which tilts the footplate within the oval window, stiffening the ossicular chain and reducing the transmission of sounds through the middle ear. Sound in either the ipsilateral or the contralateral ear can excite the reflex, and the maximum excitation occurs with binaural sound. The excitation path begins with the auditory nerve, which, in turn, excites neurons within the cochlear nucleus (CN). Output from the CN leads to excitation of the motoneurons. The stapedius reflex comes into effect after about 50 ms. Either noise or tonal stimulation can initiate the reflex. However, reflex thresholds are relatively high, being in normal hearing humans on the order of 75 dB SPL for broad band noise and 90 dB SPL for pure tones. The degree of sound attenuation depends strongly on sound frequency, with low-frequency sounds attenuated more than high-frequency sounds. The maximum attenuation occurs for frequencies near 1 kHz. The stapedius muscle can also be activated without acoustic stimulation: for example, during (and in anticipation of) vocalization or chewing, and (in some individuals) under voluntary control. Thus, it can be expected that also a descending control pathway from the central nervous system exists (Liberman and Guinan, 1998). It is assumed that the main function of the stapedius reflex is to protect the inner ear from acoustic overexposure.

2.3 Pure-tone audiometry

Pure-tone audiometry (PTA) tests a subject's hearing ability with respect to pure tones. In contrast to speech intelligibility tests, a frequency-dependent analysis is possible. However, more complex sound processing, including the ability to separate phonemes and thus to understand speech in either a quiet or noisy environment, is not possible by means of PTA. However, PTA is accredited a key role in clinical practice to quantify hearing loss and to examine and evaluate loudness perception.

2.3.1 Hearing threshold determination

The pure-tone hearing threshold in quiet indicates the sound pressure level of a pure tone stimulus that is just audible to the listener. The pure-tone hearing threshold measurement constitutes a prominent behavioral hearing test which is commonly used in clinical diagnostics for identifying individual hearing threshold levels and which is helpful in the determination of the degree, type, and configuration of a hearing loss. The measurement provides ear and frequency specific thresholds by using pure tones to elicit place specific responses in the cochlea, so that the configuration of a hearing loss can be identified. As the measurement technique can both be applied with air and bone conduction, the type of hearing loss (sound conductive or sensorineural hearing loss) can be identified via the air-bone gap. Usually, for air conduction measurements, supra-aural headphones are used for stimulus presentation. Conventional PTA frequencies usually range from 0.25 to 8 kHz. Although PTA has many clinical benefits, it is not perfect at identifying all hearing losses, such as e.g. 'dead regions', i.e. a hearing loss due to a distinct decline of IHCs within a small cochlear region (Moore, 2001).

Calibration of the test environment, the equipment and the stimuli is needed before testing. Especially, for each PTA headphone, so-called reference-equivalent sound pressure levels (RETSPL) have to be determined. These values are derived from the average sound pressure levels which had to be applied at a specific frequency and for a sufficiently large test group of normal hearing subjects at hearing threshold. The sound pressure level is commonly measured with a specific acoustic coupler.

The test procedure can be conducted manually or computer controlled. There are several different psychophysical methods proposed in literature, which can be applied for measuring absolute hearing thresholds. Classical methods date back to the 19th century and were first described by Gustav Theodor Fechner in 1860. Most of these classical methods are characterized by a fixed sequence of test runs and include several series of decreasing and increasing runs. The stimulus level is either controlled by the examiner or by the listener in such a way that the situations "tone inaudible" and "tone just audible" follow each other in sequence. The hearing threshold for each run is determined as the midpoint between the last audible and first inaudible level. The subject's hearing threshold at a specific frequency is then determined by averaging the hearing thresholds of all runs.

One of the most commonly used modifications of the classical method of tracking is the so-called Békésy tracking (Békésy, 1947), which was introduced as an adaptive method and can be used to automatically detect hearing thresholds. In this method, the subject controls the direction in which the stimulus level varies (i.e., the stimulus level is increased as long as the subject does not respond and is decreased when a response occurs), while the test frequency is slowly swept from lower to higher frequencies. The result is a zigzag line which varies continuously along frequency. When applying moving average methods, the smoothed line represents the hearing threshold. If test frequency is kept constant for a sequence of several turning points (i.e., reversals), the method is called staircase or up-down method (Cornsweet, 1962). After obtaining a default number of reversals (usually six to eight), the threshold is defined as the average of an even number of reversal points excluding the first trial run.

In general, these methods are relatively fast but can produce several biases. The first issue is anticipation, which is caused by the subject's awareness that the turning points determine a change in response. Anticipation produces better ascending thresholds and worse descending thresholds. The second issue is habituation, which creates an opposite effect, and occurs when the subject becomes accustomed to responding either "audible" in the descending runs or "inaudible" in the ascending runs. For this reason, thresholds are raised in ascending runs and improved in descending runs. Also, it is always easier for the subject to follow a tone that is audible and decreasing in amplitude than to detect a tone that was previously inaudible. This means that when measuring thresholds with sounds decreasing in amplitude, the point at which the sound becomes inaudible will always be lower than the point at which it returns to awareness. This phenomenon is known as hysteresis effect. Another problem may be related to step size. Too large a step size compromises accuracy of the measurement as the actual threshold may be between two stimulus levels.

There are several other methods, which do not bear these problems, but which commonly require substantially more time. In the method of constant stimuli the tester sets the stimulus levels and presents them at completely random order. The subject responds with "audible" or "inaudible" after each presentation. The stimuli are presented many times at each level and the threshold is defined as the stimulus level at which the subject scored 50 % correct answers. "Catch" trials (where the tone is in fact absent) may be included. Another common method is the two-interval alternative forced choice (2-AFC) method, in which the subject is confronted with the choice of two intervals with a sound presented in one of the two intervals and no sound in the other. The subject has then to decide in which interval the signal occurred. The advantage of this methods is that the subject cannot predict the occurrence of a signal since it randomly occurs in one of the two (or more) intervals.

When recording pure-tone thresholds with small frequency increments of about 50 Hz, i.e. pure-tone threshold fine structure, a quasi-periodic pattern of dips and peaks can be observed across frequency. The reason for pure-tone threshold fine structure and its significance have remained hitherto rather obscure. Some studies suggested dips in pure-tone threshold fine structure to be a sign of beginning hearing loss e.g. due to ototoxic aspirin consumption (Long and Tubis, 1988). This measurement technique might then be a tool to detect beginning or temporary hearing disorders which cannot be detected by standard PTA at octave frequencies. Other studies suggested that dips and peaks occur due to internal resonances resulting from energy reflected from the middle ear back to the cochlea due to the impedance mismatch at the stapes (Shera and Zweig, 1993). This resonance effect is expected to enhance the response of the basilar membrane to sounds at some frequencies, and reduce it at others resulting in minima and maxima in the pure-tone threshold fine structure.

2.3.2 Determination of loudness perception

Loudness measurement procedures evaluate a subject's perception of loudness concerning a pure-tone at a specific frequency. Loudness functions are helpful in clinical practice to get information about the status of supra-threshold hearing. The relationship between stimulus level and subjective loudness perception is important for the hearing aid fitting process since hearing aids have to compensate both for the loss of sensitivity and compression.

There are several methods of measuring loudness perception in the supra-threshold hearing area. There are both absolute and relative loudness measurement procedures. Relative procedures include relative loudness estimation with an anchor sound, relative loudness production, and loudness matching. For relative loudness estimation (e.g., Hellman and Zwislocki, 1961), the subject has to numerically evaluate the loudness of a sound with respect to an anchor sound which is provided with a given numeric reference value. For relative loudness production (e.g., Geiger and Firestone, 1933; Zwicker, 1958), the subject has to alter the volume of a test sound in such a way that it achieves a certain loudness ratio (e.g., doubling or halving) in comparison to a reference sound. For the method of loudness matching (e.g., Steinberg and Gardner, 1937), which is based on the phenomenon of loudness summation, the subject has to alter the volume of a pure-tone test sound in such a way that it is as loud as a reference sound consisting of a tone complex, i.e. a superposition of several pure tones. All these measurement procedures start from the assumption that a subject is capable of making relational classifications or adjustments of the loudness of a test tone in comparison to a reference tone. This assumption is, however, not generally true, and for untrained subjects often very difficult. Furthermore, all these methods are largely dependent on the parameterization of the reference sound. However, details shall not be discussed here. Absolute loudness measurement procedures include absolute loudness scaling (e.g., Stevens, 1957) and categorical loudness scaling (e.g., Allen *et al.*, 1990; Brand and Hohmann, 2002). For absolute loudness scaling, the subject has to assign a number to the test sound reflecting the individual loudness perception. Either the number can be chosen freely, i.e. without giving any reference value, or by limiting values to a given range of numeric values. For the first alternative, a problem of normalization occurs since the subject can choose any range of real numbers. Especially for large numeric values, there is a logarithmic response bias, i.e. for large numbers rather the logarithm of the number is evaluated and not the absolute value. This means that, e.g., the difference between 1000 and 999 is recognized as much lower than the difference between 10 and 9, although the difference for both cases amounts to 1. These influences cannot be compensated by normalization. The second alternative excludes these problems. However, the problem of an inter-individually varying perception of numbers and a difficult and for the untrained subject uncommon process of assigning loudness to a numeric value remains. In an effort to avoid these problems, another absolute loudness measurement procedure was introduced: categorical loudness scaling (CLS). This technique has hitherto attained the highest clinical acceptance and thus shall be explained in the following in some more detail.

CLS is a loudness measurement technique that is commonly applied in audiological diagnostics and, especially, in fitting hearing aids (e.g., Pascoe, 1978). The main advantage of CLS is that the procedure is quite easy to understand for inexperienced subjects. For CLS, the subject has to assign the perceived loudness of a test stimulus to one of several categories in a scale. The method is susceptible to a range of parameters.

The most important basic parameter is the quantity and labeling of the categories. Normally, the categories are marked with common verbal expressions such as "inaudible", "quiet", or "loud" (see Fig. 2.13). When dividing the scale in more than seven categories (usually labeled "inaudible", "very quiet", "quiet", "medium volume", "loud", "very loud", and "extremely loud"), the other categories normally remain unlabeled and are inserted between the labeled ones, resulting in eleven categories. Although the number of categories is normally set to seven or eleven (which is the most commonly used scale), numbers of categories from five to fifty have been proposed. Furthermore, there are one-stage and multi-stage procedures. One-stage procedures use just one category scale, whereas multi-stage procedures make use of one rough estimation scale and one or several fine resolution subscales. In general, more categories do not necessarily provide a better accuracy since the subject's natural resolution is limited. Thus, eleven categories are commonly considered enough for the human resolving power even if successive stimuli with small level variations could be resolved better concerning their loudness relative to each other.

The loudness categories are usually assigned to numeric values for further mathematical analysis. The numeric values are usually labeled with the pseudo-unit CU (= categorical unit). In the most common assignment strategy, loudness categories are assigned to

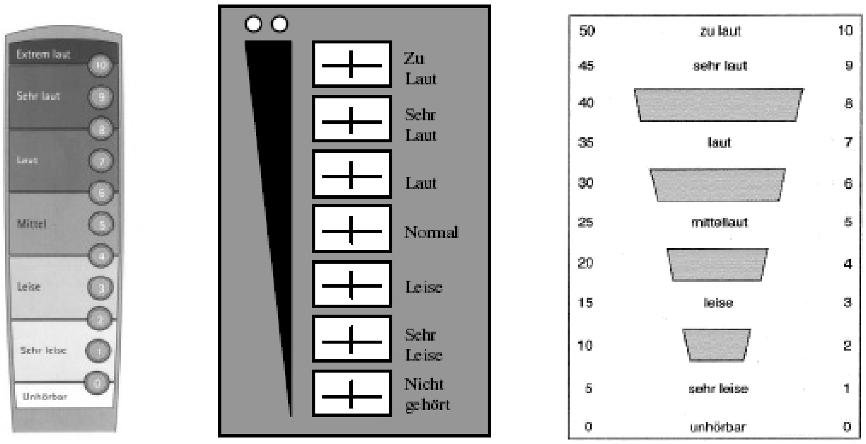

Figure 2.13: Graphical user interfaces of different categorical loudness scaling devices (from left to right: Phonak Claro; Madsen Aurical; Kollmeier, 1997)

values from 0 (="inaudible") to 50 (="extremely loud") with a step size of 5 (Kollmeier, 1997). The equidistant division is arbitrary and could also contain other numeric values. Furthermore, it is not clear if the different loudness categories are linearly represented in the loudness perception of each subject, which is suggested by the linear numeric assignment. This may result in a distorted representation of loudness perception.

Another aspect is the presented stimulus level range, which could be fixed or adapted to the hearing area of the subject. In general, a stimulus level range covering the entire hearing area is suggested to be favorable in order to avoid range effects which result in deviations in loudness perception dependent on the presented level range. This is due to the fact that subjects tend to use the entire range of categories even if perceived loudness does not correspond to the labeling of the category.

Random presentation is usually favored against continuous upward or downward sequences since hysteresis effects were observed for these sequences. This is due to the fact that small level changes are evaluated relative to each other resulting in a more frequent change in loudness category. Frequencies can also be tested either sequentially or randomly. Random presentation has the advantage that a relative evaluation between successive stimuli is avoided. However, a disadvantage is that especially untrained subjects may be irritated by randomly changing frequencies. For sequential presentation of frequencies, a disadvantage may be that the evaluation of loudness at the last frequencies is possibly influenced by reduced concentration and/or learning effects.

There are diverging opinions about the advantage or disadvantage of an orientation phase. An advantage of including an orientation phase might be that subjects get an overview of the presented level range and thus may be better prepared for the task. Also, the orientation phase can be used to determine the threshold of uncomfortable levels. A disadvantage might be that the subject is influenced by knowing the range of the levels and already assigns the presented level range beforehand to the range of loudness categories.

Several studies about loudness in normal hearing subjects and subjects suffering from sensorineural hearing loss showed that loudness behavior bears a good resemblance to basilar membrane characteristics, exhibiting compressive loudness functions for normal hearing subjects and steeper, less compressive loudness functions (i.e., recruitment) for hearing-impaired subjects (e.g., Hellman and Meiselman, 1990, 1993; Oxenham and Plack, 1997; Schlauch *et al.*, 1998; Moore et al., 1999). Consequently, the basilar membrane action and thus the influence of the OHC system seems to affect the shape of the loudness function (Yates *et al.*, 1990), although it can be expected that there are other more complex influences in the actual loudness encoding process (Relkin and Doucet, 1997; Moore and Glasberg, 2004).

2.3.3 General problems using psychoacoustic measurement procedures

Psychoacoustic measurement methods bear some general problems. Both pure-tone threshold and loudness are behavioral measures as they rely on the patient's response to a stimulus. Therefore, these measurement techniques can only be used in sane adults and older children who are capable of coping with the test procedure. There are special measurement methods for children as, e.g., play audiometry. However, these techniques are not very precise.

The perception of an acoustic stimulus is in general not only dependent on the nominal sound pressure level, which could be measured physically, but is also dependent on the spectral composition of the stimulus and the general functional status of the hearing organ. These factors influence the perception of an acoustic stimulus dependent on its specific stimulus frequency and level. This is the main effect, which is intended to be measured exclusively. However, there are some unwanted side-effects inherent to psychoacoustic measurement procedures, which superimpose on the main effect.

First, the behavioral measure itself is often difficult to record and depends on the applied measuring procedure, the exact instruction given to the subject, and the design and handling of the user response device. The influence of these factors can be reduced by using a standardized instruction and an identical simple-to-use response device for all subjects.

Second, multifarious external influencing factors, which are mainly due to psychological processes, cannot be adequately captured and removed from the data. These influencing factors are dependent on the subject and for one subject also dependent on time and include the current state of mind (e.g., stress, fatigue), different listening habits and experiences, the previous impact of sound to the ear, and the personal attitude towards the presented sound. A sound with equal nominal sound pressure level can be experienced in a different way dependent on the situation. For example, if a person listens intentionally to music, the loudness might be rated differently as when listening to the same music with the same sound pressure level played by a neighbor while the person does not want to be distracted during reading a text book or while falling asleep. In this case the loudness might be rated much louder. Moreover, the power of concentration plays a major role for psychoacoustic tests. This might be lower especially for children or older subjects.

Additionally, the determination of loudness perception as a behavioral measure, bears the inherent problem that there is no physical measure for the evaluation and numeric representation of absolute loudness. This further complicates mathematical analysis. Only very imprecise statements, as "quiet" or "loud", are common in colloquial usage and are thus also limiting the possibilities of spontaneous absolute evaluation of loudness perception.

Moreover, the quality of the results achieved with a specific measuring procedure is dependent on its complexity. This factor influences the maintenance of concentration. Also, the more a subject is familiar with the task, the better and more reproducible the results will be. Here, a general question is, if a subject must be familiar with a given task beforehand or if it can be trained in the course of several repetitions of the task. However, when a subject is trained, the question is, if the responses still reflect the same statement which would be given spontaneously by an untrained subject.

2.4 Impedance audiometry

2.4.1 Tympanometry

Tympanometry is an objective examination technique used to test the condition of the middle ear by measuring the acoustic admittance of the tympanic membrane (e.g., Schuster, 1934; Zwislocki, 1957; Terkildsen and Nielsen, 1960). In the evaluation of hearing loss, tympanometry is a valuable component in the distinction between sensorineural and sound conductive hearing loss.

The basis of operation is that, while changing the static pressure in the ear canal, a probe tone with a typical frequency of 226 Hz is sent into the ear canal. The sound strikes the tympanic membrane causing a vibration of the middle ear. Some of the sound is reflected back and picked up by a microphone placed in the ear canal. The more sound that enters the middle ear, the less is reflected back and vice versa. The fraction of reflected sound energy depends on the acoustic admittance of the ear drum. For tympanometry measurements, the additional pressure imposed on the static pressure in the ear canal is usually changed from -400 to $+200$ daPa. By changing the pressure within the ear canal, the ear drum is bent from its starting position and thus alters its acoustic admittance and by that the amount of reflected energy. For proper operation an airtight closure of the ear canal by the tympanometric ear probe is indispensable.

Basically, the sound pressure level of the probe tone, which is reflected back from the ear drum is measured and then converted into a measure of admittance, which is in a clinical setting denoted as middle ear compliance. The unit for the compliance is millimho (mmho) or cubic centimeters (cm^3 or cc). The relationship between the amplitude of the reflected signal and the middle ear compliance can be described in the following way: if more sound is reflected back, the middle ear is stiffer and therefore the compliance is lower.

Normally, the air pressure in the ear canal is the same as the ambient pressure since the Eustachian tube opens periodically (e.g., when swallowing) to ventilate the middle ear and to equalize pressure differences. In a healthy middle ear, maximum sound transmission through the middle ear and with that maximum compliance occurs when the air pressure in the ear canal is equal to air pressure in the middle ear. Normal middle ear function is characterized by a maximum compliance occurring in the pressure variation range of −150 daPa to +100 daPa with the value of compliance ranging from 0.2 to 2.5 mmho.

2.4.2 Stapedius reflex measurement

The stapedius reflex describes the contraction of the stapedius muscle in response to acoustic stimulation. The activation of the stapedius reflex can be monitored by recording the middle ear admittance (e.g., Metz, 1952). The reflex threshold can be investigated for different sound stimuli (e.g., pure tones with differing frequencies, or broad band noise). Due to the activation of the stapedius reflex, the acoustic admittance of the ossicular chain and with that the compliance of the ear drum decreases, i.e. a higher fraction of sound energy is reflected from the ear drum. To determine the reflex threshold, the time course of the acoustic admittance is measured for stimulation with increasing sound pressure levels. For sound conductive hearing loss, the reflex is expected to be elevated or not detectable. For sensory hearing loss, the reflex is usually similar compared to normal hearing. For neural hearing loss, the reflex is commonly not detectable or at least significantly elevated.

2.5 Otoacoustic emissions

"Ja so gar zwey Flutes douces geben, wenn man c" und das a" 'rein zusammen bläset, noch den dritten Klang, nemlich ein f, welches zu probieren stehet."

Georg Andreas Sorge (1745)

The phenomenon of sound generated by the ear itself has first been described by the composer, organist and musical theoretician Georg Andreas Sorge in 1745 and shortly afterward by the composer and violinist Giuseppe Tartini (1754), who named the found emission from the ear "terzo suono" (i.e., third tone) and made use of it in his famous "Devil's trill sonata". More than 200 years later, the presence of otoacoustic emissions in human ears could be proved experimentally by Kemp (1976, 1978).

Up to now, the underlying processes for the generation of otoacoustic emissions within the inner ear are not yet completely understood. The following explanations are therefore based on an established model which is commonly accepted by the scientific community.

Otoacoustic emissions are sounds that are supposed to be generated as a byproduct of the active, nonlinear amplification process of OHCs within the inner ear (Kemp, 1986; Brownell, 1990). The emission is transmitted via the middle ear to the outer ear canal, where it can be recorded non-invasively by means of a sensitive microphone. Since otoacoustic emissions are supposed to reflect the functional operability of OHCs, they seem to be suitable to evaluate cochlear integrity. Otoacoustic emissions are the only audiometric test that is capable of selectively assessing cochlear dysfunction.

2.5.1 Classification of otoacoustic emissions

There are several types of otoacoustic emissions. Spontaneous otoacoustic emissions (SOAEs) occur spontaneously without any acoustic stimulation as a direct consequence of cellular force generation of OHCs (Burns *et al.* 1998). SOAEs can be recorded in about $\frac{2}{3}$ of the normal hearing population with a higher prevalence in females than in males (Penner and Zhang, 1997). In contrast to previous speculations, there was no distinct correlation to the occurrence of tinnitus (Penner and Burns, 1987). This type of emission has yet not gained any clinical significance. In contrast, evoked otoacoustic emissions occur due to acoustic stimulation. They can be divided in two main subtypes, depending on the type of stimulus (transient or stationary) which is applied to elicit the particular type of emission. The following types of evoked otoacoustic emissions can be distinguished:

Transiently evoked otoacoustic emissions (TEOAEs) are elicited by transient clicks. These broad band signals stimulate a large part of the cochlea within a short period of time. The recorded overall response can be seen as the sum of responses from different locations (i.e., frequencies) within the cochlea. Since signals from different places in the cochlea exhibit different delay times, the overall response can be broken down into particular responses from the different cochlear locations. However, frequencies above 4 kHz are difficult to record, since for higher frequencies the delay time is too short to be able to separate the stimulus artifact properly from the response. TEOAEs are commonly used in clinical practice for quick hearing screening purposes. A major field of application is in universal newborn hearing screening (UNHS) programs. TEOAEs can usually be detected in ears with mild sensory hearing losses of up to about 30 dB HL. The TEOAE measurement technique was first introduced by Kemp in 1978.

Stimulus frequency otoacoustic emissions (SFOAEs) are produced by a single stationary pure tone. The detection of the emission is, however, complicated by the superposition of stimulus and response. The response can only be separated from the stimulus by making use of the nonlinear properties of the emission response. This measurement technique has hitherto merely gained scientific relevance.

Distortion product otoacoustic emissions (DPOAEs) are elicited by stationary stimulation with two pure tones. DPOAEs are supposed to occur as a direct result of the nonlinearity of the cochlear mechanical amplifier, which produces (as any other nonlinear active device) distortion products of different order. In the human ear, both quadratic as well as cubic distortion products are detectable. However, the most prominent distortion product found in the human ear is the cubic difference tone at $f_{dp} = 2f_1 - f_2$, with f_1 being the lower stimulus frequency and f_2 the higher one (Gorga *et al.*, 2000a). DPOAEs are very sensitive to variations in both stimulus frequency ratio f_2/f_1 and stimulus level ratio L_2/L_1. DPOAEs are widely used in clinical practice for screening purposes (e.g., UNHS) and for a more detailed objective examination of OHC functionality. DPOAEs can usually be elicited in ears with sensory hearing losses of up to about 40 to 50 dB HL, representing approximately the range of the cochlear amplifier (Davis, 1983; Ruggero *et al.*, 1997).

2.5.2 Generation mechanism of distortion product otoacoustic emissions (DPOAEs)

Since the DPOAE measurement technique was extensively used in this work, some more details concerning its generation shall be given in the following. Also some problems inherent to the measurement technique shall be disclosed.

The place of generation of the DPOAE is supposed to be located alongside the basilar membrane in the area of overlap of the two traveling waves near the characteristic place of the primary tone frequency f_2. This place, x_2, is suggested to be the location of the main source of DPOAE generation according to the two-sources interference model (Whitehead *et al.*, 1992; Brown *et al.*, 1996; Shera and Guinan, 1999; Talmadge *et al.*, 1999). A basic DPOAE generation model is shown in Fig. 2.14.

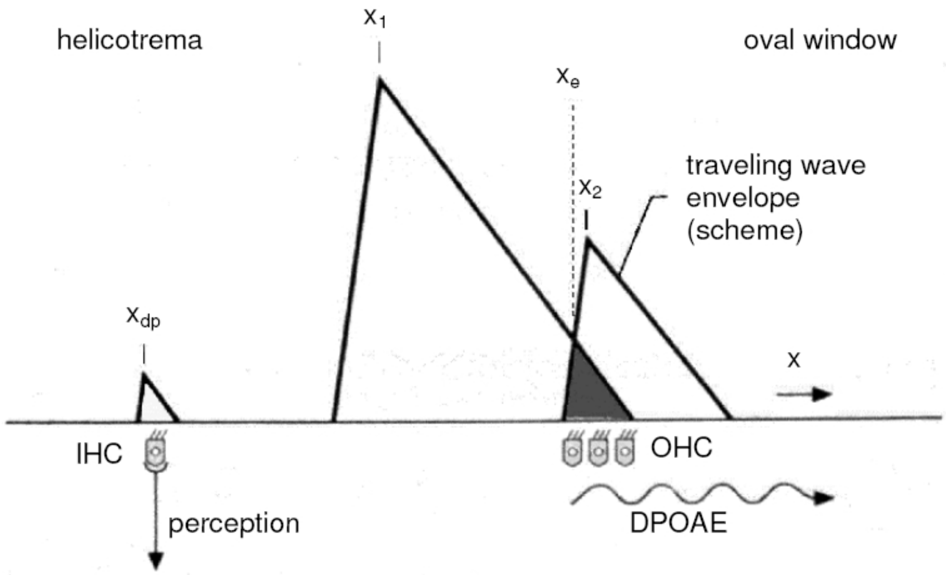

Figure 2.14: Schematic drawing of the DPOAE generation model (Janssen, 2000)

Both primary tones are characterized by their respective amplitude (L_2, L_1) and frequency (f_2, f_1) and become manifest in two traveling waves on the basilar membrane. These traveling waves exhibit maxima at their particular characteristic places (x_2, x_1). Due to the asymmetric envelope of the traveling wave and its steep slope towards the helicotrema, the maximum of the area of overlap, x_e, is close to the x_2 place. OHCs in the small area of overlap around x_e are supposed to predominantly contribute to the generation of the emission. Thus, the main generation site of the DPOAE is expected to be close to the characteristic place of f_2. This assumption is supported by the fact that iso-suppression tuning curves exhibit their characteristic frequency at f_2 (Kummer *et al.*, 1995; Gorga *et al.*, 2003a). The frequency resolution and even more the amplitude of the emission strongly depend on the size of the area of overlap and with that on the frequency and level ratio of the two primaries.

Regarding Fig. 2.14, one can imagine that for a fixed frequency ratio and a constant L_2, a change in L_1 may have an enormous effect on the size of the area of overlap. When reducing L_1 steadily, starting from an optimum value, the area of overlap gets smaller until it vanishes and no emission is generated any more. When increasing L_1, the area of overlap increases as well, but the emission amplitude diminishes again. This effect could be reproduced experimentally when recording DPOAEs with a fixed frequency ratio and constant L_2 but varying L_1 (Kummer *et al.*, 2000; Whitehead *et al.*, 1995a,b). The optimum primary tone level setting varies inter-individually and across frequency. Due to the fact that finding an optimum setting for each individual and for each test frequency is very time-consuming, and thus not clinically relevant, usually a compromise has to be accepted by using a heuristical optimum, which can be derived from optimum parameter settings averaged across a sufficiently large group of normal hearing subjects and across several frequencies. Such an optimum was empirically determined by Kummer *et al.* (2000) and can be described by Eq. 2.4, which quantifies the frequency ratio of the two primaries, and by Eq. 2.5, which quantifies the level ratio of the two primaries, the so-called 'scissor paradigm'. These equations were specified for frequencies f_2 between 1 and 8 kHz and levels L_2 up to 65 dB SPL.

$$\frac{f_2}{f_1} = 1.2 \tag{2.4}$$

$$L_1 = 0.4L_2 + 39 \tag{2.5}$$

In the area of overlap (see Fig. 2.14), the distortion products are generated due to the nonlinearity of the mechanical amplifier. Here, only the distortion product at $f_{dp} = 2f_1 - f_2$ shall be examined. A part of the emission energy, which is generated near f_2, is now relayed basally via the middle ear and the ear drum towards the outer ear canal. The other part of the emission energy is relayed apically towards the helicotrema, where a maximum deflection of the basilar membrane occurs at x_{dp}, i.e. at the characteristic place of f_{dp} alongside the basilar membrane. Supposed the emission level is large enough, the basilar membrane deflection at x_{dp} would trigger nerve impulses, which may lead to a hearing sensation at f_{dp}. However, normally the DPOAE amplitude is 30 to 60 dB lower than the primaries and thus is masked by them, making the emission inaudible.

According to the two-sources interference model (Whitehead *et al.*, 1992; Brown *et al.*, 1996; Shera and Guinan, 1999; Talmadge *et al.*, 1999), the secondary DPOAE generator at x_{dp} contributes to the overall emission because some of the energy that has traveled apically from the region of overlap near x_2 is reflected from the x_{dp} place and is from there transmitted basally towards the outer ear canal where it interferes with the main emission from the primary generator place at x_2. Thus, energy from both interacting sources yield the composite DPOAE signal. The fraction from the secondary generator is phase-delayed to the fraction from the primary generator. The resulting interferences with the strongly varying phase-delay from the secondary generator are commonly regarded as a source of strongly varying amplitudes between neighboring frequencies (He and Schmiedt, 1993; Heitmann *et al.*, 1998; Talmadge *et al.*, 1999; Mauermann and Kollmeier, 2004). Alternating dips and peaks are supposed to occur due to constructive and destructive superposition of the two sources. This phenomenon can be observed when recording DPOAEs with a high frequency resolution, i.e. DPOAE fine structure. Also, the amount and phase delay of energy reflected from the middle ear back into the cochlea might play some role in the depth of DPOAE fine structure (Shera and Zweig, 1993). If reflected energy reaches the characteristic place of f_{dp} for one frequency in phase and for a neighboring frequency out of phase with the original signal, an increase in depth of DPOAE fine structure may be possible.

There were contradictory results concerning the influence of hearing loss on DPOAE fine structure properties. Mauermann *et al.* (1999) showed that characteristic properties of DPOAE fine structure vanished in subjects with a prominent hearing loss at $2f_1 - f_2$, whereas the characteristic properties remained in subjects with a sharp hearing loss at f_2. In contrast, He and Schmiedt (1996) did not find any distinct differences with hearing loss.

In an attempt to separate the two DPOAE sources, DPOAEs have been measured using a method of time windowing (Knight and Kemp, 2001; Kaluri and Shera, 2001; Mauermann and Kollmeier, 2004; Shaffer and Dhar, 2006). However, this method is very time-consuming and thus not relevant for clinical practice. Also, the application of a selective suppressor tone presented close to f_{dp} has been suggested (Heitmann *et al.*, 1998; Shaffer and Dhar, 2004). However, this method is strongly dependent on the proper setting of the suppressor stimulus, which may vary inter-individually and dependent on the setting of the two primaries. Both methods showed that the occurrence of dips and peaks in DPOAE fine structure, and with that the influence of the second DPOAE source, could be reduced.

Although DPOAE fine structure is similar in its appearance to pure-tone threshold fine structure, there seems to be no direct relationship between both measures, since maxima and minima of both fine structures commonly occur at different frequencies (Mauermann *et al.*, 2004). Also, DPOAE fine structure turned out to be more sensitive towards cochlear damage compared to pure-tone threshold fine structure (Mauermann *et al.*, 1999).

DPOAE amplitudes recorded in the outer ear canal also depend on several other influencing factors. A decisive role holds middle ear function. For example, a stiffening of the chain of ossicles in the middle ear results in reduced DPOAE amplitudes since both the incoming stimulus levels and the transmitted emission is attenuated by the reduced capability of the middle ear to properly transmit sound from the outer ear to the inner ear and vice versa. Hence, in sound conductive hearing loss, DPOAEs are difficult to measure, even with a mild hearing loss (Margolis, 2002). DPOAE amplitudes, as a byproduct of cochlear nonlinear sound amplification, are moreover strongly dependent on the functional operability of the cochlear amplifier and are hence reduced or even disappear in subjects with sensory hearing loss (Mills and Rubel, 1994). Even minute changes in the functioning of OHCs, caused, for example, by low-level noise exposure (Skellet *et al.*, 1996), increased body temperature due to fever (O'Brien, 1994), administration of salicylate (McFadden and Plattsmier, 1984), or alteration of body posture (Frank *et al.*, 2000) are known to affect the amplitude of otoacoustic emissions.

Ear canal volume and ear drum impedance are crucial factors in influencing DPOAE amplitudes also across normal hearing subjects, since the attenuation of the emission amplitude is related to both middle ear parameters. The inter-individual variance of the DPOAE level in normal hearing subjects is hence very high with a standard deviation exceeding 10 dB (Kemp *et al.*, 1986; Probst *et al.*, 1987; Bonfils and Uziel, 1989; Smurzynski and Kim 1992). The intra-individual variance of the DPOAE level is, however, much smaller, but depends distinctly on the signal-to-noise ratio (SNR). Recently, Janssen *et al.* (2005a) showed that repetitive DPOAE measurements with unchanged sound probe position exhibited an exponentially increasing standard deviation of DPOAE level with increasing SNR. For example, at an SNR of 10 dB, the standard deviation amounts to 1.8 dB, at an SNR of 20 dB to 0.7 dB, and at an SNR of 40 dB to 0.1 dB. This means that the higher the SNR, the higher the reliability of the DPOAE measurement. This finding is important with respect to the evaluation of small DPOAE changes.

There are also some general limitations of DPOAE measurements:

- electric microphone noise, physiological noise (breathing, swallowing, blood flow) and ambient acoustic noise do not allow for measurements at very low stimulus levels. Especially below 500 Hz, reliable OAE measurements are not possible even at high stimulus levels.

- limited frequency range of the sound probe's electroacoustic transducers makes high-frequency OAE measurements difficult.

- standing waves in the outer ear canal make a defined stimulus setting difficult to obtain (see Sec. 3.4).

Considering all these influencing factors and the ones mentioned further above, it is easy to see how DPOAE measures can be misinterpreted.

2.5.3 Evaluation and clinical applications of DPOAEs

The possibility to measure DPOAEs comparably easy and non-invasively, and the fact that emissions are already present at the day of birth (Abdala, 2000), makes them a valuable measurement technique especially in postnatal audiometric diagnostics, but also for enhanced differential diagnostics in adults. Hence, the main current applications in clinical diagnostics are:

- universal newborn hearing screening (UNHS)
- proof of a cochlear hearing-loss along with tympanometry and auditory brainstem responses
- quantitative evaluation of hearing loss and recruitment

In order to detect hearing deficits in UNHS, handheld devices are in use, which offer easy-to handle presets for measurements of otoacoustic emissions (TEOAEs and/or DPOAEs) and auditory evoked potentials. These screening methods allow for a differentiation between normal hearing (”pass”) and hearing damage (”fail”). Hearing screening serves as a simple test for early detection of a hearing lesion. If a ”fail” occurs, routinely an enhanced and more detailed audiometric test battery is applied in order to check if a serious lesion is evident. Directly after birth, the percentage of ”fail” responses is higher compared to the results from a second test some days after birth. This is suggested to be due to residual amniotic fluid in the tympanic cavity resulting in a temporary sound conductive hearing loss. There are no quick tests up to now to distinguish between a temporary sound conductive and a cochlear hearing loss. Further efforts of the author concerning this topic are presented in Chapter 5, when examining hearing status in neonates directly after birth and about a month later.

Otoacoustic emissions have a potential beyond hearing screening and can also be used for a detailed examination of cochlear functionality. Especially DPOAEs can be useful in quantitatively evaluating cochlear sensitivity, compression, and frequency selectivity. Since DPOAEs are closely related to the operability of the cochlear amplifier (Mills and Rubel, 1998), they are capable of describing cochlear lesions related to OHC dysfunction. However, major hearing losses exceeding about 50 dB HL cannot be examined since the cochlear amplifier merely operates in the low-to-mid-level region. Also, a damage of IHCs or lesions at higher stages of the auditory path, e.g., neural or central disorders, cannot be detected by means of DPOAEs alone. However, together with other objective measurements, such as tympanometry and auditory brainstem responses, the clinical practitioner possesses an extensive test battery in order to differentiate between cochlear, neural, and sound conductive hearing loss. Due to the fact that a majority of about 90 % of all hearing disorders can be attributed to OHC dysfunction, DPOAEs are a powerful means to selectively examine cochlear status (Hall and Lutman, 1999; Attias *et al.*, 2001; Marshall *et al.*, 2001; Janssen *et al.*, 2005a). Hence, DPOAEs are helpful in clinical practice and also in examining non-cooperative subjects such as malingerers, aggravating persons or mentally retarded patients.

DPOAEs provide quantitative information about the range and operational characteristics of the cochlear amplifier, i.e., sensitivity, compression, and frequency selectivity. There are several DPOAE measures shown in Fig. 2.15 that are used for assessing the functioning of the cochlear amplifier.

(A) DPOAE grams (Fig. 2.15A) plot the DPOAE level L_{dp} as a function of f_2 (the main DPOAE generation site) for selected combinations of primary-tone levels L_1 and L_2. It should be emphasized that DPOAE grams reflect the sensitivity of the cochlear amplifier best when recorded at close-to-threshold stimulus levels (Janssen *et al.*, 1998; Kummer *et al.*, 1998; Dorn *et al.*, 2001). DPOAE grams when recorded with narrow frequency spacing of f_2 (DPOAE fine structure) may give information about pure-tone threshold fine structure. However, due to the superposition of the second DPOAE source (He and Schmiedt, 1993, 1996, 1997; Shera and Guinan 1999) the correlation between the two measures is not clear. The DPOAE fine structure is commonly characterized by alternately varying amplitudes, i.e. dips and peaks. In normal hearing, DPOAE grams are close to each other at high and more separated at low stimulus levels, reflecting cochlear nonlinear sound processing. In cochlear hearing loss, DPOAE grams are more separated even at high stimulus levels, revealing a loss of compression of the cochlear amplifier (Janssen *et al.*, 1998; Kummer *et al.*, 1998; Neely *et al.*, 2003).

(B) DPOAE level I/O functions (Fig. 2.15B) plot the DPOAE level L_{dp} as a function of primary tone level L_2 for a selected f_2 (test frequency f_{test}) and thus reflect dynamics of the cochlear amplifier at the f_2 place in the cochlea (Dorn *et al.*, 2001). In normal hearing, in response to low-level stimuli, DPOAE level I/O functions exhibit steep slopes, while at high stimulus levels, slopes decrease, thus mirroring the strong amplification at low and decreasing amplification (saturation) at moderate sound pressure levels. However, this is true only when a stimulus setting is used, which accounts for the different compression of the primary tones at the f_2 place (Kummer *et al.*, 2000). In subjects with cochlear hearing loss, the DPOAE level I/O function is linearized and compared to I/O functions from normal hearing subjects also steeper at higher primary tone levels (Janssen *et al.*, 1995a,b, 1998; Kummer *et al.*, 1998; Dorn *et al.*, 2001; Boege and Janssen, 2002; Neely *et al.*, 2003). Moreover, a simplified estimation of DPOAE threshold can be derived from the lowest L_2 at which a valid emission occurs.

(C) DPOAE pressure I/O functions (Fig. 2.15C) plot the DPOAE pressure p_{dp} (instead of the DPOAE level L_{dp}) as a function of the primary tone level L_2. Due to the logarithmic dependency of the DPOAE level on the primary tone level, there is a linear dependency between DPOAE pressure p_{dp} and primary tone level L_2 (Boege and Janssen, 2002). Thus, DPOAE data can easily be fitted by linear regression analysis. The intersection point of the linear regression line with the L_2-axis at $p_{dp} = 0$ Pa can then serve as an estimate of the stimulus level at the DPOAE threshold, i.e., $L_{dp,th}$ (Boege and Janssen, 2002).

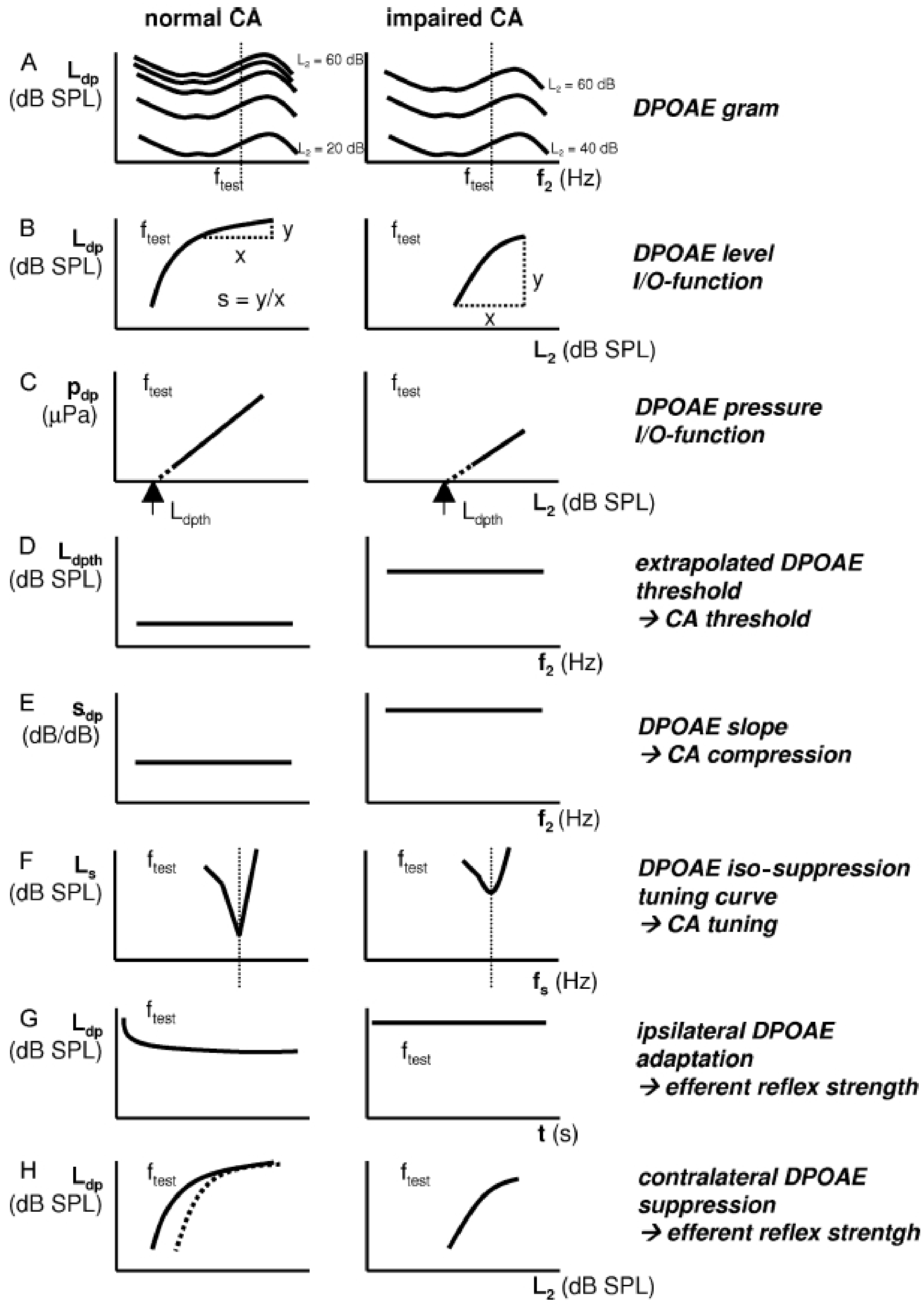

Figure 2.15: Schematic presentation of commonly used graphic renditions of DPOAE data assessment. All plots are shown for a normal hearing subject, i.e. with normal cochlear amplifier (CA), at left, and a hearing-impaired subject, i.e. with impaired CA, at right. The term commonly used for the respective DPOAE measurement plot is given on the right-hand side of each row. The physiological parameters that can be derived from the DPOAE measures are indicated by an arrow at the respective term (Janssen and Müller, 2008)

(D) Estimated threshold level $L_{dp,th}$ (Fig. 2.15D) plotted across frequency f_2 provides a measure for estimating hearing threshold at the f_2 place in the cochlea. Note that changes in DPOAE level with frequency do not have an influence on $L_{dp,th}$ if the separation of the DPOAE grams is independent of frequency. In studies with normal hearing subjects and subjects with cochlear hearing loss, $L_{dp,th}$ was found to be significantly correlated to audiometric pure-tone thresholds. By introducing several criteria for evaluating the reliability of the regression line, the mean difference between $L_{dp,th}$ and pure-tone threshold could be reduced to -2.5 dB with a standard deviation of 10.9 dB (Boege and Janssen, 2002). Similar results could be reproduced by Gorga *et al.* (2003b).

(E) DPOAE slope (Fig. 2.15E) calculated from DPOAE level I/O functions (e.g., between stimulus levels L_2 of 40 and 60 dB SPL) indicates compression of the cochlear amplifier. When plotted across frequency, a slope profile can be established. In ears with cochlear hearing loss, the slope s_{dp} of the DPOAE level I/O function increases with increasing hearing loss, indicating loss of compression (Janssen *et al.*, 1998; Kummer *et al.*, 1998).

(F) DPOAE iso-suppression tuning curves (Fig. 2.15F) mirror frequency selectivity of the cochlear amplifier at the f_2 place in the cochlea. They plot the level L_s of an ipsilateral suppressor tone at which the DPOAE level L_{dp} is decreased by a particular amount (e.g., 3 dB) across the frequency of the suppressor tone f_s. DPOAE iso-suppression tuning curves exhibit the V-shape of neural tuning curves. In a cochlear hearing loss, the tip of the tuning curve disappears, revealing loss of both sensitivity and frequency selectivity of the cochlear amplifier (Kummer *et al.*, 1995; Abdala *et al.*, 1996; Gorga *et al.*, 2003a).

(G) Ipsilateral DPOAE adaptation (Fig. 2.15G) plots the DPOAE level L_{dp} as a function of time at a selected f_2 beginning at the stimulus onset. The difference between the DPOAE level at onset and the level at steady state is supposed to indicate the change in OHC motility as controlled by MOC efferents and is thus suggested to serve as a measure for evaluating the reflex strength of the crossed MOC efferents (Liberman *et al.*, 1996; Agrama *et al.*, 1998; Kim *et al.*, 2001; Bassim *et al.*, 2003; Meinke *et al.*, 2005).

(H) Contralateral DPOAE suppression (Fig. 2.15H) represents the difference between the DPOAE level L_{dp} measured in the absence and in the presence of contralateral acoustic stimulation (CAS). The difference in DPOAE level due to CAS is assumed to indicate altered OHC motility due to the impact of MOC feedback and is hence suggested to serve as a measure for evaluating the reflex strength of the uncrossed MOC efferents. (Collet *et al.*, 1990a; Puel and Rebillard, 1990; Moulin *et al.*, 1993; Williams and Brown, 1995; Puria *et al.*, 1996; Maison *et al.*, 2000; Janssen *et al.*, 2003).

Clinically relevant measurements are currently DPOAE grams and I/O functions, and their derived measures of DPOAE amplitude, threshold, and slope (see Fig. 2.15, panels

A–D). Measures derived from DPOAE phase are so far clinically not evaluated. Iso-suppression tuning curves have up to now only gained scientific relevance and are not commonly applied in clinical diagnostics.

Ipsilateral DPOAE adaptation and contralateral DPOAE suppression measurements are relatively new measures for evaluating the reflex strength of either the crossed or uncrossed MOC feedback loop. However, their interpretation is difficult due to a lack of sufficient knowledge about the functioning of the efferent MOC system, about the representation of efferent reflex strength in ipsilateral DPOAE adaptation or contralateral DPOAE suppression data, and about proper parameterization of the stimuli. The clinical significance of both measurements is currently negligible, since it is still under discussion how to properly analyze and make clinical use of the data.

The influence of the efferent MOC system on OHC motility and its measurability by means of otoacoustic emissions (DPOAE/TEOAE) has been strongly investigated in both animal and human studies in recent years. Research has mainly focused on the two basic methods of ipsilateral DPOAE adaptation and contralateral DPOAE/TEOAE suppression. Contralateral suppression has been extensively studied in animals (e.g., Puel and Rebillard, 1990; Puria *et al.*, 1996) and humans (e.g., Collet *et al.*, 1990a; Veuillet *et al.*, 1991; Moulin *et al.*, 1993; Williams and Brown, 1995; Maison *et al.*, 2000). The observed change in DPOAE level due to CAS was found to be more commonly a decreasing effect, i.e. suppression, than an increasing effect, i.e. enhancement, and amounted to only some dB, depending on the type of the contralateral stimulus and the primary tone level setting. In general, with increasing contralateral stimulus bandwidth and level, and with decreasing primary tone level, the suppression effect increased (e.g., Chéry-Croze *et al.*, 1993; Janssen *et al.*, 2003). However, in the literature there are no data concerning systematic $L_2|L_1$ variation across a major primary tone level range for contralateral DPOAE suppression in humans. Compared to contralateral DPOAE suppression there is little data concerning ipsilateral DPOAE adaptation in the literature. Ipsilateral DPOAE adaptation, first measured by Liberman *et al.* (1996) in cats, was reported to exhibit a decrease in steady-state DPOAE level of up to 6 dB. In humans, however, DPOAE adaptation was observed to be lower than 1 dB on average across subjects (Agrama *et al.*, 1998; Kim *et al.*, 2001; Bassim *et al.*, 2003). The time course of DPOAE adaptation was found to be best approximated by a two-exponential function with a rapid (about 100 ms) and a slow (1 to 1.5 s) component (Kim *et al.*, 2001; Bassim *et al.*, 2003). Due to the rather small contralateral DPOAE suppression and ipsilateral DPOAE adaptation effects observed in humans, the clinical applicability of DPOAEs for investigating the function of the MOC efferents seems to be restricted. Maison and Liberman (2000) paved the way for getting higher DPOAE adaptation effects. They showed that in guinea pigs at particular $L_2|L_1$ level combinations, predominantly in notched regions of DPOAE I/O functions, a small shift in primary tone level could yield a large bipolar change in adaptation magnitude, typically progressing from an increasing (i.e., enhancement) to a decreasing (i.e., suppression) post-onset time course. The difference between maximum suppression and maximum enhancement amounted up to 30 dB. Kujawa and Liberman (2001) confirmed the above results and showed that after section of the MOCB, large

DPOAE adaptation magnitudes as well as notches in DPOAE I/O functions disappeared. Until now, bipolar changes of that amount have not been found in humans even though in some studies DPOAE adaptation behavior was examined when changing primary tone levels within a wide range (Kim *et al.*, 2001; Meinke *et al.*, 2005). When applying both ipsilateral DPOAE adaptation and contralateral DPOAE suppression in the same sample of guinea-pigs, it could be shown that both measures, although they were different in magnitude, exhibited similar properties in frequency and level dependence (Kujawa and Liberman, 2001). The usability of ipsilateral DPOAE adaptation or contralateral DPOAE suppression in humans in a clinical context was examined in this work and is described in Chapter 6. Possible future applications, which may include a determination of cochlear vulnerability (Maison and Liberman, 2000) or a detection of neural disorders (James *et al.*, 2002), were investigated in this work when studying noise-induced hearing loss (see Chapter 7) and age-related changes in hearing (see Chapter 8).

Furthermore, there is some evidence that DPOAE I/O functions and loudness I/O functions may show some common characteristics. The basis for this assumption is that the perception of loudness is supposed to be proportional to the effective stimulation of IHCs and with that to the amplitude of basilar membrane deflection (Steinberg and Gardner, 1937; Schlauch *et al.*, 1998) which by itself is influenced by the amplification of OHCs. Since the nonlinear activity of OHCs is supposed to be the reason for the existence of otoacoustic emissions, there seems to be a common basis for DPOAEs and loudness. However, loudness perception is also dependent on the operational status of IHCs and neural processing, which cannot be identified by means of DPOAEs. Thus, congruent behavior can only be expected for normal hearing subjects and subjects with OHC-related cochlear hearing loss. Since a singular lesion of OHCs is rare, although mostly predominant, only an approximation of the loudness function by the DPOAE I/O function can be expected. Neely *et al.* (2003) showed for normal hearing subjects a correlation between the slope of DPOAE I/O functions and the slope of loudness functions derived from Fletcher and Munson (1933). This was true, however, only for averaged data. The individual variability of compression was found to be rather large. Further investigations of the author are presented in Chapter 4 where the usability of DPOAEs as a means of fitting hearing aids is examined.

3 Instrumentation and methods

3.1 Hardware

In the following, the basic hardware components of the measurement system, which was applied for pure-tone threshold, categorical loudness scaling (CLS), and DPOAE measurements, shall be presented. An overview of the principle components of the applied measurement system can be seen in Fig. 3.1.

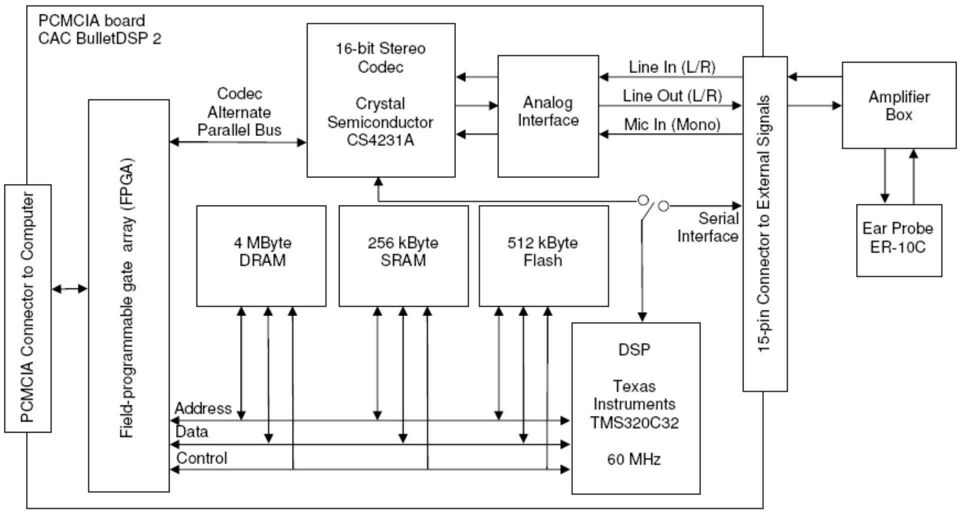

Figure 3.1: Overview of the measurement system and its basic hardware components

The main hardware components shall be outlined in the following. These include a digital signal processor (DSP) for basic signal pre-processing (see Sec. 3.2), an audio codec for digital/analog (D/A) conversion of the stimulus signals and analog/digital (A/D) conversion of the microphone signal, an amplifier box, and an ear probe. All hardware components are commercially available and are part of a commercial DPOAE measurement system (Starkey DP2000).

The DSP and the codec are on-board components of a PCMCIA board (Communication Automation Corporation BulletDSP 2) that can be connected to a laptop, which is responsible for the flow control (see Sec. 3.3). The PCMCIA board provides on-board periphery. This includes a 24-bit address register, a 32-bit data register, a 16-bit control register, and different memory sections, i.e. volatile cache (SRAM: 256 kByte) and working memory (DRAM: 4 MByte), and non-volatile memory for storing firmware (Flash memory: 512

kByte). A field programmable gate array controls the communications between each of the elements of the board. For further information, please have a look at the user manual (Communication Automation Corporation, 1997).

The on-board DSP, a Texas Instruments TMS320C32-60, is a 32-bit floating-point signal processor. Operating on a clock frequency of 60 MHz, the DSP can execute 30 million instructions per second (MIPS). Since the arithmetic logic unit (ALU) and the multiplier may execute in parallel in a single instruction cycle, the DSP is rated at 60 million floating-point operations per second (MFLOPS) peak. Furthermore, the DSP provides 2 MByte of on-chip RAM and two direct memory access (DMA) co-processors. The external memory interface provides access to data and program code with a 24-bit address bus and a 32-bit data bus. The serial port is used to connect the DSP to the audio codec. Further information about the DSP is provided in the data sheet (Texas Instruments, 1996).

The audio subsystem consists of a Crystal Semiconductor CS4231A audio codec, which provides stereo line-level inputs and outputs and a mono microphone level input. The digital interfaces of left and right channels are multiplexed into a single serial data bus. The codec is full duplex and features programmable sampling rate (5.51 to 48 kHz), input gain (0 to +22.5 dB), and output attenuation (0 to −94.5 dB). The A/D and D/A converters use delta-sigma modulation with 64-fold over-sampling and linear 16-bit quantization. Moreover, the audio inputs include on-chip anti-aliasing filters, whereas the audio outputs include on-chip reconstruction filters for smoothing the analog output signal. The total dynamic range (TDR), which describes the ratio of the power of a full-scale signal to that of the lowest obtainable noise floor at full attenuation, amounted to 93 dB. In comparison, the maximum achievable dynamic range due to the applied 16-bit quantization would amount to 96 dB. The total harmonic distortion (THD), which defines the ratio of the sum of the powers of the first five harmonic components of the signal to the power of its fundamental, was specified to be below 0.2 %. Further information about the codec can be derived from the data sheet (Crystal Semiconductor, 1994).

The amplifier box is part of the Starkey DPOAE measurement system and was developed by Mimosa Acoustics. It can be directly connected to the 15-pin PCMCIA board output. The amplifier box includes a microphone preamplifier and equalization section which provides a rather constant microphone output across frequency. Since the box includes a microphone preamplifier, the line level inputs of the codec were used. Also, the loudspeaker output is smoothed by a low-pass filter. For loudness measurements an additional commercial audio power amplifier box based on a Toshiba TA8217P (see Toshiba, 2002) was cascaded to the Mimosa amplifier box. This was done since the maximum output sound pressure level, when using the Mimosa amplifier box alone, amounted to only about 70 to 85 dB SPL depending on frequency. This was considered to be too low for CLS measurements. THD amounted to 0.2 % for the Mimosa amplifier alone, and increased to 0.8 % when including the cascaded additional amplifier (see Müller, 2002).

The recording of DPOAEs requires the use of a highly sensitive low-noise microphone and loudspeakers need to exhibit a low distortion factor to minimize technical distortion. For DPOAE recording, separate loudspeakers are commonly used for each primary tone in

Figure 3.2: DPOAE ear probe (Etymotic ER-10C)

order to exclude technically generated distortion components. Both the microphone and the loudspeakers of the ear probe need to be miniaturized so that the ear probe is small enough (especially in newborns) to be placed inside the ear canal. Thus, a specialized DPOAE ear probe (Etymotic Research ER-10C), which accounted for the above aspects, was used (see Fig. 3.2). The microphone noise is rated at −17 dB SPL at 1 kHz. The ear probe can be used with replaceable foam ear tips of different sizes to fit ear canal dimensions from newborns to adults. The ear probe cable is extremely soft in order to absorb mechanically induced sounds.

Contralateral acoustic stimuli were generated via a standard computer soundcard. For application of the contralateral acoustic stimulus, a Fischer-Zoth FZ-PRC1 ear probe with only one loudspeaker and no microphone channel was used.

3.2 Firmware

The firmware was custom-made to fit the requirements for the implementation of the different measurement techniques applied in the studies presented in Chapters 4 to 8. The main specified sound processing features included:

- output of one or more simultaneous stationary stimulus signals with their separation on the two line output channels
- averaging of the microphone response signal in a sum buffer, or alternatively
- continuous recording of the microphone response signal in a buffer without averaging
- discarding a certain number of initial recording buffers when averaging in a sum buffer in order to avoid adaptation effects when intending to measure the steady-state DPOAE amplitude

The main adjustable parameters were sample rate (5.51 to 48 kHz), output attenuation (0 to −94.5 dB in steps of 1.5 dB), input gain (0 to +22.5 dB in steps of 1.5 dB), duration of the stimulus (up to 20 s), and the number of discarded input buffers.

The firmware of the DSP communicated with the host application, which was realized as a MATLAB-specific (Mathworks) dynamically linked library (DLL). This allows calling the host application functions from MATLAB-based software (see Sec. 3.3). Calls of host application functions trigger the call of particular DSP routines. All hardware-specific functions were written in the programming language C.

The BulletDSP board is distributed with an application programming interface (API) package, which contains device drivers, host and DSP libraries, diagnostics and utility programs and which makes it unnecessary for the user to program communications with the board at the register level. C-callable functions are provided to initialize and reset the DSP, download and start DSP programs, transfer data between the host and the DSP, and control the operation of the card. The DSP library contains functions to initialize and control the codec (see Communication Automation Corporation, 1997).

The written host application provided MATLAB-callable functions to initialize the DSP and to download and start the DSP program, to set codec parameters (i.e., sample rate, left and right output attenuation, left input gain), and to record either averaged or continuous microphone responses. Output parameters handed over to the DSP included one buffer for each of the two output channels, the number of repetitions of the stimulus buffers, the number of discarded response buffers, and optionally a normalized fade in/out envelope for multiplication with the stimulus signal at the start/end of the signal. For stimulus generation, only stationary signals were used, since the stimulus buffers were downloaded to the DSP just once with the buffers being repeatedly shifted via DMA to the codec without reloading. Since stimulus buffers were repeated continuously, they had to contain signals with an integer multiple of their cycle time being equal to the duration of the stimulus buffer. Thus, only a number of discrete frequencies were producible.

The written DSP application was confined to some very basic operations, which mainly included storage management of incoming microphone data. Further sound processing, such as execution of fast Fourier transformation (FFT) and artifact handling, was implemented in MATLAB software (see Sec. 3.3). The DSP routine initialized the codec, and activated and deactivated DMA operation for shifting out the stimulus buffers and reading in the response buffers. The response buffers were then either added up in a sum buffer or continuously stored in a circular buffer, which was able to hold four response buffers at a time. The sum buffer was uploaded by the host application as soon as the DSP flagged that the designated number of response buffers had been read. In contrast, the circular buffer was continuously uploaded by the host application and was read into a response buffer that was big enough to keep the entire time response. If one of the four buffers, which comprised the circular buffer, was filled with new data, the DSP indicated this by an interrupt to the host application, which thereupon uploaded the particular buffer and appended it to the current response buffer. In the meantime, data from the codec was transferred by the DMA into the next circular buffer element. This procedure was repeated until the designated number of response buffers had been read and the calling DSP program failed to maintain the global variables (buffer pointers and size variables) that were driving the DMA operation. As soon as the end of the recording procedure was signaled by the DSP, the response buffer was handed over by the host application to the MATLAB software environment. For stimulus output, a single zero buffer was shifted out prior to each stimulus buffer in order to make sure that the codec had reached a steady state after setting codec parameters.

3.3 Software

The controlling software for pure-tone threshold, CLS, and DPOAE measurements was custom-made using MATLAB. The main features shall be explained in the following. Measurement software was developed with respect to offer automated measuring procedures, which is an important aspect for guaranteeing test consistency and for simplifying the usability of the measurement system for non-specialist operators.

The graphical user interface (GUI) included some general sections, which comprised input options for personal data such as name, first name, birthday, gender, and measured ear. Also, audiometric pure-tone hearing thresholds, derived from a clinical audiometer, could be entered and served as a reference to the measured data. Options to choose between different calibration methods (see Sec. 3.4) and their parameterization were available. In the following subsections, the measurement-specific parameterization options and the respective GUIs are presented.

3.3.1 Hearing threshold determination

For determining pure-tone hearing thresholds via ear probe, a staircase method (see Sec. 2.3.1) was implemented similarly to the method used by Boege and Janssen (2002). The subjects were instructed to press or release a mouse button as long as a hearing sensation was present or not, respectively. The sound pressure level of the stimulus was computer-controlled dependent on the input of the subject, i.e. the sound pressure level decreased as long as the stimulus was rated "audible" and increased as long as the stimulus was rated "inaudible". Stimulus sound pressure levels were limited to 80 dB SPL for safety reasons. Stimuli were presented as a pulsed pure-tone sequence. The GUI (see Fig. 3.3) offered several parameter sections.

The 'DSP Parameters' section provided input options for basic stimulus parameters, i.e. sample rate (5.51 to 48 kHz) and stimulus buffer size (1024, 2048, 4096, or 8192). The setting of these two parameters determined the frequency (Δf) and time resolution (Δt) of the stimulus. These values were related to the sample rate f_s and buffer size N_{buffer} as given in Eq. 3.1.

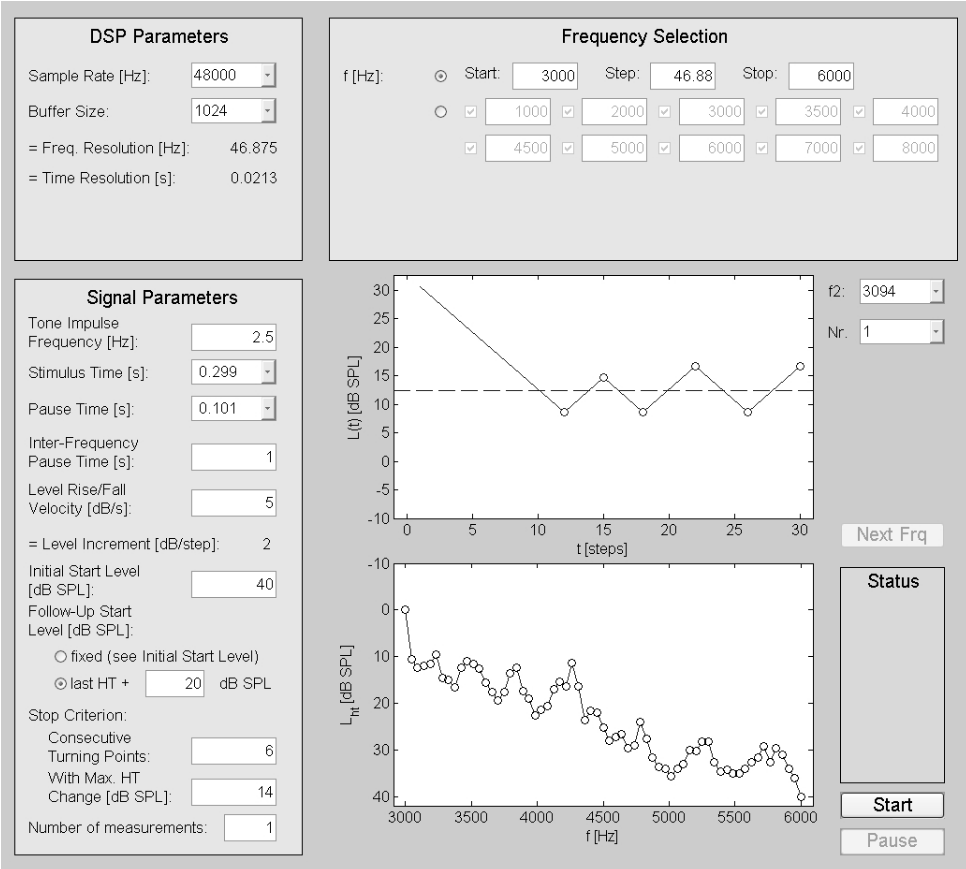

Figure 3.3: Pure-tone threshold measurement GUI and case example

$$\Delta f = \frac{1}{\Delta t} = \frac{f_s}{N_{buffer}} \tag{3.1}$$

The sample rate was set to 48 kHz and the buffer size to 1024 samples. This resulted in a frequency resolution of 47 Hz, being small enough for recording pure-tone threshold fine structure and in a time resolution of 21 ms, being small enough for pulsed stimulus output.

The 'Signal Parameters' section offered parameters to control the stimulus sequence and stop criteria. Stimulus sequence parameters included input options for tone impulse frequency, which controlled the repetition rate of the pure tone, and for stimulus and pause time, which determined the stimulus-to-pause ratio for a given tone impulse frequency and time resolution. The inter-frequency pause time determined the pause time when proceeding in the measurement sequence to the next test frequency. The level rise/fall velocity specified the level increment or decrement per second. Also, the initial (i.e., for the first test frequency) and follow-up (i.e., for all following test frequencies) start level could be set. The follow-up start level could be fixed or adaptive, i.e. dependent on the pure-tone threshold level determined at the previous test frequency. For the adaptive method, an offset to the previous pure-tone threshold level could be set. The stop criteria included two parameters, the number of consecutive valid turning points (i.e., reversals from audible to inaudible or vice versa) and the maximum change in sound pressure level between two consecutive turning points, which defined these turning points as valid. Moreover, the number of measurements (i.e., repetitions) for a fixed parameter setting could be selected.

The 'Frequency Selection' unit allowed for input of the test frequencies in two basic ways. First, test frequencies could be selected by choosing a start and stop frequency together with a step size. This method was thought for pure-tone threshold fine structure measurements with constant step size. Second, up to ten test frequencies could be selected manually. This method was thought for pure-tone threshold measurements with unequally spaced test frequencies, e.g. at standard audiometric test frequencies (0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz).

The typical stimulus parameter setting and a measurement example can be seen in Fig. 3.3. The graphical representation of the measurement data shows both the stimulus level time course due to the response of the subject at a single selectable test frequency (top) and the determined pure-tone thresholds in dB SPL across all test frequencies (bottom). The dashed line in the top plot shows the determined pure-tone threshold for the given stimulus level time course. It was calculated as the average across the sound pressure levels at all of the valid consecutive turning points, i.e. in this case across the last six turning points. The number of valid consecutive turning points had to be an even number to balance reversals from audible to inaudible and vice versa. During the measurement the status box in the bottom right corner showed the operator information about the current stimulus frequency and sound pressure level setting. With the 'Next Frequency' pushbutton, a measurement at a specific test frequency could be stopped and the measurement continued with the next test frequency. However, this option was only used when a subject was not able to respond properly, e.g., due to a hearing loss exceeding the sound pressure level limit. Moreover, start, pause, and stop buttons allowed for control of the measurement procedure. The stop button is not visible in Fig. 3.3 since the start button was relabeled as stop button after the measurement was started.

3.3.2 Categorical loudness scaling (CLS)

For measuring loudness perception via ear probe, a CLS measurement procedure (see Sec. 2.3.2) was implemented as part of the author's diploma thesis (Müller, 2002). CLS was chosen due to its clinical significance in hearing aid fitting. The GUI offered several parameterization options and is shown in Fig. 3.4. Fixed parameters, which were not directly accessible in the GUI were the sample rate and the buffer size, which were set in a configuration file to 48 kHz and 1024 samples, respectively.

The 'Frequency Selection' unit allowed for selection of up to three test frequencies. The frequency presentation strategy could be set to sequential (i.e., measurement at one test frequency is finished before starting the next) or mixed (i.e., randomly changing mea-

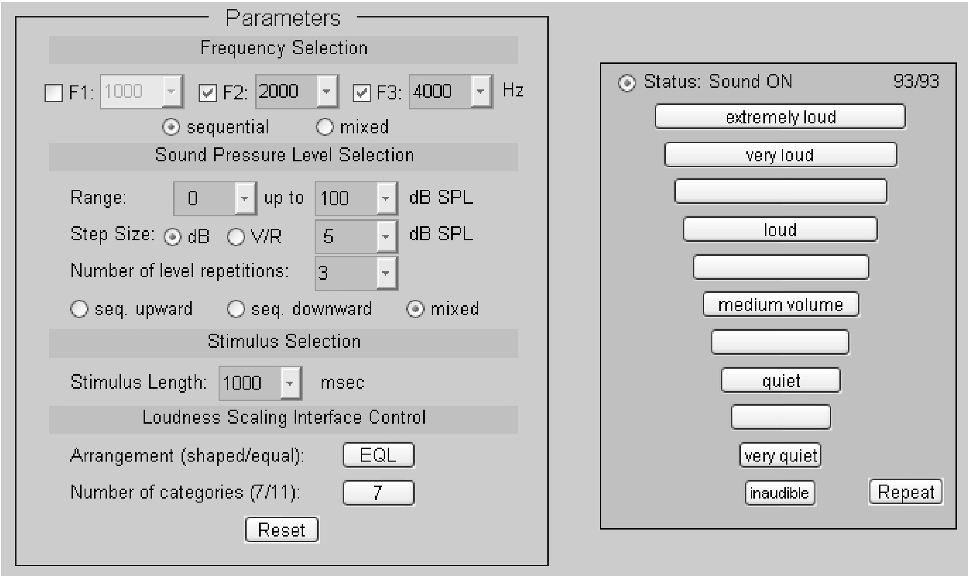

Figure 3.4: CLS measurement GUI

surement of several test frequencies). Parameters related to sound pressure level could be adjusted in the 'Sound Pressure Level Selection' unit. The available parameters included the sound pressure level range, step size, number of level repetitions, and the presentation strategy. The step size could be either selected in dB or as values per range (V/R), i.e. the available level range was divided up into a number of equidistant sound pressure levels (e.g., number of categories). The level presentation strategy could be set to sequential upward or downward, or mixed. The stimulus duration could be set in the 'Stimulus Selection' unit. The applied stimulus parameter setting can be seen in Fig. 3.4.

The 'Loudness Scaling Interface Control' section allowed for a change in the graphic representation of the subject response input interface. It allowed switching between a graphically scaled (triangular shape as plotted in Fig. 3.4) or unscaled (each scale is represented by a pushbutton with equal width) input interface. Also the number of categories could be set to seven (only the labeled categories) or eleven (see Fig. 3.4). The input interface contained beside the category pushbuttons for evaluating the perceived loudness, a repeat pushbutton for repeating the last signal, and a status box, which signaled if a sound was present or not, and showed the remaining number of loudness evaluations. The subjects were instructed to make, as far as possible, spontaneous evaluations and to make use of the repeat button only in an exceptional case. For further analysis, loudness categories were assigned to numbers from 0 (="inaudible") to 50 (="extremely loud") in steps of 5 (see Sec. 2.3.2).

3.3.3 Distortion product otoacoustic emissions (DPOAEs)

For recording DPOAEs (see Sec. 2.5), a DPOAE measurement module was implemented. It included the measurement and graphical representation of DPOAE grams, DPOAE

I/O functions, extrapolated DPOAE thresholds, ipsilateral DPOAE adaptation, and contralateral DPOAE suppression (see Fig. 2.15). For all data, both DPOAE level and phase could be analyzed and plotted. The GUI offered several parameter sections in order to control stimulus and response parameters and is shown in Fig. 3.5.

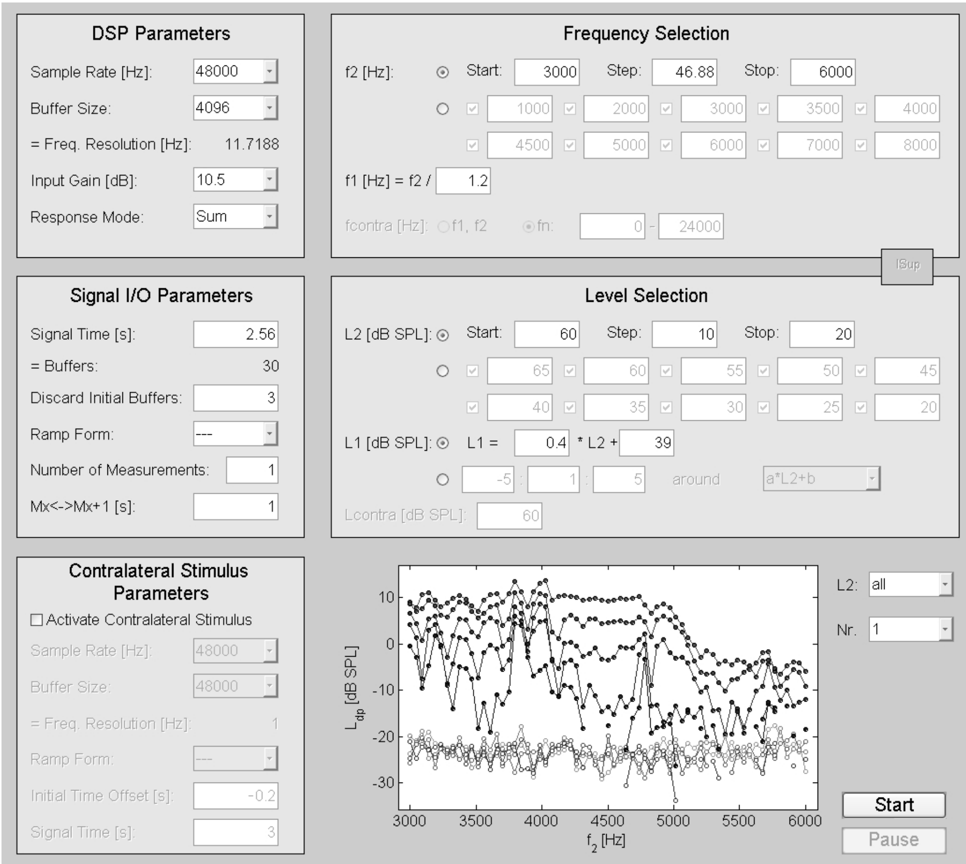

Figure 3.5: DPOAE measurement GUI and case example of DPOAE fine structure measurement

The 'DSP Parameters' section included the sample rate (5.51 to 48 kHz) and the stimulus/response buffer size (1024, 2048, 4096, or 8192), which were by default set to 48 kHz and 4096 samples, respectively. This setting yields a frequency resolution of 11.7 Hz. Additional DSP response parameters were the input gain (0 to +22.5 dB) and the response mode. The input gain was constantly set to +10.5 dB, whereas the response mode allowed for a selection between buffer averaging ('sum' mode) and continuous recording ('stream' mode). The latter was, however, only used for DPOAE adaptation measurements. The 'Signal I/O Parameters' section offered several basic options concerning stimulus and response parameters. The signal time determined the duration of the stimulus and was restricted to a maximum of 20 s (i.e., $20s \cdot 48000Hz \cdot 32bit = 3.7MByte$) since working memory was limited to 4 MByte (see Sec. 3.1). In 'sum' mode, the signal time also defined the number of averaged response buffers. Signal averaging yields a suppression of additive noise, since noise as a stochastic signal is canceled partly due to the averaging process whereas the approximately deterministic DPOAE signal is not canceled. Theoretically, averaging across a number of n buffers reduces the signal-to-noise ratio (SNR) by the factor $\sqrt{n}$. Furthermore, the number of discarded initial response buffers could be defined. This parameter was necessary in order to exclude the initial time span in which a rapid adaptation effect yields a change in DPOAE amplitude until steady state is reached after about 100 ms (see Sec. 2.5.3). By default, three buffers (equivalent to 256 ms) were discarded. The optional parameter 'Ramp Form' determined the fade in/out shape of the signal. The number of measurements (i.e., repetitions) for a particular measurement setting could be adjusted (e.g., for reproducibility tests) as well as the pause time between two measurement settings.

Primary tone frequency f_2 and level L_2 could be set either in 'start, step, stop' mode, or by manually entering up to ten values. The primary tone frequency ratio was by default set to 1.2. L_1 could be adjusted by the linear function $L_1 = aL_2 + b$, which was consistently parameterized with $a = 0.4$ and $b = 39$ (see Sec. 2.5.2). L_1 could also be changed for a fixed L_2 around a center level, which was set according to the equation above. This parameter option was implemented to record DPOAEs within a wide matrix of primary tone level combinations $L_2|L_1$.

The contralateral acoustic stimulation (CAS) mode could be switched on or off. In CAS mode, primary tone stimuli were generated first in the absence and then in the presence of CAS. The sample rate and the buffer size for CAS generation were constantly set to 48 kHz and 48000 samples. The initial time offset defined the offset of the CAS to the start of the ipsilateral stimuli (i.e., negative values indicated that CAS started prior to the ipsilateral stimuli), whereas the signal time defined CAS duration. Furthermore, the frequency composition of CAS could be switched between ipsilateral primary tone frequencies (f_1, f_2) and broad band noise, which was the default option. The CAS sound pressure level for broad band noise was constantly set to 60 dB SPL.

Some further parameters could be set in the menu bar. An important parameter section included measurement interrupt handling, which defined measurement conditions that marked a response as invalid. If one or more of the selected and parameterized conditions occurred, the measurement procedure was interrupted. The valid options included:

- minimum SNR value
- maximum deviation from a reference table of noise floor levels determined in a sound-proof cabin
- maximum increase in noise floor level between two successive measurement points
- check for technically distorted signals, defined as signals which included at least 6 out of 10 distortion products with an SNR of more than a user-defined value
- check for clipped signals.

The operation (i.e., either repeat or continue measurement), which should be executed at such an interrupt, could be selected either due to manual decision by the user or due to automatic processing. Moreover, cumulative measurements could be conducted, i.e. if a response exhibited a low SNR (i.e., below a user-defined minimum), another response with the same stimulus setting was added to the first response and the overall response was then analyzed. This allowed shorter measurement times for high-level emissions, whereas measurement time was increased for low-level emissions.

A typical stimulus parameter setting and a measurement example of DPOAE fine structure is shown in Fig. 3.5. The graphical representation shows the DPOAE level L_{dp} plotted above frequency f_2 with the stimulus level as additional parameter. The bottom lines represent the noise floor level L_{nf}. The noise floor was calculated as the average across noise levels at six frequencies adjacent to the DPOAE frequency f_{dp} (i.e., $f_{dp} \pm \Delta f$, $\pm 3\Delta f$, and $\pm 5\Delta f$). The spectrum could be shown when clicking on the particular measurement point in the plot (see Fig. 3.6). During the measurement, a status box showed measurement information about the current stimulus frequency and level setting. Start, pause, and stop buttons allowed for control of the measurement procedure. Other graphic renditions, beside the DPOAE gram plot, included the DPOAE I/O function, the three-dimensional DPOAE plot (for L_2,L_1 matrix), and the DPOAE envelope time course. Further evaluation features include for DPOAE I/O function analysis, the implementation of DPOAE threshold estimation by means of linear regression (Boege and Janssen, 2002) and for DPOAE time course analysis, the implementation of a one- or two-exponential nonlinear simplex fitting procedure, which allows for obtaining the least-squared difference between the DPOAE envelope level and the fitting function (Kim *et al.*, 2001).

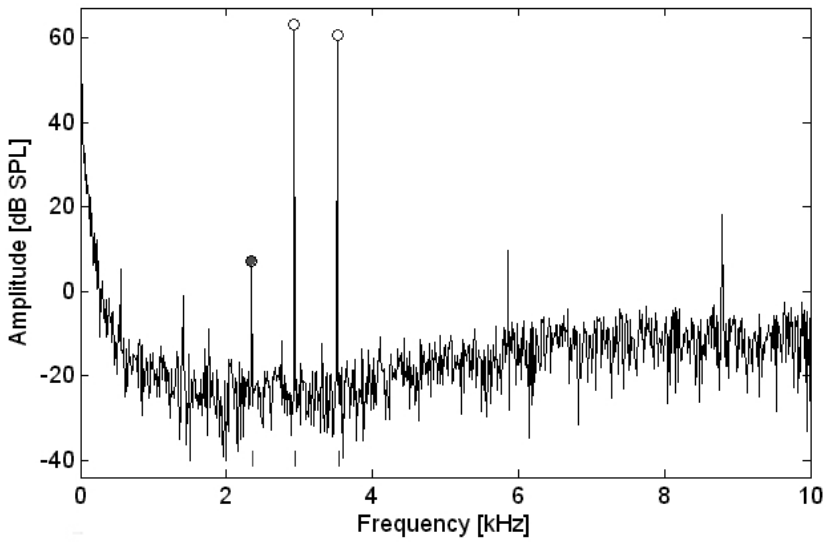

Figure 3.6: Typical spectrum of a DPOAE response

For analyzing steady-state DPOAE amplitudes, the spectrum (see Fig. 3.6) was calculated from the averaged time-domain response signal by means of FFT. This allowed for automatic evaluation of the microphone response signals. The two vertical lines with the open circles represent the two primary tone levels (left: L_1, right: L_2), the vertical line with the filled circle represents the DPOAE level L_{dp}. The noise floor L_{nf} is represented by the lines adjacent to the DPOAE frequency and amounted in this case example to about -24 dB SPL.

For analyzing the DPOAE time course (see Fig. 3.7), an envelope detection method was implemented (see Kim *et al.*, 2001). First, the FFT was performed on the complete pressure waveform. A band of frequencies surrounding the DPOAE frequency was selected. These frequency components were shifted down in such a way that the DPOAE frequency was positioned at the zero frequency. A low-pass filter extending around the zero frequency was applied to the shifted spectrum. The shape (e.g., Blackman type) and the cutoff frequency of the filter could be selected. Then the negative frequencies were cut off and an inverse FFT was performed on the remaining spectral components. This resulted in a complex-valued signal spanning the duration of the original waveform. The level-versus-time function corresponded to the temporal envelope of the DPOAE component.

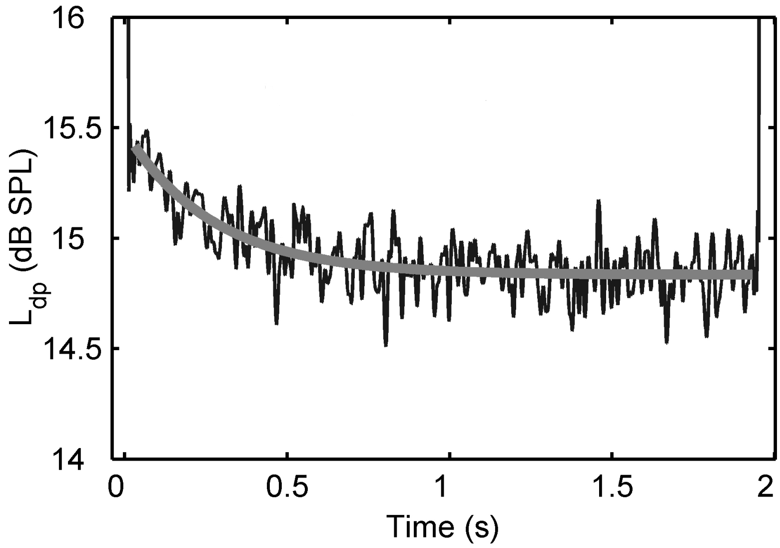

Figure 3.7: Typical DPOAE envelope time course with one-exponential fitting function

3.4 Stimulus calibration

The aim of stimulus calibration is to apply defined sound pressure levels at the adequate place of stimulation. This is a crucial prerequisite to relate the response to the applied stimulus to a definable physical measure. For audiometric measurements, a defined sound pressure level at the ear drum should be applied. However, there is no simple relationship between voltage at the ear probe loudspeaker and sound pressure level at the ear drum due to the load-dependent frequency response of the loudspeaker, which is dependent on inter-individual varying ear drum impedance and ear canal geometry (Hudde, 1983).

Psychoacoustic measurements, such as the determination of pure-tone hearing thresholds or loudness perception, are therefore normally conducted by using headphones since their calibration is relatively simple due to their rather load-independent frequency response, which yields rather constant stimulus levels across subjects. This is important to ensure proper data interpretation and comparability. In the present work, standard pure-tone audiometry was also conducted by using headphones and hence served as a reference measurement. However, pure-tone threshold and CLS measurements were additionally accomplished by using an ear probe loudspeaker in order to improve the comparability to DPOAE measurements which needed to be performed by using ear probe loudspeakers and microphone. In literature, there are several methods suggested to calibrate stimuli when applied via ear probe. Two calibration methods, which were implemented in the measurement system, shall be explained in the following.

The most commonly used calibration method is the in-the-ear adjustment strategy, which is based on the measurement of the sound pressure level at the ear probe microphone for a constant voltage at the loudspeaker (Whitehead *et al.*, 1995c). However, the ear probe microphone is located in the outer ear canal, while the relevant magnitude for the quantification of stimulus levels is the sound pressure level at the ear drum. Thus, dependent on ear canal length and middle-ear impedance, there is a frequency-dependent deviance of unknown quantity between the nominal sound pressure level at the tip of the ear probe and the actual sound-pressure level at the eardrum due to standing wave effects (Siegel, 1994), which yield place-fixed nodes and antinodes in the waveform due to interference of the primary stimulus wave with its reflection from the ear drum.

The standing wave effect is illustrated in Fig. 3.8 for the case of a reverberant termination, which is characterized by a 100 % reflection and a phase shift of 0^o. Largest differences between the amplitude at the reverberant termination and the microphone occur with the microphone located at the place of wave nodes. This is the case at frequencies f_n, which exhibit wave lengths λ_n that are related to the distance between the microphone and the tympanum l_{MT} as shown in Eq. 3.2.

$$\lambda_n = \frac{4l_{MT}}{2n+1}, f_n = \frac{(2n+1)c}{4l_{MT}}, n = 0,\, 1,\, 2, \ldots \infty \tag{3.2}$$

This formula only holds for reverberant termination, which is not quite true for the real ear drum, which shows an inter-individually varying and frequency-dependent reflection amplitude and phase (Stinson *et al.*, 1982). Since the ear drum is not completely reverberant there is also the opposite effect of a larger sound pressure level at the microphone compared to that at the ear drum. The deviation between sound pressure level at the microphone and sound pressure level at the ear drum is usually largest around frequencies corresponding to $l_{MT} = \frac{\lambda}{4}$ and $\frac{\lambda}{2}$ and can amount up to 20 dB (Siegel, 1994). Thus, problems become serious around 3 to 4 kHz and above 6 kHz in adults (e.g., $l_{MT} = 20$ mm corresponds with $f_0 = 4150$ Hz), but are less important in newborns and infants due to their smaller ear canal length (Keefe *et al.*, 1993).

Another calibration method is the constant voltage adjustment which is a coupler-based reference calibration strategy. In this method, the loudspeaker is not directly calibrated in the subject's ear but in a reference coupler or ear simulator. The strategy was modified by recording several frequency responses for different ear canal lengths (see Müller *et al.*,

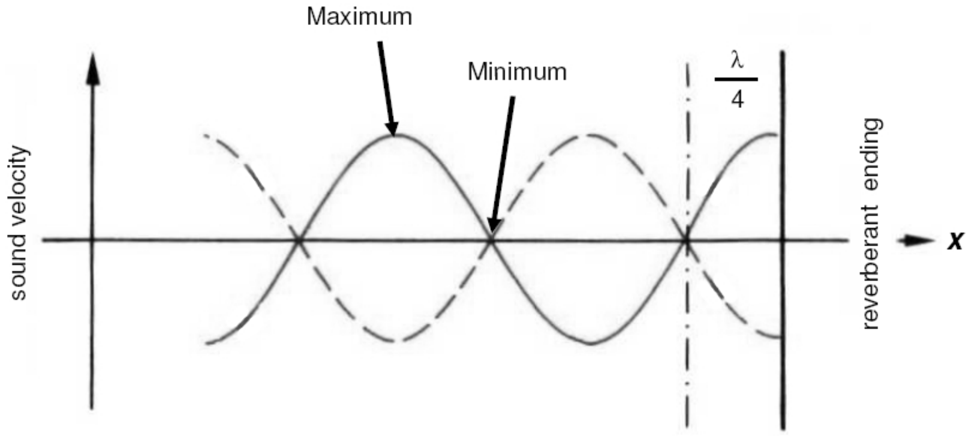

Figure 3.8: Standing wave for a reverberant ending

2004; Oswald, 2005). For a constant loudspeaker voltage, both the sound pressure level at the ear probe microphone and at the microphone of the ear simulator (corresponding to the place of the ear drum) was recorded. In this work, a Brüel&Kjær 4157 ear simulator was used as reference coupler. Eleven sets of paired frequency responses (from ear probe microphone and modeled ear drum position) for distances between ear drum microphone and modeled ear drum from 15 to 45 mm in steps of 3 mm were recorded and saved in a reference data bank. For calibration, the individual frequency response was recorded at the ear probe microphone. Then, the best fitting ear probe frequency response from the reference data bank was chosen by selecting the frequency response with the least distance in a given frequency range. For the selected ear probe frequency response, the associated ear drum frequency response recorded in the ear simulator was used as calibration curve. Additional ear canal volume adjustment was possible by shifting the ear drum frequency response by the level difference between real and reference ear probe frequency response at 1 kHz, a frequency where no major standing wave effect was expected. The advantage of this strategy is that standing wave phenomena do not play a role since the sound pressure level at the ear simulator microphone (= modeled ear drum position) is not subject to the standing wave problem. However, the main remaining error source is the individually varying difference between real ear canal and coupler transfer function, which only models typical ear canal and ear drum parameters. For a more detailed description of this calibration method please refer to Müller (2002), Müller *et al.* (2004), and Oswald (2005).

Despite the known problems, for most of the studies in this work, the in-the-ear calibration method was applied since this calibration method is widely used by other study groups and thus more data is available for comparison to the achieved results. Also, the DPOAE stimulus level paradigm used in this work (see Sec. 2.5.2), was developed and optimized for the in-the-ear calibration method. The quality of the coupler-based reference calibration and the optimization of the stimulus paradigm have not yet been investigated in more detail.

It has to be kept in mind, that the calibration method has a major impact on the stimulus sound pressure level accuracy and thus on the recorded DPOAE response when using ear probes. The primary tone levels L_2 and L_1 may deviate differently from their target level and hence may yield a variation in DPOAE level and with that a variation in the shape and the compression of DPOAE I/O functions (see Müller *et al.*, 2004) complicating inter-individual comparability. Figure 3.9 illustrates the influence of calibration on DPOAE I/O functions. The left panel shows L_{dp} recorded for in-the-ear and coupler-based reference calibration with the same target primary tone levels. It could be observed that in-the-ear calibration yielded higher L_{dp} values, possibly due to higher real primary tone levels. This assumption was supported by the fact that when the I/O function derived with in-the-ear calibration was shifted by 13 dB SPL along the L_2 axis, both I/O functions exhibited a similar course (Fig. 3.9, right panel).

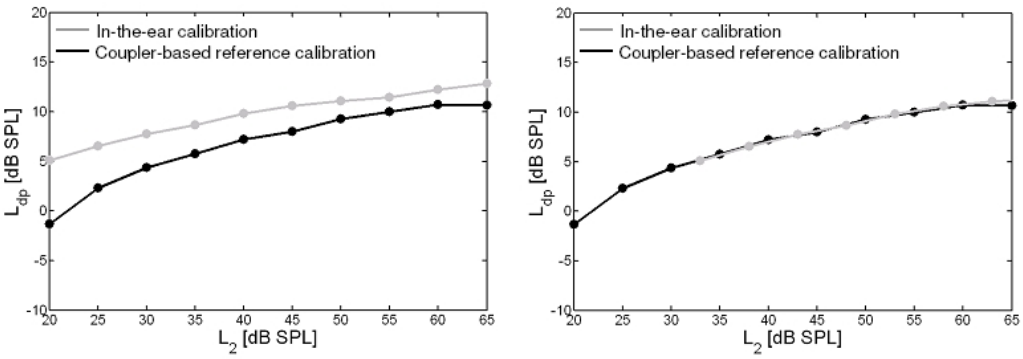

Figure 3.9: Impact of the calibration method on DPOAE I/O functions recorded at 4 kHz in a subject with an estimated ear canal length of about 22 mm. Left panel: original DPOAE I/O functions. Right panel: DPOAE I/O function for in-the-ear calibration shifted 13 dB SPL along the L_2 axis (adopted from Müller *et al.*, 2004)

4 Implications for objective hearing aid fitting by means of DPOAEs

Hearing aids are primarily useful in improving the hearing and speech comprehension of people who suffer from sensorineural hearing loss that results from damage to the outer hair cells (OHCs) of the inner ear. The damage can occur as a result of disease, aging, injury from noise or certain pharmaceuticals (see Sec. 2.2). Retrocochlear or central lesions as well as damage to inner hair cells (IHCs) cannot be compensated by hearing aids. Also, lost discriminatory power, which normally accompanies sensorineural hearing loss, cannot be restored by a hearing aid. A hearing aid magnifies sound vibrations entering the ear. Surviving hair cells detect the larger vibrations and convert them into neural signals that are passed along to the auditory cortex. The greater the damage to a person's OHCs, the more severe the hearing loss, and the greater the hearing aid amplification needed to make up the difference. Modern digital dynamic compression hearing aids are capable of frequency-specific and level-dependent amplification of sound signals. Usually, hearing aid fitting relies on psychoacoustic measurements and is mainly based on categorical loudness scaling (CLS) which is used to determine the subject's loudness growth. This requires the subject's cooperation, which cannot be taken for granted in all subjects. Especially, in newborns or young children a sufficient cooperation cannot be expected. About 1 to 6 out of 1000 newborns are born with a congenital hearing defect (Bachmann and Arvedson, 1998). Since hearing is a vital part for a young child's proper speech, language, and cognitive development, on the one hand an early detection of hearing disorders in newborns is necessary, which can be accomplished by means of universal newborn hearing screening (UNHS) (see also Chapter 5). On the other hand, proper treatment is necessary by hearing aid fitting at an early stage. However, the conventional hearing aid fitting procedures cannot be applied. At the moment, in non-cooperative children, hearing aids are fitted according to normative data. Hence, it is an important task to develop objective hearing aid adjustment methods, which do not rely on the subject's cooperation. This problem was investigated in the following study and a possible approach, which was developed within this study, shall be presented.

An objective and noninvasive measurement procedure giving evidence of the nonlinear cochlear function in humans is the recording of DPOAE I/O functions (see Sec. 2.5), which show compressive behavior for normal hearing subjects and gradually increasing linear behavior as hearing loss increases (e.g., Kummer *et al.*, 1998; Neely *et al.*, 2003). These observations suggest that DPOAEs could be a reliable measure to diagnose dysfunctions of sound processing on the stage of the cochlear amplifier. In comparison, psychoacoustic experiments (e.g., Steinberg and Gardner, 1937; Schlauch *et al.*, 1998) show that loudness behavior bears a good resemblance to basilar membrane characteristics (see Sec. 2.3.2), exhibiting compressive loudness functions for normal hearing subjects and steeper, less compressive loudness functions (i.e., recruitment) for hearing-impaired subjects. Altogether, both DPOAEs and loudness are supposed to be influenced by basilar membrane displacement and thus by OHC functionality and therefore provide an insight into cochlear sound processing in humans. However, any IHC damage or dysfunctions on the neural or central level that have an influence on loudness sensation cannot be recognized with DPOAEs. On account of this, it seems to be reasonable to compare objective DPOAE with subjective loudness measurements in order to examine the possibility of using DPOAE I/O functions as a means of estimating loudness perception in ears with a hearing loss related to OHC damage, which is the most common cause for sensorineural hearing loss. DPOAEs would then offer the potential of basic hearing aid adjustment for non-cooperative patients.

Neely *et al.* (2003) already showed that there is a correlation between DPOAEs and loudness. They compared the Fletcher and Munson (1933) loudness function with DPOAE growth functions both plotted on a logarithmic scale, basically focusing on an absolute comparison of compression in normal-hearing subjects. This study showed that both the Fletcher and Munson loudness function and the averaged DPOAE I/O data in normal hearing subjects could be described by similar logarithmic functions resulting in equal compression. They concluded that this suggests that the same source of nonlinearity determines the growth of both I/O functions. Also DPOAE I/O functions of hearing-impaired subjects were recorded to show that the slope of DPOAE growth functions gradually increased with advancing hearing loss. However, inter-individual variability was reported to be quite high. Consequently, Neely *et al.* stated that individual predictions of loudness might be difficult. A previous work of Müller (2002) investigated the clinical applicability of different loudness measurement techniques. CLS measurements were found to be best suited for determining loudness perception. Moreover, DPOAE and CLS I/O functions were compared in a group of normal hearing subjects. The data from the normal hearing subjects served as a basis for the following study, which, however, extended the work of Müller (2002) and Neely *et al.* (2003) by measuring and comparing both CLS and DPOAE I/O functions in a subject sample of cochlear hearing loss patients and by using the same measurement system and ear probe. The main purpose of the following study was to examine the relation between DPOAE and loudness and hence to investigate the feasibility of using DPOAE I/O functions as a means of fundamental objective hearing aid adjustment in cochlear hearing loss patients.

4.1 Material and methods

4.1.1 Subjects

Ten subjects with normal hearing and nine patients suffering from moderate hearing loss participated in the present study. Data was collected only from one ear per subject.

The normal hearing subjects (7 male, 3 female) were aged between 25 and 30 years. Measurements were conducted at 2, 3, 3.5 and 4 kHz. According to clinical audiometry their hearing loss was 15 dB HL or lower in the examined frequency range. Hearing loss at 3.5 kHz was derived from interpolation between 3 and 4 kHz since it is not an audiometer frequency. The patients (6 male, 3 female) were aged between 14 and 67 years and were examined at minimum one of the test frequencies used with normal hearing subjects, depending on the possibility to get suitable DPOAE I/O functions. Hearing losses ranged from 20 to 45 dB HL, exclusively regarding the hearing loss at the individual frequencies which were used in the measurement procedure on each subject. Hearing loss was presumably due to cochlear defect considering clinical history, tympanometry, and auditory brainstem response measurements, which excluded middle ear and retrocochlear disorders.

4.1.2 Stimulus generation

DPOAE and CLS measurements were conducted with the same hardware and sound probe (see Sec. 3.1) using custom-made software (see Sec. 3.3). For CLS measurements, an additional customized amplifier was used to generate high-level sine signals of up to 100 dB SPL. Signal levels were adjusted according to a modified coupler-based reference calibration strategy with ear canal volume adjustment at 1 kHz. The reference curves were recorded for a fixed distance from ear probe microphone to ear simulator microphone of 25 mm. The coupler-based reference calibration was used in this study since it was expected to result in smaller inter-individual variability in the measurement frequency range compared to in-the ear calibration (see Sec. 3.4).

4.1.3 DPOAE measurement procedure

L_2 was set to a maximum of 65 dB SPL and was decreased in steps of 5 dB to a minimum of 20 dB SPL. L_1 was set according to the equation $L_1 = 0.4L_2 + 39$ dB SPL. The averaging time for recording DPOAEs was 4 s. DPOAEs were accepted as valid for an SNR exceeding 6 dB. If a DPOAE value failed to fulfill this criterion, the measurement of this point in the DPOAE I/O function was repeated up to three times. Each measurement of a complete DPOAE I/O function for a specific frequency was repeated twice (for three patients with qualitatively good DPOAE I/O functions the measurement was just conducted once) in order to get both general information about repeatability and to increase certainty in the decision to erase outliers or inconsistent data. Outliers were defined as (*i*) data that were at least 10 dB above the adjoining lower and upper DPOAE levels or (*ii*) data that occurred below L_2 levels at which no valid data could have been measured. Inconsistent data were defined either as (*i*) data that led to a local negative slope of the DPOAE I/O function in the upper L_2 region or (*ii*) data that resulted in a relative local increase of slope in the lower L_2 region and which often ran parallel to the course of the noise floor. All in all, in the normal hearing group 46 values (i.e., 5.8 %) and in the hearing-impaired group 40 values (i.e., 17.4 %) were excluded from further analysis. The overall measurement duration for all test frequencies amounted to about 5 to 10 minutes.

4.1.4 CLS measurement procedure

For CLS measurement, sine tone signals with a frequency at f_2 were used in order to assure best possible comparability to DPOAE measurements. Before the actual subjective estimation process was started, the individual maximal tolerable level was determined in a pre-measurement orientation phase to ensure that the subject was not exposed to levels that would cause any painful sensation. The lowest level was always set to 0 dB SPL. For the actual CLS measurement procedure all stimulus levels from 0 dB SPL in steps of 5 dB to maximum 100 dB SPL were presented three times in random order. The length of the stimulus was 1 s. Frequencies were tested successively. The response scale consisted of 11 graphically scaled response alternatives, partly titled with common language expressions for loudness (see Sec. 3.3.2). Subjects were instructed to evaluate the presented signals as spontaneously as possible on the given scale and independently of the previously offered signals, merely considering absolute loudness sensation. Data were analyzed and outliers removed. Outliers were defined as (*i*) data that were at a certain stimulus level at least three categories away from the median at that level and at least two categories above/below the maximum/minimum categorical value at the adjoining upper/lower stimulus level and (*ii*) data that were categorized as audible even if there were exclusively "inaudible" estimates at minimum two higher stimulus levels. Altogether, in the normal hearing group 6 values (i.e., 0.2 %) and in the group of hearing-impaired subjects 7 values (i.e., 0.8 %) were discarded. The overall measurement duration for all test frequencies amounted to about 10 minutes.

4.2 Results

Discrete DPOAE and CLS data of all ten normal hearing subjects were averaged separately for each frequency to obtain normative I/O functions. These functions were then used for comparisons to single frequency-specific I/O functions of hearing-impaired subjects. For both DPOAE and CLS data averaging was done throughout for each input level.

4.2.1 Normative data

DPOAE data

Figure 4.1A shows average DPOAE sound pressure levels as a function of L_2 for each test frequency (2, 3, 3.5, 4 kHz) for the normal hearing group. All I/O functions, independent of test frequency, had a similar compressive shape (compression = 1/slope for extrapolated

I/O functions at $L_2 = 65$ dB SPL for 2 kHz: 5.5 dB/dB, 3 kHz: 5.6 dB/dB, 3.5 kHz: 6.1 dB/dB, and 4 kHz: 5.9 dB/dB, mean across all frequencies: 5.8 dB/dB) and were mainly different in respect to absolute DPOAE levels. It is important to note that the shift ΔL_{dp} of a DPOAE I/O function presented in a logarithmic scale (Fig. 4.1A) is, as shown in Eq. 4.1, equivalent to a multiplication with a factor m of the DPOAE I/O function plotted in a linear scale (Fig. 4.1C).

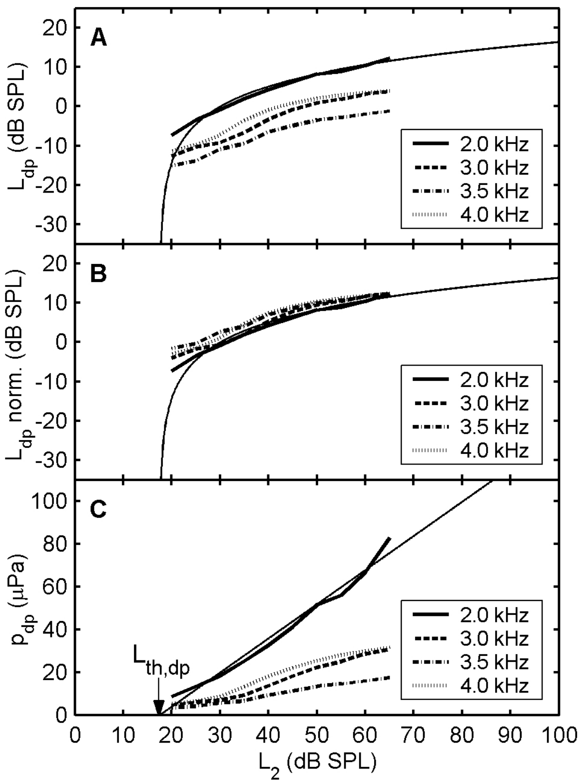

Figure 4.1: DPOAE I/O functions for 2, 3, 3.5, and 4 kHz for the normal hearing group. Panel (A) shows DPOAE data in logarithmic scale, panel (B) normalized DPOAE data in logarithmic scale, and panel (C) DPOAE data in linear scale. $L_{th,dp}$ in panel (C) shows the DPOAE threshold level, which serves as an estimate for hearing threshold. In each panel bold lines represent discrete DPOAE data, whereas the single thin line exemplifies linear DPOAE data extrapolation for 2 kHz.

$$\log(p_{dp} \cdot m) = \log(p_{dp}) + \log(m) = L_{dp} + \Delta L_{dp} \tag{4.1}$$

Thus, the slope of the DPOAE I/O function in a linear plot is highly contingent on the magnitude of the DPOAEs in a logarithmic plot. Since influences on DPOAE magnitude other than OHC damage, e.g., ear canal length, middle ear impedance, individual cochlear conditions, or calibration errors, cannot be excluded, DPOAE data were normalized.

Normalization was executed by setting the maximum value of a DPOAE I/O function, which was located at the maximum stimulus level ($L_2 = 65$ dB SPL), to a defined value, e.g., to the maximum DPOAE level of one of the DPOAE I/O functions used for relative comparison. The result of this procedure applied to the DPOAE I/O functions from Fig. 4.1A is shown in Fig. 4.1B. Please note that all DPOAE I/O functions in logarithmic scale still have the same shape and thus the same compression as in Fig. 4.1A, but now coincide at $L_2 = 65$ dB SPL.

Moreover, linear extrapolation lines were fitted to the discrete mean DPOAE data given in sound pressure p_{dp} (Boege and Janssen, 2002). Examples of extrapolation curves are shown for the 2 kHz test frequency in logarithmic (Figs. 4.1A and 4.1B) as well as in linear (Fig. 4.1C) DPOAE scale. It is important to note that the hearing threshold estimation is independent of normalization, since a multiplication with a constant factor m (see Eq. 4.1) results in a rotation of the linearly scaled DPOAE I/O function around the rotation point at $p_{dp} = 0$ Pa, which remains zero when multiplied with any factor. The standard deviation of the DPOAE level across all individual mean DPOAE I/O functions (inter-individual repeatability) of the normal hearing group was on an average 6.4 dB, but amounted dependent on frequency and level to more than 10 dB. In contrast, the average difference of DPOAE level between two successive measurement runs in one subject (intra-individual repeatability) was only 0.8 dB. The compression at $L_2 = 65$ dB SPL of the individually extrapolated DPOAE I/O function of each normal hearing subject plotted in a logarithmic scale ranged between 3.9 and 8.9 dB/dB and amounted on average to 5.9 ± 1.2 dB/dB.

CLS data

Figure 4.2 shows CLS data averaged across the normal hearing subjects. Categorical loudness is plotted as a function of the stimulus level L in the commonly used linear (categorical loudness in CU) (Fig. 4.2B) and in logarithmic scale (categorical loudness in 20log(CU)) (Fig. 4.2A). The unusual logarithmic plot was chosen to better visualize the similar behavior of loudness functions in comparison to DPOAE I/O functions plotted in logarithmic scale. All CLS I/O functions, independent of frequency, had in logarithmic presentation a similar compressive shape (compression for extrapolated I/O functions at $L = 65$ dB SPL for 2 kHz: 6.7 dB/dB, 3 kHz: 6.3 dB/dB, 3.5 kHz: 6.2 dB/dB, and 4kHz: 6.2 dB/dB, mean across all frequencies: 6.3 dB/dB) and approximately equal absolute loudness values.

Linear extrapolation lines were fitted to the average CLS values given in a linear scale. There would also have been other strategies for extrapolating CLS data (e.g., two extrapolation lines for different level sections or polynomial of second order), but linear extrapolation was chosen to provide best possible comparability to linear DPOAE I/O function extrapolation. For the calculation of linear extrapolation lines, mean values equal zero were excluded in order to avoid the flattening of extrapolation lines dependent on the number of levels which were exclusively rated 'inaudible'. An example of linear extrapolation is shown for the 2 kHz test frequency for categorical loudness in linear scale

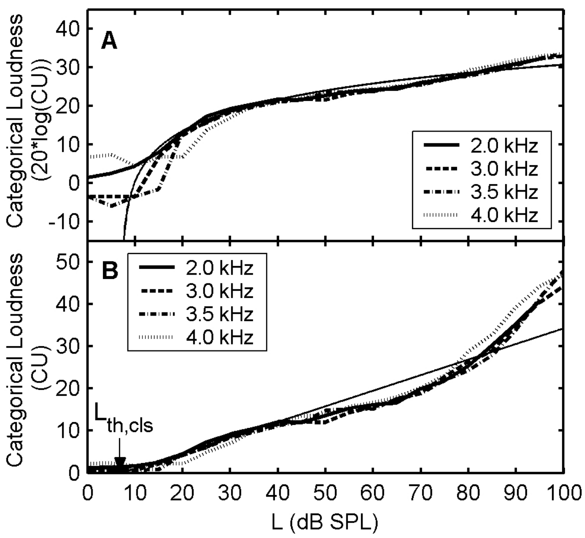

Figure 4.2: CLS I/O functions for 2, 3, 3.5, and 4 kHz for the normal hearing group. Panel (A) shows CLS data in logarithmic scale, panel (B) CLS data in linear scale. $L_{th,cls}$ in panel (B) shows the CLS threshold level, which serves as an estimate for hearing threshold. In each panel bold lines represent discrete CLS data, the single thin line exemplifies the linear CLS data extrapolation for 2 kHz.

(Fig. 4.2B) and transferred to logarithmic scale (Fig. 4.2A). The estimated CLS threshold level $L_{th,cls}$ was defined analogously to the DPOAE approach as the stimulus level L at which the extrapolation line equals 0 CU (Fig. 4.2B).

Standard deviations of categorical loudness in a linear plot (not shown) across individual mean CLS I/O functions (inter-individual repeatability) were calculated for the normal hearing group. On an average across all levels it amounted to 3.0 CU and was thus lower than one category step. In contrast, the average difference between the maximum and minimum categorical loudness value at a certain level for three repetitive measurements in one subject (intra-individual repeatability) amounted to 4.2 CU. The compression at $L = 65$ dB SPL of the individually extrapolated CLS I/O functions of each normal-hearing subject plotted in a logarithmic scale ranged between 3.6 and 8.1 dB/dB and amounted on average to 6.0 ± 0.9 dB/dB.

When comparing extrapolations of normative CLS and DPOAE data presented on a logarithmic scale, a close correspondence was apparent, even if the exemplarily presented threshold estimates at the test frequency of 2 kHz differed about 10 dB (compare the intersection points with the stimulus level axis $L_{th,dp}$ in Fig. 4.1C for DPOAE and $L_{th,cls}$ in Fig. 4.2B for CLS). On average across all test frequencies, the threshold level estimates $L_{th,dp}$ and $L_{th,cls}$ of the normative functions differed about 5 dB (not shown are the differences $L_{th,dp} - L_{th,cls}$ at 3 kHz: 6 dB, 3.5 kHz: 1 dB, and 4 kHz: 2 dB). Moreover, the compression values of the extrapolated normative CLS and DPOAE I/O functions were quantitatively very similar to each other and differed on average by only 0.5 dB/dB. Regarding individual DPOAE and CLS I/O functions of each normal hearing subject, compression was for both measures in a similar range with an average difference between DPOAE and CLS compression of only 0.2 dB/dB but with a standard deviation of 1.6 dB/dB.

4.2.2 Hearing loss case examples

Comparison of DPOAE and CLS data

Two hearing loss case examples and their respective DPOAE (Figs. 4.3A and 4.4A), normalized DPOAE (Figs. 4.3B and 4.4B) and CLS (Figs. 4.3C and 4.4C) data are presented in comparison to normative data (compare Figs. 4.1 and 4.2). Patient P1 was afflicted with a hearing loss of 30 dB HL at 4 kHz (Figs. 4.3A–C), while patient P2 suffered from a hearing loss of 45 dB HL at 3 kHz (Fig. 4.4A–C). Bold lines in the figures symbolize discrete, thin lines extrapolated data.

DPOAE I/O functions were for both hearing-impaired subjects (solid lines) in comparison to normative data (dashed lines) less compressive, consequently steeper and also lower in respect to absolute DPOAE levels (Figs. 4.3A and 4.4). The described effects were more distinct in patient P2, reflecting the higher hearing loss for this patient. The compression of the extrapolated I/O functions at $L_2 = 65$ dB SPL amounted to 3.0 dB/dB (P1) and 2.2 dB/dB (P2), respectively, whereas the absolute difference in DPOAE level at $L_2 = 65$ dB SPL in comparison to the respective normative I/O function amounted to 5.5 dB (P1) and 7.2 dB (P2), respectively. Normalization of DPOAE I/O functions was executed to compensate for these deviations (Figs. 4.3B and 4.4B). The estimated hearing thresholds $L_{th,dp}$ due to linear extrapolation of DPOAE data were for the hearing-impaired subjects 39 dB SPL (P1) and 46 dB SPL (P2). Presupposed that in the regarded frequency range dB SPL is approximately equal to dB HL, the DPOAE threshold level estimates were with a difference of 9 dB (P1) and 1 dB (P2), especially for patient P2 very close to the respective audiogram hearing threshold, which was, however, determined with a 5-dB resolution only.

CLS I/O functions for both hearing-impaired subjects were less compressive than the normative functions (Figs. 4.3C and 4.4C). As for DPOAE data, the effects were more distinct in case example P2. The compression of the extrapolated I/O functions at $L =$ 65 dB SPL amounted to 3.4 dB/dB (P1) and 2.4 dB/dB (P2). The discrete CLS values for the hearing-impaired patients above about $L = 55$ dB SPL (P1) and $L = 90$ dB SPL (P2), respectively, were of similar magnitude as for the average normal hearing subject. The estimated hearing thresholds, $L_{th,cls}$, due to linear extrapolation of CLS data were for the hearing-impaired subjects 36 dB SPL (P1) and 44 dB SPL (P2). Once again making use of the assumption that in the studied frequency range dB SPL is very close to dB HL, the CLS threshold level estimates exhibited a good resemblance to the respective audiogram hearing thresholds with a difference of 6 dB (P1) and -1 dB (P2).

All in all, for both patients DPOAE and CLS behavior were qualitatively similar. Both DPOAE and CLS data for both patients showed a steeper, less compressive course of

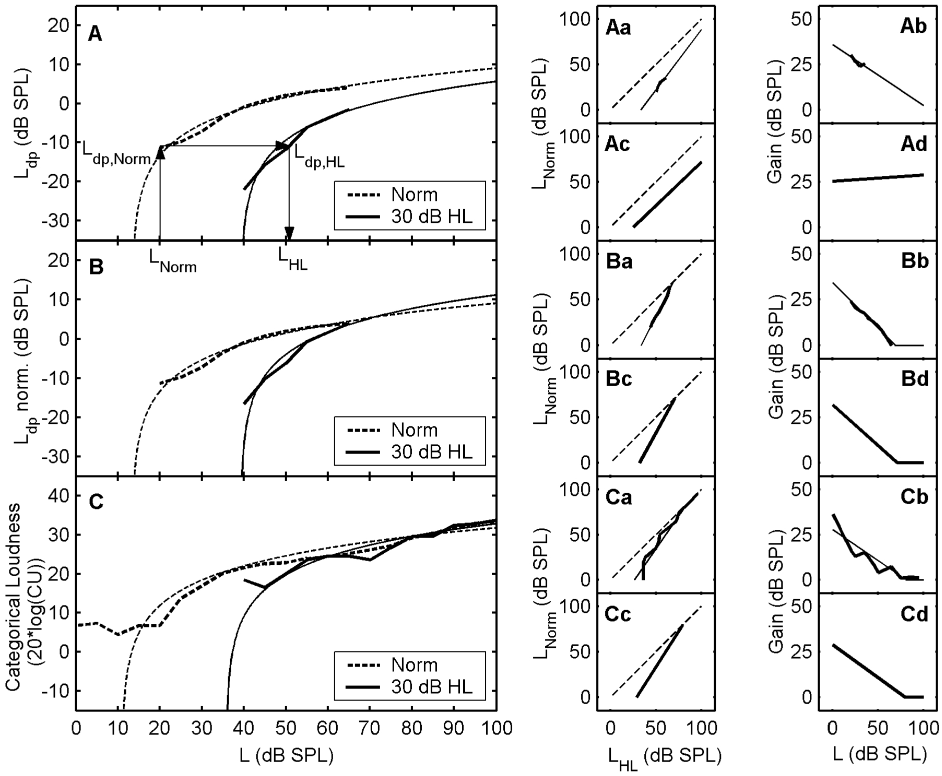

Figure 4.3: Data of case example P1 with a hearing loss of 30 dB HL at 4 kHz is shown in comparison to normative data. Panel (A) shows DPOAE, panel (B) normalized DPOAE, and panel (C) CLS data on a logarithmic scale. Bold lines represent discrete, thin lines extrapolated data. Panels (Aa), (Ba), and (Ca) show discrete values of L_{Norm} plotted above L_{HL} (relative growth function) for the respective discrete measuring data (bold solid lines) and extrapolations of the discrete relative growth functions (thin solid lines). Panels (Ac), (Bc), and (Cc) show relative growth functions for the respective extrapolated measuring data (bold solid lines). The thin dashed lines represent the respective normative function $L_{Norm} = L_{HL}$. Panels (Ab), (Bb), and (Cb) show gain functions for the respective discrete measuring data (bold solid lines) and extrapolations of the discrete gain functions (thin solid lines). Panels (Ad), (Bd), and (Cd) show gain functions for the respective extrapolated measuring data.

the I/O functions in comparison to normative data. For DPOAE and CLS data this effect was more distinct in patient P2 who exhibited the greater hearing loss. For both hearing-impaired subjects, compression and hearing threshold estimates were similar when obtained by extrapolated CLS and DPOAE I/O functions. Compression differences between extrapolated CLS and DPOAE I/O functions at $L_2 = 65$ dB SPL were with 0.4 dB/dB (P1) and 0.2 dB/dB (P2) quite low and estimated threshold level differences $L_{th,dp} - L_{th,cls}$ amounted to only 3 dB (P1) and 2 dB (P2).

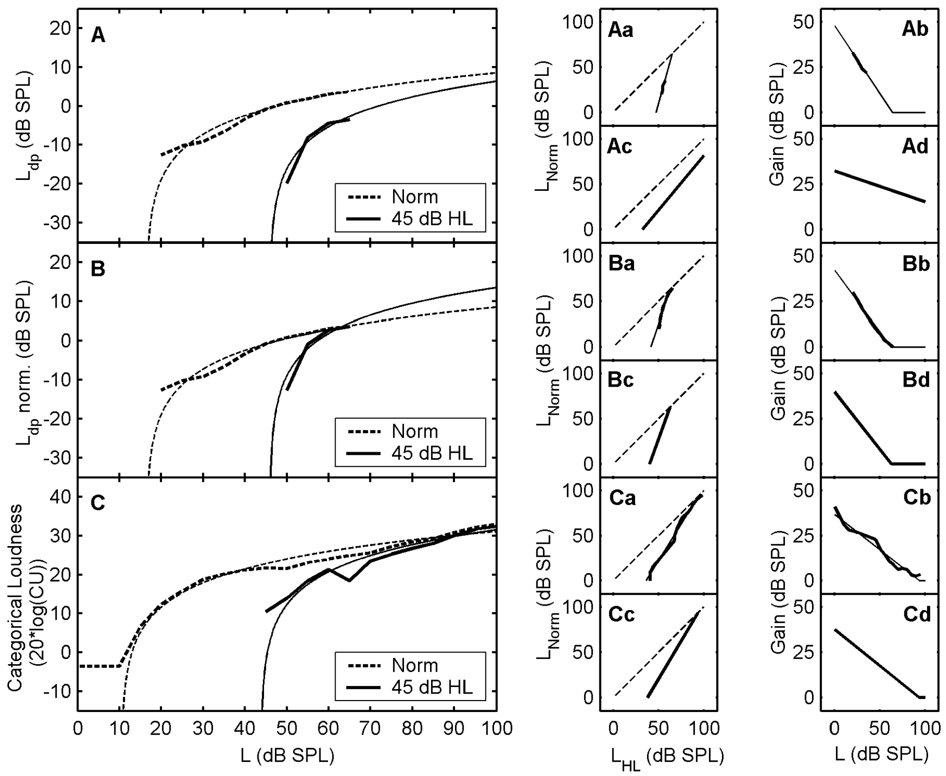

Figure 4.4: Data of case example P2 with a hearing loss of 45 dB HL at 3 kHz is shown in comparison to normative data. For the meaning of each panel see the descriptions in Fig. 4.3.

Estimation of gain for compensating loss of sensitivity and compression

The normal hearing and the hearing-impaired subjects were compared relatively to each other for both DPOAE and CLS data. The chosen procedure for comparison was derived from a strategy used by Steinberg and Gardner (1937). The basic steps in the procedure of comparison are illustrated for discrete DPOAE data in Fig. 4.3A. The approach for CLS and extrapolated data is analogous to this. For each stimulus level, designated as L_{Norm}, the respective corresponding DPOAE level of the normal hearing group $L_{dp,Norm}$ was compared to the DPOAE level data of the hearing-impaired subject in order to find the stimulus level, designated as L_{HL} , that was required to elicit the same DPOAE level $L_{dp,HL}$ ($= L_{dp,Norm}$) in the hearing-impaired subject. For comparing discrete data, linear interpolation was used, because discrete numerical DPOAE and CLS values were usually not identical for the normal hearing group and the hearing-impaired subject. So, in most cases no exact matches would have been found without interpolation. Moreover, if there was no unequivocal decision due to several possible matches in the data of the hearing-impaired subject (this situation occurred if data were not monotonically increasing), the corresponding L_{Norm} value was skipped. All valid data are displayed in a graph with L_{Norm} plotted above L_{HL} (Fig. 4.3Aa). Both discrete values (bold solid line) and the extrapolation line calculated on the basis of these discrete values (thin solid line) are shown. These functions, which are in the following referred to as relative growth functions, visualize the relative growth behavior of the I/O function of the hearing-impaired subject in comparison to the normative I/O function, which is in this plot displayed by the function $L_{Norm} = L_{HL}$ (dashed line). The deviation $L_{HL} - L_{Norm}$, which represents the level-dependent gain for hearing aid adjustment, was calculated for each L_{Norm} and is plotted as a function of L $(= L_{Norm})$ in Fig. 4.3Ab. Gain representation is displayed for discrete values (bold line) and for the extrapolation line computed on the basis of the discrete gain values (thin line). Figures 4.3Ac and 4.3Ad show relative growth and gain functions for extrapolated DPOAE data. Moreover, L_{HL} values, which failed the criterion $L_{HL}(L_{Norm}) \geq L_{Norm}$ and would thus have led to negative gain values, were set to $L_{HL} = L_{Norm}$ (compare, e.g., Fig. 4.3Bb) since level-dependent attenuation did not seem to be reasonable for hearing-aid adjustment.

For both case examples, relative growth and gain functions are plotted on the right-hand side of Figs. 4.3 and 4.4. In the following, further examinations are restricted to the presentation of the resulting gain functions (panels b and d), since they shall constitute the basis for hearing aid adjustment. CLS gain functions (Figs. 4.3Cb, 4.3Cd, 4.4Cb, and 4.4Cd) were considered as particular reference for comparisons between CLS and DPOAE gain functions. At first glance, one can observe for both case examples that most of the gain functions had a similar shape. However, gain functions calculated on the basis of extrapolated non-normalized DPOAE data (Figs. 4.3Ad and 4.4Ad) resulted in an exceedingly deviant behavior and made up a poor fit for CLS gain estimation. For both case examples best resemblance was achieved when comparing extrapolated CLS data (Figs. 4.3Cd and 4.4Cd) with extrapolated normalized DPOAE data (Figs. 4.3Bd and 4.4Bd). The resulting gain differences $gain_{CLS}(L) - gain_{normDP}(L)$ at $L = 0$ dB SPL were for both hearing-impaired subjects quite small and amounted to -3 dB (P1) and -2 dB (P2). However, the level at which gain became zero was especially in case example P2 for normalized DPOAE gain estimation far apart from CLS gain estimation. The level difference amounted to 3 dB (P1) and 9 dB (P2). Consequently, comparisons of CLS and normalized DPOAE gain estimations resulted in a maximum gain difference of 3 dB (P1) and 11 dB (P2).

Altogether, it is important to notice that gain estimations based on DPOAE measurements were highly influenced by the magnitude of the DPOAE levels and thus by the deviation between normative and hearing loss data. For both case examples normalization of DPOAE data resulted in an improvement of gain estimations compared to gain functions based on non-normalized DPOAE data, especially when extrapolated data were used.

4.2.3 Comparison of DPOAE and CLS I/O and gain functions for pooled data

Data of all nine hearing-impaired subjects were included in a joint comparison between DPOAE and CLS data. DPOAE and CLS I/O functions and their respective compressions and estimated threshold levels were compared to each other for each hearing-impaired subject. The difference between the estimated threshold levels $L_{th,dp} - L_{th,cls}$ amounted on average to 4 ± 6 dB. The difference between the estimated thresholds and the audiometric thresholds (given in dB HL, which is supposed to be approximately equal to dB SPL in the studied frequency range) were for the estimated DPOAE threshold levels on average 8 ± 7 dB and for the estimated CLS threshold levels 5 ± 8 dB. The average compression amounted to 3.0 dB/dB (DPOAE) and 3.5 dB/dB (CLS) and thus resulted in a mean difference in compression between CLS and DPOAE I/O functions, which amounted to 0.5 ± 0.7 dB/dB.

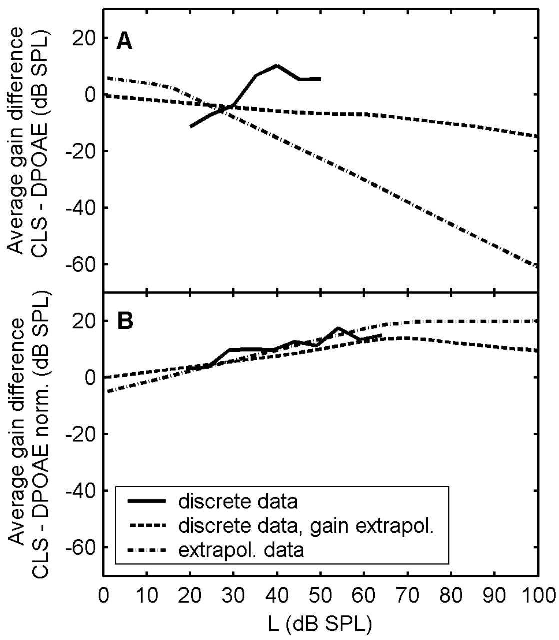

Figure 4.5: Average difference of level-dependent gain between CLS and DPOAE (A) or normalized DPOAE (B), respectively, across all frequencies and all hearing-impaired subjects. In each panel solid lines represent gain differences calculated on the basis of discrete measuring data, dashed lines represent gain differences calculated on the basis of extrapolated discrete gain functions, and dash-dotted lines represent gain differences calculated on the basis of extrapolated measuring data.

Comparing DPOAE and CLS gain functions, each of the 14 single-frequency data sets of the nine hearing-impaired subjects was compared to the respective normative function. This procedure was in each case done for non-normalized DPOAE, normalized DPOAE, and CLS data. The difference between the gain functions based on CLS and non-normalized DPOAE (Fig. 4.5a) or normalized DPOAE (Fig. 4.5b) was calculated and averaged for all test frequencies and across all 14 gain difference functions of all hearing-impaired subjects. Using extrapolated I/O functions, average gain differences were calculated and plotted in steps of 5 dB between 0 and 100 dB SPL.

First of all, gain differences between CLS and non-normalized DPOAE (Fig. 4.5a) are described. Examining discrete CLS and DPOAE data (solid line), it must be mentioned that just a small fraction of all existing data was available for averaging. The higher the stimulus level, the fewer points were available. Data at levels above $L = 55$ dB SPL were excluded, since there were two or fewer points left for statistical analysis. Average gain differences ranged from -11 dB at $L = 20$ dB SPL to 10 dB at $L = 40$ dB SPL with an average standard deviation (not shown) of 12 dB. Mean gain differences in extrapolated gain functions calculated on the basis of discrete DPOAE and CLS data (dashed line) were 0 dB at $L = 0$ dB SPL and -15 dB at $L = 100$ dB SPL. The average standard deviation across all levels amounted to 29 dB. Especially for extrapolated data (dash-dotted line), mean gain differences were extremely high, ranging from 6 dB at $L = 0$ dB SPL to a maximum of -62 dB at $L = 100$ dB SPL, and were furthermore accompanied by enormous standard deviations with a mean across all levels of 59 dB.

When looking at the gain differences between CLS and normalized DPOAE (Fig. 4.5b), it is striking that the discrepancies, especially for extrapolated data, were considerably lower. Further, the mean as well as the standard deviation (not shown) of the gain difference were in a rather similar range of magnitude for discrete and extrapolated data. To begin with, discrete data results (solid line) are described. Maximum average gain difference between CLS and normalized DPOAE amounted to 17 dB at $L = 55$ dB SPL, while minimum gain difference was 3 dB at $L = 20$ dB SPL. The average standard deviation across all levels amounted to 13 dB. Extrapolated gain values computed on the basis of discrete data (dashed line) achieved best results with regard to gain difference and its variability. Average gain differences ranged from 0 dB at $L = 0$ dB SPL to 14 dB at $L = 70$ dB SPL. Between $L = 0$ and 70 dB SPL gain differences increased continuously and then decreased above $L = 70$ dB SPL. Standard deviations were quite constant at 9 dB. A similar behavior occurred when examining gain difference functions computed on the basis of extrapolated CLS and normalized DPOAE data (dash-dotted line). Gain differences ranged on average from -5 dB at $L = 0$ dB SPL to 20 dB at $L = 100$ dB SPL (standard deviation: 11 dB). Thus, in comparison to normalized DPOAE data CLS data resulted on average in shallower gain functions with a gain of zero at higher stimulus levels. For normalized DPOAE data gain became zero at levels around $L = 65$ dB SPL due to the implemented normalization strategy, which forced discrete DPOAE levels of the normative and hearing loss I/O function to be equal at this stimulus level.

Consequently, using discrete data, the absolute difference in gain estimation was fairly similar between non-normalized and normalized DPOAE data. For extrapolated I/O functions, normalized DPOAE data resulted in better estimations of gain than non-normalized DPOAE data compared to the reference CLS gain functions. Especially for extrapolated functions standard deviations were much lower using normalized DPOAE data. Altogether, discrete normalized DPOAE data and extrapolated gain functions yielded the best performance when compared to CLS data.

4.3 Discussion

The main aim of the study was to compare DPOAEs to loudness estimations with regard to the potentiality of DPOAEs to determine characteristic quantities of the impaired ear and to derive objective dynamic compression hearing aid fitting parameters by estimating level-dependent gain. In the following the achieved results are discussed.

Relationship between DPOAE and CLS

DPOAEs, an objective quantity, and loudness, a subjective quantity, were found to be on average closely related to each other. Both loudness and DPOAE I/O functions exhibited similar behavior when plotted on a logarithmic scale. This is manifested in similar threshold level estimates (the average difference between DPOAE and CLS threshold level estimates was 5 dB for the normal hearing group and 4 dB for the individual hearing-impaired subjects) and compression (the average difference between DPOAE and CLS compression at $L_2 = 65$ dB SPL was 0.5 dB/dB for both the normal hearing group and for the individual hearing-impaired subjects). The slope of loudness and DPOAE I/O functions increased with increasing hearing loss (compression decreased on average for both DPOAE and CLS I/O functions by 2.8 dB/dB for hearing-impaired subjects in comparison to the normal-hearing group; compare also case examples in Figs. 4.3 and 4.4) and is therefore suggested to reflect loss of cochlear sensitivity and compression. This confirms the results of Neely *et al.* (2003) and suggests that both DPOAE and loudness growth may be determined by the same source of nonlinearity. Since DPOAEs directly reflect cochlear compression, loudness seems to be essentially formed by peripheral sound processing mechanisms. However, it remains questionable if there is a direct relationship between DPOAE and loudness, i.e., if loudness is exclusively due to cochlear sound processing or if it is additionally affected by retrocochlear mechanisms.

The similarity of DPOAE and CLS threshold estimates and compression was furthermore consistently manifested in the small difference of the calculated gain functions (Fig. 4.5). However, small differences and low standard deviations were only achieved if the calculation of gain was based on normalized DPOAE data. The close relationship between the gain functions derived from DPOAE and loudness measurements (compare Fig. 4.3Bb and 4.3Bd, 4.4Bb and 4.4Bd) suggests that DPOAEs may permit objective assessment of recruitment and hence may provide parameters for an input-level-dependent compensation of the cochlear defect of hearing loss ears. Since extrapolated gain functions based on discrete normalized DPOAE data yielded the most accurate gain estimation (gain differences ranged from 0 to 14 dB SPL with an average standard deviation of 9 dB) it is recommended to apply this strategy for the derivation of basic parameters for the adjustment of dynamic compression hearing aids. However, there were some fundamental problems when comparing loudness and DPOAE data, which shall be discussed in the following. Some proposals are given for the solution of these problems.

Comparison of quantities with different units

Absolute comparisons between two different quantities are subject to the selected numerical representation (e.g., loudness categories could be associated with any sequence of numbers) and the chosen style of graphic representation (e.g., linear or logarithmic plot). Therefore, a relative comparison strategy, which was deduced from Steinberg and Gardner (1937) and which is independent of the scaling of the measured data, was applied in our study to examine deviations in DPOAE and CLS I/O functions between normal hearing and hearing-impaired subjects. Nevertheless, a comparison between DPOAE and loudness is difficult since both measures are totally different with respect to their nature (DPOAEs are a physiological and loudness is a psychophysical measure) and their kind of stimulation (two-tone versus single-tone stimulation).

Influence of calibration errors

The relevant magnitude for the generation of DPOAEs and for the generation of loudness is the actual sound pressure level at the ear drum. In general, calibration errors yield a deviance of unknown quantity between actual and nominal sound pressure levels (see Sec. 3.4). The magnitude of the deviation varies, particularly with individual influencing factors such as ear canal length and middle ear impedance. The calibration error at f_2 occurs uniformly in DPOAE and CLS measurements, but deteriorates inter-individual comparability of I/O functions. For DPOAE measurements, however, calibration errors may occur with different magnitude at the two primary tone frequencies f_1 and f_2. If the calibration errors at the two primary tone frequencies result in a deviation of the two primary tone stimulus levels from an optimal stimulus paradigm, this usually results in an additional stimulus-level-dependent change in DPOAE level and thus may cause a change in the shape and thus the compression of the DPOAE I/O function (see Chapter 3.4). It should be emphasized that an additional source of error in the compression estimate may result from the deviation between the individual optimal stimulus paradigm and the applied constant stimulus paradigm. This is in accordance with the observations of Neely *et al.* (2003), who found the compression of DPOAE I/O functions plotted on a logarithmic scale to be highly variable (compression at $L_2 = 65$ dB SPL ranged from 1.8 to 7.6) among normal hearing subjects, suggesting that this effect might occur at least partly due to calibration errors. The same effect, though a little less distinct, was existent in our CLS and DPOAE I/O functions of normal hearing subjects, which showed a similar variance in compression at $L_2 = 65$ dB SPL and ranged between 3.9 and 8.9 dB/dB (DPOAE) and between 3.6 and 8.1 dB/dB (CLS) for normal hearing subjects. However, the standard deviation of compression was only 1.2 dB/dB for DPOAE and 0.9 dB/dB for CLS. We believe that this variance in compression, which deteriorates the individual quality of gain estimations, is mainly due to calibration errors. However, calibration errors might be less influential in neonates or young children who exhibit smaller ear canal lengths and with that calibration errors at higher frequencies (see Sec. 3.4).

Influence of inter-individual variability of DPOAE level and categorical loudness

Calibration errors, which vary considerably among subjects, are supposed to have an undesired impact on the magnitude of DPOAE and CLS data and hence on the resultant inter-individual variance. Moreover, the ear canal length and the middle ear transfer function are supposed to directly influence the propagation of DPOAEs through the middle ear and outer ear canal and may cause an individually differing attenuation of DPOAE amplitude, which may bring about increased inter-individual deviations in DPOAE level. The inter-individual deviance of CLS data (average standard deviation: 3.0 CU) was within the reproducibility of a single person (average difference: 4.2 CU). In contrast, the deviation of DPOAE level was substantial across normal hearing subjects (average standard deviation: 6.4 dB). The deviation should be lower, proceeding on the assumption that the single influencing factor is OHC damage, which should hardly be existent in the tested normal hearing subjects. In comparison, DPOAE levels were quite constant for successive measurements within a single subject (average difference: 0.8 dB), suggesting that the DPOAE amplitude hardly varies within a short period of time when measured with an unaltered ear probe position. Therefore, it is likely that the absolute variance of DPOAE level is not only dependent on OHC dysfunction, but also on other side effects, which can be of external (ear canal length, middle ear impedance, calibration error) or intra-cochlear origin (i.e., dysfunction of the cochlear amplifier). We believe that the external components are more influential on the DPOAE amplitude and thus obstructive to relative comparisons of different DPOAE I/O functions. The fact that there is a high variability in DPOAE magnitude, but only a small variability in loudness across frequency (compare Figs. 4.1A and 4.2A), may disprove intra-cochlear effects because intra-cochlear variability is supposed to influence both DPOAEs and loudness. It is assumed that calibration errors and ear canal parameters are influencing DPOAEs more than loudness measurements because the DPOAE amplitude is highly sensitive to slight deviations from the individual optimal primary tone level setting. Also, ear canal volume influences the backward sound propagation of the DPOAE to the microphone and hence yields an inter-individually varying attenuation of DPOAE amplitude. To compensate for these undesired effects, a normalization strategy was implemented.

Reasonableness of DPOAE normalization

The applied normalization procedure with an equalization of DPOAE levels at a constant stimulus level of $L_2 = 65$ dB SPL (see Fig. 4.1B, 4.3B, and 4.4B) was chosen, because $L_2 = 65$ dB SPL was the highest stimulus level at which DPOAEs could be measured without getting distorted signals due to microphone clipping effects. Other stimulus levels could have been chosen for normalization by using extrapolations, but since there was no a priori evidence for any optimal solution, $L_2 = 65$ dB SPL was arbitrarily selected. It is interesting to note that results of DPOAE gain functions could have been further improved by executing an individual DPOAE shift, making use of knowledge about behavior of individual CLS data. Using this strategy, gain differences between DPOAE- and CLS-based computation amounted to a maximum of just about 2 dB (not shown in results).

However, this approach is not reasonable if the main aim is to develop a method for objective hearing aid adjustment on the exclusive basis of DPOAEs. Thus, one of the most prominent and influencing factors was the difference in absolute magnitude of DPOAE I/O functions. This problem is directly linked to the question to what extent the amplitude differences result due to OHC dysfunction or due to non-pathological impacts. Therefore, further improvements in DPOAE measuring techniques and especially in the quality of calibration are necessary to minimize the influence of undesired side effects.

Applicability of the proposed hearing aid fitting strategy by means of DPOAEs in clinical practice

The proposed hearing aid adjustment strategy is only a small step on the way to non-cooperative hearing aid adjustment in clinical practice. Influencing factors are, as discussed before, individually varying DPOAE amplitudes even in normal hearing ears and calibration errors. Moreover, DPOAEs are only capable of detecting dysfunctions on the stage of the cochlear amplifier and not on the stage of IHCs or along the retrocochlear auditory pathway. However, OHC dysfunction is the most common hearing disorder. Another limiting factor for the application of the proposed strategy in clinical practice is that with the available commercial DPOAE measurement systems and ear probes one can only elicit DPOAEs free of artifacts at stimulus levels of up to 65 dB SPL. Thus, DPOAEs are currently only useful in detecting loss in sensitivity and compression in hearing-impaired subjects with cochlear hearing losses of up to 50 dB HL and hence predictions of level-dependent gain are only possible for impaired ears of that category. Despite these restrictions, the proposed strategy for providing objective hearing aid adjustment parameters (i.e., the gain for compensating loss of sensitivity and compression of the impaired ear) is expected to be beneficial in non-cooperative patients with mild to moderate cochlear hearing losses. For higher hearing losses and hearing losses with an IHC or retro-cochlear component, other measurement techniques, which are capable of examining the entire auditory pathway, as e.g. brainstem-evoked potentials, could probably further expand the scope of application of the proposed method.

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5 Differentiation between middle ear and cochlear hearing loss by means of DPOAEs

Universal newborn hearing screening (UNHS) is an important part of the postnatal test battery giving usually a "pass"/"fail" decision which indicates either normal hearing or hearing loss. Audiologic screening methods include measurements of auditory brainstem responses and otoacoustic emissions (TEOAEs/DPOAEs), which in combination have been shown to accurately diagnose sensorineural hearing loss in newborns. However, screening results can be corrupted the first days after birth due to remnants of amniotic fluid in the tympanic cavity. This becomes noticeable as a temporary sound conductive hearing loss. The detection of a transitory sound conductive hearing loss might help to reduce the false refer rate during early postnatal hearing screening. Usually, UNHS is conducted within a few days after birth as long as the newborns stay at the clinic. Thus, it would be beneficial for the evaluation of UNHS results and for avoiding costly follow-up examinations to develop a method, which allows for an objective differentiation between sensorineural and sound conductive hearing loss.

DPOAEs are known to reflect the status of the cochlear amplifier (see Sec. 2.5.3). DPOAE I/O functions provide an insight into frequency-specific sensitivity of the cochlear amplifier by estimated DPOAE thresholds. Moreover, DPOAE I/O functions provide an additional measure, i.e. the slope of the I/O function, which is able to estimate cochlear compression. Due to the linear sound processing of the middle ear, one can assume that the DPOAE growth behavior remains to a great extent unaltered with a sound conduction dysfunction. In fact, when inducing a middle ear dysfunction by filling the bulla with physiological saline solution in guinea pigs, the slope of the DPOAE I/O functions was not significantly affected revealing normal compressive sound processing. In contrast, when the guinea pigs were exposed to noise, the slope of the DPOAE I/O function differed significantly from that found before noise exposure (Gehr *et al.*, 2004). These findings suggest DPOAE I/O functions to allow for a differentiation between middle and inner ear dysfunction. The purpose of the present study was to apply extrapolated DPOAE I/O functions in neonates in order to find out whether and to what extent this new method is able to estimate hearing thresholds and to differentiate between sound conductive and cochlear hearing loss under hearing screening conditions.

5.1 Material and methods

5.1.1 Subjects

There were no selection criteria for participation in the study. The study was performed under realistic test conditions since DPOAE measurements were conducted either in the neonatal care unit (first measurement) or at the baby's home (follow-up measurement). In total, 127 ears from 102 babies were investigated (first measurement). In 8 ears measurements had to be stopped because the babies woke up. In one ear neither TEOAEs nor DPOAEs could be found. DPOAE measurements were conducted immediately after UNHS using TEOAEs. In most of the babies only one ear was measured in order to not stress the babies unnecessarily. Thus, the population of the present study consisted of 118 ears of 93 babies. The age varied from 27 hours to 10 days (mean age = 3.2 days). Postconceptional age ranged between 36 weeks and 41 weeks. These ears are referred to as the neonate group. DPOAE measurements were performed in a quiet room of the neonatal care unit in the gynecological hospital of the Technische Universität München during spontaneous sleep. Most of the parents did not agree in a second measurement. Thus, from the 93 neonates only 16 babies (21 ears) were tested in a follow-up study at least four weeks after the birth at their parents' home. These ears are referred to as the follow-up neonate group. DPOAEs were measured after feeding during natural sleep. A quiet room was chosen and the babies were lying in their cradle.

For comparison, DPOAEs were measured in 26 ears of 14 adults (7 females, 7 males) with normal hearing (mean age = 24.7 years) and in 189 ears of 98 patients suffering from cochlear hearing loss. According to pure-tone audiometry the hearing loss of the normal hearing subjects was equal to or lower than 15 dB HL in the examined frequency range. Audiometric hearing thresholds of the cochlear hearing loss ears were sampled in five groups ranging from −5 dB HL to 40 dB HL in steps of 10 dB (group 1: −5 and 0 dB HL, group 2: 5 and 10 dB HL, group 3: 15 and 20 dB HL, group 4: 25 and 30 dB HL, and group 5: 35 and 40 dB HL). Please note that group 1 and 2 does not mean normal hearing ears. In these ears normal thresholds were found at some frequencies only. The classification was done because it is believed that a cochlear hearing loss ear is not normal, even if its audiometric thresholds are normal within a limited cochlear region. Middle ear and retrocochlear disorders were excluded by tympanometry and auditory brainstem responses. Measurements were performed in a sound-proof cabin while normal hearing subjects and patients were seated in a comfortable recliner.

5.1.2 Stimulus generation and DPOAE measurement procedure

DPOAE measurements were conducted with the hardware described in Sec. 3.1. Standard clinical DPOAE software, which was developed in the laboratory of experimental audiology at Technische Universität München was used. Signal levels were adjusted according to in-the-ear calibration (see Sec. 3.4).

DPOAE measurements were conducted at eleven f_2 frequencies (i.e., at 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7 and 8 kHz) beginning with the highest one. However, for establishing hearing loss classes in the cochlear hearing loss ears only audiometer frequencies (1.5, 2, 3, 4, 6, and 8 kHz) were considered. L_2 was decreased from 65 to 20 dB SPL in steps of 5 dB. L_1 was set according to the equation $L_1 = 0.4L_2 + 39$ dB SPL. The maximum averaging time for recording DPOAEs was 4 s. After an average time of 2 s a subtotal was established. If the SNR was higher than 20 dB the measurement was stopped and the DPOAE was accepted as valid. If the SNR was lower than 20 dB after 2 s the measurement was continued for another 2 s. In this case DPOAEs were accepted as valid for an SNR exceeding 6 dB. The measurement duration per ear amounted up to about 8 minutes (at 11 frequencies and 10 levels).

Linear extrapolation lines were fitted to the discrete DPOAE data (see Sec. 2.5.3). The estimated DPOAE threshold level L_{dpth} was defined as the stimulus level L_2 at which the linear extrapolation equaled $p_{dp} = 0$ Pa. The slope s_{dp} of the extrapolated DPOAE I/O functions in a logarithmic plot was calculated according to Eq. 5.1. The DPOAE compression $k_{dp}(L_2)$ was defined as the reciprocal value of the slope $s_{dp}(L_2)^{-1}$. The criteria for accepting a DPOAE I/O function as valid were as follows: (*i*) I/O functions had to consist of at least three successive data points, (*ii)* the coefficient of determination for the linear regression had to exceed 0.8, and (*iii*) the slope of the regression line had to be positive.

$$s_{dp}(L_2) = \frac{20}{\ln 10} \cdot \frac{a}{aL_2 + b} \tag{5.1}$$

5.2 Results

5.2.1 DPOAE test performance

In the normal hearing subject sample (26 ears) hearing threshold estimation could be performed in almost all ears at most test frequencies (e.g., 21/26 ears, i.e. 80 %, at 3 kHz; 26/26 at 5 kHz), with the exception of $f_2 = 8$ kHz, where in only 17 ears, i.e. 65 %, the criteria for extrapolation were fulfilled. In contrast, in the neonate group (118 ears) the percentage of ears in which hearing threshold estimation could be yielded was lower and reached a maximum of 88/118 ears, i.e. 75 %, at 5 and 6 kHz. Especially at the lower test frequencies the test performance was distinctly worse (e.g., 39/118, i.e. 33.1 %, at 1.5 kHz), which can be attributed to the higher noise floor. Similar test performance was obtained in the follow-up neonate group (see Tab. 5.1).

The mean noise floor level varied across frequency from −14.3 dB SPL at 1.5 kHz to −21.9 dB SPL at 4.5 kHz in the normal hearing subjects, from −3.1 dB SPL at 1.5 kHz to −15.3 dB SPL at 4.5 kHz in the neonates, and from 2.6 dB SPL at 1.5 kHz to −15.0 dB SPL at 4.5 kHz in the follow-up neonates (see Tab. 5.1). The higher noise floor level in the neonates, especially at low test frequencies, can be attributed to the fact

$f2$ (kHz)	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	6.0	7.0	8.0
$L_{\mathrm{dpth,norm}}$	18.9±9.0	17.6±15.8	14.8±7.6	10.8±11.4	11.2±6.7	10.6±13.7	11.5±11.4	16.0±14.0	25.1±8.3	31.3±8.9	31.9±9.0
26 ears	$n=24$	$n=24$	$n=24$	$n=21$	$n=25$	$n=25$	$n=25$	$n=26$	$n=25$	$n=25$	$n=17$
$L_{\mathrm{dpth,15-20HL}}$	26.6±8.7	27.0±16.1		25.7±13.1		21.6±15.7			32.5±13.1		39.8±10.9
	$n=13/21$	$n=23/37$		$n=16/29$		$n=29/31$			$n=40/56$		$n=7/42$
$L_{\mathrm{dpth,25-30HL}}$	32.2±12.5	21.7±7.2		38.8±6.5		34.1±8.6			41.3±7.6		17.4
	$n=5/7$	$n=3/8$		$n=6/10$		$n=14/18$			$n=16/35$		$n=1/18$
$L_{\mathrm{dpth,35-40HL}}$				42.3±4.9		41.3±5.9			42.5±7.6		42.4
				$n=7/14$		$n=9/15$			$n=4/17$		$n=1/18$
$L_{\mathrm{dpth,neonate}}$	24.6±11.0	27.0±9.0	23.6±11.1	25.7±9.3	18.9±8.7	21.0±8.9	21.1±9.0	24.3±9.4	29.5±9.8	32.7±9.7	36.0±8.3
118 ears	$n=39$	$n=56$	$n=54$	$n=53$	$n=49$	$n=65$	$n=87$	$n=88$	$n=88$	$n=85$	$n=78$
$L_{\mathrm{dpth,follow\text{-}up}}$	21.2±12.4	24.0±21.1	19.0±12.2	17.9±14.8	13.2±10.6	13.3±12.8	19.6±12.2	17.9±12.2	23.4±8.1	27.8±10.1	33.8±6.9
21 ears	$n=7$	$n=9$	$n=9$	$n=9$	$n=10$	$n=14$	$n=16$	$n=19$	$n=17$	$n=16$	$n=16$
$k_{\mathrm{dp,norm}}$	4.2±1.0	4.3±1.8	4.6±0.9	5.1±1.3	5.0±0.8	5.1±1.6	5.0±1.3	4.5±1.6	3.4±1.0	2.7±1.0	2.7±1.0
$k_{\mathrm{dp,15-20HL}}$	3.3±1.0	3.2±1.8		3.4±1.5		3.8±1.8			2.6±1.5		1.7±1.3
$k_{\mathrm{dp,25-30HL}}$	2.6±1.4	3.7		1.8±0.7		2.4±1.0			1.6±0.9		4.3
$k_{\mathrm{dp,35-40HL}}$				1.5±0.6		1.6±0.7			1.4±0.9		1.5
$k_{\mathrm{dp,neonate}}$	3.5±1.3	3.2±1.0	3.6±1.3	3.4±1.1	4.2±1.0	3.9±1.0	3.9±1.0	3.5±1.1	2.9±1.1	2.6±1.1	2.2±1.0
$k_{\mathrm{dp,follow\text{-}up}}$	3.9±1.4	3.6±2.4	4.1±1.4	4.3±1.7	4.8±1.2	4.8±1.5	4.1±1.4	4.3±1.4	3.6±1.0	3.1±1.2	2.4±0.8
$L_{\mathrm{nf,norm}}$	−14.3±1.9	−16.8±2.0	−19.9±2.8	−20.5±2.7	−19.9±2.9	−20.9±3.1	−21.9±3.2	−21.8±3.1	−21.4±3.1	−19.1±3.4	−18.1±3.0
$L_{\mathrm{nf,neonate}}$	−3.1±7.2	−7.6±6.2	−10.7±6.5	−9.8±6.8	−14.8±5.4	−14.6±6.0	−15.3±5.2	−13.8±4.7	−13.3±4.2	−13.6±4.9	−14.4±4.0
$L_{\mathrm{nf,follow\text{-}up}}$	2.6±9.7	−4.5±8.0	−10.8±6.4	−9.3±7.3	−10.8±6.5	−11.9±6.6	−15.0±5.6	−13.2±5.3	−14.7±4.5	−12.3±5.4	−13.2±4.4

Table 5.1: DPOAE threshold level L_{dpth}, compression k_{dp} (at $L_2 = 55$ dB SPL), and number of ears where criteria for estimating the DPOAE threshold from extrapolated DPOAE I/O functions were fulfilled for the normal hearing adult, neonate, follow-up neonate, and cochlear hearing loss groups across f_2 frequencies (mean ± standard deviation). Additionally, the noise floor level L_{nf} (mean ± standard deviation) for the normal hearing adult, neonate, and follow-up neonate groups across f_2 frequencies is listed.

that the measurements in the neonates were performed at the hospital or at the baby's home, whereas the measurements in the normal hearing subjects were performed in a sound-proof cabin. Furthermore, despite the fact that neonates were measured during natural sleep, slight movements of the head or heavy breathing could deteriorate noise floor levels. In contrast, adults were fully cooperative and were instructed to calmly rest on the recliner.

At $f_2 = 8$ kHz, the test performance was nearly the same in the neonates (66.1 %) compared to that found in the normal hearing subject sample (65.4 %). This can be attributed to the fact that the neonates exhibited higher emission levels at the high test frequencies compared to those found in the ears of the normal hearing subject sample (see Fig. 5.1). The percentage of cochlear hearing loss ears, in which the hearing threshold estimation could be achieved, varied with frequency and hearing loss. The percentage was lowest at $f_2 = 8$ kHz. The best performance occurred at $f_2 = 3$, 4 and 6 kHz (see Tab. 5.1).

5.2.2 DPOAE grams and DPOAE I/O functions in neonates, normal hearing subjects, and cochlear hearing loss patients

Figure 5.1 shows DPOAE grams obtained in the neonate group, the follow-up neonate group (upper panels), the normal hearing subject sample, and the 15–20 dB HL cochlear hearing loss samples (lower panels). The DPOAE level, L_{dp}, found in the follow-up neonate group was considerably higher compared to that found in the neonate group, predominantly for mid and high frequencies. When comparing the DPOAE grams of the normal hearing subject sample to that of the neonate group, DPOAE levels differed most in the low and high frequency region, especially at 8 kHz. In both neonate ears and normal hearing adult ears DPOAE grams were close together at high and more separated at low primary tone levels revealing compressive DPOAE growth. In contrast to that, DPOAE grams of the 15–20 dB HL cochlear hearing loss ears exhibited lower DPOAE levels and were more separated. The standard deviation of the DPOAE level at the highest did not differ much from that at the lowest primary tone level. The 6 dB SNR criterion is therefore supposed to be strong enough for ensuring reliable DPOAE measurements.

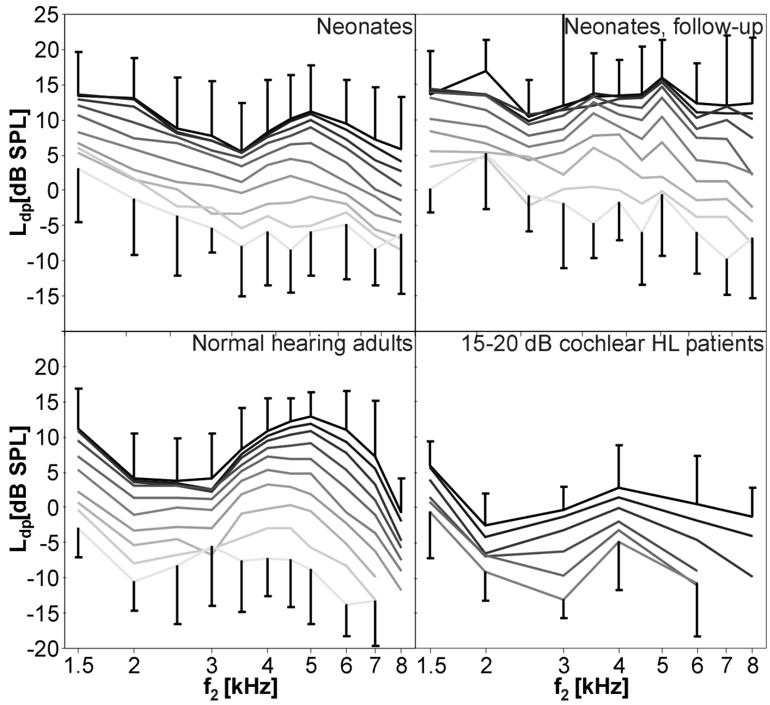

Figure 5.1: Mean DPOAE grams for four different experimental populations: neonates, follow-up neonates, normal hearing adults and a group of patients with a cochlear hearing loss of 15 and 20 dB HL. DPOAE grams are plotted for all primary tone levels decreasing from L_2 = 65 dB SPL (black line) to L_2 = 20 dB SPL (light gray line, in the first three plots). In the cochlear HL group DPOAEs could only be recorded down to L_2 = 40 dB SPL. Standard deviations are shown for the highest and lowest possible L_2.

For a better visualization of the DPOAE growth behavior, DPOAE data are plotted in the form of DPOAE I/O functions for the neonate group, the follow-up neonate group, and the normal hearing subject sample (Fig. 5.2, left panel) as well as for the cochlear hearing loss samples (Fig. 5.2, right panel). The DPOAE level, L_{dp}, was averaged across f_2 for all subjects. The DPOAE level of the neonate group was lower compared to that found in the follow-up neonate group. On average across L_2, the difference amounted to 2.8 dB. The difference between the neonates and the normal hearing subjects amounted to 2.5 dB, the difference between the follow-up neonates and the normal hearing subjects to 5.3 dB. The DPOAE level of the follow-up neonates differed significantly from that of the neonates and the normal hearing subjects (with the exception of follow-up neonates at L_2 = 20 and 25 dB SPL). The neonate group (despite the lower DPOAE level), the follow-up neonate group, and the normal hearing subject sample exhibited similar DPOAE growth behavior. In contrast, the DPOAE I/O functions of the cochlear hearing loss ears exhibited a continuous increase of the slope of the I/O function with increasing hearing loss (Fig. 5.2, right panel).

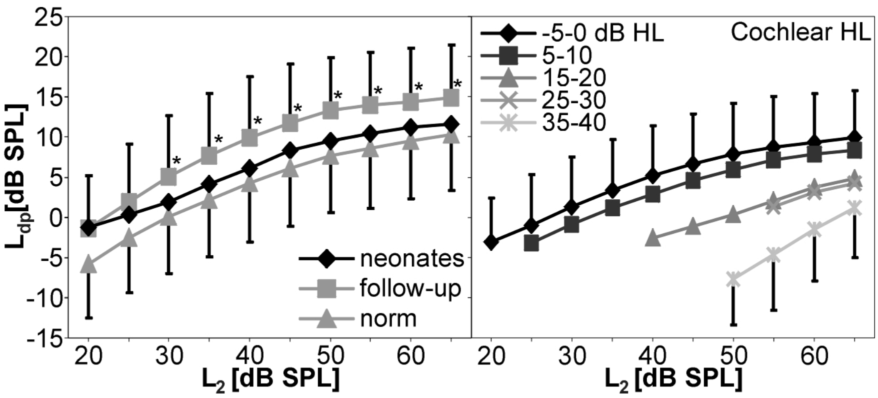

Figure 5.2: Left panel: mean DPOAE I/O functions across all f_2 frequencies for neonates, follow-up neonates and normal hearing adults. * : $p < 0.05$ (t-test). Right panel: mean DPOAE I/O functions across all f_2 frequencies for different cochlear hearing loss groups.

5.2.3 DPOAE threshold and compression estimates - normal hearing versus neonatal hearing and cochlear hearing loss

The linear fitting procedure for estimating the DPOAE threshold level is shown in Fig. 5.3. The left panel exemplarily plots DPOAE I/O functions at f_2 = 4 kHz in a logarithmic scale (L_{dp} across L_2). Both DPOAE I/O functions were derived from the same neonate ear after birth (black diamonds) and 4 weeks later (grey squares). The right panel plots the same data in a semi-logarithmic scale (p_{dp} across L_2). The intersection point between the linear regression line (dashed line in the right panel of Fig. 5.3) and the primary tone level axis (p_{dp} = 0 Pa) served as the DPOAE threshold level estimate. The estimated DPOAE threshold level for the first measurement amounted to $L_{dpth,neonate}$ = 28.4 dB SPL and improved for the follow-up measurement to $L_{dpth,follow-up}$ = 21.9 SPL. The dashed lines in the left panel of Fig. 5.3 show the regression lines presented in logarithmic scale. The compression k_{dp} of the extrapolated I/O function calculated at L_2 = 55 dB SPL was smaller in the first measurement compared to that of the follow-up measurement ($k_{dp,neonate}$ = 3.1 dB/dB, $k_{dp,follow-up}$ = 3.8 dB/dB).

Figure 5.4 (left panel) plots the estimated DPOAE threshold for the neonate group and the cochlear hearing loss samples relatively to the normal hearing subject sample across

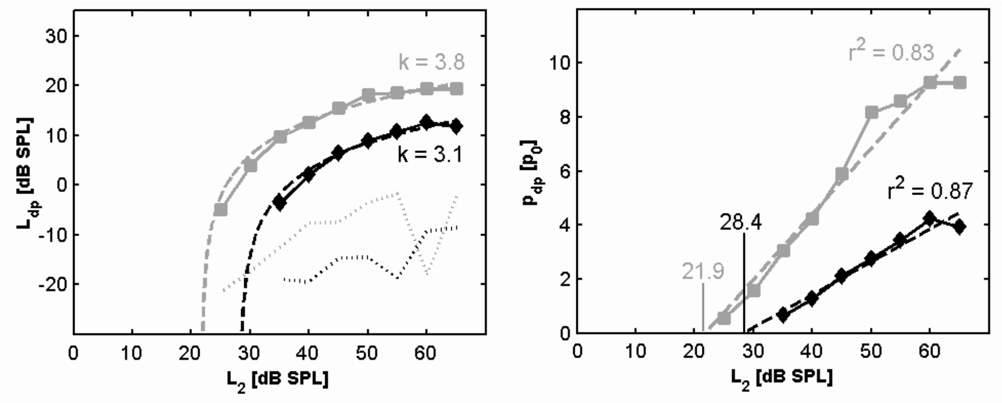

Figure 5.3: DPOAE I/O functions shown in logarithmic (left panel) and semi-logarithmic (right panel) scale for one neonate at $f_2 = 4$ kHz: early measurement (black diamonds) and the respective follow-up measurement (gray squares). Extrapolation of the DPOAE I/O function using linear regression analysis yields L_{dpth} values at the intersection point between linear regression line and abscissa in the right panel. Compression k_{dp} of the extrapolated I/O function was calculated at $L_2 = 55$ dB SPL. Dotted lines in the left panel show noise floor levels. The coefficient of determination r^2 is displayed for each regression line.

f_2. For example, at $f_2 = 4$ kHz the such estimated hearing loss (eHL) amounted to $L_{dpth,follow-up} - L_{dpth,norm} = 2.7$ dB for the follow-up neonate ears and to $L_{dpth,neonate} - L_{dpth,norm} = 10.4$ dB for the early postnatal neonate ears. The estimated hearing loss for the cochlear hearing loss samples amounted to $L_{dpth,HL} - L_{dpth,norm} = 0.1$ dB for the −5–0 dB HL sample, 5.6 dB for the 5–10 dB HL sample, 10.9 dB for the 15–20 dB HL sample, 23.5 dB for the 25–30 dB HL sample, and 30.6 dB for the 35–40 dB HL sample. When comparing the estimated hearing loss (eHL) and the behavioral hearing loss (HL) in the cochlear hearing loss ears, an underestimation of the hearing loss was obvious. Its degree varied with frequency and amount of hearing loss. The estimation error (i.e., $HL - eHL$) was lowest in the mid-frequency region and highest in the high and low frequency regions. The rationale for presenting the data following a clinical audiogram form was to allow an overview on changes between the different groups as well as on frequency and hearing-loss-specific changes within one group.

Figure 5.4 (right panel) plots the estimated DPOAE compression $k_{dp}(L_2)$ calculated at $L_2 = 55$ dB SPL for the two neonate groups and the cochlear hearing loss samples relatively to that of the normal hearing subject sample ($k_{dp,norm}$) across f_2. In the following, the compression ratio $k_{dp,norm}/k_{dp}$ is referred to as the estimated compression loss (eCL). For example, at $f_2 = 4$ kHz, eCL amounted to $k_{dp,norm}/k_{dp,neonate} = 1.3$ for the neonate ears and to $k_{dp,norm}/k_{dp,follow-up} = 1.1$ for the follow-up neonate ears, to $k_{dp,norm}/k_{dp,HL} =$ 1.0 (for −5–0 dB HL) 1.1 (5–10 dB HL), 1.3 (15–20 dB HL), 2.1 (25–30 dB HL), and 3.2 (35–40 dB HL) for the cochlear hearing loss samples. That means compression in the neonates was lower compared to that of the follow-up neonates. Compression of the

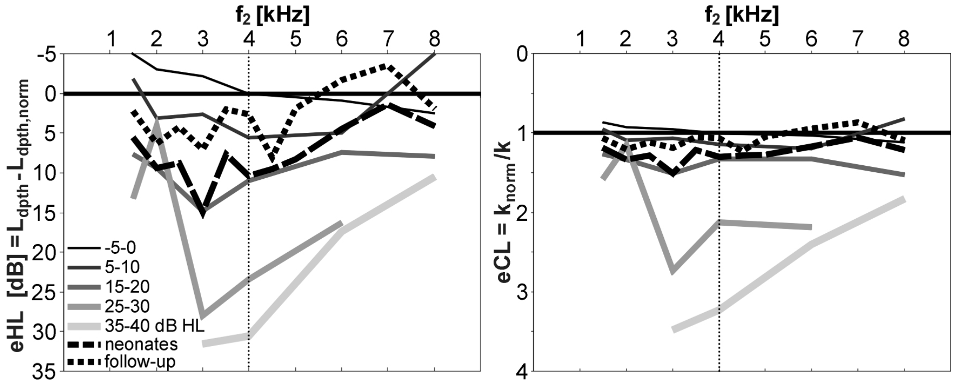

Figure 5.4: Left panel: Estimated hearing loss (eHL) in audiogram form. Mean L_{dpth} of the different HL classes and the two neonate groups is normalized with mean $L_{dpth,norm}$ of the normal hearing subject sample at the respective frequencies. Right panel: estimated compression loss (eCL) in audiogram form. Mean k_{dp} of the different HL classes and the two neonate groups is normalized with mean $k_{dp,norm}$ of the normal hearing subject sample at the respective frequencies. A ratio of $eCL = 1$ represents normal hearing.

neonates was quite similar to that of the 15–20 dB HL cochlear hearing loss sample. Only in cochlear hearing loss ears with hearing losses exceeding 20 dB HL a considerably higher compression loss was found.

Statistical differences in eHL and eCL between the groups were examined (unpaired t-test). This was done for $f_2 = 4$ kHz only. In the cochlear hearing loss ears, the estimated hearing loss (eHL) differed significantly ($p < 0.05$) in all groups with the exception of the respective neighboring groups (−5–0 dB HL group compared to 5–10 dB HL group, 5–10 dB HL group compared to 15–20 dB HL group, etc.). In the neonate and follow-up neonate ears, the estimated hearing loss (eHL) differed significantly, however, the estimated compression loss (eCL) did not. The estimated compression loss (eCL) differed significantly ($p < 0.05$) in all cochlear hearing loss groups with the exception of the −5–0 dB HL group compared to the 5–10 dB HL group, and the 5–10 dB HL group compared to the 15–20 dB HL group.

The fact that k_{dp} decreased with increasing cochlear hearing loss suggests the compression to provide an additional measure for quantifying cochlear hearing loss and for differentiating between sound conductive and cochlear hearing loss, at least for the mid frequency range. To test this hypothesis, the compression $k_{dp}(L_2)$ was calculated at $L_2 = 65$, 60, 55, 50, and 45 dB SPL for the different groups (see Fig. 5.5). With increasing cochlear hearing loss the compression decreased quite linearly. This was true for all L_2. The standard deviation was quite similar across hearing loss classes and L_2.

The statistical difference of DPOAE compression k_{dp} in the cochlear hearing loss groups was determined (Mann-Whitney test). When comparing neighboring cochlear hearing loss groups, k_{dp} differed significantly (with the exception of the 35–40 dB HL group at $L_2 = 45$ and 50 dB SPL). Thus, k_{dp} is suggested to provide a quantitative measure for

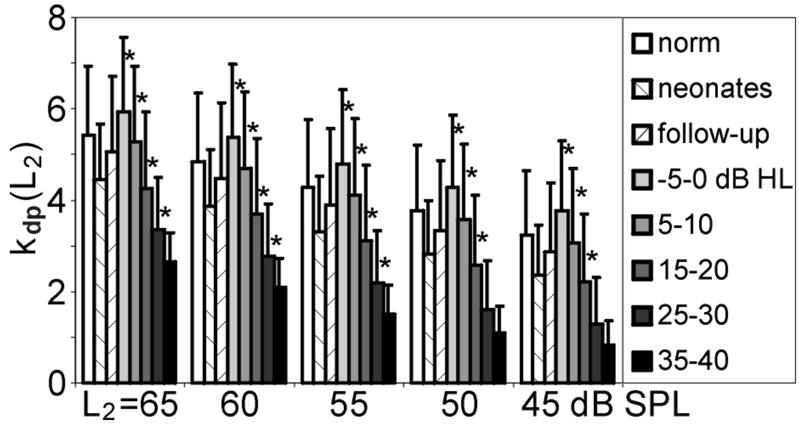

Figure 5.5: Mean and standard deviation of compression k_{dp} calculated at various primary tone levels L_2 of the extrapolated DPOAE I/O functions for neonates, follow-up neonates, normal hearing adults and different groups of cochlear hearing loss. * : $p < 0.05$ (Mann-Whitney test).

assessing cochlear compression. Mean DPOAE compression k_{dp} in the neonate, the follow-up neonate, and the norm group were within the range of the −5–0 dB HL and 15–20 dB HL cochlear hearing loss groups and was significantly lower ($p < 0.001$) when compared to the cochlear hearing loss groups exceeding 15–20 dB HL. In view of a differentiation between transitory sound conductive and persisting cochlear hearing loss in neonates this is an important finding. Table 5.1 presents the mean and standard deviation of the estimated DPOAE threshold level L_{dpth} and the DPOAE compression k_{dp} for the neonate, follow-up neonate, normal hearing, and cochlear hearing loss ears.

5.2.4 Modeling DPOAE I/O functions in sound conductive and cochlear hearing loss

For a better understanding of the different DPOAE behavior in sound conductive and cochlear hearing loss ears and hence for developing a strategy for differentiating between middle ear and cochlear disorders, a simple model was introduced (see Fig. 5.6). In that model a sound conductive hearing loss (A, B, and C) was modeled by shifting the normal hearing reference DPOAE I/O function (which was adopted from the DPOAE I/O function of the normal hearing subject sample at 4 kHz, where the average estimated DPOAE threshold level amounted to 10.6 dB SPL, see Tab. 5.1) to the same degree on the L_2-axis (representing the damping of the primary tone levels) as well as on the L_{dp}-axis (representing the damping of the DPOAE). The shift on the L_2-axis in the logarithmic plot (A, B, and C in the left panel of Fig. 5.6) resulted in a shift of the intersection point of the I/O function in the semi-logarithmic plot and hence in a change of the estimated DPOAE threshold level (being 20, 30, and 40 dB SPL corresponding to a hearing loss of 10, 20, und 30 dB HL with the normal hearing I/O function as a reference; see A, B, and C in the right panel of Fig. 5.6). Furthermore, it resulted in an increase of the slope at a fixed

L_2 level. In contrast, the shift on the L_{dp}-axis did neither change the estimated DPOAE threshold level nor the slope. However, it resulted in a significant decrease of L_{dp} also at high primary tone levels.

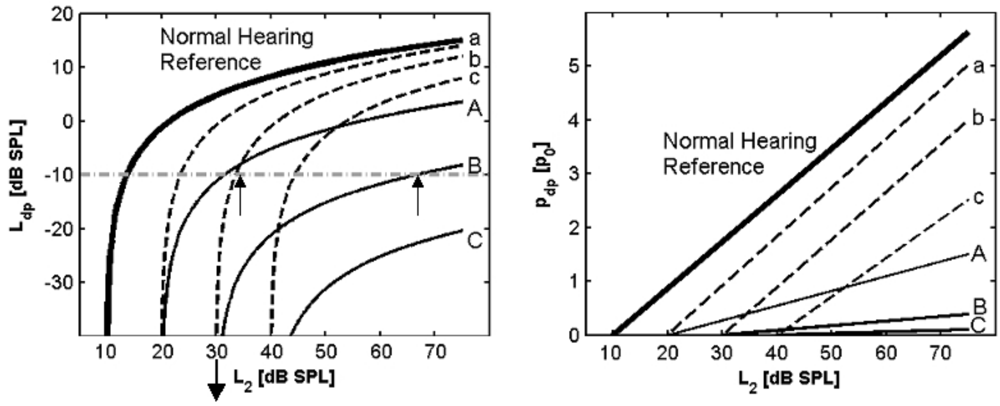

Figure 5.6: DPOAE model functions simulating cochlear and middle ear disorders shown in logarithmic (left panel) and semi-logarithmic scale (right panel). The thick solid line represents a normal hearing reference subject with an estimated DPOAE threshold level of 10 dB SPL. Solid curves (A), (B), and (C) represent 10, 20, and 30 dB HL sound conductive hearing loss. Dashed curves (a), (b), and (c) represent 10, 20, and 30 dB HL cochlear hearing loss. The horizontal line in the left panel indicates the DPOAE detection threshold (L_{nf} + 6 dB). Thin arrows indicate the different DPOAE detection thresholds, whereas the thick arrow indicates the estimated DPOAE threshold in the case of the 20 dB HL cochlear and the 20 dB HL sound conductive hearing loss example.

For simulating DPOAE behavior in cochlear hearing loss, DPOAE I/O functions were used which were modeled on extrapolated DPOAE I/O functions from the cochlear hearing loss ears of the study (a, b, and c in the left panel of Fig. 5.6) resulting in an estimated DPOAE threshold level of 20, 30, and 40 dB SPL corresponding to a hearing loss of 10, 20, und 30 dB HL (a, b, and c in the right panel of Fig. 5.6). The slope at a fixed L_2 level increased with increasing hearing loss. In comparison to the sound conductive hearing loss I/O functions (A, B, C) the shift on the L_{dp}-axis of the cochlear hearing loss I/O functions (a, b, c) was considerably lower (left panel of Fig. 5.6).

To summarize, in both middle-ear and cochlear disorder, an increase of hearing loss could be expected to result in an increase of the slope of the DPOAE I/O function at a certain fixed L_2 level, even if the reasons for the change in slope are of a different nature. In sound conductive hearing loss there was a shift of the DPOAE I/O function along the L_2-axis which shifts the fixed point at which the slope is calculated to lower L_2 levels. In contrast, the increase in slope in cochlear hearing loss was suggested to be a result of a change in the nonlinear compressive sound processing of the cochlear amplifier. The main difference between sound conductive and cochlear hearing loss can thus be found in the absolute magnitude of DPOAE level L_{dp} especially at the higher primary tone levels. In sound conductive hearing loss, the shift on the L_{dp}-axis was much higher compared to that in cochlear hearing loss. When comparing the 30 dB HL DPOAE I/O functions of the sound conductive and the cochlear hearing loss, a difference in the DPOAE level of almost 30 dB was evident (compare C and c in the left panel of Fig. 5.6). In contrast, the slope was nearly the same in both conditions. This was also true for the 10 and 20 dB HL DPOAE I/O functions (compare A and a, and B and b in the left panel of Fig. 5.6). That means the slope of the DPOAE I/O function in the model does not allow a differentiation between sound conductive and cochlear hearing loss of the same degree.

In the model, the DPOAE level at a 20 dB HL sound conductive hearing loss amounted to only −10 dB SPL at the highest L_2 (see B in the left panel of Fig. 5.6). Supposing a noise floor level of −16 dB SPL and a minimum SNR of 6 dB, a reliable DPOAE measurement would be possible if the DPOAE level exceeded −10 dB SPL. This DPOAE detection threshold is indicated in Fig. 5.6. On this condition, in the presence of a 20 dB HL sound conductive hearing loss, DPOAEs would be measurable only at the highest L_2 resulting in a large difference between the estimated DPOAE threshold and the DPOAE detection threshold level (see arrows in Fig. 5.6). In contrast, the DPOAE level of the 20 dB HL cochlear hearing loss amounted to almost 10 dB SPL at the highest L_2 in the model (see b in the left panel of Fig. 5.6). Thus, despite the 20 dB HL cochlear hearing loss a reliable DPOAE measurement would be achieved at L_2 down to almost 30 dB SPL resulting in a small difference between the estimated DPOAE threshold and the DPOAE detection threshold level (see arrows in Fig. 5.6). At a 30 dB HL sound conductive hearing loss the DPOAE level was below the DPOAE detection threshold (see C in Fig. 5.6). In contrast, at a 30 dB HL cochlear hearing loss the detection threshold level and the estimated DPOAE threshold level (which is 40 dB SPL) hardly differed. Even at a 40 dB HL cochlear hearing loss the difference between the estimated DPOAE threshold and the DPOAE detection threshold level was very small. Thus, the difference of the two measures can be considered as a means for differentiating between sound conductive and cochlear hearing loss.

5.2.5 Frequency-specific DPOAE behavior in neonates

DPOAE data of a single neonate ear (3 days old) demonstrates that the DPOAE level and the estimated hearing threshold considerably varied with frequency. The DPOAE grams (see Fig. 5.7) were close together at the higher (upper curves) and more separated at the lower primary tone levels (lower curves) revealing normal compressive cochlear sound processing. The DPOAE level was lower at the higher test frequencies (around 4 kHz) compared to that found at the lower test frequencies (around 2 kHz). When comparing the DPOAE I/O functions at 2 and 4 kHz a considerable change in the DPOAE level was obvious, the difference being almost 10 dB. However, both I/O functions exhibited the same compressive shape.

The downward shift of the DPOAE I/O function and the change in the DPOAE level were comparable with that found in the model in the case of the simulated sound conductive hearing loss (see B in Fig. 5.6). However, when comparing the neonate DPOAE I/O functions with that of the model in the case of a 10 dB HL cochlear hearing loss, a completely

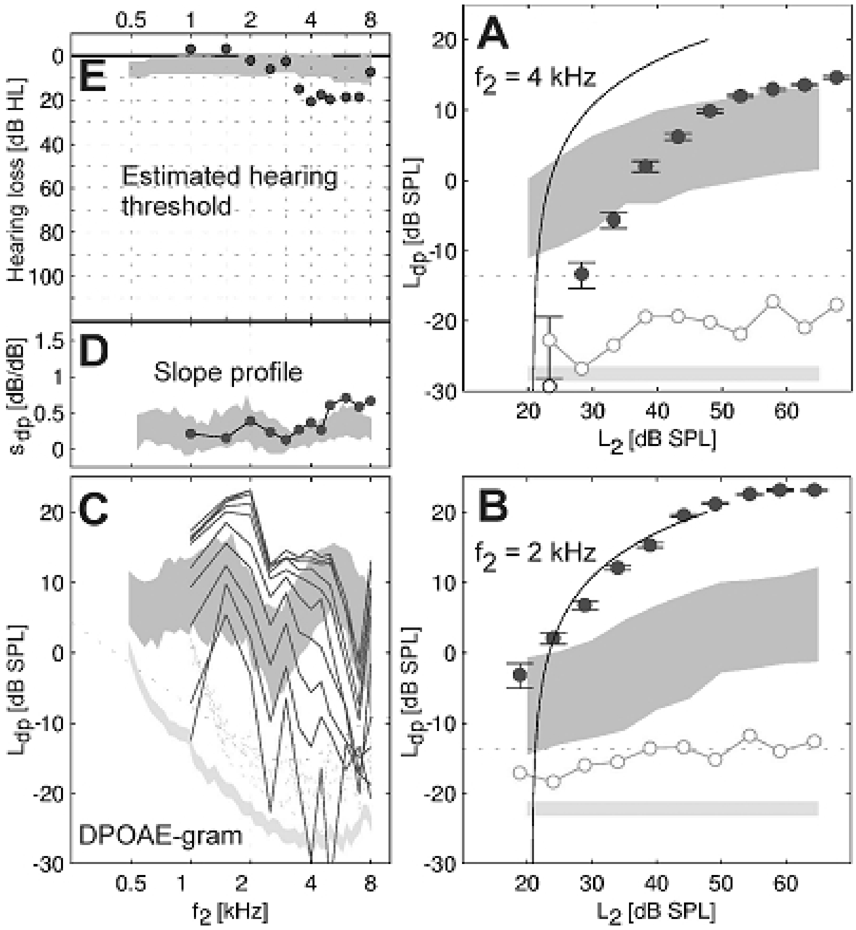

Figure 5.7: Case example of a newborn (3 days old). DPOAE I/O functions at 4 kHz (A) and 2 kHz (B). DPOAE grams and slope of the DPOAE I/O functions are plotted in panels (C) and (D). The estimated hearing threshold derived from extrapolated DPOAE I/O functions are shown in panel (E). Shaded areas show normative data (standard deviation of the normal hearing subject sample). In panels (A) and (B) the noise floor is indicated by open circles, in panel (C) by dotted lines. The bottom gray area in panel (C) indicates a typical noise floor in the sound-proof cabin where measurements in normal hearing subjects and patients with cochlear hearing loss were performed.

different I/O behavior was obvious since the DPOAE level only slightly decreased in the high primary tone level range (see a in Fig. 5.6). This was quite different from that found in the neonate ear where a difference in DPOAE level of almost 10 dB was present in the entire primary tone level range. The slight increase in slope for test frequencies above 4 kHz (see Fig. 5.7D) was compatible with the findings of the model where a slight change in slope was present in the case of sound conductive hearing loss.

Figure 5.8 shows mean and standard deviation of the DPOAE level obtained in the 21 follow-up neonate ears during the first and second measurement. At f_2 = 1.5 kHz there was no difference in the DPOAE level. At the other test frequencies the DPOAE level differed considerably, being lower in the early postnatal period (compare the first and follow-up measurements in Fig. 5.8). The highest difference in the DPOAE level was found at $f_2 = 3.5$ kHz and amounted to almost 10 dB at $L_2 = 65$ dB SPL. As in the single neonate ear, the average DPOAE level in the pooled data obtained in the first measurement was highest at the lowest test frequency and decreased almost continuously with increasing test frequency (compare Fig. 5.7C and Fig. 5.8). In contrast, follow-up data exhibited DPOAE levels which were almost independent of test frequency being around 10–15 dB SPL at $L_2 = 65$ dB SPL (see Fig. 5.8).

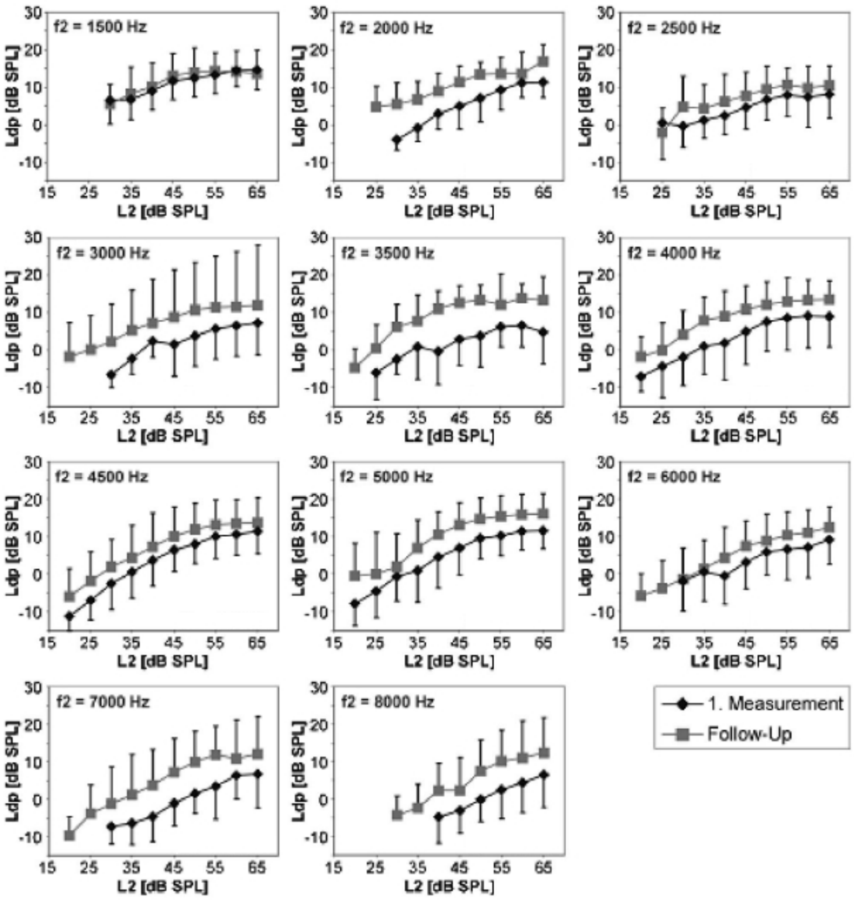

Figure 5.8: Mean and standard deviation of DPOAE I/O functions of the first (black) and follow-up (grey) measurement in the neonate ears for all test frequencies (for the numbers of ears for each frequency see Tab. 5.1).

In the pooled data, there was a clear downward shift when comparing the DPOAE I/O functions obtained in the follow-up and first measurement. This DPOAE behavior was true for all frequencies except 1.5 kHz and corresponds to that found in the model in the case of sound conductive hearing loss, where a considerable decrease in DPOAE level was obvious nearly independent of the primary tone level (compare A in Fig. 5.6 to Fig. 5.8). The frequency-specific change in the DPOAE level observed in the early postnatal period, the downward shift of the DPOAE I/O functions along the L_{dp}-axis, and the increase of the DPOAE level in the follow-up measurement indicate a transitory sound conductive hearing loss during the early postnatal period.

5.3 Discussion

In the present study the question of whether extrapolated DPOAE I/O functions are able to estimate hearing loss and to differentiate between middle ear and cochlear disorders in neonates was addressed. In the following the achieved results are discussed.

Influence of different ear canal lengths on DPOAEs in neonates and adults

The variation of the DPOAE level with test frequency was higher in the normal hearing adult subjects compared to that in the neonate ears. The higher variation of DPOAE level with test frequency in the normal hearing ears in comparison to the neonate ears can be attributed to calibration errors. Due to standing waves, the sound pressure at the tip of the sound probe can differ considerably to that measured at the ear drum. This is true especially in outer ear canals with large lengths (see Sec. 3.4). As a consequence, suboptimal primary tone stimulation was more likely in the adult subjects which exhibited larger ear canal length. This results in DPOAE I/O functions which do not reflect cochlear non-linearity and hence do not estimate hearing threshold with a sufficient accuracy. The fact that the variation of the DPOAE level (Fig. 5.1, normal hearing adults) and the underestimation of the hearing threshold (Fig. 5.4, cochlear hearing loss patients) was highest in the $\lambda/4$ and $\lambda/2$ range ($f_2 = 3$ and 8 kHz) supports this assumption. Thus, for improving hearing threshold estimation in the mid and high frequency range, the stimulus calibration has to be improved. However, the influence of calibration errors may be lower in neonate ears since their ear canal length is smaller and thus calibration effects are supposed to occur at higher frequencies.

Influence of cochlear maturation or amniotic fluid on DPOAEs in early postnatal measurements

The DPOAE level was smaller and estimated hearing thresholds were higher during the early postnatal period compared to that found in the follow-up measurement four weeks later. The question is: what is the reason for the increase in DPOAE level and the decrease in the estimated hearing threshold when comparing the DPOAE measures obtained in the early postnatal period (mean age 3.2 days) and 4 weeks later? A change in the outer ear canal volume can be excluded since the ear canal volume should be larger in the follow-up neonate ears than in the neonate ears. Consequently, the DPOAE level should decrease and not increase over time. The lower DPOAE level in the neonate ears is therefore suggested to be caused by other impacts, i.e., either sound conductive hearing loss or cochlear immaturity.

According to previous literature, DPOAEs of term-born neonates appear to be adult-like. This was found to be true for various parameters like the shape of I/O functions or iso-suppression tuning (Abdala, 1998, 2001). However, in more recent publications several differences between neonates (term-born and premature) and adults are reported. Especially, premature neonates show non-adult-like behavior of DPOAE iso-suppression tuning and linearized DPOAE I/O functions (Abdala, 2000, 2003; Abdala and Chatterjee, 2003). These differences led to the assumption that the cochlear amplifier maturates closely around term birth or in the first months of postnatal life. The analysis of optimum f_2/f_1 ratios for DPOAE measurements (Brown *et al.*, 2000; Vento *et al.*, 2004) may also give information about cochlear maturation, but these data should not be overrated, because of problems with calibration and the different sizes of outer ear canals between various age groups.

It is known from literature that any manipulation of the middle ear results in a change of DPOAE level. For example, when changing the middle ear's stiffness by changing the atmospheric pressure (e.g., Osterhamel *et al.*, 1993) or changing the middle ear's mass by filling the bulla with fluid or during otitis media with effusion (e.g., Ueda *et al.*, 1998) the DPOAE level is reported to decrease. Priner *et al.* (2003) recorded DPOAEs in newborn guinea pigs and reported increasing DPOAE levels from birth until the fourth day of life. This increase in the DPOAE level was accompanied by reduced amounts of residual amniotic fluid in the bulla. Gehr *et al.* (2004) simulated middle ear effusion by filling the bulla of guinea pigs with saline solution and found a clear downward shift of DPOAE functions with the slope being hardly affected. Moreover, they compared the slope of the treated guinea pigs with that of guinea pigs which were exposed to white noise with a level of 115 dB SPL for 2.5 h on two consecutive days and found the slope to be significantly increased.

Moreover, in the present study the DPOAE level was found to vary with test frequency in the early postnatal period and was almost independent of test frequency in the follow-up measurement. As explained in Sec. 2.2, increasing stiffness affects the low, whereas increasing mass affects the high test frequencies. Thus, increased middle ear mass due to amniotic fluid and/or increased stiffness due to Eustachian tube dysfunction are suggested to be the most likely reasons for the observed hearing loss in the neonate group of the present study. Increasing mass and stiffness would affect both high and low frequencies, i.e. the change in hearing threshold is not restricted to the high frequency range. This could be an explanation for the findings of the pooled data (see Fig. 5.8) which showed a decrease in the DPOAE level in a broader frequency range compared to that observed in the single neonate ear (see Fig. 5.7). Also, the clear downward shift of the DPOAE I/O function (see Fig. 5.8) which is typical for a sound conductive hearing loss (see model, Fig. 5.6) speaks for the presence of a sound conductive hearing loss and against cochlear maturation.

Influence of background noise on DPOAE test performance

In the normal hearing subject sample hearing threshold estimation could be performed in almost all ears at most test frequencies. In the neonates, the percentage of ears in which hearing threshold estimation could be achieved was lower, which can be attributed to the higher noise levels (see Tab. 5.1). Gorga *et al.* (2000b) described DPOAE and noise levels in a huge neonate collective (n = 2348) for a frequency range between 1 and 4 kHz and for two stimulus intensities ($L_2|L_1 = 50|65$ dB SPL, $L_2|L_1 = 75|75$ dB SPL) and reported an increasing noise level with frequency (about -10 dB SPL at $f_2 = 4$ kHz and 0 dB SPL at $f_2 = 1.5$ kHz), resulting in the most favorable SNRs at 3 and 4 kHz. In the present study, high test frequencies exhibited noise levels which were similar to that found at $f_2 = 4$ kHz (e.g., -13.3 dB SPL at $f_2 = 6$ kHz, -14.6 dB SPL at $f_2 = 8$ kHz). That means that in neonates, favorable SNRs can be achieved in the high frequency region also. This is in contrast to the normal hearing adults in which the DPOAE levels considerably decreased (due to standing wave problems) and hence favorable SNRs could not be achieved at test frequencies above 6 kHz (see Fig. 5.1). At low test frequencies the noise level was higher (-3.7 dB SPL at $f_2 = 1.5$ kHz, -7.6 dB SPL at $f_2 = 2$ kHz) and the DPOAE level was similar to that of the normal hearing adults making measurements less reliable.

The variation of the DPOAE and noise floor level was reflected in the percentage of ears in which hearing threshold estimation across frequency was possible. In the normal hearing adult ears (in which the noise level varied between -14.3 and -21.9 dB SPL) in almost all ears criteria for threshold estimation were fulfilled at all test frequencies with the exception of $f_2 = 8$ kHz (due to the low DPOAE level) where the percentage was only 65.4 %. In the neonates the percentage of ears in which hearing threshold estimation was possible varied between 33.1 % and 74.6 % across frequency being largest at mid and high test frequencies. On average, in a single neonate ear the approach enabled hearing threshold estimation at about $\frac{2}{3}$ of the test frequencies. Thus, test performance in the neonates was lower compared to that of the adults, but with respect to the worse environmental conditions sufficient test performance of the approach under hearing screening conditions is suggested. It should be emphasized that Tab. 5.1 does not list the number of ears in which valid DPOAEs could be measured but rather the number of ears in which DPOAE I/O function extrapolation criteria were met and hence DPOAE hearing threshold estimation could be performed (see Sec. 5.1.2).

Differentiation in sound conductive and cochlear hearing loss according to the introduced model and recorded DPOAE data

DPOAEs in sound conductive and cochlear hearing loss of the same degree exhibited similar compression (see model, Fig. 5.6, and data, Figs. 5.4 and 5.5) and hence a differentiation between middle ear and cochlear disorders solely by means of DPOAE compression does not seem to be possible. In contrast, in animal experiments (Gehr *et al.*, 2004) no significant change in the slope of DPOAE I/O functions was found, when comparing data of filled and unfilled bulla. The contradicting findings of the model and the measuring data in animals make a search for an additional measure necessary. A suited candidate might be the difference between the estimated DPOAE threshold (which is the intersection point between the extrapolated DPOAE I/O functions with the L_2-axis) and the DPOAE detection threshold (which is the lowest primary tone level at which a valid DPOAE is measurable).

According to the model, in cochlear hearing loss the estimated DPOAE and the DPOAE detection thresholds were close together, whereas in sound conductive hearing loss the two measures differed highly (see arrows in Fig. 5.6). Thus, from the model the difference of the two measures is suggested to be a means for differentiating between sound conductive and cochlear hearing loss. In this study, a comparison between the two measures was not conducted since DPOAE measurements were restricted to minimum primary tone levels of 20 dB SPL. Due to the large emission amplitude found in neonates, the DPOAE detection threshold is, however, expected to be below this primary tone level. Hence, the evaluation of the proposed model was not possible with the given data. To our knowledge, there is no study in literature, which compares DPOAE behavior in sound conductive and cochlear hearing loss ears, neither in neonates nor in children or adults. Thus, further studies will have to find out whether a differentiation between sound conductive and cochlear hearing loss by means of DPOAEs is actually possible.

The fact that compression differed significantly in different cochlear hearing loss groups (see Fig. 5.5) suggests compression (or slope, respectively) to be an additional measure (besides DPOAE level and estimated DPOAE threshold) for quantitatively assessing cochlear hearing loss.

Applicability of the proposed strategy for differentiation between sound conductive and cochlear hearing loss by means of DPOAEs in clinical practice

From a simple model it could be derived that DPOAE I/O functions in the presence of sound conductive hearing loss differed considerably from that which was found in the presence of cochlear hearing loss. The model and practical experience have shown that DPOAE levels are considerably lower in sound conductive hearing loss (because there is a damping of the stimulus and the DPOAE response) in comparison to those found in cochlear hearing loss (where only a reduction of the DPOAE response occurs). As a consequence, in sound conductive hearing loss exceeding 20 dB HL no DPOAEs would be measurable, whereas in cochlear hearing loss, DPOAEs would be measurable at up to about 40 to 50 dB HL. In neonates, who usually exhibit large DPOAE levels, the DPOAE detection threshold levels might be slightly larger. Nevertheless, the proposed method for differentiating between sound conductive and cochlear hearing loss may only work for small sound conductive hearing losses of up to about 20 dB HL.

In view of an application in UNHS protocols, where a fast measurement procedure is required, the measurement strategy of the present study could be modified, i.e. test time could be reduced, e.g., by reducing the number of test frequencies (e.g., $f_2 = 1.5, 2, 3, 4, 6$ kHz). Assuming an average time of 4 s per DPOAE and 5 test frequencies, the maximum test time for estimating the hearing threshold would amount to 200 s (at 10 primary tone levels). Another possibility to reduce measurement time is varying the primary tone level from low to high levels and stopping the measuring procedure if a valid DPOAE response is present at a defined low primary tone level (e.g., $L_2 = 25$ dB SPL). At these frequencies the recording of DPOAE I/O functions would then not be necessary and the hearing threshold could be considered as normal. In doing this the measuring time would then depend on the type and the degree of the hearing loss. The minimum test time would amount to 20 seconds in a healthy ear, in which a valid response is present at the lowest primary tone level. The implementation of noise-floor dependent averaging times could further improve testing time.

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6 Improvements in quantifying efferent reflex strength by means of DPOAEs

The efferent medial olivocochlear (MOC) system is supposed to alter the operability of the cochlear amplifier (see Sec. 2.2). It can be divided into the crossed and uncrossed feedback loop, which both project onto the ipsilateral OHCs and which can be examined either by means of ipsilateral DPOAE adaptation or contralateral DPOAE suppression, respectively. Both DPOAE suppression and adaptation are suggested to be a means for evaluating the MOC system's reflex strength (see Sec. 2.5.3). In previous studies in humans, MOC-related effects on DPOAEs were usually found to be rather small, suggesting that the clinical applicability of DPOAEs for investigating the function of the MOC efferents seems to be restricted. However, Maison and Liberman (2000) paved the way for getting higher DPOAE adaptation effects by finding large bipolar changes (i.e., transition from enhancement to suppression) in adaptation magnitude for a small shift in primary tone levels (see Sec. 2.5.3).

The aim of this study was to investigate the capability of quantifying the reflex strength of the MOC efferents by recording contralateral DPOAE suppression (in the following named CAS DPOAE) and ipsilateral DPOAE adaptation in humans. The main question was whether large bipolar changes in DPOAE level also occur in humans when changing the primary tone level within a small range as described by Maison and Liberman (2000) for guinea pigs. In the study, CAS DPOAE and ipsilateral DPOAE adaptation were measured at particular frequencies, i.e. when the DPOAE fine structure exhibited pronounced dips. This was done because the second DPOAE source is suggested to generate the dips and peaks in the fine structure (e.g., Mauermann and Kollmeier, 2004) and to be the reason for the observed bipolar change in DPOAE level (Kujawa and Liberman, 2001). Also, in view of a clinical application for assessing efferent MOC reflex strength, this study investigated the reproducibility of DPOAE measures.

6.1 Material and methods

6.1.1 Subjects

Seven subjects (10 ears) with normal hearing participated in the study. The subjects (4 male, 3 female) were aged between 19 and 30 years. Clinical audiometry showed that hearing thresholds were 15 dB HL or lower at audiometric test frequencies between

500 and 8000 Hz. For all subjects tympanometry showed normal middle ear function. A brief medical history was taken from each subject documenting the absence of ear-related complaints, ear infections, ear surgery, and ototoxic medication use. Moreover, ipsilateral and contralateral stapedius reflex thresholds were measured at 4 kHz. The median stapedius reflex threshold amounted to 90 dB SPL, while the minimum reflex threshold was 75 dB SPL. All measurements were conducted in a sound-attenuated cabin while subjects were seated in a comfortable recliner.

6.1.2 Stimulus generation and DPOAE recording

DPOAE measurements were recorded using the measurement system described in Chapter 3. Primary tone levels were adjusted according to an in-the-ear calibration strategy, whereas contralateral noise signals were calibrated a priori in an ear simulator (Brüel&Kjær Type 4157) with no adjustment of the individual ear canal volume.

DPOAEs were accepted as valid for SNRs exceeding 6 dB. The noise floor level was computed by averaging the levels at six frequencies located around the DPOAE frequency. During the measurement, if a DPOAE value failed to fulfill this criterion or if the noise level between two consecutive measurements increased by more than 5 dB, the measurement of the DPOAE was repeated with the current parameter setting at least twice or until the emission was accepted as valid. Technically distorted data were discarded when the levels of at least seven out of ten frequency bins at other distortion product components (e.g., $2f_2 - f_1$) around the DPOAE component at $f_{dp} = 2f_1 - f_2$ exceeded an SNR of 10 dB. The SNR criterion was not checked at single DPOAE adaptation measurements since the measurement time was, especially in cases of responses with low emission levels, too short for sufficient time domain averaging.

6.1.3 DPOAE fine structure measurement procedure

The DPOAE fine structure was measured between $f_2 = 3000$ and 5016 Hz with a frequency resolution of $\Delta f_2 = 47$ Hz. The primary tone level L_2 was set to 40, 30, and 20 dB SPL, whereas L_1 was set according to the equation $L_1 = 0.4L_2 + 39$ dB SPL. The averaging time for recording DPOAEs was set to 4.5 s and the pause time between two measurement settings to 1 s. The total measuring duration amounted to about 15 minutes.

For further evaluation, the dip depth $d_{dip,L2}(f_2)$ was calculated by adding up the DPOAE level differences between f_2 and both neighboring frequencies for a constant L_2. The overall dip depth $d_{dip}(f_2)$ was defined as the average across $d_{dip,L2}(f_2)$ for the three L_2 level settings (L_2 = 40, 30, 20 dB SPL). Equations 6.1 and 6.2 illustrate the calculation of the dip depth values.

$$d_{dip,L2}(f_2) = [L_{dp}(L_2, f_2) - L_{dp}(L_2, f_2 - \Delta f)] + [L_{dp}(L_2, f_2) - L_{dp}(L_2, f_2 + \Delta f)] \quad (6.1)$$

$$d_{dip}(f_2) = \frac{d_{dip,40}(f_2) + d_{dip,30}(f_2) + d_{dip,20}(f_2)}{3} \tag{6.2}$$

Please note that in the following the term dip depth is used synonymously with the overall dip depth d_{dip}. The standard deviation of d_{dip} across the entire frequency range was used as a measure for quantifying the roughness of DPOAE fine structure.

For reproducibility examinations, DPOAE fine structure was measured for one subject (J.M.) with the parameter setting described above, ten times on different days and eight times on one day with constant and varying ear probe position, respectively.

6.1.4 CAS DPOAE measurement procedure

CAS DPOAEs were measured at two frequencies, depending on the results of the DPOAE fine structure. The first frequency $f_{2,dip}$ was located at the deepest dip in the DPOAE fine structure. The second frequency $f_{2,flat}$ was at a location, where there was no major change of L_{dp} across frequency. If there was no completely flat region, a point at a peak in the fine structure was chosen ($d_{dip}(f_2) > -0.2$ dB).

The effect of CAS on DPOAEs was investigated at different $L_2|L_1$ combinations. L_2 was shifted from 60 down to 20 dB SPL in steps of 5 dB. For each L_2, L_1 was changed symmetrically around the center level $L_{1,center} = 0.4L_2 + 39$ dB SPL. The offset $L_{1,offset}$ around $L_{1,center}$ was changed from -10 to $+10$ dB in steps of 2 dB. Thus, altogether 99 $L_2|L_1$ combinations were examined. The averaging time for recording DPOAEs was set to 4.5 s and the pause time between two consecutive DPOAE measurements to 1 s as it was done for recording DPOAE fine structure. For each level setting, DPOAEs were recorded first in the absence and then in the presence of CAS. The contralateral stimulus was started 0.5 s before the onset of the ipsilateral primary tones and ended 0.5 s after their termination. The contralateral stimulus consisted of broadband noise which was presented with a stimulus level of 60 dB SPL. The total measuring duration for each frequency amounted to about 25 minutes.

Please note that the DPOAE level difference between measurements with and without CAS is in the following labeled $\Delta L_{dp,CAS}$. Positive values of $\Delta L_{dp,CAS}$ mean enhancement, negative values suppression. For evaluating the MOC reflex strength, corresponding to the definition of Maison and Liberman (2000), a value was defined, which in the following is referred to as peak-to-peak efferent reflex strength (PPERS). It was defined as the difference between maximum enhancement and maximum suppression. In the very few cases where no enhancement occurred, it was defined as the difference between minimum and maximum suppression.

For reproducibility examinations, the effect of CAS on DPOAEs was measured for one subject (J.M.) at one frequency ($f_{2,dip}$) ten times on different days and eight times on one day with constant and varying ear probe position, respectively.

6.1.5 Ipsilateral DPOAE adaptation measurement procedure

Corresponding to CAS DPOAE measurements, ipsilateral DPOAE adaptation was measured at frequencies $f_{2,dip}$ and $f_{2,flat}$. At least three different $L_2|L_1$ combinations were selected for each frequency. The first level combination was that one in the primary tone level matrix that resulted in maximum DPOAE suppression during CAS, while the second level combination was that one leading to maximum DPOAE enhancement during CAS. These two level combinations were chosen based on the assumption that for ipsilateral adaptation a distinct change in DPOAE level should appear if there is a similar behavior for CAS and IAS effects. However, the DPOAE level and hence the SNR at level combinations leading to maximum suppression or enhancement, respectively, were usually low. As a consequence, depending on how much time the subject could spare, additional measurements were carried out at one to four other level combinations with varying but normally rather low suppression or enhancement during CAS but with high emission levels. The DPOAE adaptation measurements were conducted immediately after DPOAE suppression measurements with the same ear probe position in order to attain best possible comparability.

DPOAE adaptation was measured using monaural primary tone stimulation in order to exclusively assess the function of the crossed MOC system. The rise/fall times of the stimuli were zero. The measurement time for recording the DPOAE time course as well as the pause time between two measurements was set to 2 s. The number of consecutive measurements for time domain averaging was set to 100. The total measuring duration for one level combination and for one frequency amounted to about 7 minutes.

In order to check the adaptation behavior in notched regions of DPOAE I/O functions, as suggested by Maison and Liberman (2000), for three subjects adaptation was measured at seven primary tone level combinations (constant L_2 and varying L_1) around a distinct notch in the DPOAE I/O function. L_2 was chosen taking into account all cross-sections of the suppression matrix with L_2 held constant while L_1 was varied, resulting in DPOAE I/O functions with L_{dp} plotted above L_1. L_2 was selected depending on which of the I/O functions showed (*i*) the most pronounced notch and (*ii*) a major bipolar change of $\Delta L_{dp,CAS}$ from suppression to enhancement. L_1 was varied from -3 to $+3$ dB in steps of 1 dB around the deepest point of the notch.

For reproducibility examinations, DPOAE adaptation was measured for one subject (J.M.) at one frequency ($f_2 = 4219$ Hz) and one level combination ($L_2|L_1 = 60|67$ dB SPL) eight times on one day with constant and varying ear probe position, respectively. The level combination was chosen since reliable DPOAE adaptation measurements were only possible at high primary tone levels.

For evaluating DPOAE adaptation, the DPOAE post-onset time course was calculated using the heterodyne technique described by Kim *et al.* (2001). A Blackman-shaped filter with a limiting frequency of 120 Hz was applied. An exponential fitting function was calculated on the basis of the DPOAE level time course. Following Kim *et al.* (2001) a nonlinear simplex fitting procedure was used to obtain the least-squared difference between the DPOAE envelope level and the exponential fitting function. For this step, a short offset period (30 ms) of the DPOAE envelope level at the beginning and the same period at the end of the stimulus were excluded in order to remove transients at the two ends. The following fitting function shown in Eq. 6.3 was applied.

$$L_{dp}(t) = L_{ss} - m \cdot exp^{\frac{-t}{\tau}} \tag{6.3}$$

$L_{dp}(t)$ is the fit for the DPOAE envelope level as a function of time t. L_{ss} represents the steady-state DPOAE level, m the magnitude, and τ the time constant of adaptation. Please note that a positive m means an increasing (enhancement) and a negative m a decreasing (suppression) adaptation time course. The initial estimate for L_{ss} was calculated from the average level of the last second of the time course signal. The initial estimate for m was set to 0.7 dB and for τ to 70 ms. The values were chosen to be within the margins of the results of other studies of DPOAE adaptation in humans (Kim *et al.*, 2001; Bassim *et al.*, 2003). The quality of the fit is given as the variance accounted for (VAF), which is defined as VAF = 1 - r where r is the ratio of (*i*) the mean-squared difference between the fitting function and the DPOAE envelope level and (*ii*) the variance of the DPOAE level. The value of VAF ranges from 0 (poor fit) to 1 (perfect fit). In this study, fitting functions were regarded as valid for VAF values exceeding 0.1.

6.2 Results

6.2.1 DPOAE fine structure and its intra-individual reproducibility and inter-individual distribution

Dips and their reproducibility in a single subject

DPOAE fine structure across frequency and its reproducibility was examined in one subject (J.M.) for three different test conditions. Measurements were conducted over several days (n = 10), and on one day with varying (n = 8) and constant (n = 8) ear probe position, respectively. The result for the worst test condition, i.e. the measurement of DPOAE fine structure on ten different days, is shown in Fig. 6.1.

The standard deviation of the DPOAE level L_{dp} was on average across frequency and primary tone levels 1.8 dB (at a mean DPOAE level of −1.1 dB SPL and a noise floor level of −26 dB SPL; see Fig. 6.1A) and was highest in dip regions of DPOAE fine structure, i.e. for lowest SNRs. The maximum standard deviation at the largest dip amounted to 4.6 dB at 4125 Hz. In general, all major dips were present in all repetition measurements and at all primary tone levels (see Fig. 6.1, panels Ba–Bc, i.e. data at L_2 = 40 to 20 dB SPL), whereas their dip depth fluctuated across measurements. The dip depth and its variability was examined at the three deepest dips of the averaged DPOAE fine structure data with d_{dip} (see Eq. 6.2) amounting to -21.0 ± 8.1 dB at f_2 = 3328 Hz, -18.0 ± 4.5 dB at 4125 Hz, and -13.6 ± 4.0 dB at 3516 Hz. The average roughness of DPOAE fine

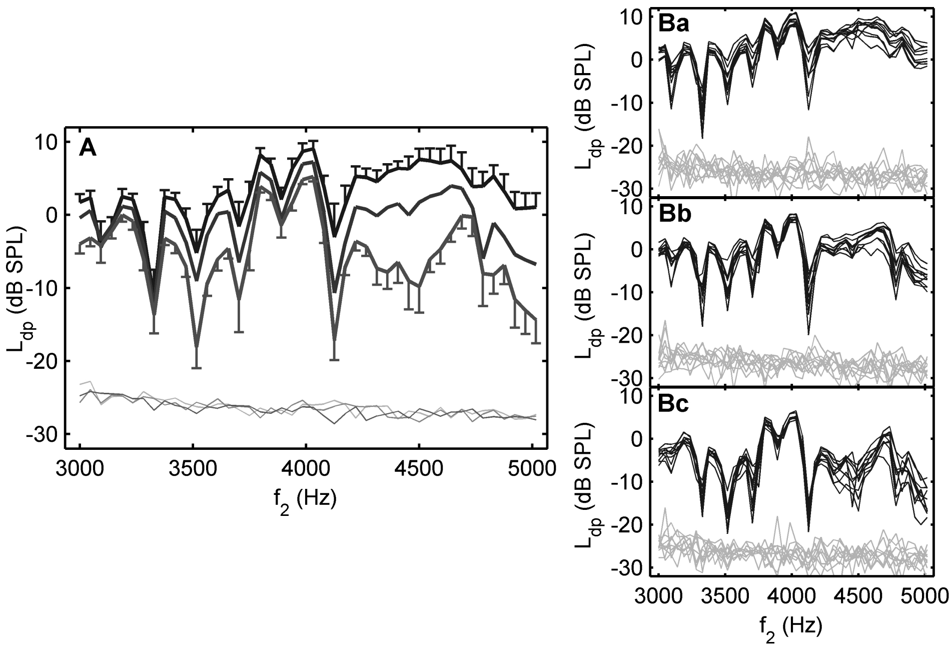

Figure 6.1: DPOAE fine structure reproducibility for one subject on ten different days. (A) The three top lines show from top to bottom mean L_{dp} plotted across frequency for L_2 = 40, 30, and 20 dB SPL. The standard deviation is given for data measured at $L_2 = 40$ and 20 dB SPL. The three bottom lines represent the particular mean noise floor levels. (B) All ten measurements in a single subject for L_2 = 40 (Ba), 30 (Bb), and 20 dB SPL (Bc).

structure R_{dp} amounted to 7.2 ± 1.0 dB. The variability of the measures obtained on one day with varying and fixed ear probe position was in general lower than that obtained on several days and can be seen in Tab. 6.1.

Distribution of dips and dip depth across subjects

DPOAE fine structure was examined in all ten ears of the seven subjects. DPOAE levels varied substantially across subjects (1.2 ± 6.9 dB SPL). The distribution of major dips ($d_{dip} < -4$ dB) is shown in Fig. 6.2 with d_{dip} plotted across the corresponding $f_{2,dip}$. The open circle and error bar show mean and standard deviation along both axes ($d_{dip} = -9.2 \pm 4.4$ dB, $f_{2,dip} = 3735 \pm 516$ Hz).

The average roughness of the DPOAE fine structure across subjects amounted to 4.2 ± 1.6 dB. Splitting the frequency range at 4 kHz, the roughness below 4 kHz was 5.6 ± 2.2 dB while the roughness above 4 kHz was substantially lower with 2.5 ± 1.5 dB. Thus, the fine structure was more pronounced and deeper dips occurred in the lower frequency region. Furthermore, the roughness increased with decreasing L_2 (4.0 dB at $L_2 = 40$ dB SPL, 4.7 dB at $L_2 = 30$ dB SPL, and 6.2 dB at $L_2 = 20$ dB SPL).

	several days	one day changed ear probe position	one day fixed ear probe position
L_{dp} (dB SPL)	-1.1 ± 1.8	-1.7 ± 1.6	-2.1 ± 1.1
$d_{dip,max}$ (dB)	-24.3 ± 4.8	-22.7 ± 4.1	-21.4 ± 2.2
R_{dp} (dB)	7.2 ± 1.0	7.0 ± 0.6	6.3 ± 0.3

Table 6.1: Mean and standard deviation of DPOAE level L_{dp}, maximum dip depth $d_{dip,max}$, and roughness of DPOAE fine structure R_{dp} in one subject and for three different measurement conditions (i.e., measurement on several days and measurement on one day with either changed or fixed ear probe position).

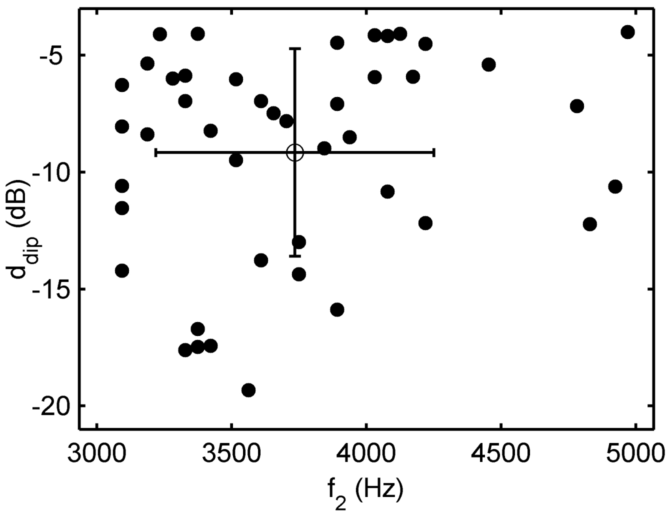

Figure 6.2: Distribution of DPOAE fine structure dips with dip depth $d_{dip} < -4$ dB for all ten ears. The mean and standard deviation are indicated by the open circle and error bars.

6.2.2 Effect of CAS on DPOAEs and its intra-individual reproducibility and inter-individual distribution

Enhancement and suppression due to CAS and its reproducibility in a single subject

The change in DPOAE level during CAS and its reproducibility was examined in one subject (J.M.) for three different test conditions: on several days (n = 10), and on one day with varying (n = 8) and constant (n = 8) ear probe position, respectively. The measurements were conducted at f_2 = 4125 Hz, a frequency at which in the DPOAE fine structure a distinct dip occurred (see Fig. 6.3).

The results for the worst test condition, i.e. the measurement on ten different days, are presented in Fig. 6.3. Figure 6.3A shows mean L_{dp} obtained in the absence (black lines) and in the presence of CAS (gray lines) for all tested primary tone level combinations.

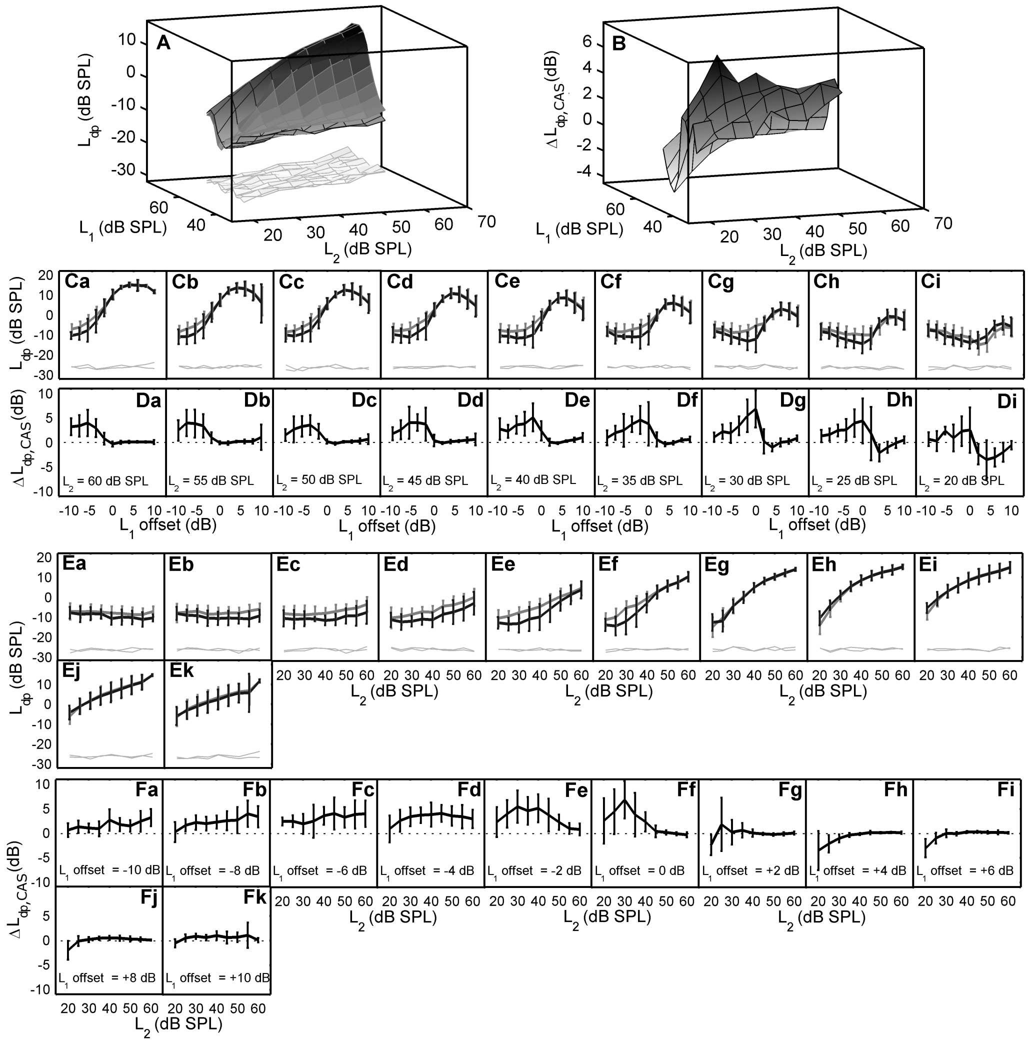

Figure 6.3: Effect of CAS on DPOAEs and its reproducibility at $f_2 = 4125$ Hz for one subject. Data were averaged across ten measurements conducted on different days. (A) Mean L_{dp} plotted above L_2 and L_1 for the condition without (black lines) and with (gray lines) CAS. The light gray area at the bottom represents the noise floor level. (B) DPOAE level difference $\Delta L_{dp,CAS}$ between measurements with and without CAS. Negative values mean suppressive, positive values enhancing behavior due to CAS. (C), (E) Cross-sections of panel A. Panel C represents cross sections with constant L_2 and varying $L_{1,offset}$ (Ca: $L_2 =$ 60 dB SPL, ..., Ci: $L_2 = 20$ dB SPL) while panel E pictures cross-sections with constant $L_{1,offset}$ (level offset from the center level $L_1 = 0.4L_2 + 39$ dB SPL) and varying L_2 (Ea: $L_{1,offset} = -10$ dB, ..., Ek: $L_1, offset = +10$ dB). Panels D (constant L_2, varying $L_{1,offset}$) and F (constant $L_{1,offset}$, varying L_2) show cross-sections of panel B. The dotted lines mark the turning point from suppression to enhancement at $\Delta L_{dp,CAS} = 0$ dB. All cross-section plots show mean and standard deviation of the repetition measurements.

Light gray lines at the bottom represent the average noise floor level. Cross-sections of Fig. 6.3A are shown in Figs. 6.3 Ca–Ci for constant L_2 (Ca: L_2 = 60 dB SPL, . . . , Ci: L_2 = 20 dB SPL) and in Figs. 6.3 Ea–Ek for constant $L_{1,offset}$ with $L_{1,offset}$ being the level offset from the center level $L_{1,center} = 0.4L_2 + 39$ dB SPL (Ea: $L_{1,offset} = -10$ dB, . . . , Ek: $L_{1,offset} = +10$ dB).

DPOAE I/O functions (L_{dp} plotted across the primary tone level of the varied parameter L_2 or $L_{1,offset}$) featured notched regions when L_2 was fixed and L_1 varied (e.g., Figs. 6.3 Cg, Ch, and Ci), while this phenomenon did not occur for the opposite case of fixed $L_{1,offset}$ and L_2 being varied (Figs. 6.3 Ea–Ek).

The change in DPOAE level $\Delta L_{dp,CAS}$ due to CAS is shown in Fig. 6.3B for all tested primary tone level combinations. Negative $\Delta L_{dp,CAS}$ values represent suppressive (L_{dp} decreases due to CAS), positive values represent enhancing (L_{dp} increases due to CAS) effects. The cross-sections of Fig. 6.3B are shown in Figs. 6.3 Da–Di for constant L_2 and in Figs. 6.3 Fa–Fk for constant $L_{1,offset}$. Please note, that a small change in L_1 in the region around the center level (i.e., $L_{1,offset} = 0$ dB) caused pronounced changes in $\Delta L_{dp,CAS}$ from enhancement to suppression (e.g., Figs. 6.3 Dg, Dh, and Di) while there were rather smooth $\Delta L_{dp,CAS}$ changes, which stretched across a wider level range, when varying L_2 (Figs. 6.3 Fa–Fk). It should be emphasized that the bipolar effect (i.e., transition from enhancement to suppression) was more pronounced at low L_2 and occurred when varying L_1 within a small level range. Regarding all cross-sections, the maximum bipolar effect occurred at the cross-section with $L_2 = 30$ dB SPL and amounted to 7.9 dB (Fig. 6.3 Dg).

This finding is important because it shows that also in humans a bipolar change in DPOAE level from enhancement to suppression is present. However, it should be emphasized that the bipolar change occurred during CAS. Please remember that in guinea-pigs the large bipolar effect was observed for ipsilateral DPOAE adaptation (see Maison and Liberman, 2000).

For the repetition measurements ($n = 10$), the mean standard deviation of L_{dp} was 3.6 dB and there were no pronounced level regions of particularly high L_{dp} variability. The average standard deviation of $\Delta L_{dp,CAS}$ amounted to 1.6 dB. The standard deviation increased in regions around DPOAE I/O function notches where CAS effects shifted from enhancement to suppression (e.g., Fig. 6.3 Dh) and increased with increasing $|\Delta L_{dp,CAS}|$. The maximum suppression amounted on average to -5.8 ± 1.9 dB and the maximum enhancement to 9.6 ± 2.3 dB. The resultant PPERS (difference between maximum suppression and maximum enhancement) was on average 15.4 ± 3.4 dB. The variability of the measures obtained on one day with varying or fixed ear probe position was once again mostly lower than that obtained on several days (see Tab. 6.2). It is important to note that the measurements on one day were conducted only for L_2 = 40, 30, and 20 dB SPL to keep the measurement time within a reasonable time period. To grant better comparability the averaged standard deviations for the ten measurements on different days were recalculated on the basis of the reduced measurement paradigm and are shown in Tab. 6.2.

	several days	one day changed ear probe position	one day fixed ear probe position
max. suppr. (dB)	-5.7 ± 1.9	-5.9 ± 2.6	-4.8 ± 1.7
max. enh. (dB)	8.2 ± 2.2	7.8 ± 1.4	7.5 ± 1.0
PPERS (dB)	13.9 ± 3.5	13.8 ± 3.0	12.3 ± 2.2

Table 6.2: Mean and standard deviation of maximum DPOAE suppression and enhancement, and peak-to-peak efferent reflex strength (PPERS) in one subject for three different measurement conditions (i.e., measurement on several days and measurement on one day with either changed or fixed ear probe position). L_2 was limited to 40, 30, and 20 dB SPL.

Enhancement and suppression due to CAS across subjects

The effect of CAS on DPOAEs was examined across all ten ears at frequencies $f_{2,dip}$ where a pronounced dip occurred in the DPOAE fine structure, and for comparison at frequencies $f_{2,flat}$ where the DPOAE fine structure was flat.

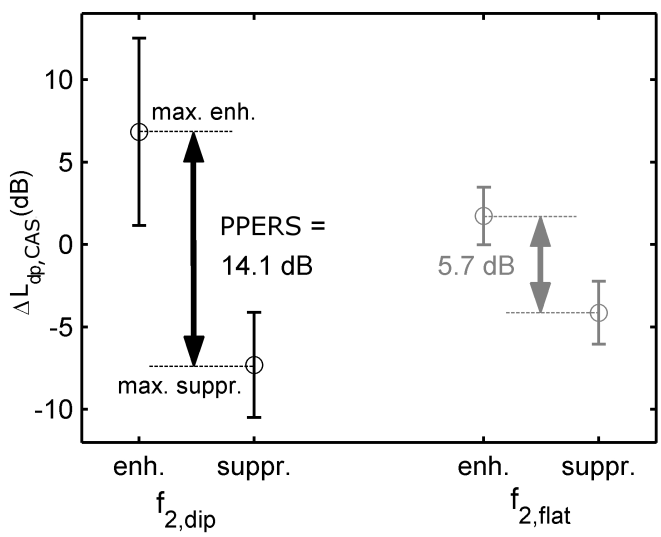

Figure 6.4: Mean and standard deviation of maximum suppression and maximum enhancement due to CAS for measurements at $f_{2,dip}$ (black) and $f_{2,flat}$ (gray) across all ten ears. The arrows show the corresponding average peak-to-peak efferent reflex strength (PPERS).

In general, for both frequencies, suppression rather than enhancement was more common. At $f_{2,dip}$ on average 67 (i.e., 69 %) and at $f_{2,flat}$ 80 (i.e., 82 %) out of 97 valid data points for each ear showed suppressive effects. Please note, that in one ear no enhancement occurred at $f_{2,flat}$. Figure 6.4 shows the mean and standard deviation for maximum suppression and enhancement at $f_{2,dip}$ (black) and $f_{2,flat}$ (gray). At $f_{2,dip}$, the average maximum suppression was -7.3 ± 3.2 dB and the average maximum enhancement 6.8 ± 5.7 dB. Thus, the resulting PPERS amounted to 14.1 ± 6.6 dB. In comparison to DPOAE level changes of only 1 to 2 dB reported in the literature when using conventional stimulus settings (e.g., Collet *et al.*, 1990a) this is an extremely large effect. In contrast, at $f_{2,flat}$, the average maximum suppression was -4.1 ± 1.9 dB and the average maximum enhancement 1.7 ± 1.7 dB, resulting in a PPERS of only 5.7 ± 2.9 dB. Comparing measurement data at $f_{2,dip}$ and at $f_{2,flat}$ both maximum suppression and maximum enhancement were significantly different ($p < 0.05$). Also, PPERS differed highly significantly ($p < 0.01$) between the two frequencies. Thus, the bipolar change in DPOAE level was considerably higher at dip frequencies than at frequencies where the fine structure was flat.

Panel A and B in Fig. 6.5 show the level combinations $L_2|L_1$ at which maximum suppression (black dots) or maximum enhancement (gray squares) occurred in each ear. Panel A shows data for measurements at $f_{2,dip}$ and panel B for measurements at $f_{2,flat}$ across all ten ears. In both panels the applied L_1 range and the L_1 center level are shown by dashed light gray lines. Regarding data obtained at $f_{2,dip}$ (Fig. 6.5A), L_2 at which maximum suppression or enhancement occurred varied across the entire L_2 range. However, a majority of points were in the low L_2 region ≤ 30 dB SPL (60 % of all points in Fig. 6.5A). Maxima were more commonly at negative $L_{1,offset}$ values. Regarding data obtained at $f_{2,flat}$ (Fig. 6.5B), both maximum suppression and enhancement occurred almost exclusively in the low L_2 region ≤ 30 dB SPL (89 % of all points in Fig. 6.5B) with L_1 values distributed nearly in equal shares around $L_{1,center}$. Panel C in Fig. 6.5 shows the level combinations $L_2|L_1$ at which major suppression (panel Ca) or enhancement (panel Cb) occurred. Major effects due to CAS were defined as $|\Delta L_{dp,CAS}| > 4$ dB. Please note that data is shown for measurements at $f_{2,dip}$ only, since nearly all major $\Delta L_{dp,CAS}$ occurred at these frequencies. The average $L_2|L_1$ was quite similar for both suppression and enhancement whereas the variability was higher across L_2 (suppression: $L_2|L_1 = 35.9 \pm 14.1|51.2 \pm 5.6$ dB SPL, enhancement: $L_2|L_1 = 38.1 \pm 12.2|51.3 \pm 4.0$ dB SPL). Especially for higher L_2 levels, L_1 was more commonly located below $L_{1,center}$ and occurred preferably between $L_1 = 45$ and 55 dB SPL (73 % of all points in Fig. 6.5Ca and Cb). In general, major CAS effects were spread across the entire L_2 level range with no distinct region preferred. However, major suppression more commonly occurred between $L_2 = 20$ and 30 dB SPL (51 % of all points in Fig. 6.5Ca).

6.2.3 Ipsilateral DPOAE adaptation and its intra-individual reproducibility and inter-individual distribution

Ipsilateral DPOAE adaptation and its reproducibility in a single subject

DPOAE adaptation and its reproducibility were examined in one subject (J.M.) for two different test conditions. Measurements were conducted eight times on one day with varying ($n = 8$) and constant ($n = 8$) sound probe position, respectively. DPOAE adaptation was quite inconsistent when measured on different days. It happened that on one day a distinct adaptation was present and on the other day not. No reproducibility measurements were therefore conducted on different days. In the following data from measurements with varying ear probe position are presented.

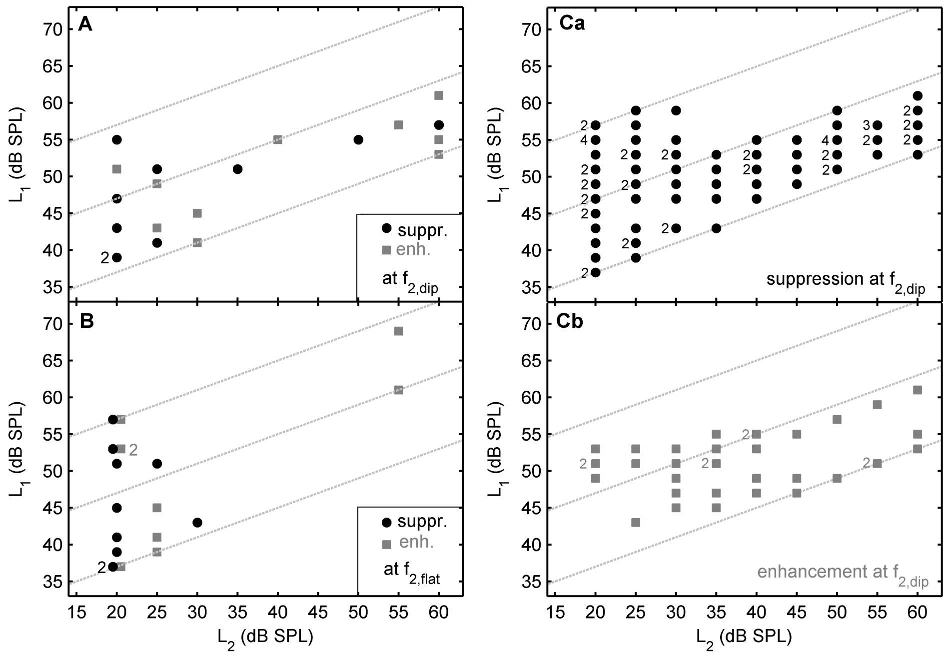

Figure 6.5: (A), (B) Distribution of maximum suppression and maximum enhancement due to CAS across their corresponding level combinations $L_2|L_1$ for all ten ears. Panel A includes data measured at dip frequencies ($f_{2,dip}$) and panel B data measured at flat frequency regions ($f_{2,flat}$) of the DPOAE fine structure. (C) Distribution of all major suppression (Ca) and enhancement (Cb) values ($|\Delta L_{dp,CAS}| > 4$ dB) due to CAS across their corresponding level combinations $L_2|L_1$ for all ten ears. Black dots show level combinations $L_2|L_1$ for suppression, gray squares for enhancement. If more than one measurement resulted in the same $L_2|L_1$ combination the respective number of similar measurement results is given. The dashed light gray lines show the L_1 center level $L_{1,center} = 0.4L_2 + 39$ dB SPL and the range in which L_1 was varied around $L_{1,center}$.

Figure 6.6 shows an example of one measurement with $L_{dp}(t)$ time course (black line) and one-exponential fitting function (grey line). For evaluating the reproducibility of DPOAE adaptation, the steady-state level L_{ss}, the adaptation magnitude m, and the adaptation time constant τ were averaged. L_{ss} amounted on average to 14.6 ± 0.5 dB SPL, m to -0.47 ± 0.12 dB, and τ to 0.372 ± 0.128 s. The average VAF was 0.41. For constant ear probe position the variability of the measures was generally lower (see Tab. 6.3).

Ipsilateral DPOAE adaptation in DPOAE I/O function notches

Ipsilateral DPOAE adaptation was measured in three subjects in DPOAE I/O function notches that occurred when varying L_2 at a fixed $L_{1,offset}$. For each subject seven adaptation measurements were conducted with L_2 being varied around the deepest point of the notch. Subject L.J. yielded three, subject T.R. one, and subject J.M. no valid adapta-

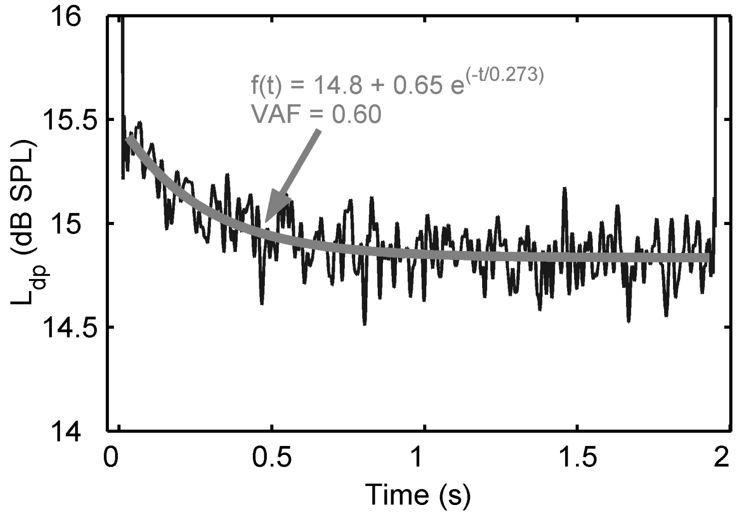

Figure 6.6: DPOAE adaptation example taken from the repetition measurements at $f_2 =$ 4219 Hz and $L_2|L_1 = 60|67$ dB SPL. The gray line shows the one-exponential fit $f(t)$. The VAF of the fitting function was 0.60.

	one day changed ear probe position	one day fixed ear probe position
L_{ss} (dB SPL	14.6 ± 0.5	14.8 ± 0.3
m (dB)	-0.47 ± 0.12	-0.66 ± 0.06
τ (s)	0.372 ± 0.128	0.247 ± 0.049

Table 6.3: Mean and standard deviation of DPOAE steady-state level L_{ss}, magnitude m, and time constant τ of DPOAE adaptation in one subject for two measurement conditions (i.e., measurement on one day with either changed or fixed ear probe position)

tion time courses (VAF > 0.1). Regarding these results only decreasing adaptation time courses occurred with an average m of -1.2 ± 0.4 dB. All in all, even when regarding fitting functions with lower VAF values, no bipolar adaptation effect could be found.

Ipsilateral DPOAE adaptation across subjects

Ipsilateral DPOAE adaptation was investigated in all ten ears at $f_{2,dip}$ and at $f_{2,flat}$ for a total of 49 ($f_{2,dip}$) and 38 ($f_{2,flat}$) level combinations. For each group there were 20 valid measurements (VAF > 0.1). The mean VAF across all valid measurements amounted to 0.36 ± 0.19. The mean DPOAE steady-state level L_{ss} was 11.2 ± 5.3 dB SPL ($f_{2,dip}$) and 12.6 ± 5.3 dB SPL ($f_{2,flat}$). The average adaptation time constant τ was 0.426 ± 0.493 s ($f_{2,dip}$) and 0.345 ± 0.154 s ($f_{2,flat}$). The mean adaptation magnitude m amounted to only -0.55 ± 0.79 dB ($f_{2,dip}$) and -0.65 ± 0.20 dB ($f_{2,flat}$). Thus, in the present human data the adaptation magnitude was very small compared to that observed in cats (6 dB, Liberman *et al.*, 1996) but similar to that observed in other human studies (e.g., Agrama *et al.*, 1998; Bassim *et al.*, 2003). A bipolar change in adaptation magnitude could be found in only one subject and amounted to 4.6 dB (-2.4 dB at $L_2|L_1 = 25|51$ dB SPL, 2.2 dB at $L_2|L_1 = 60|61$ dB SPL). In all other subjects no bipolar effect was observed. Compared to Maison and Liberman (2000), who found in guinea-pigs a bipolar change in adaptation magnitude of up to 30 dB, the effect in the present human data is very small.

6.2.4 Correlation between DPOAE measures

The relationship between DPOAE fine structure and change in DPOAE level due to CAS $\Delta L_{dp,CAS}$ was examined. In particular the relationship between the dip depth d_{dip} of DPOAE fine structure and the corresponding PPERS is shown in Fig. 6.7. Black dots show data for measurements at $f_{2,dip}$, gray points for measurements at $f_{2,flat}$. With increasing dip depth (negative values) PPERS increased, the two measures being closely correlated ($r = -0.81$). The observation that bipolar effects were most prominent in the deepest dips is important with regard to a clinical application of DPOAEs for assessing MOC reflex strength. Due to time restrictions in a clinical context, the bipolar effect cannot be explored at a large number of test frequencies. Therefore it is necessary to choose critical frequencies (e.g., $f_{2,dip}$).

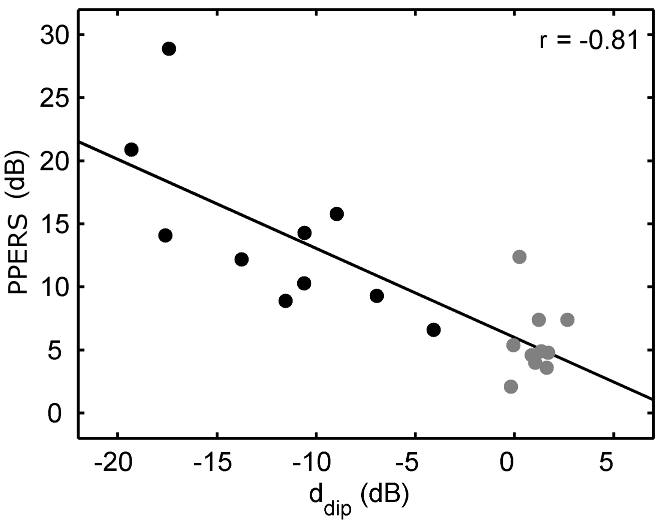

Figure 6.7: Relationship between DPOAE fine structure and CAS DPOAE data across subjects. PPERS is plotted above the corresponding dip depth d_{dip} for all ten ears. Black dots show data for measurements at $f_{2,dip}$, gray dots for measurements at $f_{2,flat}$. The regression line and the correlation r were calculated on the basis of all data points.

In Fig. 6.8 the DPOAE level change $\Delta L_{dp,CAS}$ due to CAS is plotted over the adaptation magnitude m. Black dots represent data for measurements at $f_{2,dip}$, gray points for measurements at $f_{2,flat}$. The insert figure shows a detail of the overall plot of $\Delta L_{dp,CAS}$

between −5 and +1 dB. It could be observed that the change in DPOAE level was in general lower during IAS (m varied between −2.4 and +2.2 dB) compared to that during CAS ($\Delta L_{dp,CAS}$ varied between −10.4 and +18.5 dB). It was striking that only in one subject enhancement could be observed in both measures (see $\Delta L_{dp,CAS} = +18.5$ dB in Fig. 6.8). The correlation between m and $\Delta L_{dp,CAS}$ was extremely significant ($r = 0.98$; $p < 0.001$) for measurements at $f_{2,dip}$. However, the very high correlation coefficient was mainly influenced by the two single data points at the left and right margin of Fig. 6.8, representing adaptation data from one subject at $\Delta L_{dp,CAS}$ with maximum suppression and maximum enhancement, respectively. When the two data points were excluded the correlation decreased to $r = 0.66$ but was still highly significant ($p < 0.01$). In contrast, the correlation for measurements at $f_{2,flat}$ was not significant and amounted to only $r = 0.28$. As a consequence, the data suggests a correlation between CAS DPOAE and ipsilateral DPOAE adaptation measures only for data recorded at $f_{2,dip}$.

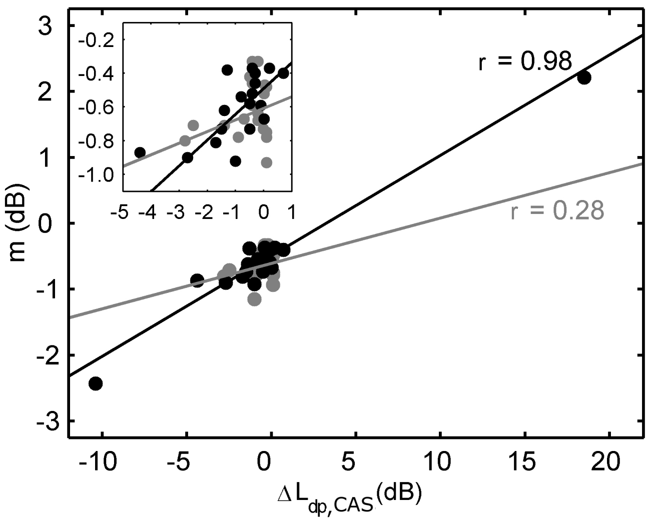

Figure 6.8: Relationship between CAS DPOAE and ipsilateral DPOAE adaptation data across subjects. Adaptation magnitude m is plotted across $\Delta L_{dp,CAS}$ for all ten ears. Black dots show data for measurements at $f_{2,dip}$, gray dots for measurements at $f_{2,flat}$. Regression lines and correlations are shown for each frequency group. The insert figure displays a detail of $\Delta L_{dp,CAS}$ between −5 and +1 dB.

6.3 Discussion

The aim of the present study was to investigate whether large bipolar changes in DPOAE level, which were reported for guinea-pigs (Maison and Liberman, 2000), are also present in humans and whether the CAS DPOAE or ipsilateral DPOAE adaptation measurement technique is better suited to detect and quantify efferent reflex strength in humans in a clinical context. In the following the achieved results are discussed.

Test performance of DPOAE measures when recorded on several days

The worst test condition was supposed to be the one with measurements on several days, which is a test situation that is nearest to clinical practice. As expected, for this test condition the highest variability was present. However, the standard deviation of PPERS was only 3.4 dB for one person on ten different days and thus was considerably lower than the average PPERS observed across subjects, which was 14.1 dB (see Fig. 6.4). Due to the large bipolar effect and the relatively small variability of the measure a good test performance of the presented approach for assessing MOC reflex strength during CAS is suggested.

In comparison, the reproducibility of DPOAE adaptation magnitude was insufficient, especially when considering that adaptation measured on consecutive days was on one day present and on the next day not. This and the fact that no distinct bipolar effects were present during IAS suggest DPOAE adaptation not to be a suited tool for investigating efferent MOC reflex strength in humans.

Frequency and level dependency of dip depth across DPOAE fine structure

In the present data, major dips occurred predominantly in the lower frequency region of the DPOAE fine structure below 4 kHz (see Fig. 6.2), which is in accordance with findings in literature (e.g., Mauermann and Kollmeier, 2004). Dips and peaks of the DPOAE fine structure are thought to be due to second DPOAE source effects (see Sec. 2.5.2). Thus, the impact of the second source seems to be higher at lower frequencies. However, the reason for this observation remains unclear. Another observation in the literature is that the roughness of the fine structure increases with decreasing L_2 (Mauermann and Kollmeier, 2004). This finding is consistent with the present data (see Fig. 6.1) and suggests the influence of the second source to be higher at near-to-threshold stimulus levels. Furthermore, the high inter-individual variability of the roughness found in the present data may be attributed to morphological differences among subjects.

Influence of the stimulus setting and the second source on CAS DPOAE effects

CAS DPOAE effects were generally larger when measured in dips of the DPOAE fine structure compared to flat regions of the DPOAE fine structure. Moreover, maximum suppression and enhancement at $f_{2,dip}$ occurred across the entire primary tone level range, but predominantly at lower L_2 and at negative $L_{1,offset}$ (see Fig. 6.5). Typically, distinct transitions from enhancement to suppression during CAS occurred in notched regions of DPOAE I/O functions (see Figs. 6.3 Ch and Dh). As shown by Maison and Liberman (2000), also in the present data large bipolar changes were noticeable for a small shift in primary tone level. In contrast to their data, in the present data transitions from enhancement to suppression occurred when varying L_1 with fixed L_2 and not the other way round. Also, primary tone level combinations eliciting maximum suppression and maximum enhancement for a single subject were not always located close to each other in the primary tone level matrix.

Supposing that notches in DPOAE I/O functions and with that also the bipolar effect is due to the second source, the observed difference between animal studies and this study in humans could be attributed to a different impact of the primaries on the second source. Since in the present data the magnitude of the bipolar effect is correlated with the dip depth of the DPOAE fine structure (see Fig. 6.7) the second source is suggested to be the underlying mechanism for the bipolar effect. The fact that maximum suppression and enhancement during CAS occurred predominantly at lower primary tone levels (see Fig. 6.5) and the observation that the roughness of DPOAE fine structure increases with decreasing primary tone level supports the idea that the second source influences the magnitude of CAS effects.

To further investigate the relationship between DPOAE fine structure, second DPOAE source, and bipolar changes in DPOAE level during CAS, additional studies are necessary. The question whether and to what extent the second DPOAE source is influencing CAS effects might be answered by performing CAS DPOAE measurements while presenting simultaneously an additional ipsilateral tone near $2f_1 - f_2$, which is supposed to suppress the second DPOAE source (Heitmann *et al.*, 1998).

Influence of the stapedius reflex on CAS DPOAE effects

Another cause for changes in DPOAE level might be the stapedius muscle reflex, which is known to be activated by acoustic stimulation from either the ipsilateral or contralateral ear (see Sec. 2.2). The activation of the stapedius reflex changes the middle ear impedance and with that the DPOAE level. In this study, the stapedius muscle reflex threshold for a 4 kHz pure tone was on average at about 90 dB SPL across subjects. Since the maximum primary tone level was set to 75 dB SPL, the influence of the stapedius muscle on the DPOAE level is suggested to be not relevant during IAS. However, reflex thresholds could be lower for broad band noise stimulation. Therefore, an impact of the stapedius muscle reflex on DPOAEs during CAS can not be excluded. However, assuming that the middle ear is a linear system, it is unlikely that the observed bipolar effect, which occurred when shifting the ipsilateral primary tone level by only 2 dB while keeping contralateral broad band noise constant, can be achieved by the activation of the stapedius muscle.

Relationship between CAS DPOAE and ipsilateral DPOAE adaptation

CAS DPOAE and ipsilateral DPOAE adaptation effects exhibited an extremely close correlation ($p < 0.001$) when including and a lower but still significant ($p < 0.01$) correlation when excluding the outliers, which represent data from only one ear (see Fig. 6.8). The close relationship was, however, only true for measurements at $f_{2,dip}$, but not for measurements at $f_{2,flat}$. The small number of valid adaptation measurements makes it difficult to properly evaluate the correlation between the two measures. Further studies are therefore necessary to investigate the impact of the uncrossed and crossed MOC efferents on OHC motility. Possibly, ipsilateral DPOAE adaptation effects could be increased when stimulating not only with the primary tones but also, as done in CAS DPOAE measurements, with additional ipsilateral broad band noise with frequency components between

f_1 and f_2 being removed by means of a notch filter. However, the influence of ipsilateral broad band noise on DPOAE recording and the proper parameterization of the notch filter would have to be investigated in the first instance.

Applicability of measuring efferent MOC reflex strength by means of DPOAEs in clinical practice

Actually, large bipolar changes were found in the present human data, but in contrast to the findings in guinea-pigs, the bipolar effect was present for CAS DPOAEs (i.e., when activating the uncrossed MOC fibers) but not for ipsilateral DPOAE adaptation (i.e., when activating the crossed MOC fibers). The bipolar effect was largest at the deepest dips of the DPOAE fine structure and PPERS amounted on average across subjects to 14 dB. This effect is much larger than that observed for conventional CAS DPOAE measurements, in which DPOAEs were measured not at critical frequencies ($f_{2,dip}$) and not at different $L_2|L_1$ combinations (e.g., Collet *et al.*, 1990a). With respect to a clinical application for assessing MOC reflex strength, a large change in DPOAE level together with good reproducibility is needed in order to assure that the obtained effect exceeds L_{dp} variability. Therefore, the presented approach and not the conventional CAS DPOAE measurement seems to be more suitable for assessing MOC reflex strength in a clinical context. However, it is important to note that a large bipolar effect seems to be present at particular frequencies ($f_{2,dip}$) and $L_2|L_1$ combinations only. The magnitude of the bipolar effect was highly correlated with the dip depth of DPOAE fine structure (see Fig. 6.7). Thus, for clinical application the bipolar effect possibly needs to be examined at only some frequencies, specifically at frequencies at which the DPOAE fine structure exhibits distinct dips.

Whether CAS DPOAEs are capable of predicting individual vulnerability to mid- or high-level noise exposure (see Sec. 2.5.3) was investigated and is described in Chapter 7. Moreover, the influence of aging on CAS DPOAEs was investigated and is described in Chapter 8.

A modified version of this chapter is published as:

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7 Further efforts to predict individual vulnerability to noise overexposure

Noise-induced hearing loss (NIHL) is known to violate the sensory cells of the hearing organ and is one of the most common hearing disorders in modern society. This aspect includes both occupational and recreational noise exposure. According to the National Institute for Occupational Safety and Health (NIOSH), in the United States approximately 30 million workers are exposed to hazardous noise on the job (NIOSH, 2001). NIHL is one of the most common occupational diseases and the second most self-reported occupational injury in the United States and Germany (NIOSH, 2001; Plinske *et al.*, 2002). Therefore, at the workplace, regulations for limiting occupational noise exposure were established: NIOSH recommendations (NIOSH, 1998) as well as European Union guidelines (European Union, 2003) define 85 dB(A) as the maximum acceptable A-weighted sound pressure level averaged across an 8-hour workday. Beyond this level, workers are obliged to wear hearing protective devices. In contrast, there are hardly any regulations concerning recreational noise exposure, which frequently exceeds the sound pressure level limits laid down for occupational noise exposure. In Germany, 25 % of adolescents, who have not been exposed to occupational noise, were found to exhibit a hearing loss (Struwe *et al.*, 1996). One of the most common sources is amplified music, whether at a concert, at a discotheque, or by using mobile music players with ear phones. Sound pressure levels at concerts or discotheques can easily exceed 100 dB(A), which is suggested to constitute a prominent risk for permanent hearing damage.

At an early stage, noise probably only causes a temporary hearing threshold shift (TTS), which may disappear within about 48 hours after noise exposure due to regeneration mechanisms provided by the inner ear (Schneider *et al.*, 2002). Permanent hearing threshold shift (PTS) is known to occur slowly over time as a cumulative process and as a result of gradually increasing irreversible damage to the cochlear sensory cells. Hence, regular high-level noise exposure, either at work or, e.g., at a discotheque, is expected to be harmful to hearing in the long run. Thus, an important concern for hearing conservation programs is, besides education and prevention, the early detection of NIHL. Furthermore, since it is known that the susceptibility to noise differs across subjects, it would be beneficial to allow for a quantification of a subject's individual vulnerability towards noise overexposure.

OHCs are known to be the most sensitive sensory cells of the inner ear and are thus most vulnerable to noise overexposure (see Sec. 2.2). Moreover, the efferent MOC system, a feedback loop to the OHCs, is supposed to provide protection from acoustic overexposure (see Sec. 2.2). Pure-tone threshold measurements assess overall hearing capability, whereas DPOAE measurements selectively assess impairment of the cochlear amplifier (see Sec. 2.5.3). CAS DPOAE measurements are suggested to quantify individual efferent MOC reflex strength (see Chapter 6).

The aim of the following two studies was to examine if there is a measurable impact on pure-tone thresholds and/or DPOAEs due to (*i*) 3 hours of high-level discotheque music or (*ii*) 7.5 hours of mid-level occupational noise. Furthermore, the capability of CAS DPOAEs to predict inter-individual susceptibility to noise was investigated.

7.1 Material and methods

7.1.1 Subjects

Discotheque music study

Fifteen (9 male, 6 female) normal hearing healthy subjects participated in the discotheque music study. Age varied from 21 to 27 years (mean: 25 years). The initial inclusion criteria for the subjects were that hearing loss according to pure-tone audiometry should not exceed 15 dB HL on both ears at audiometer frequencies (1, 2, 3, 4, and 6 kHz), and that contralateral stapedius reflex thresholds elicited with broad band noise had to exceed 70 dB SPL. In all subjects, pure-tone threshold and DPOAE fine structure was measured before and immediately after the 3-hour discotheque attendance. The time between music exposure and the commencement of the measurements amounted to less than 5 minutes. Additionally, a control measurement was conducted on the day after discotheque attendance (i.e., 8 to 14 hours after music exposure). Measurements were conducted in a sound-proof cabin, which was located nearby the discotheque, while subjects were lying on a comfortable recliner. In general, two subjects were measured simultaneously in one session. For one subject, pure-tone threshold fine structure was measured first and DPOAE fine structure second, while in the other subject the sequence was inverted. Pure-tone threshold (see Fig. 7.1A) and DPOAE fine structure (see Fig. 7.1B) were recorded before (left panel) and after (middle panel) listening to discotheque music in order to examine possible noise-induced changes in hearing or OHC functionality. The control measurements on the day after noise exposure (right panel) were conducted in order to examine recovery from noise-induced hearing dysfunction. CAS DPOAEs (see Fig. 7.1C) were measured only once before discotheque attendance in order to test their capability to determine cochlear vulnerability to three hours of high-level noise exposure.

Occupational noise study

Sixty-nine subjects participated in the occupational noise study. Subjects belonged to either of two groups. (*i*) The noise exposure group (52 male subjects) was made up of factory workers (e.g., lathe operators, polishers, etc.) employed in the metal-working

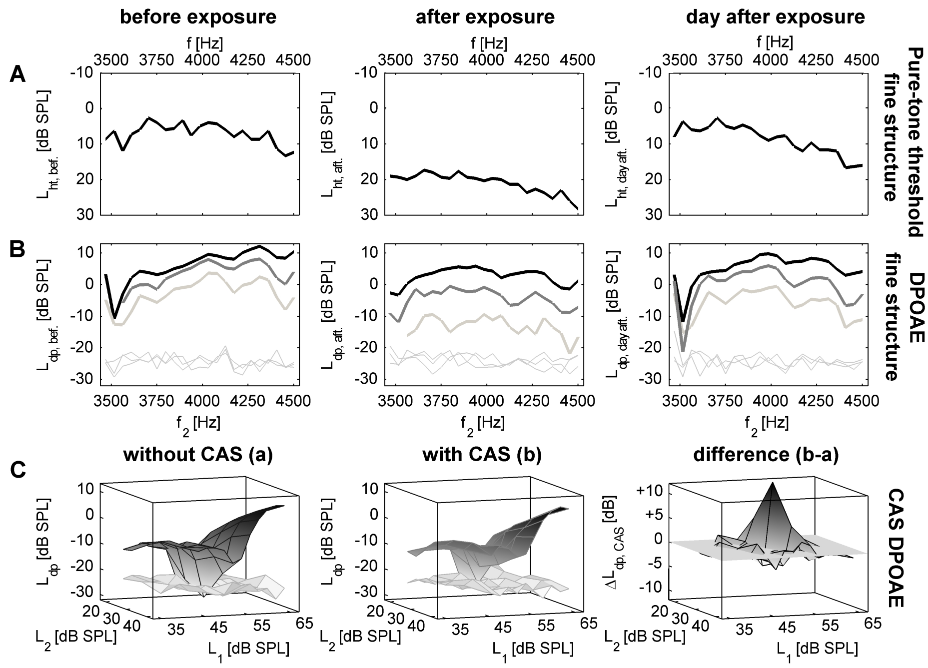

Figure 7.1: Discotheque music study case example. (A) Pure-tone threshold fine structure data taken before (left panel), immediately after (middle panel), and the day after discotheque attendance (right panel). (B) DPOAE fine structure data for L_2 = 40, 30, and 20 dB SPL (from top to bottom). Light gray lines show the particular noise floor level. (C) CAS DPOAE data recorded before work. Data is plotted for measurements without CAS (left panel), with CAS (middle panel), and as the difference between both measurements (right panel).

industry (Voith AG, Germany). They were all regularly exposed to high noise levels during their working time and had been working in noisy environments for a longer period of time, ranging from 3 to 40 years (mean: 20 years). (*ii*) The control group (6 female, 11 male subjects) consisted of clerical workers (e.g., secretary, company physician, etc.) with no major noise exposure during work. Age varied from 20 to 59 years (mean: 40 years) in the noise exposure group and from 22 to 57 years (mean: 37 years) in the control group. The only initial inclusion criterion for the subjects in both groups was that hearing loss according to pure-tone audiometry should not exceed 40 dB HL on the ipsilateral ear at 1.5, 2, 3, 4, and 6 kHz. For evaluation of CAS DPOAE measurements, hearing loss at the contralateral ear should also not exceed 40 dB HL at any tested audiometer frequency. Pure-tone thresholds were measured with headphones and a standard audiometer with a level resolution of 5 dB. All subjects were measured directly before and after work. 22 factory workers were measured in the morning shift (5.30 a.m. to 1 p.m.), 15 in the afternoon shift (1.30 p.m. to 9 p.m.), and 15 in the night shift (9.30 p.m. to 5 a.m.). All subjects in the control group started their work in the morning (on average at 8.30 a.m.) and finished their work in the afternoon (on average at 4 p.m.). The time between the pre- and post-work measurements was similar in both groups and amounted on average to about 7.5 hours. Measurements were conducted in a quiet examination room while subjects were lying on a comfortable recliner. The examination room was located near the workplace so that examinations could be conducted within a few minutes before and after work.

Pure-tone thresholds (see Fig. 7.2A) and DPOAE fine structure (see Fig. 7.2D) were recorded successively in this order before and after work so as to examine possible noise-induced changes. CAS DPOAEs (see Fig. 7.2E) were measured only once before work in order to test their capability to predict cochlear vulnerability due to mid-level noise exposure of one workday.

Please note, that in this study the number of subjects, which were considered for further evaluation, was reduced due to the application of measurement-specific exclusion criteria which were introduced in order to improve measurement reliability and comparability and which are defined and explained below (see Secs. 7.1.5 and 7.1.6).

7.1.2 Noise exposure

Discotheque music study

Noise exposure measurements were conducted in the discotheque with a calibrated mobile sound level meter (Voltcraft) every 15 minutes. The sound level meter met the requirements of IEC 60651. The noise exposure measurements revealed an average A-weighted sound pressure level of 102 dB(A) with a maximum of 106 dB(A). Individual noise exposure levels might deviate slightly from these values since measurements were place-fixed and not individual-related. The overall exposure time amounted to 3 hours for each subject.

Occupational noise study

Noise exposure measurements were conducted by the local Accident Prevention and Insurance Association (Berufsgenossenschaft Metall Süd) with a calibrated sound level meter (Norsonic) according to norm DIN 45645-2. Noise exposure measurements at different workplaces indicated that the average rating level for an 8-hour workday amounted to 82 dB(A). Energy-equivalent permanent sound levels (with time-weighting 'fast') measured at different locations in the factory ranged from 73 to 97 dB(A) whereas peak levels ranged from 92 to 118 dB(C). Individual noise exposure levels might deviate from the given values since measurements were not conducted individually for all subjects but only exemplarily at some typical workplaces. The overall exposure time amounted to about 7.5 hours for each subject.

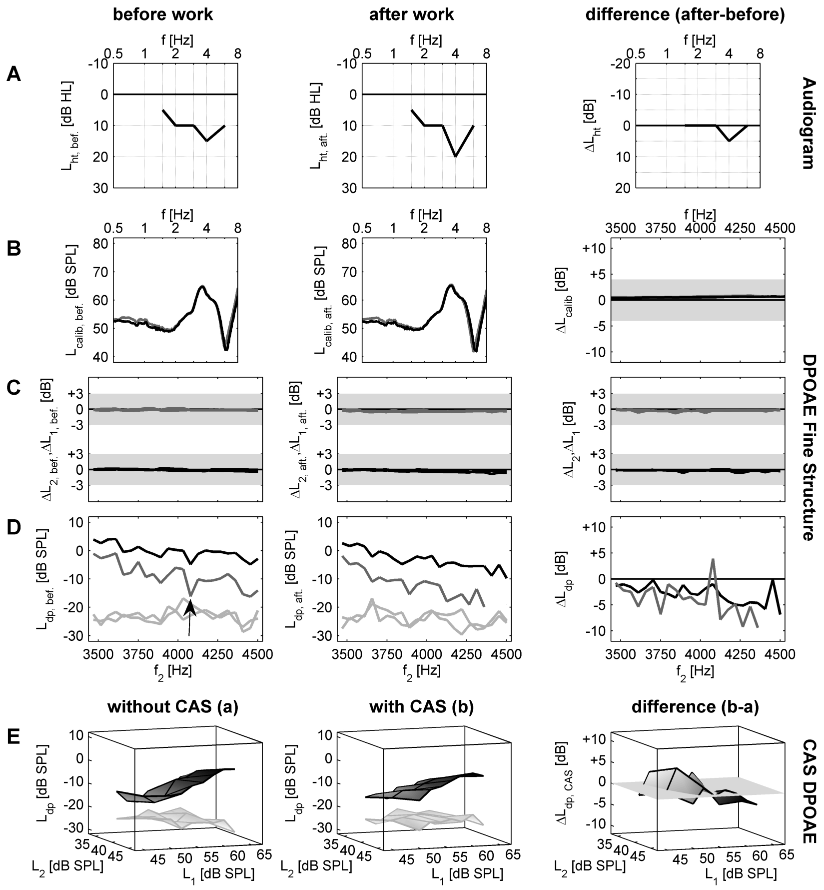

Figure 7.2: Occupational noise study case example. (A) Audiogram data taken before (left panel) and after (middle panel) work. The difference between both measurements is shown in the right panel. (B)–(D): DPOAE fine structure data plotted together with related measures as ear probe calibration stability (B) and primary tone level stability (C) which were used for evaluation of measurement stability. (B) Calibration transfer functions of both loudspeakers (black and gray line) for in-the-ear calibration (left and middle panel) and their difference in the measurement frequency range from 3.5 to 4.5 kHz (right panel). The light gray area shows the range for sufficient calibration stability (see Sec. 7.1.5). (C) Primary tone level deviations measured at the ear probe (black: ΔL_2, gray: ΔL_1) from target level (left and middle panel) and their differences (right panel). The light gray area shows the range of sufficient primary tone level stability (see Sec. 7.1.5). (D) DPOAE fine structure data (black: at $L_2 = 30$ dB SL; dark gray: at $L_2 = 20$ dB SL). Light gray lines at the bottom of the left and middle panel show the particular noise floor levels. The arrow in the left panel shows the frequency at which CAS DPOAEs were measured. (E) CAS DPOAE data recorded before work. Data is plotted for measurements without CAS (left panel), with CAS (middle panel), and as the difference between both measurements (right panel).

7.1.3 Pure-tone threshold measurement procedure

Discotheque music study

Pure-tone threshold fine structure was recorded between $f = 3469$ and 4500 Hz in steps of $\Delta f = 47$ Hz (see Fig. 7.1A). This frequency range was chosen since hearing is known to be most sensitive around 4 kHz and thus also most vulnerable to noise (McBride and Williams, 2001). In this study, pure-tone thresholds were recorded using the same measurement system and ear probe (see Chapter 3) as for DPOAE measurements to guarantee best comparability. A pulsatile tone with stimulus duration of 0.3 s and pause duration of 0.1 s was used. The starting level was initially set to 40 dB SPL for the first frequency and to 20 dB SPL above the last determined threshold for the following frequencies. The level of the pulsatile tone was changed in steps of 2 dB (= 5 dB/s). The level went down as long as the subject kept the mouse button pressed (indicating the presented sound to be audible) and went up when the button was released (indicating the presented sound to be inaudible). When six consecutive reversal points (from decreasing to increasing stimulus level, i.e. from 'audible' to 'inaudible', or vice versa) occurred within a stimulus level range of 14 dB, the measurement at the particular frequency was finished and the pure-tone threshold level was determined by averaging the stimulus levels at the last six reversal points (see Sec. 3.3.1). The measuring duration for one ear amounted on average to about 7 minutes.

Occupational noise study

Pure-tone thresholds were recorded using a standard audiometer with headphones. Measurements were conducted at audiometer frequencies (1.5, 2, 3, 4, and 6 kHz) with a level resolution of 5 dB. No pure-tone threshold fine structure measurements were conducted in this study due restrictions in available measurement time.

7.1.4 Stimulus generation and DPOAE recording

DPOAE measurements were recorded using the measurement system presented in Chapter 3. Primary tone levels were adjusted according to an in-the-ear calibration strategy, whereas contralateral noise signals were calibrated a priori in an ear simulator (Brüel&Kjær Type 4157) without adjustment of individual ear canal volume.

DPOAEs were accepted as valid for SNRs exceeding 6 dB. The noise floor level was computed by averaging the levels at six frequencies located around the DPOAE frequency. The averaging time for recording DPOAEs was initially set to 2.6 s and was doubled if there was no valid DPOAE response (i.e., SNR > 6 dB) within this time period. Technically distorted data were discarded when the levels of at least seven out of ten frequency bins at other distortion product components (e.g., $2f_2 - f_1$) around the DPOAE component at $f_{dp} = 2f_1 - f_2$ exceeded an SNR of 10 dB.

7.1.5 DPOAE fine structure measurement procedure

In both studies, DPOAE fine structure was measured between $f_2 = 3469$ and 4500 Hz with a frequency resolution of $\Delta f_2 = 47$ Hz (see Figs. 7.1B and 7.2D). For improving comparability, the frequency range was chosen similar to that for pure-tone threshold measurements from the discotheque study. Reasons for measuring DPOAE fine structure were: (*i*) several neighboring frequencies had to be analyzed to detect dips in the DPOAE fine structure where measurement conditions for CAS DPOAEs are best (see Chapter 6); (*ii*) averaging across an extended frequency range was important in order to smooth out the influence of dips and peaks in DPOAE fine structure, which might not be representative for the actual DPOAE amplitude and hence potential OHC dysfunction in the examined frequency range.

Discotheque music study

In the discotheque music study, the primary tone level L_2 was set to 40, 30 and 20 dB SPL, whereas L_1 was set according to the 'scissor paradigm' equation $L_1 = 0.4L_2 + 39$ dB SPL. L_2 levels were chosen close to pure-tone thresholds since DPOAEs are known to be most sensitive when elicited at close-to-threshold primary tone levels (see Sec. 2.5.2). The total measuring duration amounted usually to about 5 to 8 minutes. In contrast to the occupational noise study, due to the small number of subjects, in this study no further measurement-specific exclusion criteria were implemented.

In this study, from DPOAE fine structure data, extrapolated DPOAE I/O functions were derived for assessing the sensitivity of the cochlear amplifier following the method of Boege and Janssen (2002) (see Sec. 2.5.3). The following criteria were introduced for validation of the regression line: 1) there had to be at least 2 valid data points; 2) the correlation coefficient between p_{dp} and L_2, which serves as a measure for the quality of the fit, had to exceed 0.8; and 3) the slope of the linear regression line had to be larger than 0.1 μPa/dB. The resulting $L_{dp,th}$ values were limited to -10 dB HL, i.e. lower $L_{dp,th}$ were set to -10 dB HL.

Occupational noise study

In the occupational noise study, the primary tone level L_2 was set to 30 and 20 dB SL (i.e., above the individual pure-tone hearing threshold at 4 kHz). An individual level setting was used in this study since not only normal hearing subjects were allowed to participate. To guarantee that DPOAEs were measured close to threshold, L_2 was set dependent on the subject's individual audiometric threshold at 4 kHz. Also, measurements were conducted at only two primary tone levels due to restricted available measurement time. L_1 was set as before according to the 'scissor paradigm' equation. The total measuring duration amounted usually to about 3 to 5 minutes.

For evaluating DPOAE fine structure, data were exclusively used that contained at least a 2/3 majority of valid data points (i.e., n $\geq$ 30 out of 46), which were present for the same parameter setting both in measurements before and after work. Due to this criterion, which was introduced to ensure inter-individual comparability, four data sets in the noise exposure group and no data set in the control group had to be discarded, resulting in group sizes of 48 and 17, respectively.

For further improving measurement quality and for achieving reliable comparability between measurements before and after work, two additional criteria were introduced for offline analysis, i.e. calibration stability (see Fig. 7.2B) and primary tone level stability (see Fig. 7.2C). Applying these two additional criteria, which are explained in more detail below, 17 data sets for the noise exposure group and one data set for the control group had to be discarded. Results are presented both for the reduced groups where the additional criteria for measurement stability have been applied (31 factory workers, 16 office workers) and for the larger groups containing all data sets with at least 2/3 of all measurement data being valid (48 factory workers, 17 office workers). Results for the larger groups are displayed in square brackets in the following.

Calibration and primary tone level stability criteria in DPOAE fine structure measurements

Calibration stability was calculated by averaging the absolute values of differences between calibration curves recorded for DPOAE fine structure measurements before and after noise exposure. Calibration curves were analyzed in the DPOAE measurement frequency range from 3.5 to 4.5 kHz. For the occupational noise study, it was defined that the mean difference should not exceed 4 dB for each loudspeaker channel. This criterion should ensure that the shape of the calibration curve used for measuring DPOAE fine structure before and after work was quite similar in the measurement frequency range (compare left and middle panel in Fig. 7.2B).

The shape of the calibration curve is known to depend on the position of the ear probe within the ear canal, which again influences the difference between the sound pressure level at the ear drum and the sound pressure level recorded at the ear probe microphone which could differ substantially due to standing wave phenomena (see Sec. 3.4). In Fig. 7.2B, an example for a valid calibration is shown, whereas Fig. 7.3A exhibits an example for a calibration which failed the above criterion. Fig. 7.3B shows the corresponding discarded DPOAE fine structure data. This example was chosen to explain possible problems of calibration differences between measurements before and after work. Similar effects were observed in most of the data sets that were discarded due to calibration instability. In this example, the maxima and minima of the calibration curves recorded before and after work were differently pronounced and also slightly shifted across frequency (compare left and middle panel in Fig. 7.3A). These changes resulted in substantial differences in calibration across the measurement frequency range, changing in this case from highly negative to highly positive differences (right panel in Fig. 7.3A). Positive differences mean that for the calibration recorded after noise exposure (in comparison to the calibration recorded before noise exposure) a higher level at the ear probe microphone occurred for a fixed output voltage at the ear probe speaker, i.e. for a fixed level at the ear probe microphone a

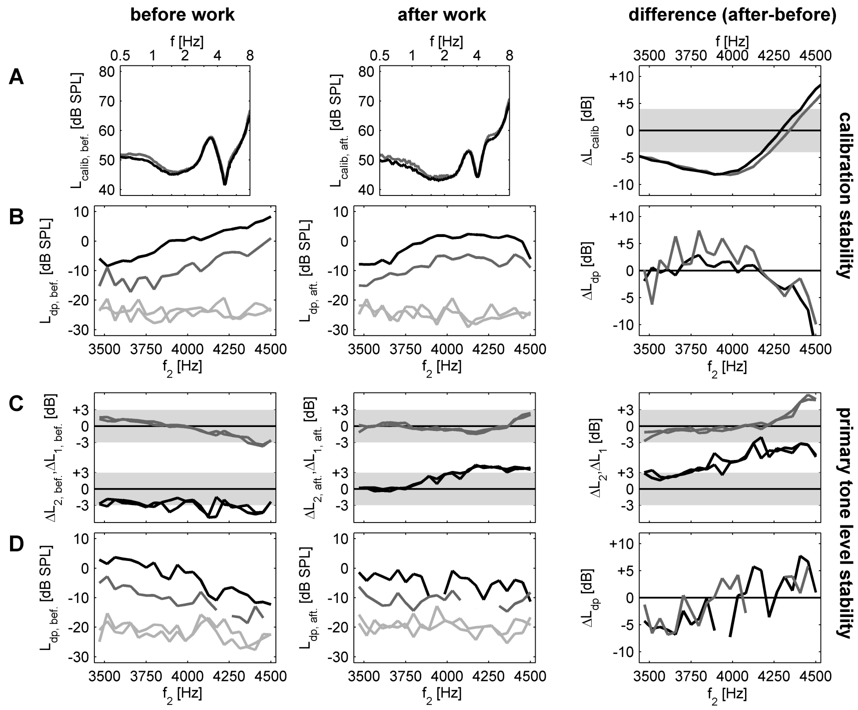

Figure 7.3: Occupational noise study case example of failed calibration stability (A) and primary tone level stability (C) criterion and the corresponding particular DPOAE fine structure (B, D). (A) In-the-ear calibration transfer functions before and after work for both loudspeakers (black and gray line) and difference between both measurements before and after work plotted in the f_2 measurement frequency range (right panel). The light gray area in the right panel shows the area in which calibration differences had to be on average so that data was accepted as valid. (B) DPOAE fine structure data for the same subject as in panel A. (C) Deviations of real level recorded at the ear probe microphone to target level before and after work for both primary tone levels (black: ΔL_2; gray: ΔL_1) and difference between both measurements before and after work (right panel). The light gray area in all panels show the area in which primary tone level deviations had to be on average so that data was accepted as valid. (D) DPOAE fine structure data for the same subject as in panel C.

lower voltage needed to be applied. A lower output voltage might result in lower levels at the ear drum supposed that the position of the ear probe was similar but not completely identical for the two measurements so that maxima and minima, which occurred due to standing wave phenomena, differed slightly. Therefore, primary tone levels at the ear drum had possibly been smaller or higher (for the same target level) where calibration exhibited positive or negative differences. This effect can be observed when comparing graphs of differences in calibration (right panel in Fig. 7.3A) to graphs of differences in DPOAE fine structure (right panel in Fig. 7.3B), which showed an inverted behavior. Thus, major changes in calibration might strongly influence the change in DPOAE level even if the particular calibration curves recorded before and after noise exposure in each case represented a valid calibration.

Stability of primary tone levels (L_2 and L_1) recorded at the ear probe microphone was taken into account by the second criterion. For this criterion the absolute values of differences between recorded levels and target levels of each measurement (within measurement stability, left and middle panel in Fig. 7.3C) and the absolute values of differences between recorded levels of measurements before and after noise exposure (before/after measurement stability, right panel in Fig. 7.3C) were calculated. Data were defined as invalid if the mean difference exceeded 3 dB. This criterion should ensure that on the one hand primary tone levels were rather constant within a DPOAE fine structure measurement and that on the other hand primary tone levels did not significantly differ between measurements before and after noise exposure. Figure 7.2C shows an example for valid primary tone level stability, whereas Fig. 7.3C exhibits an example for insufficient primary tone level stability according to the criterion above. Figure 7.3D shows the corresponding discarded DPOAE fine structure data. When comparing differences in primary tone level (right panel in Fig. 7.3C) and differences in DPOAE level (right panel in Fig. 7.3D), it can be seen that the course of both measures proceeds comparably suggesting that higher primary tone levels recorded at the ear probe microphone may directly result in higher DPOAE levels.

7.1.6 CAS DPOAE measurement procedure

DPOAE measurements with and without contralateral acoustic stimulation (CAS) were recorded at one specific frequency (see Figs. 7.1C and 7.2E), which was selected at a major dip of the DPOAE fine structure since contralateral effects were found to be larger in dips compared to flat regions of the DPOAE fine structure (see Chapter 6).

In both studies, the effect of CAS on DPOAEs (i.e., $\Delta L_{dp,CAS}$) was investigated at different $L_2|L_1$ combinations. For each level setting, DPOAEs were recorded first in the absence and then in the presence of CAS (directly following each other in the measurement sequence). The contralateral stimulus was started 0.2 s before the onset of the ipsilateral primary tones and ended 0.2 s after their termination. The contralateral stimulus consisted of broadband noise which was presented with a stimulus level of 60 dB SPL.

For evaluating efferent MOC reflex strength, two measures were defined: (i) the range between maximum and minimum $\Delta L_{dp,CAS}$, which was named peak-to-peak efferent reflex strength (PPERS) (see Chapter 6) and (ii) the absolute values $|\Delta L_{dp,CAS}|$ averaged across all level combinations, which was named average efferent reflex strength (AERS). PPERS was introduced following the method applied by Maison and Liberman (2000), who found in their guinea-pig experiments a correlation between efferent reflex strength and susceptibility to noise overexposure. In the presented studies, AERS was introduced as a more stable parameter incorporating not only the maxima but all valid measuring points. Additionally, also average as well as maximum suppression and enhancement was examined.

Discotheque music study

L_2 was varied from 40 to 20 dB SPL in steps of 5 dB. For each L_2, L_1 was changed symmetrically around the center level $L_{1,center} = 0.4L_2 + 39$ dB SPL. The offset around the center level $L_{1,offset}$ was shifted from -10 to $+10$ dB in steps of 2 dB. Thus, a total of 55 $L_2|L_1$ combinations were examined. The total measuring duration amounted to about 8 minutes. No further exclusion criteria were implemented.

Occupational noise study

For the occupational noise study, a slightly reduced paradigm was used. L_2 was varied from 30 to 20 dB SL in steps of 5 dB. For each L_2, L_1 was changed symmetrically around the center level $L_{1,center} = 0.4L_2 + 39$ dB SPL. The offset around the center level $L_{1,offset}$ was shifted from -6 to $+6$ dB in steps of 2 dB. Thus, a total of 21 $L_2|L_1$ combinations were examined. The total measuring duration amounted to about 5 minutes.

For evaluating CAS DPOAEs, data were exclusively used that contained at least a 2/3 majority of valid data points (i.e., $n \geq 14$ out of 21), which occurred for the same parameter setting both in measurements with and without CAS. Due to these criteria, five data sets in the noise exposure group and one data set in the control group had to be discarded. The basis for excluding CAS DPOAE data were either the reduced groups (applying all measurement quality criteria mentioned in Sec. 7.1.5) or the extended groups (without the stricter measurement quality criteria). Results on the basis of the extended groups are presented as before in square brackets. Group sizes for analyzing CAS DPOAE data thus were 16 [15] for the control group and 26 [43] for the noise exposure group.

7.2 Results

7.2.1 Impact of noise exposure on pure-tone threshold data

Discotheque music study

Pure-tone hearing threshold levels measured before ($L_{ht,bef.}$), immediately after ($L_{ht,aft.}$), and the day after ($L_{ht,dayaft.}$) three hours of discotheque music are presented in Fig. 7.4A.

In the first instance, the quality of pure-tone threshold measurement data was analyzed. Absolute differences in calibration transfer functions between measurements before and after noise exposure, i.e. calibration stability between measurements conducted at different times, amounted on average to 6 dB (after/before) and 4 dB (day after/before). The difference was calculated in the measurement frequency range between 3.5 and 4.5 kHz. No microphone responses were recorded for the measurement of pure-tone thresholds. Hence, no data is available about primary tone level stability.

Gray lines in Fig. 7.4A show individual data, whereas the black line shows the particular average. On average across subjects and frequencies, pure-tone thresholds L_{ht} amounted

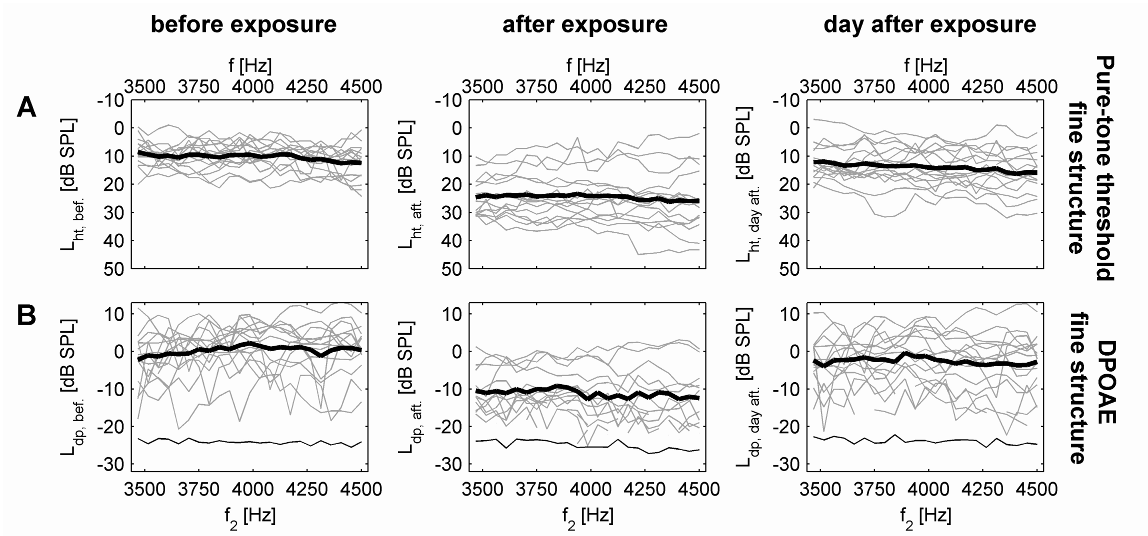

Figure 7.4: Discotheque music study: Mean data (black line) and single measurement data (light gray lines) for pure-tone threshold fine structure (A) and DPOAE fine structure (B) recorded before (left panel), immediately after (middle panel), and the day after (right panel) exposure to three hours of discotheque music. DPOAE fine structure data is shown for $L_2 = 30$ dB SPL. The dark gray line at the bottom constitutes the average noise floor.

to 10.4 ± 3.8 dB SPL before noise exposure, to 24.6 ± 8.9 dB SPL immediately after noise-exposure, and to 14.0 ± 6.5 dB SPL the day after noise exposure. Hence, pure-tone thresholds deteriorated by $+14.2 \pm 8.7$ dB due to the influence of three hours of discotheque music, which was extremely significant (Wilcoxon test, $p < 0.001$). After noise exposure, a deterioration of pure-tone thresholds occurred for all subjects, except for one, which exhibited a slight improvement. The shift in pure-tone thresholds due to noise exposure varied substantially across subjects and ranged from -1.8 to $+26.1$ dB.

The day after discotheque attendance, pure-tone thresholds largely recovered, but usually not completely. Pure tone-thresholds improved on the next day by -10.6 ± 8.6 dB, which was extremely significant ($p < 0.001$), but the difference to the baseline measurement still remained significant ($p < 0.05$) at $+3.6 \pm 4.3$ dB.

The roughness of pure-tone threshold fine structure R_{ht} was calculated as the average of absolute dip depth values across the entire measurement frequency range and was investigated for measurements before, immediately after, and the day after noise exposure. R_{ht} was largest (3.1 ± 1.3 dB) at the baseline measurement and decreased after noise exposure (2.4 ± 1.0 dB), whereas on the next day it once again slightly increased (2.6 ± 1.0 dB) but was still distinctly lower compared to baseline roughness. However, there was no significant difference between any of the measurements before, immediately after, and the day after noise exposure.

In view of examining the relationship between baseline pure-tone thresholds ($L_{ht,bef.}$) and shifts in pure-tone thresholds due to noise exposure ($\Delta L_{ht,aft.} = L_{ht,aft.} - L_{ht,bef.}$), their correlation was examined. There was no significant correlation between $L_{ht,bef.}$ and $\Delta L_{ht,aft.}$, i.e. the individual TTS and with that possibly the individual susceptibility to noise did not seem to depend on the subject's initial hearing capability. However, in this study only normal hearing subjects were allowed to participate. Hence, the variability in baseline pure-tone thresholds was rather low, complicating the comparison between both measures.

Occupational noise study

Pure-tone hearing threshold levels measured before work ($L_{ht,bef.}$) are presented in Fig. 7.5A for the noise exposure group and in Fig. 7.5B for the control group. Gray lines show individual data, whereas the black line shows the particular average. On average across subjects and frequencies, pure-tone thresholds were similar in each group and amounted to 10.3 ± 4.8 dB HL ($n = 31$) [11.1 ± 5.3 dB HL ($n = 48$)] for the factory workers and to 10.9 ± 7.6 dB HL ($n = 16$) [10.6 ± 7.5 dB HL ($n = 17$)] for the office workers. However, it should be emphasized that for the factory workers often a distinct notch in the audiogram at 4 kHz occurred, representing a typical NIHL at the most sensitive region of the cochlea. Average pure-tone threshold at 4 kHz amounted to 14.4 ± 8.3 dB HL [14.9 ± 8.8 dB HL] for the factory workers and to 9.7 ± 10.7 dB HL [9.4 ± 10.4 dB HL] for the office workers and was thus on average larger for the subjects regularly exposed to work-related noise compared to those normally working in a quiet office environment.

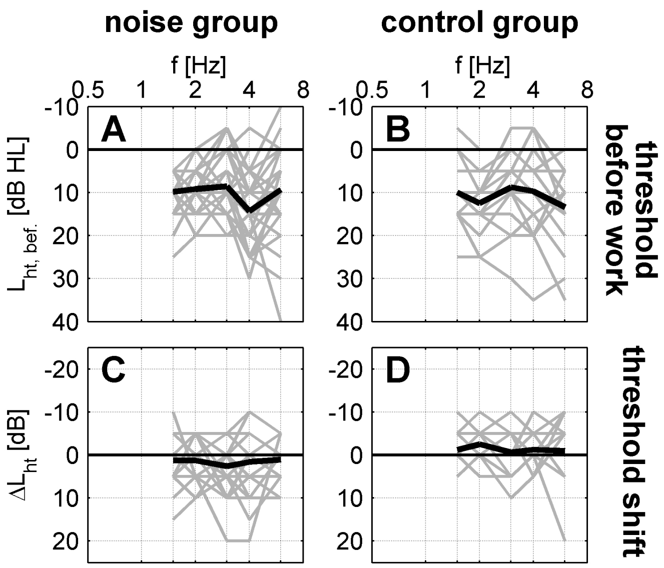

Figure 7.5: Occupational noise study: Audiogram data for noise exposure ($n = 31$) and control group ($n = 16$). Pure-tone hearing thresholds were determined at 1.5, 2, 3, 4, and 6 kHz. (A), (B) Particular average (thick black line) and individual (thin gray lines) pure-tone thresholds recorded before work (Lht,bef.). (C), (D) Particular average and individual shift in pure-tone thresholds after one workday (ΔL_{ht}).

Pure-tone hearing threshold shifts ΔL_{ht}, i.e. the difference of pure-tone thresholds obtained before and after work, are presented in Fig. 7.5C for the factory workers ($n = 31$) and in Fig. 7.5D for the office workers ($n = 16$). On average across frequencies, pure-tone threshold levels increased for the factory workers by $+1.6 \pm 3.0$ dB [$+1.8 \pm 3.0$ dB], i.e. hearing thresholds on average deteriorated, whereas for the clerical workers threshold levels decreased by -1.3 ± 3.3 dB [-1.1 ± 3.3 dB], i.e. hearing thresholds on average improved. When regarding pure-tone thresholds at 4 kHz, threshold shifts amounted to $+1.6 \pm 6.6$ dB [$+2.5 \pm 6.6$ dB] and -1.3 ± 3.9 dB [-1.2 ± 3.8 dB], respectively. Thus, when looking at data from the extended group of factory workers, hearing at 4 kHz was found to be most affected by one day of noise exposure. For the reduced group of factory workers, the deterioration in hearing capability was largest at 3 kHz (see Fig. 7.5C).

Regarding pure-tone threshold shifts averaged across all audiometer frequencies, threshold shifts were highly significant within the noise exposure group (paired t-test, $p < 0.01$ [$p < 0.001$]), whereas they were not significant within the control group. Differences in pure-tone threshold shifts between the two groups were also highly significant (unpaired t-test, $p < 0.01$). When examining pure-tone threshold shifts at 4 kHz only, results were qualitatively similar but mostly higher p-values occurred. Thus, data show that there was a small but significant change in hearing capability in the factory workers but not in the office workers after one workday.

Similar to the findings of the discotheque music study, there was no significant correlation between $L_{ht,bef.}$ and ΔL_{ht}, i.e. the individual TTS and with that the individual susceptibility to noise did not seem to depend on whether the respective subject had a good or bad hearing capability. Thus, baseline pure-tone thresholds do not seem to be an adequate predictor for TTS.

7.2.2 Impact of noise exposure on DPOAE fine structure data

Discotheque music study

On average across subjects and primary tone levels, DPOAE fine structure data sets contained 68 (before), 53 (after), and 66 (day after) valid out of 69 measuring points. The average noise floor level was independent of the time of measurement and amounted to -24 dB SPL. Absolute differences in calibration transfer functions between measurements before and after work amounted to 4 dB (after/before) and 3 dB (day after/before). The difference was calculated as for pure-tone threshold data in the measurement frequency range between 3.5 and 4.5 kHz and across both loudspeaker channels for the two primary tones. Absolute differences in primary tone levels within a measurement were rather low with 0.8 dB (before), 1.3 dB (after), and 0.4 dB (day after). The absolute differences between the measurements amounted to 1.4 dB (after/before) and 0.5 dB (day after/before).

DPOAE levels at $L_2 = 30$ dB SPL recorded before ($L_{dp,bef.}$), immediately after ($L_{dp,aft.}$), and the day after ($L_{dp,dayaft.}$) noise exposure are shown in Fig. 7.4B. Thin gray lines show individual data of the subjects in the respective group. The thick black line shows the particular average. In addition, the average background noise floor level is presented as the dark gray line at the bottom of all panels.

Average DPOAE levels amounted at $L_2 = 40$ dB SPL to 5.2 ± 5.1 (before), -4.9 ± 8.4 (after), and 3.4 ± 5.6 dB SPL (day after), at $L_2 = 30$ dB SPL to 0.3 ± 5.5 (before), -12.5 ± 6.6 (after), and -2.7 ± 6.5 dB SPL (day after), and at L_2 =20 dB SPL to -6.5 ± 5.3 (before), -17.7 ± 3.2 (after), and -9.9 ± 6.1 dB SPL (day after). As expected, L_{dp} generally decreased with decreasing primary tone level. Especially for measurements after noise exposure, at the lowest primary tone level ($L_2 = 20$ dB SPL) DPOAEs were frequently not measurable since their amplitude fell below the noise floor level. Hence, fewer data were available for evaluation and for comparison between measurements before and after noise exposure, yielding a lower expressiveness of the data. The minimum detectable DPOAE level was restricted to the detection threshold SNR $+L_{nf}$ which did hence also limit the maximum shift in DPOAE level in comparison to the baseline value. This can be seen in the reduced variability of L_{dp} across subjects at $L_2 = 20$ dB SPL for the measurement after discotheque attendance. The number of available valid data points amounted at L_2 = 40 dB SPL to 23 (before), 21 (after), and 23 (day after), at $L_2 = 30$ dB SPL to 23 (before), 19 (after), and 23 (after), and at $L_2 = 20$ dB SPL to 22 (before), 12 (after), and 20 (day after) reflecting the decline in DPOAE levels after noise exposure and especially at $L_2 = 20$ dB SPL.

The shift in DPOAE level between measurements after and before noise exposure ($\Delta L_{dp,aft.} = L_{dp,aft.} - L_{dp,bef.}$) amounted to -10.1 ± 5.1 dB at $L_2 = 40$ dB SPL, to -12.9 ± 4.9 dB at $L_2 = 30$ dB SPL, and to -11.0 ± 5.2 dB at $L_2 = 20$ dB SPL. The shift in DPOAE level at $L_2 = 20$ dB SPL could be expected to be even larger since on average about half of all measurement data became invalid due to DPOAE levels, which were below the detection threshold (SNR $+L_{nf}$) and hence could not be evaluated. The deterioration in DPOAE level was for all primary tone levels extremely significant ($p < 0.001$). The standard deviation of $\Delta L_{dp,aft.}$ of about 5 dB is supposed to demonstrate the inter-individually different effect of noise exposure on L_{dp}. All subjects exhibited a deterioration in DPOAE levels, which ranged from -3.5 to -19.2 dB at $L_2 = 40$ dB SPL, from -5.8 to -21.9 dB at $L_2 = 30$ dB SPL, and from -0.8 to -19.2 dB at $L_2 = 20$ dB SPL.

DPOAE levels recovered partially until the next day and increased by $+8.3 \pm 4.6$ dB at $L_2 = 40$ dB SPL, by $+10.0 \pm 4.3$ dB at $L_2 = 30$ dB SPL, and by $+7.9 \pm 5.6$ dB at L2 = 20 dB SPL, which was an extremely significant ($p < 0.001$) increase at all primary tone levels. However, L_{dp} did not reach the baseline value and remained at -1.9 ± 2.6 dB (L_2 = 40 dB SPL), -3.0 ± 3.2 dB ($L_2 = 30$ dB SPL), and -3.5 ± 3.2 dB ($L_2 = 20$ dB SPL) below the baseline, which was still significant for all primary tone levels ($L_2 = 40$ dB SPL: $p < 0.01$; $L_2 = 30$, 20 dB SPL: $p < 0.001$).

For evaluating the sensitivity of the cochlear amplifier, DPOAE thresholds $L_{dp,th}$ were calculated by linear regression analysis. $L_{dp,th}$ showed a similar behavior compared to DPOAE levels, but changes were in general smaller. $L_{dp,th}$ amounted to 12.4 ± 3.9 dB SPL (before), 18.8 ± 6.2 dB SPL (after), and 15.1 ± 3.6 dB SPL (day after). Hence, the estimated deterioration in cochlear sensitivity amounted to $+6.3 \pm 8.2$ dB SPL, which was a significant shift ($p < 0.05$) but distinctly lower than the shift in behavioral pure-tone thresholds, which amounted to 14.2 dB (see Sec. 7.2.1). On the next day, $L_{dp,th}$ recovered significantly ($p < 0.05$) by -5.4 ± 4.6 dB. The remaining difference compared to the baseline measurement amounted to $+2.8 \pm 2.5$ dB which was still highly significantly ($p < 0.01$) below the baseline value. For evaluating the compression of the cochlear amplifier, DPOAE slope s_{dp} (i.e., difference between L_{dp} at $L_2 = 60$ and 40 dB SPL, derived from the extrapolated regression line) was calculated. The DPOAE slope changed slightly across time and amounted to 0.24 ± 0.03 dB/dB (before), 0.30 ± 0.06 dB/dB (after), and 0.26 ± 0.03 dB/dB (day after). The differences between the measurements before, after, and the day after noise exposure were rather small but significant (after/before, day after/before: $p < 0.05$; day after/after: $p < 0.01$). These findings suggest that both sensitivity and compression of the cochlear amplifier deteriorated after three hours of high-level discotheque music.

The roughness of DPOAE fine structure R_{dp} was calculated as the average of absolute dip depth values across the entire measurement frequency range and was investigated before, immediately after, and the day after noise exposure. Roughness generally increased with increasing primary tone level. Also, R_{dp} was generally largest at the baseline measurement. However, there was no consistent behavior when comparing measurements conducted before and after or before and the day after noise exposure. There was also no significant change in R_{dp} due to noise exposure or recovery. This result was true for all primary tone levels.

In order to investigate if changes in OHC function due to noise exposure can be evaluated by means of individual baseline DPOAE levels, the relationship between baseline DPOAE levels ($L_{dp,bef.}$) and shifts in DPOAE levels ($\Delta L_{dp,aft.}$) was examined. There was no significant correlation between $\Delta L_{dp,aft.}$ and $L_{dp,bef.}$ except for $L_2 = 20$ dB SPL. However, at $L_2 = 20$ dB SPL the shift in DPOAE level $\Delta L_{dp,aft.}$ might have been influenced by the baseline DPOAE level $L_{dp,bef.}$ since for larger $L_{dp,bef.}$ a larger $\Delta L_{dp,aft.}$ was possible than for a lower $L_{dp,bef.}$ due to a larger separation from the constant noise floor level. This means that for the present data there seems to be no consistent relationship between baseline DPOAE level and temporary changes in cochlear amplifier functionality.

Occupational noise study

On average across subjects, DPOAE fine structure data sets contained 44 valid out of 46 measuring points. The average noise floor level was independent of group membership and amounted to -24 dB SPL resulting in an average SNR of 18 dB for the noise exposure group and 21 dB for the control group. Due to these SNRs, it could be expected that the DPOAE level L_{dp} exhibited a test-retest-variability of less than 1 dB (see Janssen *et al.*, 2005a). Differences in calibration transfer functions between measurements before and after work amounted to 2.0 dB [3.1 dB] (noise exposure group) and 1.4 dB [1.7 dB] (control group), respectively. Primary tone level differences within a measurement (see Sec. 7.1.5) amounted to 0.7 dB [0.8 dB] and 0.6 dB [0.7 dB] for the particular groups, while primary tone level differences between measurements before and after work (see Sec. 7.1.5) amounted to 0.8 dB [1.0 dB] (noise exposure group) and 0.7 dB [0.7 dB] (control group), respectively. Thus, measurement conditions were expected to be good enough to reliably detect small changes in DPOAE level.

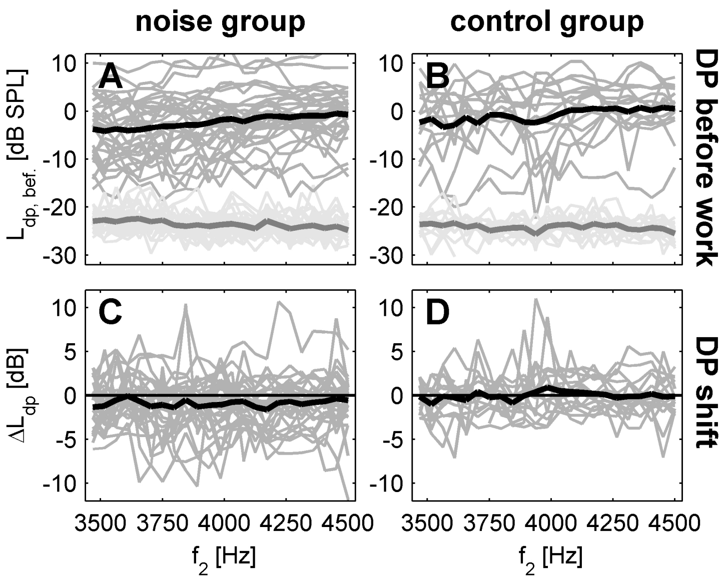

Figure 7.6: Occupational noise study: DPOAE fine structure data for noise exposure ($n = 31$) and control group ($n = 16$). All data are shown for $L_2 = 30$ dB SL. (A), (B) Particular average (thick black line) and individual (thin gray lines) DPOAE levels recorded before work ($L_{dp,bef.}$). The thick dark gray line and the thin light gray lines at the bottom of each plot show the respective average and individual background noise floor levels. (C), (D) Particular average and individual shift in DPOAE level after one workday (ΔL_{dp}).

DPOAE levels recorded before work ($L_{dp,bef.}$) at $L_2 = 30$ dB SL are shown for factory workers ($n = 31$) in Fig. 7.6A and for office workers ($n = 16$) in Fig. 7.6B. Thin dark gray lines show individual data of the subjects in the respective group. The thick black line shows the particular average. In addition, background noise floor levels are presented as the lines at the bottom of panel A and B (thick dark gray line: average; thin light gray lines: individual data). $L_{dp,bef.}$ recorded at $L_2 = 30$ dB SL and averaged across the entire measurement frequency range and all subjects was lower for the factory workers (-2.3 ± 5.6 dB SPL [-2.6 ± 5.6 dB SPL]) than for the office workers (-1.0 ± 5.5 dB SPL [-1.0 ± 5.4 dB SPL]). For $L_2 = 20$ dB SL, mean L_{dp} was as expected substantially lower for both groups (noise exposure group: -8.2 ± 5.9 dB SPL [-8.1 ± 5.7 dB SPL]; control group: -6.8 ± 5.1 dB SPL [-7.0 ± 5.0 dB SPL]).

The shift in DPOAE level ΔL_{dp}, i.e. the difference of DPOAE levels obtained before and after work, is presented in Fig. 7.6C and 7.6D for both groups. ΔL_{dp} was analyzed across the entire measurement frequency range and amounted for $L_2 = 30$ dB SL to -0.9 ± 2.1 dB [-0.8 ± 3.6 dB] for the factory workers and to 0.0 ± 1.4 dB [$+0.3 \pm 1.9$ dB] for the office workers, while for $L_2 = 20$ dB SL the effect was in general slightly larger and amounted to -1.0 ± 2.4 dB [-1.0 ± 3.7 dB] (noise exposure group) and to 0.0 ± 1.6 dB [$+0.4 \pm 2.2$ dB] (control group). The shift in DPOAE level was significant for the factory workers (paired t-test, $p < 0.05$), but not for the office workers. Differences in ΔL_{dp} between the groups were not significant (unpaired t-test). This means, there was, similar to the finding for behavioral pure-tone thresholds, a small but significant decrease in DPOAE level, revealing an impact on cochlear amplifier function after only one workday in the factory. This is also consistent with the findings from the discotheque music study, where, however, a larger effect was observable.

The average change in DPOAE slope (i.e., difference between ΔL_{dp} at $L_2 = 30$ dB SL and ΔL_{dp} at $L_2 = 20$ dB SL) increased for the factory workers (+0.3 dB/dB) and decreased for the office workers (-0.2 dB/dB). An increase in slope of DPOAE growth means a loss of compression of the cochlear amplifier (e.g., Kummer *et al.*, 1998) and is thus an additional indication that noise exposure had an impact on cochlear amplifier function of the factory workers after one workday. Due to lack of sufficient data, DPOAE thresholds $L_{dp,th}$ were not investigated.

The roughness of DPOAE fine structure R_{dp} was calculated as in the other study as the average of absolute dip depth values across the entire measurement frequency range and was investigated before and after work for both test groups. For the factory workers, roughness evaluated across both primary tone levels increased slightly after work, whereas for the office workers R_{dp} slightly decreased. However, there was no significant change in R_{dp} due to noise exposure.

Similar to the findings from the discotheque music study, there was no significant correlation between ΔL_{dp} and $L_{dp,bef.}$, i.e. for the present occupational noise exposure data the absolute DPOAE level does not seem to be related to temporary changes in cochlear amplifier function.

7.2.3 Relationship between pure-tone threshold and DPOAE fine structure before and after noise exposure

Discotheque music study

When examining the relationship between pure-tone threshold and DPOAE fine structure data, only data recorded before and after noise exposure was examined. On average across subjects, pure-tone threshold and DPOAE fine structure data showed similar behavior (see Secs. 7.2.1 and 7.2.2), i.e. pure-tone thresholds and DPOAE levels deteriorated after noise exposure. However, when looking at individual data, pure-tone threshold and DPOAE fine structure data did not always exhibit congruent behavior, but also divergent behavior. So, the question was whether there is any correlation between objective and behavioral measures. Figure 7.7 shows different case examples for congruent and divergent behavior.

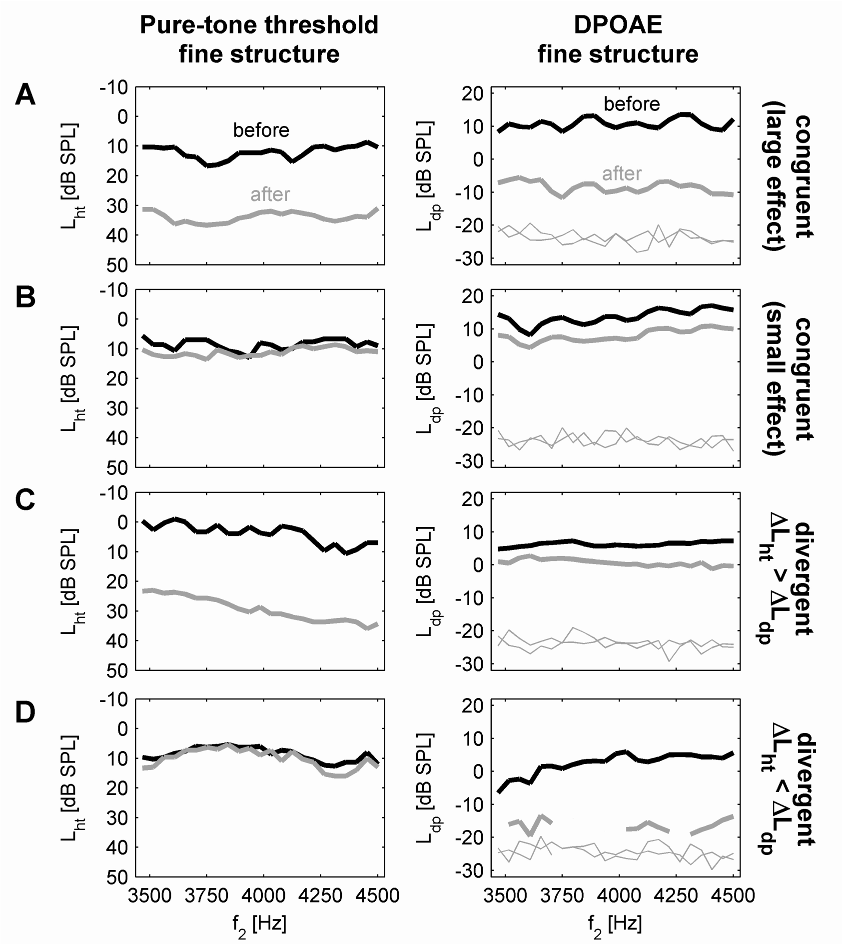

Figure 7.7: Discotheque music study: Case examples of congruent (A, B) and divergent (C, D) behavior between pure-tone threshold (left panels) and DPOAE fine structure at $L_2 = 40$ dB SPL (right panels) before (black line) and after (gray line) noise exposure. For DPOAE fine structure, the thin light gray lines at the bottom of each panel constitute the noise floor.

Left panels show pure-tone threshold data, whereas right panels show DPOAE data recorded at $L_2 = 40$ dB SPL. Data derived from measurements before noise exposure are plotted as black line, whereas data derived from measurements after noise exposure are plotted as gray line. For DPOAE data, noise floor levels are additionally plotted as thin gray lines at the bottom of each DPOAE plot. The first example (Fig. 7.7A) shows a congruent and rather large deterioration in both measures, which amounted in this case example on average across frequencies to 22 dB for pure-tone thresholds and to 19 dB for DPOAE levels. The second example in panel B also shows a congruent but rather small deterioration in both measures, which amounted to only 3 dB ($\Delta L_{ht,aft.}$) and 6 dB ($\Delta L_{dp,aft.}$), respectively. When setting the threshold of congruent behavior for an average absolute difference between measures to 8 dB, 9 out of 15 subjects exhibited a congruent behavior. Two examples for divergent behavior between measures can be seen in Fig. 7.7C and 7.7D. The most common case, which was present at 5 out of 6 subjects with divergent behavior, was that pure-tone thresholds exhibited a large deterioration, whereas DPOAE levels only exhibited a small deterioration (Fig. 7.7C). In the shown case example, $\Delta L_{ht,aft.}$ amounted to 25 dB and $\Delta L_{dp,aft.}$ to 6 dB. In one exceptional case, the opposite effect of a small deterioration in pure-tone thresholds of 2 dB and a large deterioration in DPOAE levels of 19 dB occurred (Fig. 7.7D).

In order to evaluate the significance of these results, the calibration stability between measurements before and after noise exposure and between pure-tone threshold and DPOAE fine structure measurements was analyzed, since calibration differences are expected to have a major influence on the deviation of the real primary tone level from the target level. Therefore, in a first step the average difference in the calibration transfer function between measurements after and before noise exposure ($\Delta L_{calib,aft.} = L_{calib,aft.} - L_{calib,bef.}$) was calculated for both types of measurements. A positive difference means a higher level at the microphone for constant output voltage for the measurement after noise exposure. However, the higher level might have arisen due to standing wave effects and hence might not be associated with a higher level at the ear drum (see Sec. 7.1.5). Thus, the true stimulus level might be reduced in the measurement after noise exposure resulting possibly in an increased shift in pure-tone threshold $\Delta L_{ht,aft.}$ or an increased shift in DPOAE level $\Delta L_{dp,aft.}$, respectively. The opposite effect may occur for negative differences in calibration transfer function $\Delta L_{calib,aft.}$. That this effect actually occurs is supported by the finding that the correlation between the particular $\Delta L_{calib,aft.}$ and $\Delta L_{ht,aft.}$ or $\Delta L_{dp,aft.}$ was rather large and amounted to 0.81 and −0.53, respectively. For evaluating differences between the two measurement methods (i.e., pure-tone threshold and DPOAE fine structure) the difference between $\Delta L_{ht,calib,aft.}$ (for pure-tone threshold measurements) and $\Delta L_{dp,calib,aft.}$ (for DPOAE fine structure measurements) was calculated. A negative value means that $\Delta L_{ht,aft.}$ was expected to be lower than $\Delta L_{dp,aft.}$, a positive value means that $\Delta L_{ht,aft.}$ was expected to be larger than $\Delta L_{dp,aft.}$. Calibration differences between the measurement methods amounted on average across all measurements to −2.7 dB and ranged from −8.0 to 6.3 dB. However, there was one outlier, where the difference amounted to −17.9 dB. This extremely high difference occurred for the case example, which showed a distinct divergent behavior with a small deterioration in pure-tone thresholds $\Delta L_{ht,aft.}$ and a large deterioration in DPOAE level $\Delta L_{dp,aft.}$. This effect could be explained by calibration errors. The correlation between calibration differences and differences in deterioration determined across both measurement methods amounted to 0.84 and was thus rather large suggesting a major impact of calibration on the divergent behavior found when comparing the results of both pure-tone threshold and DPOAE fine structure.

In the following, pure-tone threshold and DPOAE fine structure data are compared for baseline data ($L_{ht,bef.}$, $L_{dp,bef.}$) and for shifts due to noise exposure ($\Delta L_{ht,aft.}$, $\Delta L_{dp,aft.}$). Figure 7.8 shows scatter plots including data across all subjects and frequencies, illustrating the relationship between behavioral and objective measures. DPOAE data is shown for $L_2 = 40$ (Fig. 7.8a), 30 (b), 20 dB SPL (c). Panel A shows the relationship between baseline data ($L_{ht,bef.}$, $L_{dp,bef.}$). The correlations increased with increasing primary tone level and amounted to $r = -0.27$ at $L_2 = 40$ dB SPL, $r = -0.44$ at $L_2 = 30$ dB SPL, and $r = -0.50$ at $L_2 = 20$ dB SPL and were all significant. The number of valid data for comparison decreased from 345 at L_2 = 40 dB SPL to 328 at L_2 = 20 dB SPL. When examining data averaged across frequencies, correlations across subjects (n = 15) also increased with increasing primary tone levels and amounted to $r = -0.42$ at L_2 = 40 dB SPL, $r = -0.56$ at L_2 = 30 dB SPL, and $r = -0.67$ at L_2 = 20 dB SPL. Correlations were significant for the lower primary tone levels (L_2 = 30 dB SPL: $p < 0.05$; L_2 = 20 dB SPL: $p < 0.01$). Thus, a relationship between baseline pure-tone thresholds and DPOAE levels could be found for the present data.

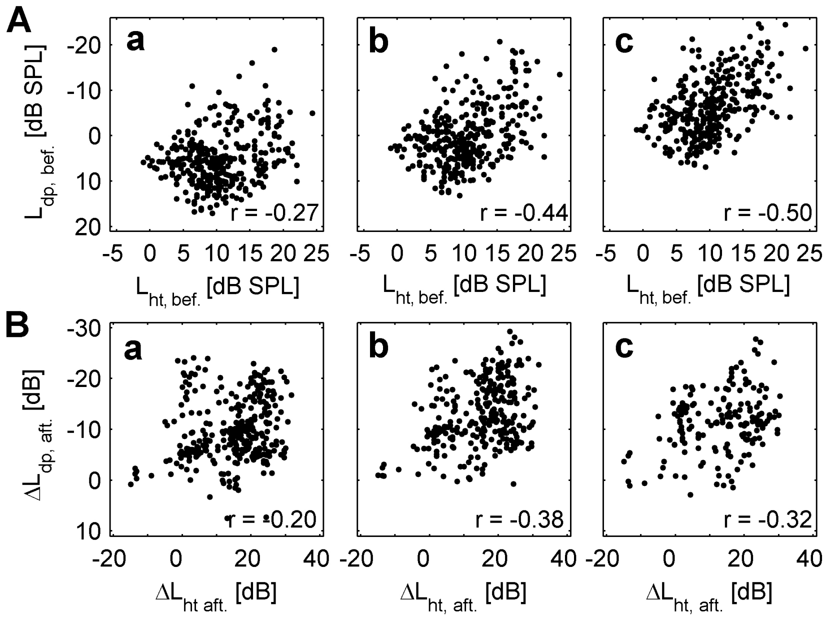

Figure 7.8: Discotheque music study: (A) Correlation between $L_{dp,bef.}$ and $L_{ht,bef.}$. (B) Correlation between $\Delta L_{dp,aft.}$ and $\Delta L_{ht,aft.}$. DPOAE data is shown for primary tone levels L_2 = 40 dB SPL (a), 30 dB SPL (b), and 20 dB SPL (c).

Panel B demonstrates the relationship between shifts in both measures after noise exposure ($\Delta L_{ht,aft.}$, $\Delta L_{dp,aft.}$). The correlation was largest for the middle primary tone level and amounted to $r = -0.20$ at L_2 = 40 dB SPL, $r = -0.38$ at L_2 = 30 dB SPL, and $r = -0.32$ at L_2 = 20 dB SPL. All correlations were significant. The number of valid data for comparison decreased from 320 at L_2 = 40 dB SPL to 179 at L_2 = 20 dB SPL. When examining data averaged across frequencies, correlations across subjects (n = 15) exhibited similar behavior with maximum correlation for the middle primary tone level. Correlations amounted to $r = -0.19$ at L_2 = 40 dB SPL, $r = -0.36$ at L_2 = 30 dB SPL, and $r = -0.31$ at L_2 = 20 dB SPL but were not significant due to the rather small number of subjects. Hence, no general correlation could be found for the deterioration in both measures. This finding is supported by the fact that in some subjects a divergent behavior between the deterioration in both measures ($\Delta L_{ht,aft.}$ and $\Delta L_{dp,aft.}$) was found. However, the question remains whether there is no general correlation between the behavioral and the objective measure or whether the correlation is actually present but is corrupted by an inter-individually varying influence of calibration errors.

It is interesting to note that there was an extremely significant correlation ($p < 0.001$) between both measures when comparing data recorded on the day after noise exposure ($L_{ht,dayaft.}$ and $L_{dp,dayaft.}$). This was true for all primary tone levels. Correlations amounted to $r = -0.80$ at $L_2 = 40$ dB SPL, $r = -0.88$ at $L_2 = 30$ dB SPL, and $r = -0.90$ at $L_2 = 20$ dB SPL. Thus, correlations improved on the day after noise exposure compared to the correlations for baseline measurements.

When comparing baseline pure-tone threshold ($L_{ht,bef.}$) and shift in DPOAE level ($\Delta L_{dp,aft.}$) there was a significant correlation for DPOAE data recorded at $L_2 = 20$ dB SPL ($r = 0.60$, $p < 0.05$) but no correlation for DPOAE data recorded at the other two primary tone levels ($r = -0.28$ at $L_2 = 40$ dB SPL; $r = 0.19$ at $L_2 = 30$ dB SPL). Hence, since there was no consistent correlation across primary tone levels, no clear relationship between $L_{ht,bef.}$ and $\Delta L_{dp,aft.}$ was evident. Also, there was no correlation between baseline DPOAE level $L_{dp,bef.}$ and shift in pure-tone threshold $\Delta L_{ht,aft.}$ (= TTS) for all primary tone levels.

Occupational noise study

In the occupational noise study, pure-tone thresholds and DPOAE fine structure data exhibited on average similar behavior for both groups (see Secs. 7.2.1 and 7.2.2), i.e. pure-tone thresholds and DPOAE levels deteriorated for the factory workers, whereas they improved or remained unchanged for the office workers. However, when looking at individual data, pure-tone thresholds and DPOAE levels did not always exhibit congruent behavior, i.e. for some subjects DPOAE levels improved during the day while pure-tone thresholds deteriorated and vice versa. So, the question was once again whether there is any correlation between objective and behavioral measures. In the following, pure-tone thresholds at 4 kHz and DPOAE fine structure averaged across both primary tone levels and the entire measurement frequency range (between 3.5 and 4.5 kHz) are compared. Figure 7.9 shows scatter plots for the factory workers ($n = 31$), illustrating the relationship between behavioral and objective measures. For examining correlations, baseline values and their changes during the day were compared.

There was no correlation between shift in pure-tone threshold (ΔL_{ht}) and shift in DPOAE level (ΔL_{dp}) after one workday (Fig. 7.9A) for both the noise exposure group ($r = 0.13$ [0.01]) and the control group ($r = 0.22$ [0.21]). This means that changes in hearing at different stages of the auditory pathway were not correlated, as one may expect at least for the noise-exposed factory workers. When comparing baseline pure-tone threshold ($L_{ht,bef.}$) and shift in DPOAE level (ΔL_{dp}) (Fig. 7.9C), correlations were once again not significant and amounted to 0.24 [0.25] for the factory workers and to 0.30 [0.13] for the office workers. When comparing shift in pure-tone threshold (ΔL_{ht}) and baseline DPOAE level ($L_{dp,bef.}$) (Fig. 7.9B) there was a minor inverse correlation (noise exposure group: -0.33 [-0.30]; control group: -0.24 [-0.24]), i.e. the lower the initial DPOAE level, the higher the pure-tone threshold shift. However, only data for the extended noise exposure group ($n = 48$) revealed a significant correlation ($p < 0.05$). When comparing baseline pure-tone threshold ($L_{ht,bef.}$) and DPOAE level ($L_{dp,bef.}$) there was once again no

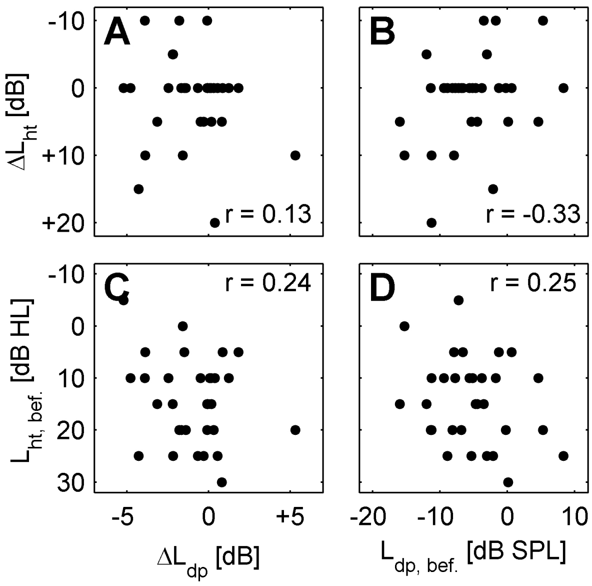

Figure 7.9: Occupational noise study: Scatter plots for comparing pure-tone threshold data obtained at 4 kHz and DPOAE fine structure data averaged over primary tone levels and frequencies in the noise exposure group ($n = 31$). Baseline values measured before work ($L_{ht,bef.}$, $L_{dp,bef.}$) as well as shifts which occurred after one workday (ΔL_{ht}, ΔL_{dp}) were evaluated.

significant correlation for both groups (noise exposure group: 0.25 [0.11]; control group: 0.25 [0.26]), i.e. subjects exhibiting a major baseline hearing loss at 4 kHz did not generally exhibit low baseline DPOAE levels and vice versa. In summary, there was no distinct correlation between measures for hearing capability and cochlear amplifier functionality in the occupational noise exposure study. These results are similar to the findings of the discotheque music study, where, however, a significant correlation between baseline data was found.

7.2.4 CAS DPOAE data

Discotheque music study

On average across subjects, CAS DPOAE data sets contained 50 valid out of 55 measuring points (for an example of CAS DPOAEs see Fig. 7.1C). The average noise floor level for both groups amounted to −24 dB SPL resulting in an average SNR of 20 dB and hence in an expected test-retest-variability of L_{dp} being close to 0.7 dB (see Janssen *et al.*, 2005a). Primary tone level differences between measurements with and without CAS amounted on average across all primary tone level combinations and across all subjects to 0.05 dB and were hence negligible. Thus, measurement conditions were expected to be good enough for reliably detecting small changes in DPOAE level during CAS.

The absolute change in DPOAE level due to CAS $|\Delta L_{dp,CAS}|$ amounted on average across all primary tone level combinations and across all subjects to 1.7 dB. Thus, average $|\Delta L_{dp,CAS}|$ was distinctly larger than the expected test-retest variability of 0.7 dB. Furthermore, only 31 % of all valid data were within the σ-boundary given by Janssen *et al.* (2005a) (compare also Fig. 7.10), which would contain 68 % of all valid data if only test-retest variability would influence the result, and only 56 % were within the 2σ-boundary, which would contain 95 % of all valid data due to test-retest variability. This indicates that the effects observed for CAS data were predominantly influenced by efferent activity and not by measurement inaccuracy.

On average across all subjects, suppression (decrease in DPOAE level due to CAS) occurred in 65 % of all valid data and hence more often than enhancement (increase in DPOAE level due to CAS) with the absolute magnitude of suppression values being with -1.5 dB on average slightly lower to that of enhancement values, which amounted to $+1.9$ dB. Maximum suppression amounted on average to -4.4 dB and was hence also lower in absolute magnitude than average maximum enhancement which amounted to $+5.9$ dB. The resulting measures of efferent reflex strength amounted for PPERS to 10.3 ± 2.8 dB, and for AERS to 1.7 ± 0.6 dB. In general, measures of efferent reflex strength varied across subjects and ranged for PPERS from 6.1 to 15.6 dB and for AERS from 0.8 to 3.0 dB.

Occupational noise study

On average across subjects, CAS DPOAE data sets contained 20 valid out of 21 measuring points (for an example of CAS DPOAEs see Fig. 7.2E). The average noise floor level for both groups amounted as in the discotheque music study to -24 dB SPL resulting in an average SNR of 17 dB and hence in an expected test-retest-variability of L_{dp} being close to 1 dB (see Janssen *et al.*, 2005a). Please note, that for maximum suppression or enhancement, the SNR was on average lower than the SNR that occurred when averaging across all level combinations. In Fig. 7.10, maximum suppression and enhancement values are plotted above the respective SNR. The solid line curve shows the expected standard deviation σ (dotted line: 2σ) of L_{dp} representing the test-retest variability according to Janssen *et al.* (2005a). When using L_{dp} measured without CAS as reference level, the SNR amounted to about 16 dB at level combinations with maximum suppression (circles in Fig. 7.10) and to about 12 dB at level combinations exhibiting maximum enhancement (asterisks in Fig. 7.10). Thus, the average change in DPOAE level $\Delta L_{dp,CAS}$ at the extreme values was well above the expected test-retest variability of about 1.5 dB (see Janssen *et al.*, 2005a). This can also be seen in Fig. 7.10 since only about 20 % of all maxima were below the 2σ curve (dotted line) which would contain 95 % of all data due to test-retest variability if CAS would not exert any influence on OHCs. Therefore, one can conclude that the observed changes in DPOAE level were also in this study mainly due to CAS and not due to measurement inaccuracy. Primary tone level differences between measurements with and without CAS amounted to 0.05 dB for both groups and were hence again negligible. Thus, measurement conditions were also in this study expected to be good enough for reliably detecting small changes in DPOAE level during CAS.

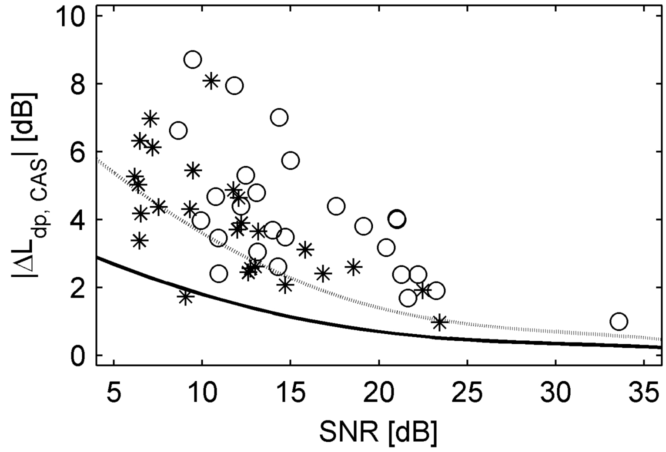

Figure 7.10: Occupational noise study: Relationship between maximum suppression or enhancement of DPOAE level during CAS and SNR. Maximum suppression (circles) and maximum enhancement (asterisks) are both shown as positive values (i.e., minus sign was omitted for suppression values). SNR values were taken from measurements without CAS. The solid line exhibits the standard deviation σ of L_{dp} (obtained from Janssen *et al.*, 2005a) and the dotted line displays 2σ of L_{dp}. These lines indicate that if CAS did not play any role in modifying DPOAE amplitude, 68 % (σ) or 95 % (2σ), respectively, of all data would be within the particular boundary due to L_{dp} test-retest variability.

The absolute change in DPOAE level due to CAS $|\Delta L_{dp,CAS}|$ was on average quite similar between groups and amounted to 1.6 dB [1.7 dB] for the factory workers and to 1.9 dB [1.9 dB] for the office workers. Thus, average $|\Delta L_{dp,CAS}|$ was larger than the expected test-retest variability of 1 dB. For both groups, suppression occurred more often (noise group: 58 %; control group: 61 %) than enhancement with the magnitude of suppression values being on average similar to that of enhancement values. Maximum suppression amounted on average to −4.1 dB [−4.4 dB] for the factory workers and to −4.5 dB [−4.3 dB] for the office workers and was thus again similar to maximum enhancement which amounted to +4.0 dB [+4.1 dB] and +4.1 dB [+4.0 dB], respectively.

The resulting measures of efferent reflex strength amounted for PPERS to 8.1 ± 2.9 [8.5 ± 3.7] dB for the factory workers and to 8.6 ± 4.3 dB [8.3 ± 4.3 dB] for the office workers, and for AERS to 1.6 ± 0.7 dB [$1.7 \pm .8$ dB] for the factory workers and to 1.9 ± 1.1 dB [1.9 ± 1.1 dB] for the office workers. In general, measures of efferent reflex strength varied across subjects and ranged for PPERS from 2.0 to 12.9 dB [19.1 dB] for the factory workers and from 2.1 to 18.4 dB for the office workers. In comparison, AERS ranged from 0.6 to 3.2 dB [0.5 to 3.8 dB] for the factory workers and from 0.4 to 4.3 dB for the office workers. Thus, PPERS and AERS were on average slightly larger in the group of office workers but were in the same order of magnitude for both groups.

7.2.5 Relationship between CAS DPOAE, pure-tone threshold, and DPOAE fine structure

For evaluation of CAS DPOAE data, peak-to-peak efferent reflex strength (PPERS) and average efferent reflex strength (AERS) were calculated (see Sec. 7.1.6). In addition, also maximum and average suppression, and maximum and average enhancement were examined. Please note, that for all measures the absolute value was used (i.e., sign of suppression values was inverted) for yielding clearness of results. For examining the usability of the applied measures of efferent reflex strength in determining inter-individual vulnerability to noise overexposure, their correlation to pure-tone threshold and DPOAE fine structure measures was analyzed.

Discotheque music study

Figure 7.11 shows correlations between measures of efferent reflex strength (PPERS, AERS, average suppression and enhancement) and baseline or shift in pure-tone threshold and DPOAE fine structure data at L_2 = 40 dB SPL. There was no significant correlation between any measure of efferent reflex strength and shift in pure-tone threshold ($\Delta L_{ht,aft.}$) (Fig. 7.11Aa–Da) or shift in DPOAE level ($\Delta L_{dp,aft.}$) (Fig. 7.11Ac–Dc) at any primary tone level.

In contrast, some measures of efferent reflex strength were correlated with baseline pure-tone threshold or DPOAE fine structure data. For baseline pure-tone thresholds ($L_{ht,bef.}$), AERS ($r = 0.57$, $p < 0.05$), maximum suppression ($r = 0.69$, $p < 0.01$), and average suppression ($r = 0.53$, $p < 0.05$) exhibited a significant positive correlation, i.e. efferent reflex strength increased with increasing baseline hearing loss. However, it is important to note that baseline hearing loss was quite similar across subjects since all subjects exhibited normal hearing in clinical audiogram testing (i.e., < 15 dB HL). This is reflected in the rather flat distribution of data (i.e., with similar $L_{ht,bef.}$) in the correlation plots (see Fig. 7.11Ab–Db). For baseline DPOAE fine structure data (i.e., $L_{dp,bef.}$), AERS ($r_{30} = -0.55$, $r_{20} = -0.58$, $p < 0.05$) and maximum suppression ($r_{30} = -0.55$, $r_{20} = -0.58$, $p < 0.05$) exhibited a significant negative correlation at L_2 = 30 and 20 dB SPL, while average enhancement exhibited a significant negative correlation at all primary tone levels ($p < 0.05$). This means that with decreasing DPOAE level in the DPOAE fine structure measurement the magnitude of efferent reflex strength increased (Fig. 7.11Ad–Dd).

Occupational noise study

For comparison to pure-tone thresholds or DPOAE fine structure data, only CAS DPOAE data from the noise exposure group was evaluated, because only for this group a noticeable effect due to noise exposure was expected. In the following, just the reduced noise exposure group ($n = 26$) is described. However, results were qualitatively similar when analyzing data from the extended noise exposure group ($n = 43$).

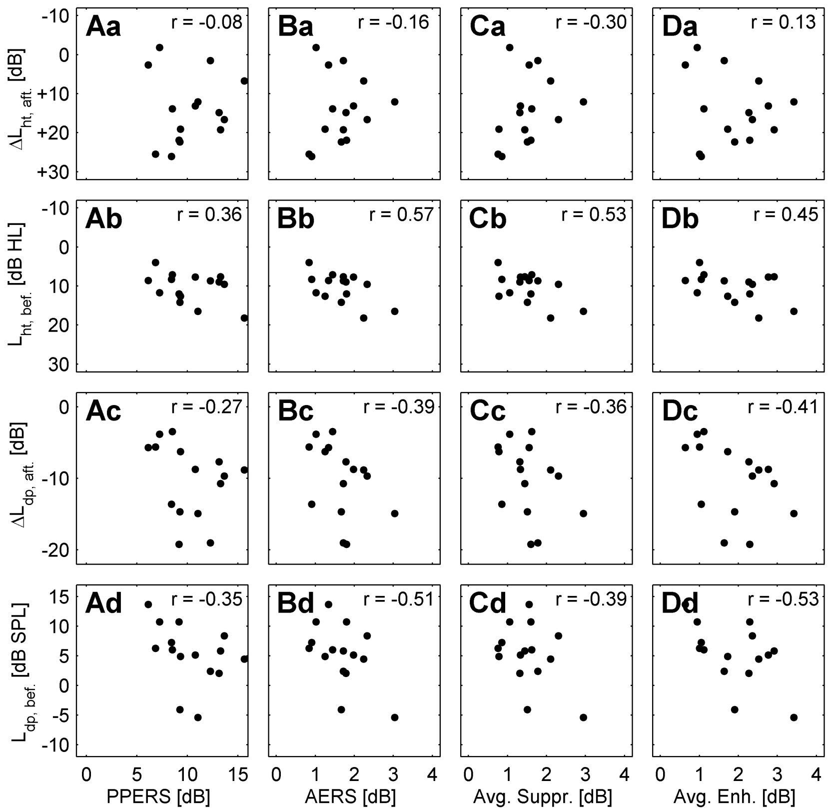

Figure 7.11: Discotheque music study: Scatter plots comparing CAS DPOAE data to pure-tone threshold or DPOAE fine structure data. Shown measures of efferent reflex strength are peak-to-peak efferent reflex strength (PPERS: column A), average efferent reflex strength (AERS: column B), average suppression (column C), and average enhancement (column D). Please note that suppression values were plotted as positive values to improve clarity. For pure-tone threshold and DPOAE fine structure data, baseline values measured before work (row b: $L_{ht,bef.}$; row d: $L_{dp,bef.}$) and shifts which occurred after one workday (row a: $\Delta L_{ht,bef.}$; row c: $\Delta L_{dp,bef.}$) were evaluated.

There was no significant correlation between PPERS or AERS and shift in pure-tone threshold (ΔL_{ht}) (Fig. 7.12Aa, Ba) or baseline pure-tone threshold obtained before work ($L_{ht,bef.}$) (Fig. 7.12Ab, Bb). This result was also independent of whether pure-tone threshold levels were examined at all audiometer frequencies or at 4 kHz only. Significant negative correlations ($p < 0.05$) only occurred when comparing baseline pure-tone thresholds at 4 kHz with maximum suppression ($r = -0.49$) or average suppression ($r = -0.40$; Fig. 7.12Cb) while there was no such correlation when examining maximum or average enhancement (Fig. 7.12Db). The negative correlation between maximum or average suppression and hearing threshold means that in subjects with large suppression, the baseline hearing threshold was low and vice versa. This finding is in contrast to the finding from the discotheque music study, where suppression and enhancement increased with increasing hearing loss.

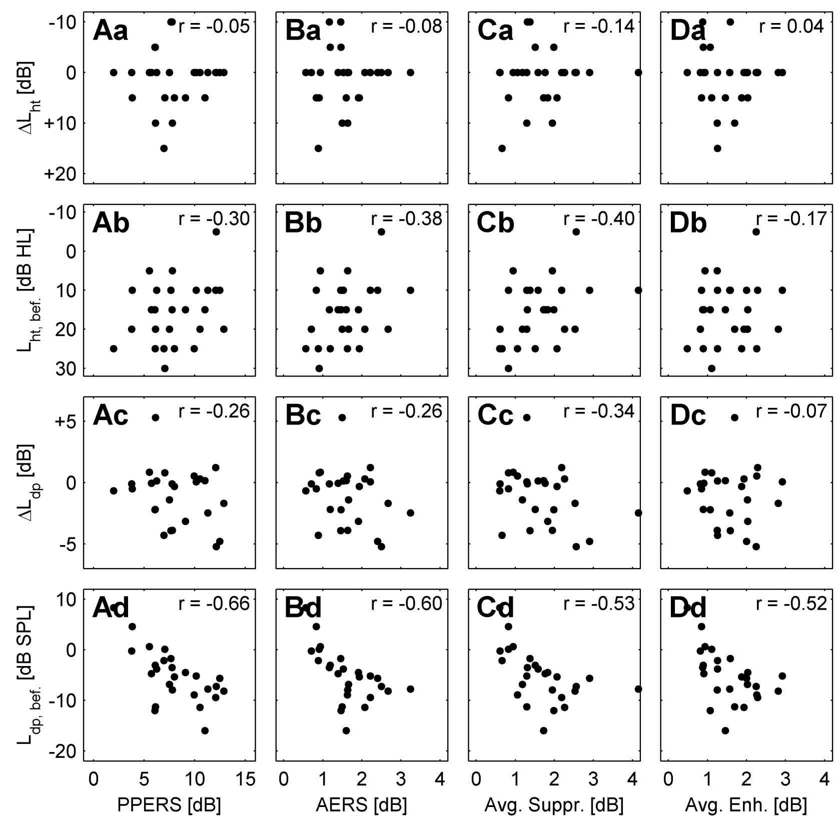

Figure 7.12: Occupational noise study: Scatter plots comparing CAS DPOAE data to pure-tone threshold (at 4 kHz) or DPOAE fine structure data for the noise exposure group ($n = 26$). For more details see Fig. 7.11.

There was no significant correlation between PPERS or AERS and shift in DPOAE level (ΔL_{dp}) after work (Fig. 7.12Ac, Bc). A significant negative correlation ($p < 0.05$) only occurred when comparing shift in DPOAE level and maximum suppression ($r = 0.40$), i.e. in subjects with large suppression, the decrease in DPOAE level was low and vice versa. However, due to the relatively small sample size the 95 % confidence interval is rather large resulting in a high probability of a false positive finding.

Similar to the findings in the discotheque music study, there were significant negative correlations between baseline DPOAE level $L_{dp,bef.}$ and PPERS ($r = -0.66$; $p < 0.001$; Fig. 7.12Ad) and when compared to AERS ($r = -0.60$; $p < 0.01$; Fig. 7.12Bd), i.e. efferent reflex strength was more pronounced for subjects with low DPOAE levels in DPOAE fine structure data. Furthermore, there were also significant correlations between $L_{dp,bef.}$ and maximum suppression ($r = -0.57$), average suppression ($r = -0.53$; Fig. 7.12Cd), maximum enhancement ($r = -0.48$) and average enhancement ($r = -0.52$; Fig. 7.12Dd).

Regarding the results of both studies, data showed that there was no distinct correlation between the applied measures of efferent reflex strength and change in hearing capability or cochlear amplifier functionality. This indicates that the applied measures of efferent reflex strength are not suitable to predict susceptibility to noise exposure either at peripheral or central stages of the auditory pathway. The observed correlation between efferent reflex strength and baseline DPOAE level means that large suppression and enhancement, respectively, occurred preferably in subjects with low DPOAE levels. Correlations between measures of efferent reflex strength and baseline pure-tone threshold were ambivalent and exhibited an increase in magnitude of efferent reflex strength either with raised (discotheque music study) or lowered (occupational noise study) hearing thresholds.

7.3 Discussion

The present study should in the first instance answer the question whether there are any measurable changes in hearing capability in subjects exposed to noise of different intensity and duration and what measure (DPOAE or pure-tone threshold) is more sensitive. Moreover, the question should be answered, whether CAS DPOAEs with the applied parameter setting are capable of predicting individual cochlear vulnerability to noise overexposure. In the following the achieved results are discussed.

Influence of differing noise exposure across subjects

The intention behind both studies was to conduct field studies with natural noise exposure of different intensity and duration. Thus, a discotheque and a factory in the metal-working industry were chosen, since both are typical recreational or occupational environments where high noise levels occur. Due to logistic reasons it was not possible to record the noise exposure for each subject, i.e. individual-related noise exposure. However, noise exposure measurements were conducted at a fixed place in the discotheque during noise exposure and at typical workplaces beforehand by an approved institution. All workplaces of the factory workers participating in the study were declared as industrial noise areas, which means that the rating level for an 8-hour workday usually exceeds 80 dB(A). It is important to note that, inherent to the principles of a field study, noise exposure was presumably differing to some extent between the subjects. Especially for the examined factory workers a higher variability is expected since they were working at different locations within the factory and at different time and days. Thus, some of the inter-individual variation in the measures is likely to be due to inter-individually differing noise exposure. This has to be kept in mind when analyzing the results of the presented studies.

Factory workers exhibited a 4 kHz notch in the audiogram

When comparing baseline data of the factory workers to that of the office workers (see Sec. 7.2.1) it could be observed that pure-tone thresholds averaged across audiometer frequencies (1.5, 2, 3, 4, and 6 kHz) were similar between groups (factory workers: 10.3 dB HL; office workers: 10.9 dB HL). Thus, both groups were comparable in view of baseline hearing capability. However, factory workers exhibited a distinct notch in pure-tone thresholds at 4 kHz with a difference being as large as 4.7 dB (factory workers: 14.4

dB HL; office workers: 9.7 dB HL). The 4 kHz notch is a typical sign for noise-induced hearing loss (NIHL) since the frequency range around 4 kHz is the most sensitive region of the cochlea and thus is supposed to be damaged first (McBride and Williams, 2001). Considering the fact that the factory workers were employed in the metal-working industry for about 20 years on average, long-term hazardous noise exposure is presumed to be the reason for the increased hearing loss at 4 kHz.

Impact of noise exposure on pure-tone thresholds and DPOAE levels

One of the most striking findings of the noise exposure studies was that both pure-tone thresholds and DPOAE levels deteriorated significantly due to noise. This effect was much larger for the subjects exposed to high-level discotheque music for three hours (more than 10 dB) compared to the factory workers who were exposed to mid-level occupational noise for one workday (about 1 to 2 dB). However, a small but significant change in both measures also occurred for the factory workers whereas there was no significant change for the office workers (see Secs. 7.2.1 and 7.2.2). Also, the decrease in DPOAE level was associated with an increase in DPOAE slope for the discotheque attendants and the factory workers, revealing both a loss of sensitivity and compression of the cochlear amplifier. Moreover, DPOAE levels were found to deteriorate most at low primary tone levels suggesting that OHCs are most sensitive at close-to-threshold sound pressure levels. Hence, DPOAEs are supposed to offer best comparability to pure-tone thresholds when recorded at close-to-threshold L_2 levels. The observed deteriorations in both pure-tone threshold and DPOAE level mean that there is a measurable impact on hearing capability and on cochlear amplifier functionality after three hours of discotheque music exposure and also after only one workday of occupational noise exposure. Admittedly, a decrease of 1 dB in DPOAE level, which was observed in the occupational noise study, is quite small, but given the fact that most factory employees accomplish their work over a long period of time day after day in a noisy environment, one may predict that DPOAE levels and therefore OHC sensitivity and hearing capability are likely to deteriorate irreversibly over time. The 4 kHz notch in the audiogram of the factory workers supports this prediction. For the discotheque music attendants the shift of more than 10 dB in both measures and the incomplete recovery of pure-tone threshold and DPOAE fine structure on the next day may suggest a large impact on hearing capability on the long run. However, the question remains whether a large shift in pure-tone threshold or DPOAE level is actually associated with a large temporary damage (i.e., hearing capability or OHC functionality is reduced due to noise-induced degenerative processes) or whether it is in fact a sign of a large protective effect (i.e., hearing capability or OHC functionality is reduced due to protective processes, which possibly shut down OHC activity).

The presented findings are partly in line with observations from other studies. Seixas *et al.* (2005) and Lapsley Miller *et al.* (2006) both found a significant shift in DPOAE level in construction industry apprentices and in subjects exposed to noise on an aircraft carrier, respectively. However, they both did not find significant shifts in pure-tone thresholds. This discrepancy might be explained by the fact that in their studies PTS were considered whereas in the present studies presumably mainly TTS occurred and the underlying mechanisms for PTS and TTS are supposed to be different (Saunders *et al.*, 1985; Nordmann *et al.*, 2000). Reuter and Hammershøi (2007) reported that for symphony orchestra musicians, no significant shift occurred either in pure-tone thresholds or in DPOAE levels after 4 hours of rehearsal (ca. 80 dB(A)). However, Strasser *et al.* (1999) found TTS in subjects exposed for 1 hour to noise or music with a level of 94 dB(A), respectively. Engdahl (1996) found both a shift in pure-tone threshold and DPOAE level in subjects exposed for 10 minutes to third octave band noise around 2 kHz with 102 dB SPL. The shift in both measures was even larger when noise exposure was accompanied by physical exercise of the subjects. This result was explained by changes in metabolic processes due to an increase in body temperature (Lindgren and Axelsson, 1988). This aspect could also play a role for most subjects in the presented studies since both at the discotheque and at the factory, subjects were frequently physically strained. The discrepancies found in literature might be explained by differences in experimental setup including differing intensities and durations of noise exposure and differing parameter settings for DPOAE measurements.

Both pure-tone threshold and DPOAE level exhibited a significant shift within the noise exposure group and thus showed no preference for one of the methods being more sensitive. In the occupational noise study, differences in shifts between groups were only significant for pure-tone thresholds but not for DPOAE levels. This seems to be due to the fact that for office workers pure-tone thresholds on average increased (though not significantly) whereas DPOAE levels remained constant. This resulted in a more pronounced and thus significant difference between groups for pure-tone thresholds compared to DPOAE levels. There is no reasonable explanation for the increase in pure-tone threshold that was observed for the office workers. However, perhaps office workers were sleepier and thus less attentive in the morning than in the afternoon resulting in a higher discrepancy between real and stated pure-tone threshold prior to work.

Given these findings, both DPOAEs and pure-tone thresholds were sensitive enough to detect minor changes in hearing capability, which amounted to only 1 dB on average across subjects in the occupational noise study. Moreover, in addition to pure-tone threshold measurements, speech discrimination tests might be applied in further studies, since these tests were found to be more powerful than audiometric tests to detect early stages of hearing loss (Preyer *et al.*, 2001). However, with respect to applicability in occupational hearing conservation programs, it should be emphasized that DPOAEs have the advantage of being a quick objective method that does not require concentration and compliance of the workers and thus might be a more reliable test procedure in occupational medicine, since lack of concentration and compliance is a frequently reported problem in occupational medicine.

Recovery from noise exposure on the day after discotheque attendance

In the discotheque study, also the recovery from noise exposure was examined. In most cases, both pure-tone thresholds and DPOAE levels did not reach the baseline value in measurements conducted the day after noise exposure (i.e., 8 to 14 hours after discotheque attendance). Difference amounted on average to +3.6 dB for pure-tone thresholds and to a maximum of −3.5 dB for DPOAE levels at the lowest primary tone level $L_2 = 20$ dB SPL. Thus, both overall hearing capability and OHC functionality still exhibited deterioration from noise exposure. With respect to evaluate individual susceptibility to noise exposure, also the magnitude of recovery on the day after noise exposure could have been used as an indicator for noise vulnerability. However, recovery cannot be directly compared across subjects since the time from the measurement immediately after noise exposure to the measurement the day after noise exposure was varying substantially across subjects from 8 to 14 hours due to organizational reasons. Reconstruction mechanisms of the inner ear, however, are known to occur over 48 hours after noise exposure.

Influence of calibration on measurements at different points of time

Problems with DPOAE recording (or other measures recorded via ear probe) can occur when comparing DPOAE data obtained at different times and thus with different ear probe positions. This may result in a differing calibration of sound pressure along the outer ear canal and with that in differing primary tone levels at the ear drum resulting in a worse stability of the measure. Also, ear probe position and with that primary tone levels must not vary during a single measurement procedure. These problems were addressed in both studies by introducing and evaluating two criteria, calibration stability and primary tone level stability, which should guarantee on the one hand measurement comparability between measurements before and after work and on the other hand measurement stability during a single measurement procedure. However, inter-individually different calibration errors due to standing wave problems, which may result in inter-individually different primary tone levels at the ear drum, could not be ruled out.

In the occupational noise study, when comparing results from the extended groups to the results from the reduced groups, where the additional stability criteria were applied, it could be observed that results were in most cases qualitatively alike and mostly exhibited a similar trend. Thus, when analyzing averaged data there was generally not much difference between the extended and reduced groups since the errors which occurred due to the problems mentioned above got eliminated as a result of the averaging process. However, when looking at individual data and correlations between measures, results often improved when analyzing data from the reduced groups. Therefore, when conducting experiments with follow-up measurements it is very important to keep in mind that problems can occur due to different measuring conditions. Thus, when applying DPOAE measurements in occupational medicine for monitoring noise-induced changes in cochlear amplifier function, methods have to be developed for minimizing calibration errors and for maintaining a constant ear probe position for subsequent measurements.

Relationship between baseline pure-tone thresholds or DPOAEs and their respective shift after noise exposure

Both pure-tone thresholds and DPOAE levels measured before work were not correlated to their respective shifts after work (see Secs. 7.2.1 and 7.2.2), i.e. baseline pure-tone thresholds did not affect the amount of TTS and baseline DPOAE levels did not affect the amount of shift in DPOAE level. Thus, both baseline measures do not seem to be able to predict cochlear vulnerability to short-term noise exposure. In the following, two assumptions were made to explain this finding: (*i*) baseline values are measures that include long-term influences on hearing, i.e. baseline pure-tone thresholds are equivalent to PTS acquired over lifetime and baseline DPOAE levels reveal at least partly permanent damage of the cochlear amplifier; (*ii*) shifts in pure-tone threshold and DPOAE level are measures that reflect predominantly temporary changes in hearing capability, i.e. shifts in pure-tone threshold are equivalent to TTS occurring due to work-related noise and shifts in DPOAE level show temporary alterations on OHC level, which might recover over time. In the light of these assumptions, the fact that there is no correlation between baseline values and their respective shifts does not surprise, since PTS and TTS are supposed to occur due to different mechanisms and thus may not be directly related to each other (Nordmann *et al.*, 2000).

Another problem that occurs when comparing inter-individual DPOAE data is that the baseline DPOAE level is not only influenced by the operational capability of the cochlear amplifier but also by other parameters such as ear canal volume or middle ear impedance, which differ across subjects. This yields an additional inter-individual variation of the DPOAE level which does not reflect any differences in the operational capability of the cochlear amplifier. This fact further complicates the comparison between baseline DPOAE levels and shifts in DPOAE levels and thus may reduce their correlation.

Relationship between shifts in pure-tone thresholds and shifts in DPOAE levels after noise exposure

There was no general congruent behavior and thus no significant correlation across subjects between shift in pure-tone threshold and shift in DPOAE level when data was averaged across frequencies (see Sec. 7.2.3). In both studies, both congruent and divergent behavior was observed. In general, the finding that there was no correlation between the shift in both measures is in line with other studies in humans, in which temporary or permanent shifts in pure-tone threshold and OAEs due to noise exposure were compared and were found to be not closely correlated (e.g., Engdahl, 1996; Lapsley Miller *et al.*, 2006).

Some of the observed differences between shifts in pure-tone threshold and shifts in DPOAE level might be explained by the fact that both measurements were conducted in succession and thus at different points of the TTS recovery function. It has been shown that TTS decreases after noise exposure, following a logarithmic function of post-exposure time whereas the time until complete recovery varies strongly between subjects and could last up to several hours (e.g., Mills *et al.*, 1979; Laroche *et al.*, 1989; Patuzzi, 1998, 2002). Similar effects of recovery over time have also been observed for DPOAEs (e.g., Sutton *et al.*, 1994). Therefore, in the present study it could be expected that the shift in pure-tone threshold (TTS), which was measured first in the occupational noise study, would be slightly higher than the shift in DPOAE level, which was measured second. However, such an effect could not be observed generally and also the prominent divergent behavior between shift in pure-tone threshold and shift in DPOAE level, which occurred in some subjects, cannot be explained by time differences between the measurements. Physiologically, the finding of higher shifts in pure-tone threshold and small shifts in DPOAE level, which was observed in 5 out of 15 subjects from the discotheque music study (in 3 subjects pure-tone thresholds were measured first, while in 2 subjects DPOAEs were measured first), could also be explained in the way that pure-tone thresholds as a behavioral measure do not only include OHC dysfunction but also retrocochlear processes. In these cases the observed larger TTS may be expected to result not only from OHC dysfunction but also from retrocochlear or central dysfunctions.

However, the most influential impact on divergent behavior and hence differing shifts in pure-tone threshold and DPOAE level is expected to be the difference in calibration errors between the two measurement techniques. This conclusion was supported by the fact that in the discotheque music study the correlation between the difference in calibration errors was highly correlated to the difference in shifts in pure-tone threshold and DPOAE fine structure. Hence, it cannot be ruled out that there is actually a correlation between the shift in both measures, which was, however, possibly masked by the larger effect due to calibration errors. Especially, for the occupational noise study, the noise-induced effect in both measures was rather small, so that also the influence of a random shift due to measurement test-retest variability might be predominant at least for some individuals and thus possibly also masks the actual effect due to noise.

Relationship between baseline pure-tone thresholds and baseline DPOAE levels

Moreover, there was also no general congruent behavior for baseline data (pure-tone threshold and DPOAE level before work), which is supposed to reflect permanent deteriorations in hearing and cochlear amplifier functionality. The result that there was no correlation in the occupational noise study could imply that changes in cochlear amplifier function are not directly reflected in subjective sensation. This seems to hold true for both temporary and permanent changes in hearing capability. A reason why there was no such correlation might be that the subjective perception of hearing loss and alterations in the operational capability of OHCs may occur at different periods in time, i.e. OAEs may decrease prior to changes in audiometric thresholds (see Lapsley Miller *et al.*, 2006). The fact that DPOAEs may be an early indicator of hearing disorder has already been proposed by Preyer *et al.* (2001), who found that in patients with hypercholesterolemia, DPOAEs became pathological prior to observable losses in audiometric thresholds. This observation could be due to retro-cochlear compensation mechanisms which may postpone the subjective sensation of beginning impairment of the cochlear amplifier. Also, as explained above, inter-individually differing DPOAE amplitude, which may be due to extrinsic causes (e.g., ear canal volume, ear drum impedance), may complicate the comparison between the two measures and may hide a possibly existent physiological relationship.

A possible congruent behavior was implied by the findings from the discotheque music study, where a significant correlation between baseline measures was found. A major difference in the parameter setting of both studies was the stimulus level setting, which was fixed in the discotheque study but was variable in the occupational noise study. In the latter study, L_2 was set in dB SL, i.e. according to the individual hearing threshold at 4 kHz. Hence, DPOAE amplitudes were measured always close to threshold and thus may be constantly low independent of hearing loss, which may deteriorate correlations.

Relationship between baseline DPOAE level and TTS

In the occupational noise exposure study, there was a minor correlation between shift in pure-tone threshold and baseline DPOAE level, i.e. the lower the DPOAE level measured before work, the higher the hearing loss due to noise (see Sec. 7.2.3). The correlation was, however, only significant for the extended group ($n = 48$) but not for the reduced group of factory workers ($n = 31$). Furthermore, there was no such correlation in the discotheque music study. Lapsley Miller *et al.* (2006) found an increased probability for PTS for subjects with absent or low baseline DPOAE levels for long-term (6 months) noise-exposed subjects. They explained this finding with a possible subclinical impairment of OHCs due to prior noise exposure which makes the ear more vulnerable to acquire hearing loss. The hearing loss might then come into effect on the stage of subjective perception with the application of additional hazardous noise. They further suggested that DPOAEs might then be useful as a means of early detection or prediction of NIHL. The present findings do not clearly support the assumption of a relationship between baseline DPOAE levels and NIHL, which was found for PTS, to be true for TTS.

Efferent reflex strength as a predictor for susceptibility to hazardous noise

In order to analyze the usability of CAS DPOAEs with respect to predict individual vulnerability to hazardous noise, several measures of efferent reflex strength (PPERS, AERS, maximum suppression and enhancement, and average suppression and enhancement) were compared to shifts in either pure-tone threshold or DPOAE level (see Sec. 7.2.5). One can speculate that shifts in one or both measures are suited to predict noise-induced impairment after one workday and hence might be related to noise vulnerability, i.e. 'tender' ears would exhibit a larger deterioration of one or both measures compared to 'tough' ears.

In the presented studies, there was no clear correlation between any measure of efferent reflex strength and shifts in pure-tone threshold or DPOAE level. In the occupational noise study, there was only a minor correlation between maximum suppression and shifts in DPOAE level but no correlation for all other measures of efferent reflex strength. Thus, the applied measures of efferent reflex strength do not seem to be capable of reliably predicting temporary changes in pure-tone thresholds or DPOAE levels due to either three hours of discotheque music or occupational noise exposure of one workday. This result is in line with a previous study of Wagner *et al.* (2005) who found no correlation between contralateral DPOAE suppression and the amount of TTS for subjects exposed to impulse noise (gun shots). In contrast, Engdahl (1996) found a correlation between contralateral DPOAE suppression and reduction in DPOAE level due to 10 minutes of high-level noise exposure. In both studies, CAS DPOAEs were not measured at specific frequencies and not within a wide primary tone level range.

However, the finding of the present study that suggests efferent reflex strength not to be closely correlated to temporary shifts in either pure-tone threshold or DPOAE level, does not allow for an ultimate statement about efferent reflex strength and its ability to predict individual susceptibility to noise overexposure. One reason could be indeed that the physiological function of the efferent MOC system is not to protect the acoustic organ from noise overexposure as suggested by other studies (e.g., Kirk and Smith, 2003). However, another reason could be that the applied measures of efferent reflex strength derived from CAS DPOAEs were not suited to properly capture the protective effect of the MOC system. Maison and Liberman (2000), who found a correlation between efferent MOC reflex strength and PTS in guinea-pigs, used in their study a measure for efferent reflex strength that was derived from ipsilateral DPOAE adaptation measurements and not from CAS DPOAEs. However, ipsilateral DPOAE adaptation was found not to be a reliable measure in humans and hence does not seem to be a suited means for assessing efferent reflex strength (see Chapter 6). Also, since the effect on pure-tone threshold and DPOAE level due to noise exposure of one workday was on average quite small, it could be possible that both measures were not precise enough and hence measurement variability did not allow for a reliable comparison between magnitude of efferent reflex strength and temporary shifts in either pure-tone threshold or DPOAE level. However, noise-induced effects were much larger in the discotheque music study where also no correlation between any measure of efferent reflex strength and shifts in pure-tone threshold or DPOAE level could be observed. In general, the influence of calibration errors was found to be a prominent side effect which might deteriorate correlations. Inter-individually varying noise exposure levels (especially at the different workplaces in the factory) could further corrupt the correlation between the measures. Moreover, the inclusion criterion that hearing thresholds should not exceed 40 dB HL (which was introduced in the occupational noise study in order to make sure that DPOAEs could be adequately measured) and the restriction to normal hearing subjects in the discotheque music study might have biased the noise exposure groups towards subjects with a low susceptibility to noise. This might have been true especially for some of the long-time noise-exposed workers. Maybe, noise vulnerability is also better reflected in permanent impairment of the cochlear amplifier and with that in permanent hearing loss and not in temporary impairment at all. Therefore, further CAS DPOAE measurements in subjects suffering from permanent hearing impairment (= PTS) due to long-term noise exposure need to be conducted in larger cohort studies for answering the question whether and to what extent CAS DPOAEs may provide a means for predicting the ear's susceptibility to hazardous noise. Also, the magnitude of recovery from noise exposure may be an alternative measure to quantify individual vulnerability to noise. Hence, further studies which systematically compare CAS DPOAEs and recovery of pure-tone thresholds or DPOAE levels from noise overexposure, have to be conducted.

Moreover, there are some general problems when comparing data from different noise-exposed subjects with respect to finding a measure for predicting individual noise vulnerability. The main problem is to find a homogeneous group that consists in the best case of subjects with similar age, similar medical history, similar recreational and occupational noise exposure, but different vulnerability to noise. Furthermore, noise exposure intensities should be large enough to evoke substantial damages that are larger than individual test-retest variability. Also, it is not clear if vulnerability to noise is a constant factor or changes over time due to external influences (e.g. age, drugs, and environmental noise). In this context, it is interesting to note that animal studies revealed that a moderate-level noise exposure prior to a hazardous noise exposure could improve protection against noise-induced damage and thus could reduce the vulnerability to noise (e.g., Canlon *et al.*, 1988; Campo *et al.*, 1991; Yoshida and Liberman, 2000).

Efferent reflex strength and OHC motility

Significant correlations were found in both studies between some measures of efferent reflex strength and baseline DPOAE levels derived from DPOAE fine structure data (see Sec. 7.2.5). There were significant correlations for AERS, maximum suppression and average enhancement ($p < 0.05$) in the discotheque music study, and for PPERS ($p < 0.001$) and AERS ($p < 0.01$) in the occupational noise study. One could argue that the change in DPOAE level during CAS $\Delta L_{dp,CAS}$ should be highest for low DPOAE levels, i.e. low SNRs and thus high test-retest variability. However, the present data showed that effects in CAS DPOAEs were larger than it would be expected due to test-retest variability (compare Fig. 7.10). This means that efferent reflex strength was largest in subjects exhibiting low baseline DPOAE levels in DPOAE fine structure measurements around 4 kHz. Thus, the MOC system possibly reduces cochlear amplification to a larger extent than it is done in subjects with a low efferent reflex strength. However, this has to be proved in further studies.

Little is known about the functioning of the efferent hearing system and whether its role is to better detect low-level signals in background noise or to protect the ear from acoustic overexposure. Nevertheless, when applying strong criteria for high test-retest stability, DPOAEs seem to be a reliable means for detecting minute changes in OHC function and thus for examining the underlying mechanism of the efferent hearing system.

8 Further efforts to determine the causes for age-related hearing loss

The issue of age-related hearing loss gains in importance due to a modern society steadily growing older. Presbycusis, i.e. age-related hearing loss, is suggested to occur as a result of an intrinsic degenerative aging process of the hearing system. The origin of age-related hearing loss is, however, still controversially discussed in literature proposing both peripheral and/or central causes. Potential peripheral causes mainly include the depletion of cochlear structures. Schuknecht (1974) described three commonly discussed types of presbycusis in humans and differentiated between (*i*) sensory presbycusis due to dysfunction of OHCs or their supporting cells, (*ii*) metabolic presbycusis due to strial atrophy resulting in a decline of endocochlear potential, and (*iii*) neural presbycusis due to loss of afferent neurons (e.g., spiral ganglions) in the cochlea. Also, more recent studies in animals and humans have proposed all of these three peripheral causes as origin of presbycusis (sensory presbycusis: e.g., Anniko, 1988; Tarnowski *et al.*, 1991; metabolic presbycusis: e.g., Gratton and Schulte, 1995; Gates *et al.*, 2002; neural presbycusis: e.g., Keithley *et al.*, 1989). Furthermore, central processes have been suggested as a reason for age-dependent hearing loss in humans. This might comprise a decline in temporal sound processing (e.g., Glasberg and Moore, 1988; Snell, 1997), a dysfunction of the central auditory connections, nuclei, and auditory cortex (e.g., Welsh *et al.*, 1985), or a deterioration of the efferent enervation of OHCs by the medial olivocochlear (MOC) system (e.g., Castor *et al.*, 1994; Kim *et al.*, 2002, Jacobson *et al.*, 2003).

The operational capability of OHCs can be non-invasively investigated by means of DPOAEs, whereas efferent enervation by the MOC system can be examined by means of CAS DPOAEs (see Chapter 6). In contrast pure-tone thresholds comprise overall hearing capability and thus both cochlear and central sound processing.

When comparing DPOAEs to pure-tone thresholds, sensory and metabolic or neural presbycusis could be differentiated (Gates *et al.*, 2002). If sensory processes are the cause for presbycusis, a similar or slightly lower decline in pure-tone thresholds compared to the decline in DPOAE levels can be expected, since OHC dysfunction is at least partly reflected in diminished hearing capability. In contrast, if metabolic processes are the reason for presbycusis, a larger age-dependent decline in pure-tone hearing thresholds compared to DPOAE levels can be expected (see Sec. 2.2). It is known from animal studies that a decline in endocochlear potential results in DPOAE amplitudes to be less affected than neural thresholds (Mills *et al.*, 1993). If neural processes are the cause for presbycusis, exclusively pure-tone thresholds might be affected due to a loss of afferent neurons. In this case, a distinct increase in behavioral hearing threshold levels but normal DPOAEs can be expected.

If central processes are involved in the development of presbycusis, the function of the efferent MOC system is supposed to be affected. Besides protection from acoustic overexposure, the MOC system is supposed to improve the detection of transient low-level stimuli in the presence of background noise. In presbycusis, speech perception in background noise is known to be affected (Frisina and Frisina, 1997). This might be attributed to an aging process of the MOC system. Both Kim *et al.* (2002) and Jacobson *et al.* (2003) found an age-dependent decrease in MOC activity both in humans and animals and thus presumed that a decline of the MOC system precedes a decline of OHCs.

The purpose of the present study was to find out whether peripheral and/or central processes are involved in presbycusis. If peripheral processes (i.e., loss of OHCs, decline in endocochlear potential) are the cause of presbycusis, an increasing decline in pure-tone threshold and/or DPOAE amplitude would be expected with increasing age. If central processes (i.e., deterioration of the MOC system) are involved, the reflex strength of the MOC system, examined by CAS DPOAEs, would be expected to decrease with age. Hence, pure-tone threshold and DPOAE fine structure as well as CAS DPOAEs were measured in the same subject sample.

8.1 Material and methods

8.1.1 Subjects

Seventy-five otologically normal subjects of different age participated in the study. Subjects were defined as otologically normal, if they were in a good state of health, and did not show any symptoms of ear-related pathology in their otologic history, including absence of ototoxic drug intake, long-term noise exposure and hereditary hearing loss. This definition is similar to the enhanced definition of otologically normal subjects given by the International Standardization Organization (e.g., ISO 389-1). Subjects were aged between 10 and 82 years and were divided in five experimental groups with a constant number of 15 subjects per group. The average age of the subjects in each group was as follows: (I) children: 14 (10-16) years; (II) young adults: 25 (17-30) years; (III) middle-aged adults: 38 (31-49) years; (IV) senior adults: 61 (50-69) years; (V) old adults: 75 (70-82) years. Subjects in all age groups comprised 29 males and 46 females. The gender distribution was quite similar across age groups: (I): 10 female, 5 male; (II) 8 female, 7 male; (III) 10 female, 5 male; (IV) 10 female, 5 male; (V) 8 female, 7 male.

8.1.2 Audiometric tests

After otoscopic examination, pure-tone audiometry at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz was performed by using a calibrated audiometer (Böckhoff BCA 300) connected to a standard pure-tone audiometry headphone (Holmco PD-81). For the evaluation of middle ear function, tympanometry (Madsen Otoflex 100) was conducted using a 226 Hz probe tone. Moreover, ipsilateral and contralateral stapedius reflex thresholds were measured at 4 kHz and for broad band noise. All subjects included in the study were expected to have normal middle ear function with normal tympanometry and ipsi- and contralateral stapedius reflex thresholds exceeding 60 dB SPL for broad band noise and 90 dB SPL for 4 kHz pure tones. In each subject, the target ear for further measurements was the better ear as determined by pure-tone audiometry. Across all age groups, 41 right ears (R) and 34 left ears (L) were measured. The distribution across age groups was as follows: (I) 8L, 7R; (II) 6L, 9R; (III) 10L, 5R; (IV) 7L, 8R; (V) 4L, 11R. All measurements were conducted in a sound-treated cabin while subjects were seated in a comfortable recliner.

8.1.3 Pure-tone threshold fine structure measurement procedure

Pure-tone thresholds were recorded using the same measurement system and ear probe (see Chapter 3) as for DPOAE measurements to guarantee best comparability. Pure-tone threshold fine structure was recorded between $f = 3$ and 6 kHz in steps of $\Delta f = 47$ Hz (see example in Fig. 8.1A). A pulsatile tone with stimulus duration of 0.3 s and pause duration of 0.1 s was used. The starting level was initially set to 40 dB SPL for the first frequency and to 20 dB SPL above the last determined threshold for the following frequencies. The level of the pulsatile tone was changed in steps of 2 dB (= 5 dB/s). The level went down as long as the subject kept the mouse button pressed (indicating the presented sound to be audible) and went up when the button was released (indicating the presented sound to be inaudible). When six consecutive reversal points (from decreasing to increasing stimulus level, i.e. from sound heard to sound not heard, or vice versa) occurred within a stimulus level range of 14 dB, the measurement at the particular frequency was finished and the pure-tone threshold level was determined by averaging the stimulus levels at the last six reversal points. The measuring duration for one ear amounted on average to about 25 minutes. In six subjects (1 from group I, 1 from group III, 3 from group IV, and 1 from group V) the measurements had to be stopped in between, since the subjects were not able to concentrate on the task anymore.

The roughness of pure-tone threshold fine structure R_{ht} was calculated by averaging the absolute values of dip depth across all frequencies. The dip depth at a single frequency f_i was defined as the accumulated differences of the pure-tone thresholds at the two neighboring frequencies f_{i-1} and f_{i+1} to the pure-tone threshold at f_i, i.e. the steeper a dip or peak, the larger the absolute value of the dip depth (compare Eq. 6.1).

In order to distinguish between the two behavioral measurement techniques applied in this study, in the following the term audiometric threshold is used for hearing thresholds derived from standard pure-tone audiometry using headphones, whereas the term pure-tone threshold is used for hearing thresholds, which were derived from fine structure measurements using an ear probe.

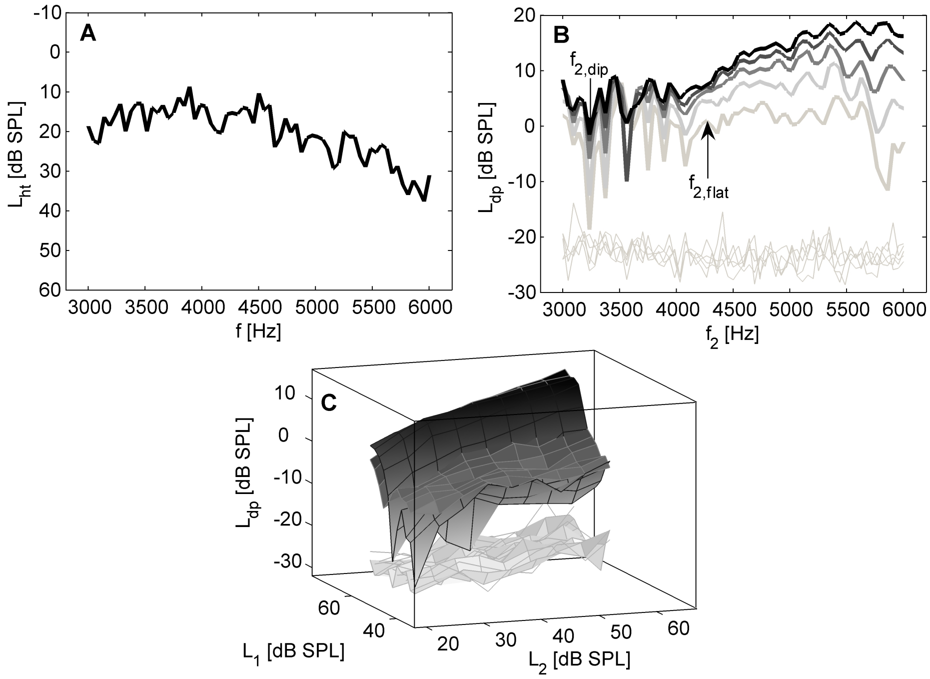

Figure 8.1: Case example of a 13-year-old girl. (A) Pure-tone threshold fine structure between 3 and 6 kHz. (B) DPOAE fine structure between 3 and 6 kHz for primary tone levels L_2 from 60 (light grey line) to 20 dB SPL (black line). The noise floor is indicated by the thin light grey lines at the bottom. The arrows mark the two frequencies of the fine structure, $f_{2,dip}$ and $f_{2,flat}$, where CAS DPOAEs were measured. (C) CAS DPOAE measurement at $f_{2,dip}$ showing measurements with (top area) and without CAS in one plot.

8.1.4 Stimulus generation and DPOAE recording

DPOAEs were recorded using the measurement system and ear probe described in Chapter 3. Primary tone levels were adjusted according to an in-the-ear calibration strategy, whereas contralateral noise signals were calibrated a priori in an ear simulator (Brüel&Kjær Type 4157) without adjustment of the individual ear canal volume.

DPOAEs were accepted as valid for SNRs exceeding 6 dB. The noise floor level was computed by averaging the levels at six frequencies located around the DPOAE frequency. The averaging time for recording DPOAEs was initially set to 2.6 s and was doubled if there was no valid response within this time period. The pause time between two measurements was set to 1 s. Technically distorted data were discarded when the levels of at least seven out of ten frequency bins at other distortion product components (e.g., $2f_2 - f_1$) around the DPOAE component at $f_{dp} = 2f_1 - f_2$ exceeded an SNR of 10 dB.

8.1.5 DPOAE fine structure measurement procedure

DPOAEs were measured between $f_2 = 3$ and 6 kHz with a frequency resolution of $\Delta f_2 =$ 47 Hz (see example in Fig. 8.1B). The primary tone level L_2 was set to 60, 50, 40, 30 and 20 dB SPL, whereas L_1 was set according to the equation $L_1 = 0.4L_2 + 39$ dB SPL. The measuring duration for one ear amounted on average to about 30 minutes.

From the DPOAE grams, extrapolated DPOAE I/O functions were derived for assessing the sensitivity of the cochlear amplifier following the method of Boege and Janssen (2002) (see Sec. 2.5.3). The following criteria were introduced for validation of the regression line: 1) there had to be at least 2 valid data points; 2) the correlation coefficient between p_{dp} and L_2, which serves as a measure for the quality of the fit, had to be exceed 0.8; and 3) the slope of the linear regression line had to be larger than 0.1 μPa/dB. The resulting $L_{dp,th}$ values were limited to -10 dB HL, i.e. lower $L_{dp,th}$ were set to -10 dB HL.

The slope s_{dp} of the DPOAE I/O function at a single frequency was calculated from the regression line which was transformed into double-logarithmic presentation (L_{dp} plotted above L_2). The slope was then calculated as the difference between the DPOAE level of the regression line $L'_{dp}(L_2)$ at $L_2 = 60$ dB SPL and at $L_2 = 40$ dB SPL divided by 20. DPOAE slope s_{dp} was used as a means for assessing the compression of the cochlear amplifier.

The roughness of DPOAE fine structure R_{dp} was calculated using the same method that was used for calculating roughness of pure-tone threshold fine structure (see Sec. 8.1.3). R_{dp} was introduced as it is expected to quantify the influence of the second DPOAE source.

8.1.6 CAS DPOAE measurement procedure

For assessing the reflex strength of the efferent MOC system, DPOAEs were measured with and without CAS at two specific frequencies. The first frequency, $f_{2,dip}$, was located at a distinct dip in the DPOAE fine structure, while the second frequency, $f_{2,flat}$, was at a location, where there was no major change of L_{dp} across frequency, i.e. in a flat region of the DPOAE fine structure (see Fig. 8.1B). This was done, since contralateral effects were found to be different in magnitude in dips and flat regions of the DPOAE fine structure (see Chapter 6).

The effect of CAS on DPOAEs at these two test frequencies was investigated at different $L_2|L_1$ combinations. L_2 was varied from 60 to 20 dB SPL in steps of 5 dB. For each L_2, L_1 was changed symmetrically around the center level $L_{1,center} = 0.4L_2 + 39$ dB SPL. The offset $L_{1,offset}$ around $L_{1,center}$ was changed from -10 to $+10$ dB in steps of 2 dB. For each level setting, DPOAEs were recorded first in the absence and then in the presence of CAS (directly following each other in the measurement sequence). The contralateral stimulus was started 0.2 s before the onset of the ipsilateral primary tones and ended 0.2 s after their termination. The contralateral stimulus consisted of broadband noise, which was presented with a stimulus level of 60 dB SPL. The total measuring duration for each frequency amounted to about 20 minutes per ear.

For 17 subjects, at least one of the two CAS DPOAE measurements could not be finished as subjects wished to stop the examination (1 from group I, 3 from group III, 5 from group IV, 8 from group V). For three subjects (1 in group IV, and 2 in group V) CAS DPOAEs were not measured at $f_{2,flat}$ due to a lack of time.

In order to quantitatively assess MOC reflex strength, the differences in DPOAE levels between measurements with and without CAS, $\Delta L_{dp,CAS}$ (see example in Fig. 8.1C), were analyzed. Corresponding to the method developed in Chapter 6, the range from maximum enhancement to maximum suppression was calculated and is referred to as peak-to-peak efferent reflex strength (PPERS). In addition, also the average absolute value of $\Delta L_{dp,CAS}$ was calculated and is termed average efferent reflex strength (AERS). AERS was introduced as a more stable parameter since all valid measurement points (and not only the extreme values) were included for analysis.

8.2 Results

8.2.1 Audiometric threshold data

Averaged audiogram data for all five age groups (black line: group I, light grey line: group V) are shown in Fig. 8.2A. It can be observed that the first three groups (with subjects aged from 10 to 49) were quite similar in hearing loss and did not show a distinct frequency dependency, i.e. average hearing loss at high frequencies was not different to that at low frequencies. In contrast, the other two groups (with subjects aged from 50 to 82) exhibited a clear deterioration in hearing capability with hearing loss being predominant at higher frequencies. The group with the oldest subjects (group V) showed the largest hearing loss exceeding that of group IV by about 10 dB at low frequencies and by about 30 dB at the highest frequency at 8 kHz. The significance of differences in audiometric thresholds between neighboring groups was investigated for each frequency separately (Wilcoxon test, $p < 0.05$). Audiometric thresholds did not exhibit a significant difference between group I and group II at any frequency and for most frequencies also not between group II and group III (only significant at 3 and 4 kHz). Between groups III and IV and groups IV and V there were, however, highly significant differences for most frequencies (III/IV: not significant at 1, 2, and 3 kHz; IV/V: not significant at 2 kHz only).

For further evaluation, audiometric threshold data were averaged once across all audiometer frequencies (i.e., from 0.25 kHz to 8 kHz) and once across the frequencies within the DPOAE and pure-tone threshold fine structure measurement frequency range (i.e., from 3 kHz to 6 kHz; results are shown in brackets). Please note that for an equal balance of frequencies and for a better comparability to DPOAE and pure-tone threshold fine structure data, also values at 5 kHz were included in the averaging process. Since data at 5 kHz were not measured, values were estimated as linear interpolation between data at

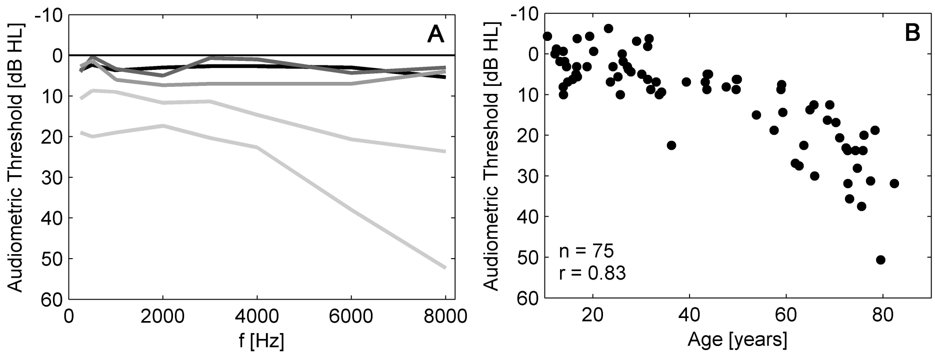

Figure 8.2: (A) Average audiogram data determined at 0.25, 0.5, 1, 2, 3, 4, 6, and 8 kHz and plotted for the five age groups (black line: group I; light grey line: group V). Hearing thresholds are given in dB HL. (B) Correlation between audiogram data averaged at 3, 4, 5, and 6 kHz and age. Audiogram data at 5 kHz was derived from linear extrapolation between data at 4 and 6 kHz.

4 and 6 kHz. Audiometric thresholds in group I and group II were similar with about 3 (I: 3, II: 2) dB HL and continually increased with increasing age to 5 (7) dB HL (III), 14 (16) dB HL (IV), and 26 (28) dB HL (V). These results emphasize that almost no hearing loss was present for groups I and II whereas the largest deterioration in hearing capability occurred for groups IV and V. The continuous increase in audiometric thresholds with increasing age is also reflected in the fact that the correlation between audiometric threshold and age across all subjects ($n = 75$; $r = 0.83$; $p < 0.001$) was extremely significant for both examined frequency ranges (see Fig. 8.2B).

However, in all age groups there were subjects with normal hearing (audiometric threshold ≤ 20 dB HL) or mild hearing loss (20 dB HL $<$ audiometric threshold ≤ 30 dB HL). When either regarding the entire audiometric frequency range from 0.25 to 8 kHz or only the fine structure measurement frequency range from 3 to 6 kHz (results shown in brackets), normal hearing could be observed in 15 (15) subjects both from group I and II, 14 (14) subjects from group III, 6 (9) subjects from group IV, and 1 (2) subject from group V, whereas mild hearing loss occurred in 1 (1) subject from group III, 5 (4) subjects from group IV, and 1 (5) subjects from group V. When averaging audiometric thresholds in the fine structure measurement frequency range from 3 to 6 kHz, the distribution of subjects from the various age groups across different hearing loss classes (with a width of 10 dB) can be seen in Tab. 8.1.

It can be observed that most of the subjects from group I to III exhibited audiometric thresholds below 10 dB HL whereas hearing thresholds in subjects from group IV ranged from 0 to 30 dB HL and in subjects from group V from 10 to a maximum of 51 dB HL. In general, the observed hearing thresholds in the different age groups of the study were in accordance with ISO 7029, which defines the statistical distribution of hearing thresholds as a function of age for otologically normal males and females from 18 to 70 years. Please note, that due to the limitation of age in ISO 7029, no comparison of hearing thresholds for age groups I and V to ISO 7029 was possible.

Hearing loss [dB HL]	≤ 0	]0–10]	]10–20]	]20–30]	> 30
10–16 years (I)	5	**10**			
17–30 years (II)	5	**10**			
31–49 years (III)	2	**12**		1	
50–69 years (IV)		4	**7**	4	
70–82 years (V)			3	**6**	**6**

Table 8.1: Number of subjects from different age groups in different hearing loss classes. Average audiometric threshold was determined as the mean value of data at 3, 4, 5, and 6 kHz. Data at 5 kHz was linearly interpolated between data measured at 4 and 6 kHz.

8.2.2 Tympanometry data

Concerning the middle ear parameters and their relation with age, no systematic change in the static compliance (I: 0.58 mmhos; II: 0.53 mmhos; III: 0.83 mmhos; IV: 0.53 mmhos; V: 0.76 mmhos) and tympanometric pressure (I: −7 daPa; II: 10 daPa; III: 9 daPa; IV: 2 daPa; V: 16 daPa) could be observed. The ear canal equivalent volume (ECV), which may have an influence on DPOAE measurements, since the ECV determines the amount of attenuation of the emission along the ear canal, exhibited on average similar values across all age groups with no clear age-related tendency. ECV amounted to 1.03 ml (I), 0.95 ml (II), 1.13 ml (III), 0.93 ml (IV), and 1.08 ml (V). These findings are in line with the results from other studies (Wiley *et al.*, 1999; Gvelesiani, 2003; Stenklev *et al.*, 2004) who also did not find age-related changes in tympanometric measures.

8.2.3 Pure-tone threshold fine structure data

Average pure-tone thresholds of the five age groups are presented in Fig. 8.3A (black line: group I, light grey line: group V). Pure-tone thresholds L_{ht} are given in dB SPL (not in dB HL as audiogram data) and amounted when averaged across frequencies to 19 ± 8 dB SPL for group II, and 20 ± 5 dB SPL for group I and III, but then notedly increased to 30 ± 9 and 34 ± 8 dB SPL for groups IV and V, respectively. Thus, similar to the audiogram results (compare Fig. 8.2A), the first three groups exhibited similar and rather low pure-tone thresholds, while there was a major increase in pure-tone threshold when proceeding with age from group III to group IV. Hence, when analyzing the significance of differences in pure-tone threshold between neighboring groups, there was only a significant ($p < 0.05$) difference between group III and IV. The correlation between L_{ht} and age across all subjects ($n = 75$; $r = 0.66$; $p < 0.001$) was lower than for audiometric thresholds but still extremely significant (see Fig. 8.3B).

When splitting up the entire frequency range into three frequency bands (3–4 kHz, 4–5 kHz, 5–6 kHz), pure-tone thresholds increased from 15 dB SPL at the lowest frequency band (3–4 kHz) to 27 dB SPL at the highest frequency band (5–6 kHz) for group I, and for the other groups from 14 to 28 dB SPL (II), from 16 to 26 dB SPL (III), from 24 to 41 dB

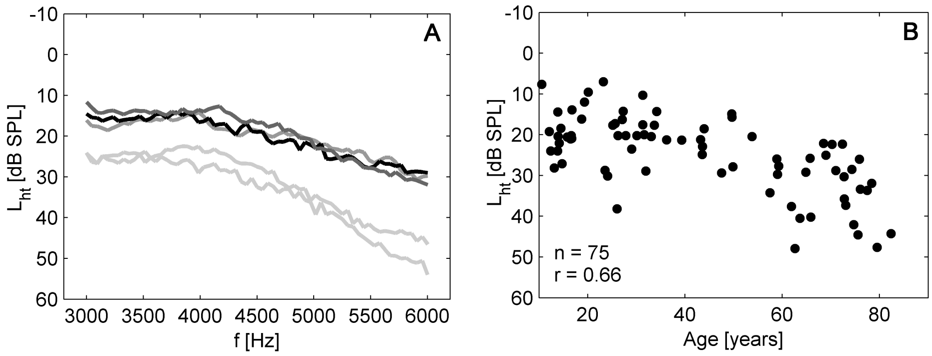

Figure 8.3: (A) Average pure-tone threshold (L_{ht}) fine structure measured between 3 and 6 kHz in the five experimental groups (black line: group I; light grey line: group V). Pure-tone threshold fine structure is given in dB SPL. (B) Correlation between pure-tone threshold data averaged between 3 and 6 kHz and age.

SPL (IV), and from 26 to 45 dB SPL (V). Thus, for all age groups, pure-tone thresholds exhibited a similar frequency dependency with increasing pure-tone thresholds towards higher frequencies. The decline in pure-tone thresholds towards the highest frequency band was, however, more prominent in groups IV and V.

The roughness of pure-tone threshold fine structure R_{ht} across the entire measurement frequency range between 3 and 6 kHz indicated no age-dependent behavior. Average R_{ht} amounted to 4.4 ± 1.2 dB (I), 3.3 ± 1.3 dB (II), 3.0 ± 0.7dB (III), 3.6 ± 2.0 dB (IV), and 4.0 ± 1.7 dB (V). Thus, minimum roughness occurred for the middle-aged adults (III), whereas roughness increased both towards younger (I and II) and older subjects (IV and V). This inconsistent behavior was also reflected in the correlation between R_{ht} and age which was not significant when evaluated across all subjects ($n = 75$; $r = 0.03$). When examining R_{ht} in three different frequency bands (3–4 kHz, 4–5 kHz, 5–6 kHz), no distinct frequency dependency could be found. However, for most age groups largest roughness occurred in the lowest frequency region.

8.2.4 DPOAE fine structure data

Average DPOAE levels L_{dp} of the five age groups are presented in Fig. 8.4A for $L_2 = 60$ dB SPL and in Fig. 8.4B for $L_2 = 30$ dB SPL (black line: group I, light grey line: group V) together with noise floor levels L_{nf} (thin light grey lines at the bottom). L_{nf} averaged across all measurement data for each group was independent of age and amounted to -24 dB SPL. However with increasing age, the number of valid data points decreased from 96 % (I) to 70 % (V). The average SNR also decreased with age from 26 dB (I) to 16 dB (V).

When averaged across the entire frequency range between 3 and 6 kHz, L_{dp} at $L_2 = 60$ dB SPL decreased with age and amounted to 8.0 ± 6.1 dB SPL (I), 7.3 ± 6.3 dB SPL (II), 5.4 ± 5.0 dB SPL (III), 0.0 ± 6.0 dB SPL (IV), and -3.2 ± 5.6 dB SPL (V). For

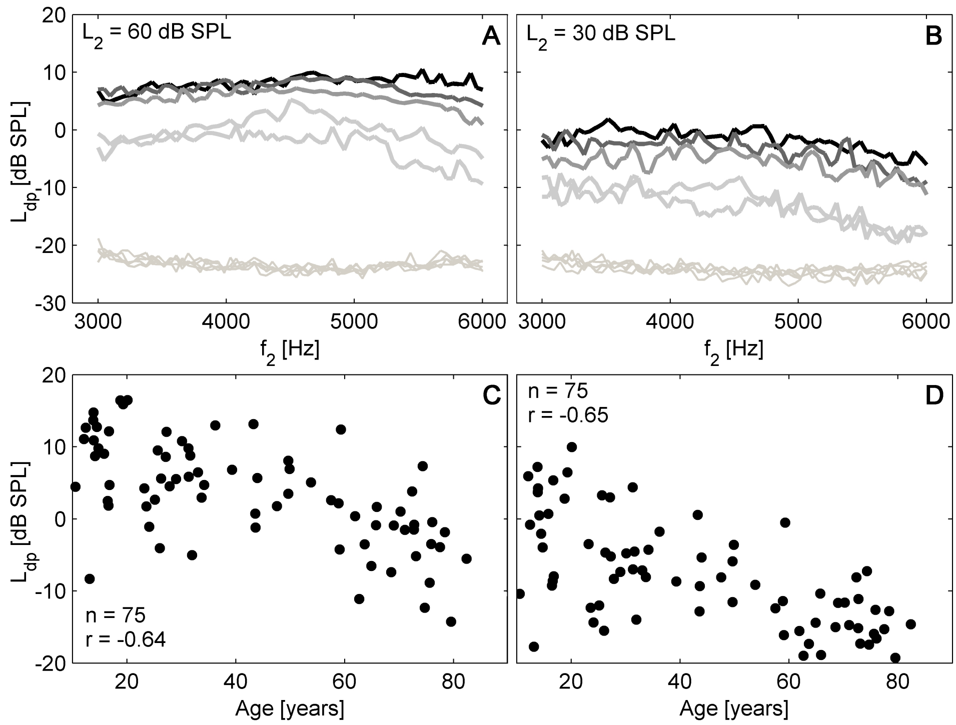

Figure 8.4: (A), (B) Average DPOAE level (L_{dp}) fine structure measured between 3 and 6 kHz in the five experimental groups (black line: group I; light grey line: group V) at the primary tone level $L_2 = 60$ dB SPL (A) and $L_2 = 30$ dB SPL (B). The noise floor is indicated by the thin light grey lines at the bottom. (C), (D) Correlation between L_{dp} data averaged between 3 and 6 kHz and age for $L_2 = 60$ dB SPL (C) and $L_2 = 30$ dB SPL (D).

$L_2 = 30$ dB SPL, L_{dp} was, as expected, smaller and amounted to -2.2 ± 7.3 dB SPL (I), -4.2 ± 7.8 dB SPL (II), -6.1 ± 4.7 dB SPL (III), -12.5 ± 5.2 dB SPL (IV), and -14.0 ± 3.4 dB SPL. Significant differences in L_{dp} for neighboring age groups (Wilcoxon test, $p < 0.05$) occurred for both primary tone levels only between group III and group IV. So, comparably to the results from pure-tone threshold fine structure data, DPOAE levels were closer together for the first three groups while there was a major decrease when proceeding to group IV and V. The correlation between L_{dp} and age across all subjects ($n = 75$; $r_{60} = -0.64$, $r_{30} = -0.65$; $p < 0.001$) was for both primary tone levels extremely significant (see Fig. 8.4, panels C and D) and was in magnitude also nearly identical to the correlation when comparing pure-tone thresholds L_{ht} to age.

In comparison, the correlation between L_{dp} and L_{ht} across all subjects was investigated. Correlations were for both primary tone levels extremely significant ($n = 75$; $r_{60} = -0.72$, $r_{30} = -0.69$; $p < 0.001$) and also slightly larger compared to the correlations between L_{dp} and age. Thus, L_{dp} both decreased with age and pure-tone threshold.

When splitting up the entire frequency range into three frequency bands (3–4 kHz, 4–5 kHz, 5–6 kHz), L_{dp} at $L_2 = 60$ dB SPL exhibited for all age groups a slight maximum in the

L_2 [dB SPL]	60	50	40	30	20
10–16 years (I)	−0.09	−0.10	−0.13	−0.10	−0.03
17–30 years (II)	−0.51	−0.59	−0.64	−0.65	−0.55
31–49 years (III)	−0.46	−0.54	−0.61	−0.59	−0.56
50–69 years (IV)	−0.29	−0.44	−0.55	−0.53	−0.42
70–82 years (V)	−0.58	−0.63	−0.56	−0.51	−0.36

Table 8.2: Correlation between DPOAE levels L_{dp}, recorded at different primary tone levels L_2, and pure-tone thresholds L_{ht} in the different age groups and across all frequencies. The maximum correlation is indicated in bold.

middle frequency band (4–5 kHz) while L_{dp} was mostly lowest in the highest frequency band (5–6 kHz). This effect was most prominent in group V where there was a clear decrease in L_{dp} from the low and middle frequency band towards higher frequencies. In contrast, at $L_2 = 30$ dB SPL, there was a continuous decrease in L_{dp} from lower to higher frequencies for all age groups.

In order to evaluate the overall capability of L_{dp} to serve as an objective means to estimate behavioral pure-tone thresholds, the correlation between L_{dp} at different L_2 and pure-tone threshold L_{ht} was investigated in the five age groups and is shown in Tab. 8.2. The correlation was calculated across all subjects in a group and across all frequencies without any averaging and thus shows the capability of L_{dp} to predict L_{ht} at a specific frequency within the measurement frequency range. Group I showed the lowest correlation among all age groups with a maximum across primary tone levels of −0.13. The correlations of groups II to V were in general much larger but rather similar and hence did not show a clear age-dependent behavior. The maximum correlation in these groups ranged from −0.55 (IV) to −0.65 (II). Maximum correlations occurred with increasing age and with that with increasing hearing loss at increasing primary tone levels (group II: at $L_2 = 30$ dB SPL; group III/IV: at $L_2 = 40$ dB SPL; group V: at $L_2 = 50$ dB SPL), i.e. closer to hearing threshold. Due to the large sample size (the maximum number of data for each group is the number of subjects multiplied by the number of frequencies, i.e., $n = 15 \cdot 65 = 975$) all maximum correlations were significant ($p < 0.001$) for each age group.

The roughness of DPOAE fine structure R_{dp} was analyzed across the entire measurement frequency range. It could be observed that average R_{dp} was largest for the two groups IV and V. Also, R_{dp} increased with decreasing primary tone levels. For $L_2 = 60$ dB SPL, R_{dp} amounted to 2.3 ± 1.5 dB (I), 1.9 ± 1.0 dB (II), 2.2 ± 1.2 dB (III), 2.9 ± 1.4 dB (IV), and 2.7 ± 0.9 dB (V) while for $L_2 = 30$ dB SPL, it amounted to 4.0 ± 1.4 dB (I), 3.7 ± 1.6 dB (II), 3.9 ± 0.9 dB (III), 5.3 ± 1.1 dB (IV), and 5.1 ± 1.1 dB (V). When analyzing the significance of differences of R_{dp} between neighboring groups (Wilcoxon test, $p < 0.05$), there was no significant difference at $L_2 = 60$ dB SPL and only one significant difference between group III and IV at $L_2 = 30$ dB SPL. However, there was no distinct age-dependent behavior evident, although R_{dp} was largest for the older subjects. The correlation between R_{dp} and age across all subjects ($n_{60} = 75$, $r_{60} = 0.22$; $n_{30} = 72$, $r_{30} = 0.44$, $p < 0.001$) was not significant at $L_2 = 60$ dB SPL, but extremely significant at $L_2 = 30$ dB SPL. In comparison, the correlations between average R_{dp} and L_{ht} across all subjects ($n = 75$; $r_{60} = 0.35$, $r_{30} = 0.53$; $p < 0.01$) were for both primary tone levels highly significant and also slightly larger compared to the correlation between R_{dp} and age. When examining R_{dp} in three different frequency bands (3–4 kHz, 4–5 kHz, 5–6 kHz), for nearly all age groups and both primary tone levels, R_{dp} was largest in the lowest frequency band, and decreased towards the middle and high frequency band. Thus, DPOAE roughness increased with decreasing L_2 and decreasing f_2. When comparing R_{dp} to R_{ht}, no significant correlation could be found in any of the five age groups.

DPOAE thresholds $L_{dp,th}$ were analyzed for the five age groups and are shown in Fig. 8.5A (black line: group I, light grey line: group V). $L_{dp,th}$ averaged across the entire frequency range between 3 and 6 kHz amounted to 14 ± 6 dB SPL (I), 16 ± 7 dB SPL (II), 17 ± 5 dB SPL (IV), 23 ± 6 dB SPL (IV), and 24 ± 5 dB SPL (V). Thus, $L_{dp,th}$ increased continuously with age. However, as it could be observed for pure-tone threshold and DPOAE level, the first three groups exhibited rather similar average values, while there was a slightly larger gap between groups III and IV. Group V was once again similar to group IV. This result was verified by testing the significance of differences in $L_{dp,th}$ between neighboring groups (Wilcoxon, $p < 0.05$). There were no significant differences. For groups III and IV the difference was at least very near to significance ($p = 0.051$). The correlation between $L_{dp,th}$ and age across all subjects ($n = 75$; $r = 0.57$; $p < 0.001$) was slightly lower than that when comparing L_{dp} or L_{ht} to age but it was still extremely significant (see Fig. 8.5B). In comparison, there was also an extremely significant correlation between $L_{dp,th}$ and L_{ht} when analyzing data across all subjects ($n = 75$; $r = 0.70$; $p < 0.001$) indicating that the estimated DPOAE threshold deteriorated with both age and hearing loss. When examining $L_{dp,th}$ across three different frequency bands (3–4 kHz, 4–5 kHz, 5–6 kHz), it became evident that $L_{dp,th}$ increased for all age groups continuously with frequency. $L_{dp,th}$ ranged from 10 dB SPL in the lowest frequency band to 18 dB SPL in the highest frequency band (I), and for the other groups from 11 to 22 dB SPL (II), from 15 to 21 dB SPL (III), 17 to 30 dB SPL (IV), and from 19 to 29 dB SPL (V). This result is similar to the finding for pure-tone threshold fine structure data, where an increase of pure-tone threshold with age and with frequency could be observed as well.

The DPOAE threshold estimation error, $L_{dp,th} - L_{ht}$, was analyzed in order to test to what extent DPOAE thresholds were reflected in behavioral hearing loss. Differences averaged across the entire frequency range amounted to -6.5 ± 7.9 dB (I), -3.1 ± 5.8 dB (II), -2.5 ± 4.2 dB (III), -6.5 ± 3.3 dB (IV), and -6.4 ± 6.0 dB (V). Thus, $L_{dp,th}$ values were on average slightly lower than L_{ht} values. This finding means that DPOAE thresholds on average underestimated behavioral thresholds, i.e. better hearing thresholds were predicted by means of DPOAEs compared to the behavioral measure. This was true for all age groups with estimation errors being lowest for groups II and III. The absolute value of the DPOAE threshold estimation error amounted to 9.8 ± 4.5 dB (I), 6.9 ± 3.1 dB (II), 5.6 ± 3.1 dB (III), 7.8 ± 2.6 dB (IV), and 9.1 ± 5.2 dB (V) and was, as expected, larger than the signed values given above, since positive and negative errors did not compensate. There was no age-dependent behavior evident, which is reflected in the fact that there was no correlation between the absolute value of the error of DPOAE threshold estimation

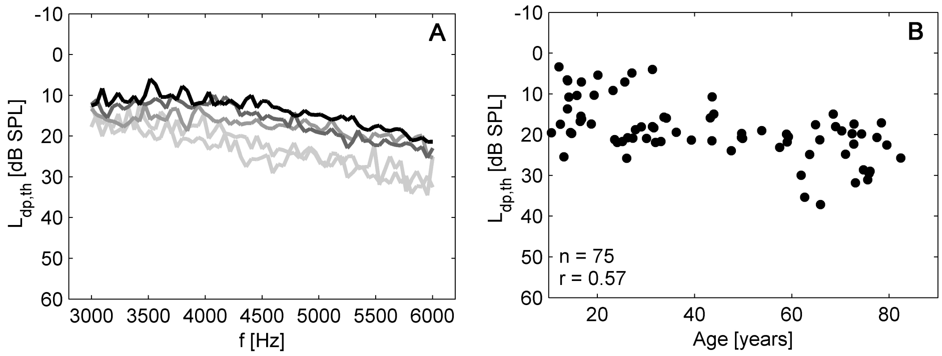

Figure 8.5: (A) Average DPOAE threshold ($L_{dp,th}$) derived from DPOAE fine structure measurements by means of linear regression analysis as described by Boege and Janssen (2002). Data is plotted for all five age groups (black line: group I; light grey line: group V). DPOAE threshold is given in dB SPL. (B) Correlation between DPOAE threshold data averaged between 3 and 6 kHz and age.

$|L_{dp,th} - L_{ht}|$ and age ($n = 75$; $r = -0.00$). Moreover, there was a slightly larger but still not significant correlation ($n = 75$; $r = -0.22$) between $|L_{dp,th} - L_{ht}|$ and L_{ht} across all subjects and with averaging across frequencies for each subject. The small negative correlation means that at least to some extent with increasing hearing loss, i.e. increasing L_{ht}, the absolute deviation of $L_{dp,th}$ from L_{ht} decreased. This result proposes that larger hearing losses were more precisely predicted by means of DPOAE threshold estimation compared to lower hearing losses. When analyzing data in separate frequency bands (3–4 kHz, 4–5 kHz, 5–6 kHz), one could observe that the largest differences between $L_{dp,th}$ and L_{ht} occurred for all age groups in the highest frequency band.

In order to further evaluate the quality of DPOAE threshold estimation, the correlation between $L_{dp,th}$ and L_{ht} was calculated across all subjects within a group and across all frequencies (i.e. there was no averaging across frequencies). This measure discloses the general capability of DPOAE threshold estimation to predict the behavioral pure-tone threshold L_{ht} at a specific frequency within the measurement frequency range. Correlations amounted to 0.26 (I), 0.67 (II), 0.62 (III), 0.73 (IV), and 0.48 (V) and thus were highest for groups II to IV with a considerable decrease towards group V and especially group I. Due to the large sample size all correlations were extremely significant. Correlations were also mostly larger (except group V) compared to the correlations between L_{dp} and L_{ht} suggesting that $L_{dp,th}$ is a better predictor for pure-tone thresholds compared to L_{dp}.

DPOAE slope s_{dp} was analyzed for the five age groups and is shown in Fig. 8.6A (black line: group I, light grey line: group V). The slope of the DPOAE I/O function was evaluated since it is supposed to be a measure for the compression of the cochlear amplifier. s_{dp} averaged across the entire frequency range between 3 and 6 kHz amounted to 0.26 ± 0.06 dB/dB (I), 0.30 ± 0.07 dB/dB (II), 0.30 ± 0.06 dB/dB (IV), 0.42 ± 0.16 dB/dB (IV), and 0.41 ± 0.09 dB/dB (V) and thus tended to increase with age revealing a decrease of compression of the cochlear amplifier. The difference between neighboring groups was significant (Wilcoxon, $p < 0.05$) between groups III and IV only. This finding is thus comparable to that for L_{dp} and $L_{dp,th}$. The correlation between s_{dp} and age across all subjects ($n = 75$; $r = 0.56$; $p < 0.001$) was similar to that observed between $L_{dp,th}$ and age and was also extremely significant (see Fig. 8.6B). In comparison, there was an even larger and also extremely significant correlation between s_{dp} and L_{ht} when analyzing data across all subjects ($n = 75$; $r = 0.69$; $p < 0.001$) indicating that the estimated DPOAE threshold deteriorated both with age and hearing loss. When splitting up the entire frequency range into three frequency bands (3–4 kHz, 4–5 kHz, 5–6 kHz), one could observe that s_{dp} continuously increased with increasing frequency.

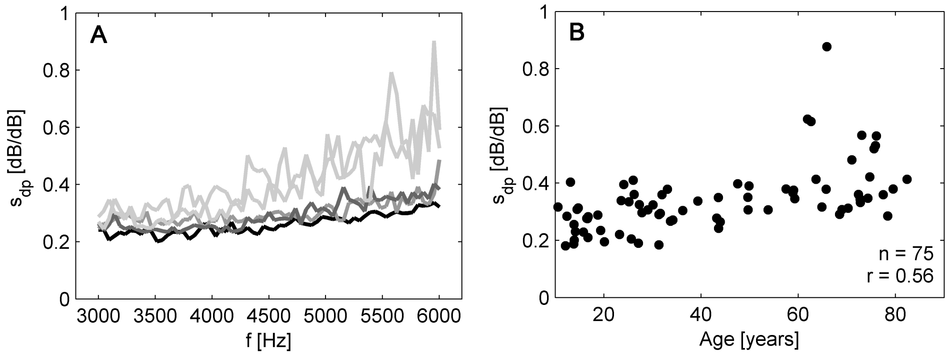

Figure 8.6: (A) Average DPOAE slope (s_{dp}) derived from DPOAE fine structure measurements by means of linear regression analysis. Data is plotted for all five age groups (black line: group I; light grey line: group V). (B) Correlation between DPOAE slope data averaged between 3 and 6 kHz and age.

8.2.5 CAS DPOAE data

For CAS DPOAE measurements, the noise floor level L_{nf} averaged across all measurement data for each group was independent of age and test frequency and amounted to -24 dB SPL. However, with increasing age, the number of valid data points decreased. Valid data points were defined as data at which both L_{dp} measured with and without CAS were valid. Results are given for $f_{2,dip}$ and in brackets for $f_{2,flat}$. The first three groups were rather similar with 89 % (91 %) for groups I and II, and 82 % (87 %) for group III. With 53 % (70 %) and 54 % (60 %) for group IV and V, respectively, much less valid data was available in the older subjects. The average SNR also decreased with age from 23 dB (26 dB) for group I to 14 dB (17 dB) for group V.

When analyzing the effect of CAS on DPOAEs, it could be observed that for both frequencies, $f_{2,dip}$ and $f_{2,flat}$, suppression occurred more often than enhancement. At $f_{2,dip}$, suppression occurred in 64 % (I), 67 % (II), 60 % (III), 63 % (IV), and 56 % (V) of all valid data points, whereas at $f_{2,flat}$ the proportion of suppression was even larger (I: 81 %; II: 82 %; III: 77 %; IV: 72 %; V: 65 %).

The magnitude of effect of CAS on DPOAEs is shown for peak-to-peak efferent reflex strength (PPERS), average efferent reflex strength (AERS), maximum enhancement and

	$f_{2,dip}$			$f_{2,flat}$		
	max. enh.	max. suppr.	**PPERS**	max. enh.	max. suppr.	**PPERS**
10–16 years (I)	9.5	−8.7	18.2 ± 6.2	3.7	−5.3	9.0 ± 3.8
17–30 years (II)	6.5	−8.7	15.2 ± 6.5	3.4	−5.6	9.0 ± 3.3
31–49 years (III)	6.8	−6.7	13.5 ± 3.7	3.3	−6.2	9.5 ± 2.2
50–69 years (IV)	6.2	−7.7	14.0 ± 5.6	4.7	−6.1	10.8 ± 3.3
70–82 years (V)	6.6	−6.3	13.0 ± 3.5	4.3	−6.4	10.7 ± 1.8
	$f_{2,dip}$			$f_{2,flat}$		
	avg. enh.	avg. suppr.	**AERS**	avg. enh.	avg. suppr.	**AERS**
10–16 years (I)	2.3	−2.3	2.4 ± 0.8	1.1	−1.4	1.4 ± 0.6
17–30 years (II)	2.0	−2.0	2.1 ± 1.1	0.9	−1.3	1.2 ± 0.4
31–49 years (III)	1.8	−1.7	1.8 ± 0.8	0.9	−1.4	1.3 ± 0.5
50–69 years (IV)	2.0	−2.1	2.0 ± 0.6	1.3	−1.5	1.5 ± 0.4
70–82 years (V)	2.0	−1.8	1.9 ± 0.5	1.2	−1.5	1.4 ± 0.4

Table 8.3: Mean maximum enhancement and suppression, and peak-to-peak efferent reflex strength (PPERS), and average enhancement and suppression, and average efferent reflex strength (AERS) in the different age groups at the two frequencies $f_{2,dip}$ and $f_{2,flat}$.

suppression, and average enhancement and suppression for all five age groups and both frequencies $f_{2,dip}$ and $f_{2,flat}$ in Tab. 8.3.

In general, it could be observed that the effect of CAS on DPOAE level $\Delta L_{dp,CAS}$ was considerably larger at $f_{2,dip}$ compared to $f_{2,flat}$. The difference was for each group statistically significant (Wilcoxon matched-pairs signed-ranks test, $p < 0.05$) for PPERS and AERS. Also, for the other measures, differences between $f_{2,dip}$ and $f_{2,flat}$ were mostly significant with a few exceptions being not significant(max. enh.: IV; max. suppr.: III, IV, V; average suppr.: III) indicating that enhancement was differing to a larger extent between the two frequencies than suppression.

The differences in PPERS or AERS across age groups were investigated more closely. In general, there was a rough trend evident, which was, however, obscured by a non-monotonic increase or decrease in measures across age, which was true especially for AERS. The magnitude of PPERS mainly decreased with age at $f_{2,dip}$ from 18.2 dB (I) to 13.0 dB (V) and slightly increased with age at $f_{2,flat}$ from 9.0 dB (I) to 10.8 dB (IV) and 10.7 dB (V), respectively. For AERS, the effect followed roughly the trend of PPERS results. At $f_{2,dip}$, AERS decreased from 2.4 dB (I) to 1.9 dB (V), whereas at $f_{2,flat}$, AERS slightly increased from 1.2 dB (II) to 1.5 dB (IV and V). When analyzing the significance of differences between neighboring age groups (Wilcoxon test, $p < 0.05$), there was for both frequencies, $f_{2,dip}$ and $f_{2,flat}$, neither a significant difference for PPERS nor for AERS. However, when examining correlations between PPERS or AERS and age across all subjects (see Fig. 8.7), correlations were significant for PPERS in both frequencies ($n_{f2,dip} = 75$, $r_{f2,dip} = -0.30$; $n_{f2,flat} = 72$, $r_{f2,flat} = 0.28$; $p < 0.05$), but not significant for AERS ($n_{f2,dip} = 75$, $r_{f2,dip} = -0.17$; $n_{f2,flat} = 72$, $r_{f2,flat} = 0.14$).

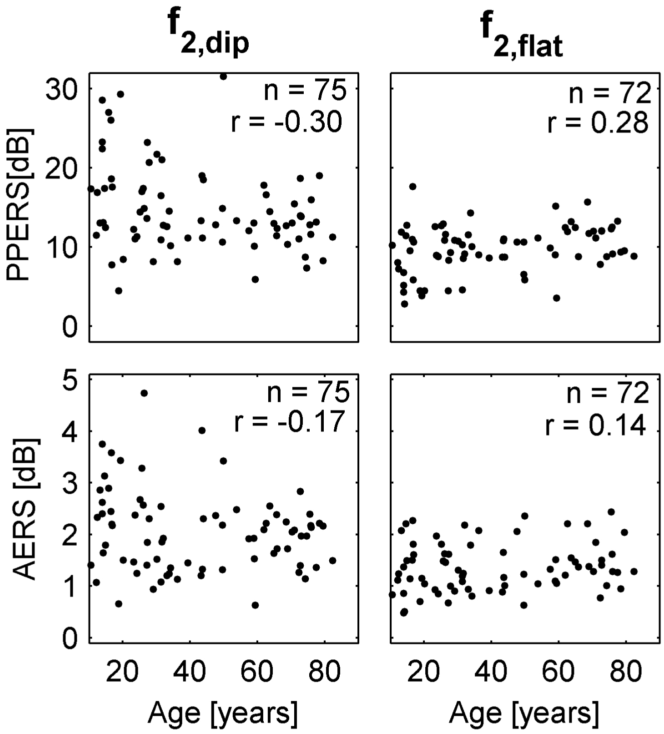

Figure 8.7: Correlation between PPERS or AERS and age at $f_{2,dip}$ (left panels) and $f_{2,flat}$ (right panels).

Correlation coefficients were negative at $f_{2,dip}$ (decrease with age) and positive at $f_{2,flat}$ (increase with age), confirming the results from analyzing the measures of efferent reflex strength across different age groups, which only exhibited a rough trend and no significant changes between neighboring age groups.

8.3 Discussion

The aim of the present study was to investigate whether age-related changes in hearing capability are due to peripheral causes (i.e., depletion of OHC activity or strial atrophy) and/or central causes (i.e., depletion of efferent MOC activity). Therefore, audiometric thresholds, pure-tone threshold fine structure, DPOAE fine structure, and CAS DPOAEs were measured in otologically normal subjects of different age. In the following the achieved results are discussed.

Audiometric threshold deteriorated with age

In the present study, it could be observed that audiometric thresholds increased with age. Compared to the younger subjects, especially the groups of senior and old adults (IV, V) exhibited noticeably elevated audiometric thresholds. This was manifested in significant differences between groups III and IV, and groups IV and V. Group IV and particularly group V also showed a distinct deterioration of hearing thresholds with increasing frequency, which might be interpreted as an indicator for sensory presbycusis since it is known that a loss of OHCs usually begins in the high-frequency range. The deterioration of audiometric thresholds with age and frequency is a typical phenomenon which is also reflected in the statistical distribution of hearing thresholds as a function of age as determined for otologically normal subjects in ISO 7029.

Although in this study only otologically normal subjects were included, it cannot be ruled out that at least some of the deterioration in hearing capability may also be due to other factors than aging. Rosen *et al.* (1962) investigated presbycusis in a relatively noise-free population in the Sudan in comparison to an age-matched industrialized American-based population and found out that hearing losses were distinctly lower in the Sudanese tribe. Thus, in an industrial society, occasional exposure to loud sounds (e.g., traffic noise), which eventually might result in permanent damage of the cochlear amplifier and with that in a deterioration of hearing threshold, is supposed to be a common issue (see also Chapter 7). This extrinsic hearing loss mingles with the age-related intrinsic hearing loss, which is intended to be examined exclusively when studying presbycusis. However, it is not possible to separate the intrinsic age-related part from the extrinsic environmental part of a subject's overall hearing loss. Therefore, when analyzing age-related effects in hearing, it seems to be at least debatable if it is helpful to cut down on the hearing loss of subjects by just examining normal hearing subjects with different age, as it was done in other studies concerning presbycusis. Assuming that the magnitude of age-related alterations may also vary across subjects, the method of including only normal hearing subjects in a study might then yield the problem that only subjects are examined who do not exhibit pronounced age-related effects. Inter-individual variations may arise due to a hereditary component (Gates *et al.*, 1999). If there is an age-related effect in a subject, one could expect that this age-related deterioration in hearing capability is also reflected in increased hearing thresholds. In an attempt to minimize this problem, in the present study only otologically normal subjects were included, which did not report on any hearing-related problems and self-reportedly did not experience any major noise-exposure or intake of ototoxic agents during their lifetime. They also did not reveal any hereditary hearing disorders. However, especially the older subjects in the present study did mostly not exhibit normal hearing (i.e., $\leq$ 20 dB HL). Hence, in the following it is assumed that the hearing loss in each subject occurred mainly due to age-related effects and not or only marginally due to extrinsic effects. However, the general problem about the influence of extrinsic noxae on hearing has to be kept in mind when analyzing the results of the present study.

Difference between pure-tone thresholds and audiometric thresholds

On first glance, there seems to be a substantial difference between pure-tone threshold fine structure data and audiometric threshold data. However, when converting audiometric data from dB HL to dB SPL, one could expect a closer resemblance to pure-tone thresholds, which are given in dB SPL, since the sound stimulus presented via ear probe was calibrated individually in dB SPL by means of in-the-ear calibration. The frequency-dependent offset between dB HL and dB SPL for audiometry data can be derived from the data sheet of the applied headphone (Holmco PD-81). The equivalent reference sound pressure level at hearing threshold, when using a coupler according to IEC 303, amounted for 3 and 4 kHz to 9 dB and for 6 kHz to 19.5 dB. These values have to be added to the audiometric threshold values given in dB HL in order to get the approximate equivalent dB SPL value. However, please note that these offset values just give an average offset from dB HL to dB SPL, which has been determined from a large number of normal hearing subjects and thus may actually vary between subjects. In the following, a comparison between the resulting audiometric thresholds and the respective pure-tone thresholds (shown in brackets) both in dB SPL is given: the particular thresholds ranged from 12 (15) dB SPL at 3 kHz to 23 (29) dB SPL at 6 kHz (I), and for the other groups from 10 (12) to 24 (32) dB SPL (II), from 16 (16) to 27 (30) dB SPL (III), from 20 (24) to 40 (47) dB SPL (IV), and from 29 (24) to 58 (54) dB SPL (V). One can observe that there still remains some difference in thresholds, with pure-tone thresholds mostly exceeding audiometric thresholds (with the exception of group V). However, considering the possible unwanted side-effects when measuring hearing thresholds by means of an ear probe, the results can be considered for the most part rather consistent. One major problem with presentation of a sound stimulus via ear probe is the occurrence of calibration errors (see Chapter 3.4). Due to standing wave phenomena during presentation of the calibration stimulus, the sound pressure level measured at the microphone in the outer ear canal may, dependent on frequency, substantially vary from the effective sound pressure level at the ear drum (Whitehead *et al.*, 1995c; Siegel, 2002). This yields inter-individually varying effective sound pressure levels which may falsify the recorded pure-tone threshold values. Thus, some of the differences between audiometric and pure-tone threshold can be explained in this way. Another minor problem might be, as explained above, the inter-individually different variation from the given offset values (derived from the data sheet of the headphone) and the actual individual offset values. However, there is no proper explanation why differences in audiometric thresholds between group IV and V are considerably larger than those observed for pure-tone thresholds.

Selection of pure-tone threshold instead of audiometric threshold for comparison to DPOAE measures

For a better comparison of peripheral and central sound processing, DPOAE and pure-tone threshold fine structure data was analyzed. It should be emphasized that pure-tone thresholds, in contrast to audiometric thresholds, were acquired within the same measurement frequency range, allowing for a better comparability, and by using the same measurement equipment, i.e., by using the same ear probe, which was applied for DPOAE measurements. In doing this, calibration-related differences in stimulus level between pure-tone threshold and DPOAE measurements might be reduced, since it is expected that the main problem of deviations at specific frequencies between sound pressure level at the microphone and sound pressure level at the ear drum occurs similarly in both DPOAE and pure-tone threshold measurements. However, it is important to note that for DPOAE measurements, calibration-related deviations influence both primary tone levels differently and thus may yield some additional inter-individual variation.

Pure-tone threshold and DPOAE level, threshold, and slope deteriorated with age

DPOAE level (L_{dp}), threshold ($L_{dp,th}$), and slope (s_{dp}) similarly decreased across the five age groups, suggesting both a loss of sensitivity (characterized by L_{dp} and $L_{dp,th}$) and compression (characterized by s_{dp}) of the cochlear amplifier with age. This finding was supported by the fact that correlations between DPOAE measures (L_{dp}, $L_{dp,th}$, and s_{dp}) and age were extremely significant. A similar result was obtained from pure-tone threshold analysis, which also yielded a deterioration of L_{ht} across all age groups and consistently an extremely significant correlation between L_{ht} and age. The most obvious deterioration occurred for DPOAEs and pure-tone thresholds in subjects above 50 years, i.e. in age groups IV and V. Significant changes between neighboring age groups occurred predominantly between age groups III and IV. It is important to keep in mind that the difference in mean age was also largest between these two groups (mean age in group III: 38 years, in group IV: 61 years). Yet, the difference in average audiometric thresholds within the measurement frequency range from 3 to 6 kHz was with 12 dB largest between groups IV and V, followed by the difference between groups III and IV, which amounted on average to 9 dB. In comparison, the difference in pure-tone thresholds was largest between groups III and IV (10 dB), whereas the difference in DPOAE thresholds was also largest between the same age groups but was, with an average of about 6 dB, considerably lower compared to that for pure-tone thresholds. The similar decline in pure-tone and DPOAE thresholds suggests that both overall hearing capability and OHC functionality are affected. Thus, presbycusis seems to be at least partly rooted in lesions on the stage of the cochlear amplifier. Similar results concerning a deterioration of the incidence, level or detection threshold of OAEs with age, were reported in earlier studies (Bonfils *et al.*, 1988; Collet *et al.*, 1990b; Satoh *et al.*, 1998) suggesting an involvement of OHC dysfunction in presbycusis. The fact that both DPOAE and pure-tone threshold data exhibited predominantly a significant difference between age groups III and IV might be an indicator that age-dependent alterations in hearing possibly become evident at the age of around 50 to 60 years. This assumption is supported by the findings of Bonfils *et al.* (1988), who found a sharp decline in OAE incidence in subjects above 60 years and a linear deterioration in OAE detection thresholds in subjects above 40 years.

Pure-tone threshold and DPOAE level, threshold, and slope deteriorated with frequency

In the present study, a clear deterioration with frequency could be observed for L_{ht} and for $L_{dp,th}$ and s_{dp}. The deterioration across frequency was larger for L_{ht} compared to $L_{dp,th}$. This effect was most prominent for group V where hearing loss was largest across all age groups. The large difference between behavioral and physiological thresholds might be due to the fact that at frequencies with a major hearing loss often no valid DPOAE threshold estimation was possible due to a lack of valid DPOAE data. Further on, there was also a distinct deterioration towards higher frequencies in L_{dp} when measured at lower primary tone levels. At higher primary tone levels, a maximum L_{dp} occurred mostly in the middle frequency range between 4 and 5 kHz and not in the lowest frequency range between 3 and 4 kHz as for measurements at lower primary tone levels. A decrease in L_{dp} towards higher frequencies was also observed in other studies (Takahashi *et al.*, 1996; Dorn *et al.*, 1998; Lonsbury-Martin *et al.*, 1991). Hence, this pattern of a sloping high frequency hearing loss with elevated hearing thresholds and diminished cochlear responses especially at high frequencies might be characteristic for presbycusis.

DPOAE level, threshold, and slope deteriorated also with increasing pure-tone thresholds - an argument against an age-related impact on hearing?

As discussed before, in the present study, an extremely significant correlation between DPOAE measures (L_{dp}, $L_{dp,th}$, and s_{dp}) and age was found suggesting that age-dependent processes yield a deterioration in cochlear amplifier functionality. However, there was also an extremely significant and quantitatively even higher correlation between DPOAE measures and pure-tone thresholds across subjects. This finding suggests that DPOAE measures were in fact mainly influenced by pure-tone thresholds, which increased with age. There are many studies about the effect of both age and hearing thresholds on otoacoustic emissions and different researchers have reported contradictory results. Some researchers found an aging effect with decrease of DPOAE amplitudes independent of hearing loss. Dorn *et al.* (1998) examined DPOAE amplitudes in subjects with normal hearing ($\leq$ 20 dB HL) at the examined frequency and with different age and found a significant main effect in age, frequency, and hearing threshold, but no significant age-by-threshold interaction and thus concluded that there may be processes intrinsic to aging alone. Lonsbury-Martin *et al.* (1991) observed in otologically normal subjects with normal hearing or mild hearing loss ($\leq$ 30 dB HL) a decrease in L_{dp} with age and frequency and hence suggested that DPOAEs are a suitable means to examine age-related hearing loss. Other researchers, however, suggested that when hearing loss was controlled, i.e. when studying the DPOAE level at subjects with different age but similar hearing threshold, no effect of age on otoacoustic emissions was found (e.g., Strouse *et al.*, 1996). The observation that emission levels deteriorate predominantly with hearing threshold and not with age was also suggested by studies from Stover and Norton (1993), Prieve and Falter (1995), and Bertoli and Probst (1997). Hence, these investigators recommended that hearing sensitivity should be included as a controlled variable when analyzing intrinsic aging effects. Also Oeken *et al.* (2000) showed that there is a significant decrease in DPOAE amplitude with age, but concluded that the main reason for this is the deterioration in pure-tone thresholds and possibly alterations of the middle ear function in elderly subjects.

Thus, the essential question remains, whether DPOAE measures deteriorated due to an aging process or predominantly due to an increase in pure-tone threshold, which occurs independent of aging, as some of the studies dealing with age-related hearing loss suggested. Hence, it once again boils down to the question whether the observed hearing loss in the older subjects can be attributed to age-related mechanisms or not. In the present study, an extremely significant correlation between age and audiometric thresholds ($r = 0.83$) or pure-tone thresholds ($r = 0.66$) could be observed although only otologically normal subjects were included in the study. This finding might be an indicator for the assumption that hearing loss occurred predominantly due to age-related effects. When trusting in this assumption, the conclusion could be drawn that age-related hearing loss occurs at least to some extent due to a deterioration of cochlear amplifier functionality.

Correlation between pure-tone threshold and DPOAE level or threshold

The question is then, to what extent the observed hearing loss could be attributed to OHC dysfunction, i.e. how close was the relationship between behavioral hearing loss, measured by means of pure-tone thresholds, and the estimated cochlear hearing loss, measured by means of DPOAEs. For answering this question, L_{dp} and $L_{dp,th}$ were evaluated concerning their correlation to behavioral thresholds L_{ht}. Correlations were calculated for each age group and across all subjects within the particular age group and across the entire measurement frequency range (3 to 6 kHz). Correlations between L_{dp} or $L_{dp,th}$ and L_{ht} were, with the exception of the group of children (I), quite large and there was no clear age-dependent behavior evident. This finding suggests that both L_{dp} and $L_{dp,th}$ are suitable measures to reproduce behavioral pure-tone thresholds. The fact that the correlation was much lower for group I can possibly be explained by a worse performance of young children in pure-tone threshold measurements due to a reduced ability of keeping up the power of concentration for a longer period of time.

Moreover, there was on average only a small deviation between $L_{dp,th}$ and L_{ht}. Deviations were largest for groups I, IV, and V with about −6.5 dB and lowest for groups II (−2.5 dB) and III (−3.1 dB). The fact that for all age groups, $L_{dp,th}$ on average underestimated behavioral thresholds L_{ht} suggests that this is a general problem of DPOAE threshold estimation and not a specific issue which occurs only in older subjects. The slightly larger deviations for groups IV and V could mean that overall hearing loss was only partially rooted in OHC dysfunction. Some studies suggested that when hearing thresholds are more affected than emission levels, a decline of the endocochlear potential due to strial atrophy may be the main patho-physiological factor for cochlear aging (Gates *et al.*, 2002; Cilento *et al.*, 2003). This factor cannot be ruled out in the present study. However, the fact that differences between behavioral and DPOAE thresholds were quite small and the fact that no correlation between $|L_{dp,th} - L_{ht}|$ and age was found across subjects ($r = 0.00$), rather suggests a decline of cochlear functionality at the stage of OHCs.

Roughness of pure-tone threshold and DPOAE fine structure

There was no clear age-dependent change in roughness of pure-tone threshold fine structure (R_{ht}) or DPOAE fine structure (R_{dp}). This was reflected in a non-monotonic progression of mean values across the five age groups and in a mostly low correlation between roughness and age. However, when analyzing R_{dp} at low primary tone levels ($L_2 = 30$ dB SPL), roughness was more pronounced and also correlations were significant with age. These findings suggest that age-dependent alterations on the roughness of DPOAE fine structure and with that possibly on the influence of the second DPOAE source are better reflected when recorded at low primary tone levels.

When comparing R_{dp} to L_{ht}, there were slightly larger correlations, which were highly significant for both primary tone levels. It is important to note that correlation coefficients were positive indicating that roughness increased with increasing hearing loss. There are contradictory observations in literature concerning the relationship between roughness and hearing capability. Mauermann *et al.* (1999) proposed from their study that the disappearance of DPOAE fine structure could commonly be associated with hearing impairment, at least when hearing loss occurred at f_{dp}, the generator place of the second DPOAE source. In contrast, He and Schmiedt (1996) found no differences dependent on age or hearing loss and concluded that DPOAE fine structure would always be observable as long as DPOAEs can be measured.

Furthermore, there was no correlation between R_{ht} and R_{dp}, suggesting that dips that occurred in DPOAE fine structure are not reflected at the same frequency in dips that occurred in pure-tone threshold fine structure. This finding is in line with observations from other studies, which compared hearing threshold fine structure to DPOAE fine structure (Mauermann *et al.*, 2004) indicating that pure-tone threshold fine structure and DPOAE fine structure occur due to different processes.

Age-related changes in MOC reflex strength

In order to investigate potential central processes which might be involved in presbycusis, efferent MOC reflex strength was examined by means of CAS DPOAEs at two specific frequencies, i.e. in a dip or in a flat region of the DPOAE fine structure. In order to avoid the influence of the stapedius reflex on CAS DPOAE measurements, ipsi- and contralateral stapedius reflex thresholds had to exceed 60 dB SPL for broad band noise and 90 dB SPL for a 4 kHz pure tone. Since the maximum primary tone level was set to 75 dB SPL and the level of the contralateral noise stimulus was set to 60 dB SPL, the influence of the stapedius muscle on the DPOAE level is suggested to be not relevant. Also, if the stapedius muscle was activated by the contralateral noise stimulus, no rapid change in suppression or enhancement of DPOAE amplitude for a small variation of primary tone levels would be expected, as it was commonly observed in the present study for CAS DPOAE measurements. Thus, the observed effects of suppression or enhancement of DPOAE amplitude can be expected to be due to CAS and not due to activation of the stapedius reflex.

The findings in the present study are divergent since CAS DPOAE data showed different behavior when either measured in dips or in flat regions of the DPOAE fine structure. In dips of the DPOAE fine structure, a decrease, whereas in flat regions, rather an increase of MOC reflex strength was observed with age. The magnitude of suppression or enhancement, and the differences between age groups were smaller at $f_{2,flat}$ than at $f_{2,dip}$. Moreover, there was only a significant correlation with age for PPERS. Hence, major age-related effects predominantly occurred at $f_{2,dip}$, suggesting that dip frequencies in the DPOAE fine structure are possibly better suited to detect age-related changes in efferent MOC functionality. When only regarding CAS DPOAE measurements at $f_{2,dip}$, the finding from the present study, implicating that there is a decrease in efferent MOC reflex strength with age, is in line with those from previous studies. Early studies on age-related changes of the efferent MOC system in humans investigated the influence of CAS on transiently evoked otoacoustic emissions and showed a decline of suppression with age (Castor *et. al.*, 1994). Kim *et al.* (2002), who investigated the influence of CAS on DPOAEs, suggested that the functional decline of the efferent MOC system precedes OHC degeneration with age. Similar age-related deficits of the efferent MOC system were observed in CBA/CaJ mice by Jacobsen *et al.* (2003) and Varghese *et al.* (2005), concluding that an age-related change in the efferent MOC system or in the operating point of OHCs (Lukashkin and Russell, 2002) may play an important role in the development of presbycusis. The physiological function of the efferent MOC system is suggested to be involved in the detection of low-level stimuli in the presence of background noise. Thus, the findings in literature and the present findings at $f_{2,dip}$, which show a slight decline in efferent MOC reflex strength with age, are in line with the finding that speech processing in background noise also declines with age (Frisina and Frisina, 1997).

Furthermore, the fraction of suppression values was larger for all age groups and both frequencies, but at $f_{2,dip}$ showed a tendency to decrease with age and to reach almost parity for the group of old adults (V). Abdala *et al.* (1999) observed in premature neonates, that DPOAE amplitude was equally likely to be suppressed or enhanced by broad band noise and suggested that contralateral enhancement may reflect a temporary stage of immaturity in OHC medial efferent fiber synapses. This hypothesis may indicate some kind of disorder in the efferent MOC system for the older subjects, where enhancement occurred more often than in younger subjects.

In summary, the findings in the present study suggest that several processes might be involved in presbycusis. There is some evidence that presbycusis is at least partly rooted in peripheral processes. Since both behavioral and DPOAE thresholds deteriorated similarly, a cochlear dysfunction on the stage of OHCs seems to be most probable. Strial atrophy can also not be ruled out completely, since pure-tone thresholds were, as it would be expected for a decline of endocochlear potentials, slightly higher than DPOAE thresholds. This was, however, true for all age groups and thus suggests being a general issue in DPOAE hearing threshold estimation rather than a specific age-related impact. Also, a slight decline in efferent MOC reflex strength can be deduced from the present findings, at least when considering data at $f_{2,dip}$, where PPERS deteriorated significantly with age. However, CAS DPOAE data and its interpretation is not yet examined thoroughly enough to draw reliable conclusions.

9 Conclusions and outlook

The presented work described efforts in improving diagnostics of the cochlear amplifier by means of distortion product otoacoustic emissions (DPOAEs). This included the improvement and development of strategies for objective hearing aid adjustment, quantification and classification of hearing loss in neonates, and quantification of efferent medial olivocochlear (MOC) reflex strength. Moreover, the impact of noise exposure of different intensity and duration on hearing and the capability of determining individual susceptibility to noise by means of DPOAEs was investigated as well as the cause for age-related hearing loss.

In order to allow for conducting the various measurement techniques which needed to be applied in the studies, a flexible measurement system was developed on the basis of a commercial device, which has been in use for clinical diagnostics. The custom-made measurement system was capable of measuring pure-tone thresholds, categorical loudness scaling (CLS), and DPOAEs. In addition to standard DPOAE measurements, two frequently used methods of quantifying efferent MOC reflex strength were implemented, i.e. contralateral DPOAE suppression and ipsilateral DPOAE adaptation. Both pure-tone thresholds and DPOAEs could be measured with high frequency resolution allowing for assessment of fine structure properties (see Chapter 3).

A novel method for objective, non-cooperative hearing aid fitting was developed and tested in Chapter 4, in which CLS and DPOAE growth functions were compared for hearing-impaired subjects. Data from normal hearing subjects were measured as part of the author's diploma thesis (see Müller, 2002; Oswald, 2005) and served as reference for comparison to data from the cochlear hearing loss patients. By using a strategy following Steinberg and Gardner (1937) similar loudness- and DPOAE-based gain functions for setting frequency- and level-dependent gain in dynamic compression hearing aids could be achieved. However, good results were only achieved for normalized DPOAE levels since non-normalized DPOAE levels were found to vary substantially in magnitude even in subjects with similar hearing properties. Hence, further studies are needed to enhance the proposed objective hearing aid adjustment strategy by improving the applied simple normalization strategy. Relevant parameters, which are suggested to influence DPOAE amplitude (e.g., ear canal volume), have to be identified and methods have to be developed which allow for quantification and compensation of these influences. Moreover, it is necessary to improve hardware abilities and increase the stimulus level output in order to make such a DPOAE-based strategy applicable for patients with major hearing losses. The behavior of DPOAE I/O functions at high-level stimuli must be further examined and compared to loudness functions. Also, other objective measurement methods, such as brainstem evoked potentials, need to be included in the strategy for better evaluation of major hearing losses.

The clinical applicability of estimating behavioral hearing thresholds by means of DPOAEs following the method of Boege and Janssen (2002) was investigated in Chapter 5. Also, the influence of sound conductive hearing loss, which frequently occurs in neonates due to residual amniotic fluid in the tympanic cavity, was examined and a model-based strategy, which might allow for differentiation between sound conductive and sensorineural hearing loss, was developed. The presented study suggests that a frequency-specific and quantitative assessment of hearing loss by means of DPOAEs is also possible in neonates under hearing screening conditions. Moreover, due to a different DPOAE behavior in sound conductive and cochlear hearing loss, the detection of sound conductive hearing loss caused by residual amniotic fluid might be possible due to a comparison between estimated DPOAE threshold and DPOAE detection threshold, which were suggested to differ highly in sound conductive hearing loss, but only marginally in cochlear hearing loss. However, further studies, where DPOAEs are measured down to hearing threshold and not only to a fixed level, need to verify the applicability of the proposed strategy. Also, the influence of the variability of DPOAE levels across subjects needs to be taken into account.

Effects due to efferent enervation of outer hair cells (OHCs) have been observed to be very small in previous studies in humans and hence clinical applicability seemed to be restricted. Much larger effects were found by Maison and Liberman (2000) in guinea-pigs when measuring ipsilateral DPOAE adaptation within a wide primary tone level range. The purpose of the study presented in Chapter 6 was to investigate in humans whether DPOAE suppression or adaptation could yield similar large bipolar changes in DPOAE level when changing primary tone levels in small steps within a wide primary tone level range. Since the observed large MOC-related effect was assigned to the influence of the secondary DPOAE source (Kujawa and Liberman, 2001), DPOAE suppression and adaptation was measured in dips and flat regions of the DPOAE fine structure, which is supposed to occur due to different impacts of the secondary generator. In the presented study, large effects were observed for contralateral DPOAE suppression in dips of the DPOAE fine structure but not in flat regions. For ipsilateral DPOAE suppression, effects were usually much smaller. Only in one subject a major bipolar change in adaptation magnitude was present. Hence, contralateral DPOAE suppression, when measured at dip frequencies and varying the primary tone level in small steps, was suggested to provide a suited tool for assessing MOC reflex strength. However, it remains unclear which intrinsic mechanisms (e.g., secondary DPOAE source) are actually responsible for the observed bipolar effect. Further studies need to examine this aspect more closely, e.g. by measuring contralateral DPOAE suppression while presenting simultaneously an additional ipsilateral tone near $2f_1 - f_2$, which is supposed to suppress the secondary DPOAE source (Heitmann *et al.*, 1998). Moreover, it remains unknown why in humans the bipolar effect is stronger during contralateral acoustic stimulation, i.e. when stimulating the uncrossed MOC feedback loop, than during ipsilateral acoustic stimulation, i.e. when stimulating the crossed MOC feedback loop, which is contrary to the findings in animals.

Further studies need to investigate the impact of the uncrossed and crossed MOC efferents on OHC motility. Ipsilateral DPOAE adaptation effects might be increased when stimulating, similar to contralateral DPOAE suppression measurements, with additional ipsilateral broad band noise. However, the influence of ipsilateral broad band noise on DPOAE recording and its proper parameterization, allowing for unobstructed generation of the emission in the region of overlap of the two primaries, would have to be investigated in the first instance.

Since noise-induced hearing loss (NIHL) is one of the most common hearing disorders, the impact of recreational and occupational noise on the operability of the cochlear amplifier and on overall hearing capability was examined by means of DPOAEs and pure-tone thresholds, respectively. Moreover, efferent MOC reflex strength, which has been suggested to protect OHCs from acoustic overexposure (Maison and Liberman, 2000), was quantified by means of contralateral DPOAE suppression (see Chapter 6). On the one hand, subjects exposed to high-level discotheque music for three hours, and on the other hand factory workers exposed to mid-level occupational noise for one workday and in comparison office workers with no major noise exposure, were examined in Chapter 7. In both studies, pure-tone thresholds as well as DPOAE levels deteriorated significantly after noise exposure. The deterioration was on average much larger in the discotheque attendants compared to the factory workers. In contrast, office workers did not show any deterioration. Hence, it can be expected that a regular temporary decline of OHC function may yield irreversible OHC damage and with that irreversible hearing impairment over time. However, no distinct correlation between efferent MOC reflex strength and shifts in pure-tone threshold or shifts in DPOAE level was found. In contrast, efferent MOC reflex strength was found to be significantly correlated to baseline DPOAE levels, i.e. a large efferent MOC reflex occurred predominantly in subjects with low DPOAE levels, possibly indicating OHC motility to be controlled by MOC activity. The present findings suggest that it is necessary to further educate people about potential dangers which may occur due to hazardous noise exposure and to inform about possibilities to protect their ears from NIHL. In addition, introducing regulations about limiting recreational noise exposure may be helpful. Furthermore, since the applied measures of efferent MOC reflex strength did not seem to be suited to predict cochlear vulnerability to noise exposure of several hours, further studies need to reveal the role of the efferent hearing system and need to investigate the underlying mechanisms for the occurrence of suppression and enhancement of DPOAE levels. In order to test whether efferent MOC reflex strength may be actually able to predict noise vulnerability, future studies need to be conducted in a more controlled environment with defined and uniform noise exposure across subjects. Also, larger cohort studies in long-term noise-exposed subjects are required to find out whether efferent MOC reflex strength is possibly better suited to predict individual susceptibility to hazardous noise in cases of permanent hearing impairment, as it was observed in guinea-pigs (Maison and Liberman, 2000), instead of temporal hearing impairment as it was observed in the present studies. Moreover, the question, which measure reflects vulnerability to acoustic overexposure best, needs to be answered. Besides changes in pure-tone thresholds or DPOAE levels after noise exposure, also the magnitude of recovery from noise exposure could serve as an indicator for noise vulnerability. Therefore, additional measurements at fixed recovery times could yield additional information about this aspect. Furthermore, since ear probe calibration was found to be a highly influential factor when comparing measurements recorded at different points of time, methods have to be established for minimizing calibration errors and for maintaining a constant ear probe position at subsequent measurements in order to guarantee proper comparability between measures when monitoring noise-induced changes across time.

Due to a steadily aging society the occurrence of age-related hearing loss gains in importance. The causes for age-related hearing loss are not yet clearly identified. In Chapter 8, pure-tone threshold and DPOAE fine structure as well as contralateral DPOAE suppression was analyzed to quantify overall hearing capability, OHC operability, and efferent MOC reflex strength (see Chapter 6) in subjects of different age in order to find out whether age-related hearing loss is more due to peripheral or central causes. Pure-tone thresholds and DPOAE levels deteriorated with age suggesting an age-related impact on the operability of the cochlear amplifier. The decline in pure-tone threshold and DPOAE level was quite similar across both measures with slightly larger effects across all age groups in the behavioral measure suggesting a deterioration in OHC functionality to be the predominant cause for presbycusis. However, a decline of the endocochlear potential due to strial atrophy could not be ruled out. Efferent MOC reflex strength deteriorated when measured in dips of the DPOAE fine structure, whereas it improved when measured in flat regions of the DPOAE fine structure. Hence, no definite conclusion could be drawn concerning the influence of central processes. Further studies need to thoroughly examine contralateral DPOAE suppression data and its interpretation with respect to the influence of the secondary DPOAE generator.

A general problem, which is supposed to be a major source of errors in all presented studies, is calibration, which is not reliable enough with respect to achieving defined sound pressure levels at the ear drum. For in-the-ear calibration, the influence of standing wave effects is known but no adequate compensation mechanisms are available. A more recently proposed calibration method, the coupler-based reference calibration (see Sec. 3.4), is not studied thoroughly enough to evaluate and quantify its inherent problems. Hence, further studies need to examine the coupler-based reference calibration and find out whether this calibration method is superior to in-the-ear calibration. Also, a reliable DPOAE stimulus paradigm has to be developed for this calibration method. In general, the improvement of ear probe calibration is supposed to be the key element for improving results derived from DPOAE measurements.

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