Assessment of the human ear's non-linear amplification process by means of distortion product oto-acoustic emissions

Thomas Janssen

Experimentelle Audiologie, Hals-Nasen-Ohrenklink, Technische Universität München, Germany
Email: T.Janssen@LRZ.TUM.de

Introduction

The discovery of oto-acoustic emissions by David Kemp in 1978 has not only changed previous thinking about cochlear sound processing, but has also produced a totally new tool for diagnosing hearing impairment. The paradoxical fact, that sound is emitted by the ear requires a sound source in the ear and was postulated by Thomas Gold in 1948. Gold suggested an active amplification process within the cochlea to align the huge range of audible sound pressure with the small range of displacement of cochlear elements. However, Gold did not know the underlying mechanism. Since the discovery of outer hair cell (OHC) motility by Brownell and co-workers in 1985 it became obvious that OHCs act as non-linear feed-back amplifiers which enhance the sensitivity and the frequency selectivity of the hearing organ.

Oto-acoustic emissions are the by-product of this nonlinear amplification process and hence can serve as a measure for evaluating cochlear integrity. Due to the non-linearity, cochlear micromechanics produce cubic distortions when stimulated with two tones simultaneously. The mechanical distortion is emitted via middle-ear into the ear canal and can be measured there by means of a highly sensitive microphone (Figure 1). There are two sound sources within the cochlea: The primary source represents mechanical distortion of OHCs in the region of overlap of the primary tone travelling waves (place-fixed OAE). The second source is fed by the traveling wave, that is generated by the mechanical distortion reaching maximum amplitude at the $2f_1$-f_2 place (wave-fixed OAE). Depending on their phase relationship the two sources interact constructively or destructively (Mauermann and Kollmeier 2004). There are different methods to minimize the influence of the second sound source: (i) suppressing the second source with an ipsilateral tone near f_2 (Heitmann et al. 1998) (ii) pulsed f_2 measurement technique (Dallhoff et al. 2013), and (iii) modulation technique (Lodwig 2013). From animal studies it is known that the efferent hearing system controls OHC motility. Two functions are discussed, i.e., detection of low-level signals in background noise and protection the ear from too loud sounds (Guinan 1996). Ipsilateral DPOAE-Adaptation and Contralateral DPOAE-Suppressions allow for evaluating the functionality of the efferent system (Liberman et al. 1996). Both measures may predict the ear's vulnerability to sound overexposure. In the following review - based on own data - it is described how DPOAE measures can assess the human ear's non-linear amplification process.

Methods

When changing the primary tone frequencies, the region of overlap is moving along the basilar membrane. In doing this, OHC functionality can be evaluated at different cochlea places. If OHCs are impaired DPOAEs appear with lower amplitude or disappear. So called DPOAE-Grams are obtained when plotting the DPOAE sound pressure level L_{DP} across primary tone frequency f_2. Like a fingerprint DPOAE-Grams mirror the hearing loss. However, close to threshold stimulation is necessary for a quantitative evaluation of hearing loss. To get information on the dynamic behavior of OHC amplifiers, DPOAEs are measured at different primary tone levels. When plotting the DPOAE-level L_{DP} across primary tone level L_2, DPOAE-Level-I/O-Functions are obtained which mirror the compressive non-linearity of OHC amplifiers when a special stimulus setting is used that accounts for the non-linear interaction of the two primary tones at the DPOAE generation site. In case of impaired outer hair cells, sensitivity and compression are decreased. For yielding a DPOAE-level growth that corresponds to the compressive non-linearity of OHC-amplifiers, primary tone levels L_1 and L_2 have to be set such that the difference between L_1 and L_2 increases with decreasing stimulus level following $L_1 = 0.4L_2 + 39$ dB SPL with $f_2/f_1=1.2$ (scissor paradigm, Kummer et al. 2000). Due to the noise floor (microphone noise, subject's breathing and blood-flow) DPOAE can not be measured at stimulus levels very close to hearing threshold levels. Therefore, DPOAE-thresholds have to be estimated. This is done by linear regression analysis using DPOAE data in the semi-logarithmic plot (DPOAE-Pressure-I/O-Functions p_{DP} (L_2)). The intersection between the linear regression line and the primary tone level axis can serve as a measure for determining DPOAE-thresholds (Boege and Janssen 2002).

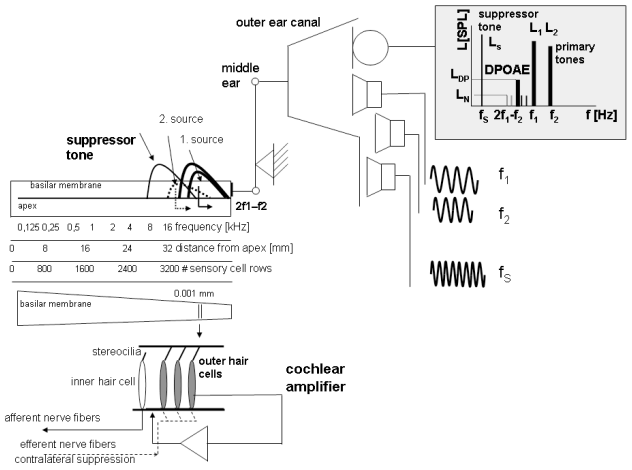

Figure 1: Schematic drawing of how to elicit and how to measure DPOAEs. DPOAEs are elicited by two primary tones with frequencies f_1, f_2 und levels L_1, L_2. When changing f_1 and f_2 ($f_2/f_1=1.2$) at fixed primary tone levels a DPOAE-Gram L_{DP} (f_2), when changing L_1 and L_2 ($L_1=0.4L_2+39$) at fixed primary tone frequencies a DPOAE-I/O-Function L_{DP} (L_2) is obtained. Iso-Suppression tuning curve plots the level L_S of the suppressor tone across suppressor tone frequency f_S at which DPOAE-level is decreased by e.g. 4 dB. There are two DPOAE sources. One is located in the overlapping region of the primary tone traveling waves (f_2-place), the other at the $2f_1$-f_2-place. Due to the non-linearity of OHC amplifiers cubic distortions of frequency $2f_1$-f_2 are generated within cochlear micromechanics that can be measured as DPOAEs by means of a microphone in the outer ear canal.

When stimulating the ear with an ipsilateral suppressor tone, tuning characteristics of OHC-amplifiers can be assessed. When plotting the suppressor tone level across suppressor tone frequency at which the DPOAE-level is suppressed by e.g. 4 dB, so called Iso-Suppression tuning curves can be established (Kummer et al. 1995). In patients with cochlear hearing loss, the tip of the tuning curve disappears. Time course of DPOAE-level $L_{dp}(t)$ mirrors the transient behaviour of OHC displacement. The reduced DPOAE-level at steady state (Ipsilateral DPOAE-Adaptation) indicates reduction of OHC motility as controlled by medial olivocochlear efferents. Contralateral DPOAE-Suppression reflects the strength of the efferent system (Maison and Liberman 2000 (guinea pigs), Müller et al. 2005 (humans)). Both measures may predict the ear's susceptibility to acoustic overexposure. A schematic drawing of the different DPOAE measures for assessing cochlear amplification is given in Figure 2.

DPOAE-Measures

DPOAE-Gram

Like a fingerprint DPOAE-Grams mirror the hearing loss when plotting DPOAE-level across f_2 revealing that OHCs around the f_2-place in the cochlea contribute most to the DPOAE. The lower the primary tone level the higher is the decrease in DPOAE-level. That means, close to threshold stimulation is necessary for a quantitative evaluation of hearing impairment (Kummer et al.1998). However, in hearing loss ears with tinnitus a discrepancy between behavioural thresholds and DPOAE-thresholds was observed in the tinnitus frequency region indicating mechanical distortion as a potential cause for tinnitus generation (Janssen et al. 1998, 2000).

To show how noise exposure in a discotheque has an impact on outer hair cell functionality high resolution (41 Hz) DPOAE-Grams were recorded between 3.5 and 4.5 kHz in 15 normally hearing subjects. DPOAEs were elicited at a close-to-threshold level at L_2 = 30 dB dBSPL. For comparison, behavioral pure tone thresholds were recorded at same frequencies. Data were recorded before, immediately after, and the day after visiting the discotheque. After noise exposure (3 hours, 102 - 106 dB (A)) the increase in behavioral thresholds was on average across frequency and subjects 14 dB, the decrease of DPOAE-level amounted to about 13 dB. Measurements at the following day revealed recovery, however recovery was not completed. Baselines were not reached yet. In an other study with factory workers small but significant changes in DPOAE-level and pure-tone threshold were observed after a 8 hours workday. Results suggest the ear's vulnerability to occupational noise even though regulations for sound exposure were met. For further details of the studies see Müller et al. 2010 and Müller and Janssen 2008.

DPOAE-I/O-Function

DPOAE-Level-I/O-Functions mirror the compressive non-linearity of OHC amplifiers when applying the 'scissor paradigm'. In case of impaired outer hair cells, DPOAE-level is decreased highest at close-to-threshold primary tone levels, revealing decrease of sensitivity and compression of cochlear amplifier at cochlea place f_2. Due to the noise floor (e.g. at 4 kHz: around minus 20 dB SPL), DPOAEs can not be measured at stimulus levels very close to hearing threshold levels. Thus. DPOAE-thresholds have to be estimated. Because of the logarithmic dependency of DPOAE-level L_{DP} on the primary tone level L_2, there is a linear dependency between DPOAE pressure p_{DP} and primary tone level L_2. 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 can serve as an estimate of the DPOAE-level at threshold L_{dpth} (Boege and Janssen 2002).

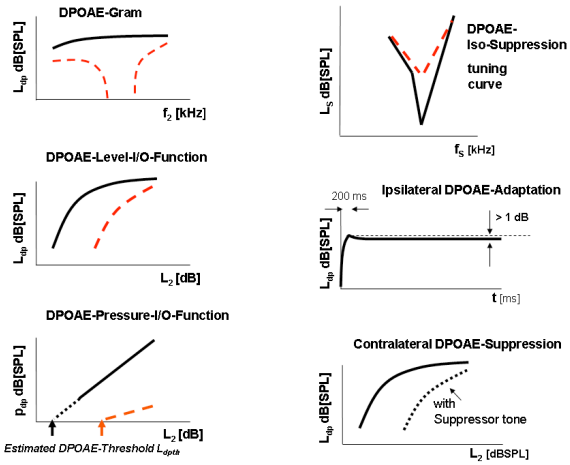

Figure 2: Schematic drawing of DPOAE measures in normal and impaired (dashed lines) ear. DPOAE-Grams $L_{dp}(f_2)$ allow for a more qualitative evaluation of OHC impairment along the cochlea, DPOAE-Level-I/O-Functions $L_{dp}(L_2)$ mirror dynamic behaviour of OHC amplifiers, extrapolated DPOAE-Pressure-I/O-Function $p_{dp}(L_2)$ allow for estimating DPOAE thresholds L_{dpth} at a specific cochlea place (f_2). DPOAE-Iso-Suppression Tuning curves $L_S(f_S)$ are able to assess tuning characteristics of OHC amplifiers. Ipsilateral DPOAE-Adaptation $L_{dp}(t)$ and contralateral DPOAE-Suppression, both controlled by the efferent hearing system, may give information about the ear's vulnerability to acoustic overexposure.

Examples of DPOAE-Level-I/O-Functions and DPOAE-Pressure-I/O-Functions are shown in Figure 3. DPOAE-Level-I/O-Function recorded in a 1 day old newborn exhibit compressive non-linearity of OHC amplifiers indicating that the cochlea is fully matured at birth. In the same newborn 4 weeks later, higher DPOAE-levels were observed. Because of the fact that there was a parallel shift of the I/O-functions (slope s of the I/O-functions is similar, s=0,26 and 0,32), a sound conductive hearing loss due to amniotic fluid in the tympanic cavity during the early post-natal period is likely. For comparison, in a patient with a cochlear hearing loss of 40 dB HL, DPOAE-level-functions are steeper (s=1.25) revealing loss of compression of outer hair cell amplifiers (Figure 3A). Data of Figure 3A are presented in a semi-logarithmic plot in Figure 3B. Data were fitted by linear regression analysis. Estimated DPOAE-threshold level L_{dpth} (intersection point of the linear regression line with the L_2-axis) is 21.9 dB SPL (newborn, 4 weeks after birth), 28.4 dB SPL (same newborn at birth), and 48,3 dB (hearing loss ear). Figure 3C shows estimated DPOAE-threshold level L_{DPTH} derived from DPOAE-I/O-functions recorded at f_2 between 1 and 8 kHz in normally hearing adults (26 ears), in newborns (118 ears), in babies with a mean age of 4 weeks (21 ears), and in cochlear hearing loss patients (189 ears) with an average hearing loss of 20 and 40 dB HL. Estimated DPOAE-thresholds were similar to that known from

behavioral pure tone thresholds, being lowest at 4 kHz.
The slope of the I/O-functions (Figure 3D) also varied with frequency, being lowest around 4 kHz revealing highest compression of OHC amplifiers in this frequency range. Data from the 4 weeks old neonate sample were closely related to that from the normally hearing adults. This is true for the estimated threshold and the slope. In contrast, the newborn group exhibited slightly higher thresholds and higher slopes. In comparison to the neonate sample, the 20 dB HL cochlear hearing loss sample shows a little bit higher thresholds and slopes. Thresholds and slopes of the 40 dB HL subject sample were considerably higher (for more detail see Janssen et al. 2005, Janssen and Müller 2008).
Estimated DPOAE-thresholds L_{DPTH} derived from recordings of DPOAE-pressure-I/O-functions at up to 51 frequencies between 0.5 and 8 kHz per ear in normally hearing adults (30 ears) and in cochlear hearing loss patients (118 ears) revealed a close relationship to the behavioural pure tone thresholds. Mean difference was 2.5 dB, standard deviation amounted to 10.9 dB. Slope of the DPOAE-I/O-function (between L_2 = 40 und 60 dB SPL) increased with increasing hearing loss from 0.2 dB/dB (normal) to 1.3 dB/dB. For more details of this study see Boege and Janssen 2002. DPOAE-thresholds and slope thus provide quantitative measures for determining loss of sensitivity and loss of compression of OHC amplifiers.

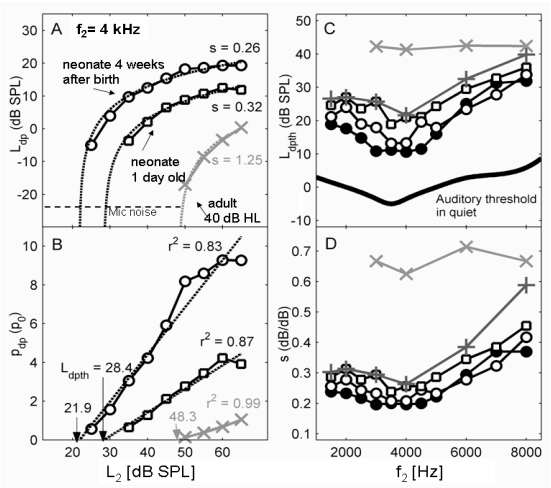

Figure 3: DPOAE-Level- (A) and DPOAE-Pressure-I/O-Functions (B) in a one day old newborn (squares), in the same newborn four weeks later (open circles), and in an adult cochlear hearing loss ear (x). DPOAE threshold level L_{dpth} was estimated by linear regression analysis (intersection between linear regression line and L_2-axis). L_{dpth} at f_2 between 1 and 8 kHz in normally hearing ears (filled circles), four weeks old neonates (open circles), newborns (open squares), 20 dB HL (+) and 40 dB HL (x) cochlear hearing loss ears (C). Slope s of DPOAE-Level-Functions are shown in D.

DPOAE-Iso-Suppression tuning curve

DPOAE-Iso-Suppression tuning curves allow for a quantitative evaluation of the tuning characteristics of OHC-amplifiers. Figure 4 shows examples of such tuning curves recorded in three subjects at different cochlear sites, at f_2 = 1, 2, 4, and 6 kHz. They exhibit an asymmetrical V-shape with sharply tuned tips. The Q-10 dB value (CF/BW_{10dB}; CF=characteristic frequency, BW_{10dB}=bandwidth at 10 dB above suppression threshold) varies from about 2 to 8. Suppression thresholds are lowest in the basal region of the cochlea. All in all, DPOAE-Iso-Suppression tuning curves share the features known from neural tuning curves in animals. Tips of the tuning curves are located near the f_2-place indicating that DPOAE generation is dominated by OHCs near the f_2-place. For more details on tuning characteristics of the cochlear amplifier see Kummer et al. 1995.

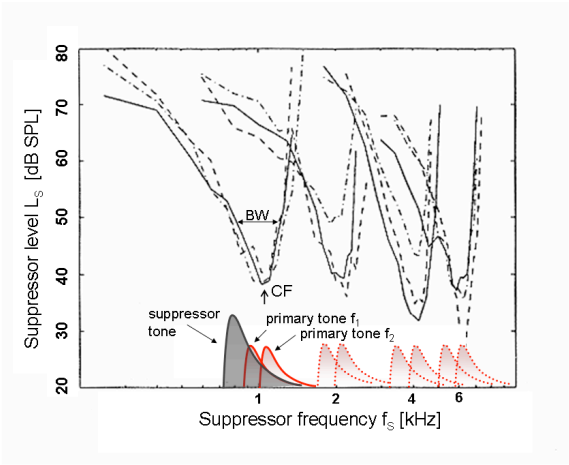

Figure 4: DPOAE-Iso-Suppression tuning curves from three subjects at four different sites in the cochlea. Suppressor tone level L_S is plotted across suppressor tone frequency f_S at which the DPOAE-level L_{DP} is suppressed by 4 dB. Travelling wave envelopes for the primary tones and the suppressor tone (as an example for suppressing the DPOAE at f_2=1 kHz) are shown schematically on the frequency-axis. CF=characteristic frequency, BW=bandwidth of the tuning curve 10 dB above threshold.

DPOAE-Adaptation and DPOAE-Suppression

The time course of DPOAE level L_{dp} mirrors the transient behaviour of outer hair cell displacement. 200 milliseconds after stimulus onset, L_{dp} - and with that outer hair cell displacement - is highest. After that, L_{dp} is reduced by 1 dB reflecting adaptation. Also, Contralateral DPOAE-Suppression, i.e., the difference between L_{dp} measured in the absence and in the presence of a contralateral acoustic stimuli, reflects the strength of the efferent system. Contralateral stimulation using noise or tones with frequencies near f_2 results in a decrease of DPOAE level. The lower the primary tone level for eliciting DPOAE the higher is the decrease in DPOAE level (Janssen et al. 2003). Suppression varies with L_1-L_2 setting and f_2. Beside suppression, enhancement (increased L_{dp}) was observed for a specific L_1-L_2 setting. The change in L_{dp} (enhancement - suppression) in normally hearing subjects was on average 14.1 dB, when f_2 corresponded to frequencies where the deepest dips in the DPOAE-Gram fine structure occurred (Müller et al. 2005).
In the discotheque study and the study with factory workers Contralateral DPOAE-Suppression was measured. However, in both studies a clear correlation between the reflex strength and the degree of noise-induced hearing loss was not found (Müller and Janssen 2008, Müller et al. 2010). Further studies are necessary to answer the question whether DPOAEs can be a tool for predicting cochlear vulnerability.

DPOAE applications

DPOAE measures can assess characteristics of normal and impaired cochlear function. DPOAE-Grams allow for a rough evaluation of cochlear hearing loss. The lower the primary tone level the better is the accordance with the behavioural hearing threshold. Due to low signal-to-noise ratios near threshold, measurements at close-to-threshold

primary tone levels are not possible. Therefore, for a quantitative assessment of cochlear hearing loss extrapolated DPOAE-I/O-functions have to be used. Both, loss of sensitivity and loss of compression can be derived from DPOAE-I/O-functions. DPOAE-Iso-suppression tuning curves allow for assessing cochlear tuning. Thus, DPOAE-I/O-functions and DPOAE-Iso-suppression tuning curves provide parameters for a non-cooperative hearing aid adjustment, especially in infants in which subjective audiometric tests fail to reliably assess the hearing loss (Müller and Janssen 2004). Compared to psycho-acoustical test procedures DPOAE measuring time is short. This is an important fact for applying DPOAEs in pediatric audiology.

Beside DPOAE-Grams, DPOAE-I/O-Functions, and DPOAE-Iso-Suppression tuning curves that allow for assessing the ear's peripheral amplification process, Ipsilateral DPOAE-Adaptation and Contralateral DPOAE-Suppression give information on the functionality of the efferent hearing system. Ipsilateral DPOAE-Adaptation mirrors the transient behaviour of outer hair cell displacement, Contralateral DPOAE-suppression can quantitatively assess the reflex strength of the efferent hearing system. Possibly, DPOAEs could be a tool for predicting the ear's susceptibility to acoustic overexposure, assuming that ears having a high reflex strength are protected in a better way than ears having a low reflex strength.

DPOAEs are able to assess sound processing on the OHC level. That means a hearing loss higher than 50-60 dB HL can not be assessed. For evaluating hearing loss within the entire range of hearing auditory steady state responses (ASSRs) have to be measured (Picton et al. 2003). Measuring ASSRs takes long time. Concurrend measurement of DPOAEs and ASSRs reduces measuring time considerably (Oswald et al. 2006, Rosner et al. 2011).

There are four main clinical applications of DPOAE measures: (i) newborn hearing screening and follow-up diagnostics, (ii) proof of a cochlear hearing loss along with tympanometry and auditory brainstem responses (topological diagnostics), (iii) quantitative evaluation of cochlear hearing loss and recruitment (loss of compression) for providing parameters for noncooperative hearing-aid-adjustment in pediatric audiology, and (iv) detecting/monitoring beginning cochlear impairment during noise exposure or ototoxic drug administration. For an overview on DPOAEs as a diagnostic tool in a clinical context see Janssen and Müller 2008, Janssen et al. 2006, 2013.

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