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Optimal L_1-L_2 primary tone level separation remains independent of test frequency in humans

Peter Kummer *, Thomas Janssen, Peter Hulin, Wolfgang Arnold

Hals-Nasen-Ohren Klinik, Klinikum rechts der Isar, Technische Universität München, Ismaninger Str. 22, 81675 Munich, Germany

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Abstract

Previous studies described a systematic asymmetry of the level of the $2f_1-f_2$ distortion product otoacoustic emission (DP) in the space of the primary tones levels L_1 and L_2 in normal-hearing humans. Optimal primary tone level separations L_1-L_2, which result in maximum DP levels, were close to $L_1=L_2$ at high levels, but continuously increased with decreasing stimulus level towards $L_1>L_2$ (Gaskill and Brown, 1990, J. Acoust. Soc. Am. 88, 821–839). At these optimal L_1-L_2, however, not only DP levels in normal hearing were maximal, but also trauma-induced DP reductions. A linear equation that approximates optimal L_1-L_2 level separations thus was suggested to be optimum for use in clinical applications (Whitehead et al., 1995, J. Acoust. Soc. Am. 97, 2359–2377). It was the aim of this study to extend the generality of optimal L_1-L_2 separations to the typical human test frequency range for f_2 frequencies between 1 and 8 kHz. DPs were measured in 22 normal-hearing human ears at 61 primary tone level combinations, with L_2 between 5 and 65 dB SPL and L_1 between 30 and 70 dB SPL ($f_2/f_1=1.2$). It was found that the systematic dependence of the maximum DP level on the L_1-L_2 separation is independent on frequency. Optimal L_1-L_2 level separations may well be approximated by a linear equation $L_1=a\,L_2+(1-a)\,b$ (after Whitehead et al., 1995) with parameters $a=0.4$ and $b=70$ dB SPL at f_2 frequencies between 1 and 8 kHz and L_2 levels between 20 and 65 dB SPL. Below $L_2=20$ dB SPL, the optimal L_1 was found to be almost constant. Following previous notions (Gaskill and Brown, 1990), an analysis of basilar membrane response data in experimental animals (after Ruggero and Rich, 1991, Hear. Res. 51, 215–230) is further presented that relates optimal L_1-L_2 separations to frequency-selective compression of the basilar membrane. Based on the assumption that optimal conditions for the DP generation are equal primary tone responses at the f_2 place, a linear increase of the optimal L_1-L_2 level separation is graphically demonstrated, similar to our results in human ears.

Key words: Distortion product otoacoustic emission; Clinical application; Human; Basilar membrane; Mechanics

1. Introduction

Distortion product otoacoustic emissions (DPs), measurable in the outer ear canal during stimulation of the ear with two primary tones of frequencies f_1 and f_2 and levels L_1 and L_2, arise from a frequency-selective compressive nonlinearity in basilar membrane (BM) mechanics (Johnstone et al., 1986; Ruggero et al., 1997) in the region of overlap of the primary tones. This nonlinearity is mainly due to the outer hair cell (OHC) function, which is thought to amplify BM motion especially at low input levels. This so-called cochlear amplifier (Davis, 1983; Dallos, 1992) is responsible for both the frequency selectivity and sensitivity of the hearing organ. Thus, DPs are suitable for a frequency-specific diagnostic of OHC function. Indeed, the DP level correlates with the hearing threshold in normal and impaired hearing (e.g., Gaskill and Brown, 1990; Martin et al., 1990; Nelson and Kimberley, 1992; Stover et al. 1996).

A number of mostly animal but also human DP studies have shown that the primary tone level is crucial for the sensitivity of DP measurements. The sensitivity to trauma increased with decreasing L_2 at primary tone levels below about 60–70 dB SPL, where DPs are vulnerable to cochlear trauma (Wiederhold et al., 1986; Sutton et al., 1994; Gorga et al., 1996; Whitehead et

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* Corresponding author. Tel.: +49 (89) 4140 2371; Fax: +49 (89) 4140 4971.

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al., 1992b, 1995a,b; Mills and Rubel, 1994; Kummer et al., 1998; Janssen et al., 1998).

Most systematically, Whitehead et al. (1995b) examined in the rabbit ototoxic ethacrynic acid-induced reductions of the DP at different L_2 levels, by systematically varying the primary tone level separation L_1-L_2. It was shown that reductions of the DP systematically depended on L_1-L_2 at different L_2: with decreasing L_2 below about $L_1=L_2=75$ dB SPL, maximum DP reductions were found when L_1-L_2 was continuously increased.

Similar to this asymmetry of trauma-induced DP reductions in L_1,L_2 space, an asymmetry of the normative DP level was first reported by Gaskill and Brown (1990). These authors reported that there is a maximum of the DP level when varying L_1-L_2 at a given L_2 and that this optimal L_1-L_2 continuously increased from 5 to 23 dB with decreasing L_2 from 55 to 25 dB SPL. At high L_2 levels between 65 and 75 dB SPL, L_1-L_2 between 0 and 10 dB were found to be optimal (Hauser and Probst, 1991; Rasmussen et al., 1993). Whitehead et al. (1995b) further elaborated this issue in humans and reported that "the L_1 values that maximize normative DPOAE amplitudes for any specified L_2 are well approximated by a simple equation",

$$L_{1\text{opt}} = a\,L_2 + (1-a)\,b \qquad (1)$$

From averaged data of eight subjects, the parameters were $a\approx 0.5$ dB/dB and $b\approx 90$ dB SPL at a primary geometric mean frequency of 2.98 kHz. From limited data at other frequencies it was concluded that a was relatively constant across frequency, but b was at a local maximum at 2.98 kHz and may vary between 65 and 85 dB SPL between 1 and 8 kHz with $f_2/f_1=1.21$. Comparison of the asymmetry of the normative DP level to that of the trauma-induced reductions of the DP level showed that they were both qualitatively and quantitatively similar. Therefore, these authors suggested that primary tone level combinations "defined by this equation were optimum for use in clinical applications".

Previously, we reported the use of such an optimized stimulus level paradigm

$$L_1 = 0.4L_2 + 39 \text{ dB}$$

evaluating the DP input/output (I/O) functions in normal-hearing and hearing-impaired humans for clinical applications, i.e., with $a=0.4$ dB/dB, $b\approx 65$ dB SPL in Eq. 1 (Janssen et al., 1995, 1998; Kummer et al., 1998), this paradigm being based on normative human data available at this time (see above, Gaskill and Brown, 1990). It was found that DPs were measurable on average within 10 dB of the average hearing threshold in both normal-hearing and moderately hearing-impaired ears. I/O functions of the DP were compressively nonlinear in normal hearing and linearized with increasing hearing loss, i.e., DP reductions were most pronounced at lowest L_2. Recently, we have demonstrated that with $L_1=0.4\ L_2+39$ dB, DP I/O functions make it possible to extrapolate to a DP threshold, which may be understood as a correlate of the mechanical hearing threshold (Boege et al., 1998). The search for optimal L_1-L_2 thus is not a trivial aim but may rather be one key to fully exploit the potential of DP I/O functions in clinical diagnostics.

This study thus was performed to extend the generality of the Gaskill and Brown (1990) and Whitehead et al. (1995b) findings to the typical human test frequency range, to provide normative data for an optimal L_1-L_2 separation. For this purpose DPs were measured in 22 normal human ears. Based on these data, one stimulus paradigm appears adequate over the typical test range in clinical applications. Furthermore, previous notions (Gaskill and Brown, 1990; Whitehead et al., 1995a) that the systematic increase of the optimal L_1-L_2 separation with decreasing L_2 may be explained on the basis of BM characteristics are further elaborated presenting a graphical analysis of BM data (after Ruggero and Rich, 1991). It is demonstrated that optimal L_1-L_2 combinations can be related to frequency-selective compression of the BM at the DP generation site at f_2.

2. DP measurements

2.1. Methods and subjects

The experimental set-up for the DP measurements was the same as that described in a previous study (Kummer et al., 1998), using Cub^{e}dis™/Etymotic (ER-10C) instrumentation (Mimosa Acoustics, NJ). The DPs were measured at 61 L_1-L_2 combinations at seven f_2 frequencies ($f_2=977$, 1465, 1953, 2979, 3955, 5957, and 7959 Hz) with a constant $f_2/f_1=1.2$ and a total sampling time of 4.096 s. At L_2 levels of 5, 10, 15, 20, 25, 35, 45, 55, 65 dB SPL, the respective L_1 levels were varied in 5-dB steps between minimally 30 and maximally 70 dB SPL, such that the optimal L_1 level could be defined (see Fig. 2 for the L_1 range at different L_2 values). By definition, optimal L_1 levels were those resulting in local maxima of the DP level at a given L_2. This definition required at least three adjacent measurement values with a signal-to-noise (S/N) ratio greater than 6 dB. The system distortion measured in an ear simulator was below the noise floor for the primary tone levels used.

A group of 22 normally hearing subjects was examined in this study. They consisted of 12 females and 10 males aged between 19 and 35 years (mean = 24.3 years). All subjects had a negative history of hearing disorders and hearing thresholds of less than 15 dB HL at octave frequencies from 0.125 to 8 kHz and from 0.75 to 6 kHz. Data were collected only from one ear per subject. The experiments were performed in accordance with the guidelines of the Declaration of Helsinki.

2.2. Results

Typical DP data collected from one individual are shown in a three-dimensional format in Fig. 1 for one frequency $f_2 = 3955$ Hz. The DP level is plotted against the primary tone levels L_1 and L_2. The shaded area indicates that the DP level was at least 6 dB above the noise floor. I/O functions obtained by varying L_1 in 5-dB steps can be read following the lines to the left, i.e., parallel to the L_1 axis, at $L_2 = 5$, 10, 15, 20, 25, 35, 45, 55, and 65 dB SPL. As the level of L_1 is increased relative to a stationary L_2 level, the DP level increases up to a local maximum and decreases again. Only at $L_2 = 65$ dB SPL did the DP level continuously increase and no local maximum was reached up to the highest L_1 at 70 dB SPL.

Contours of the data are projected into the stimulus level plane which allow easier identification of the $L_1 - L_2$ combinations where local maxima of the DP level occurred. The circles indicate the L_1 levels where a local maximum of the DP level is reached at a given L_2. This optimal L_1 level will be referred to as $L_{1\mathrm{opt}}$. The dashed diagonal line indicates $L_1 = L_2$. It can be seen that $L_{1\mathrm{opt}}$ systematically depends on L_2. Basically, $L_{1\mathrm{opt}}$ is greater than L_2 at all L_2 levels. Whereas this difference is small at high L_2 levels, it continuously increases with decreasing L_2. Thus, the optimal primary tone level separation $L_{1\mathrm{opt}} - L_2$ continuously increases with decreasing L_2. Furthermore, the data indicate the crucial role of $L_{1\mathrm{opt}}$ on the measurability of the DP at a given L_2, especially at low levels; e.g., at $L_2 = 5$ dB SPL, the DP rose out of the noise only in a 15-dB L_1 range; with both lower and higher L_1 levels, no DP was measured above the noise floor.

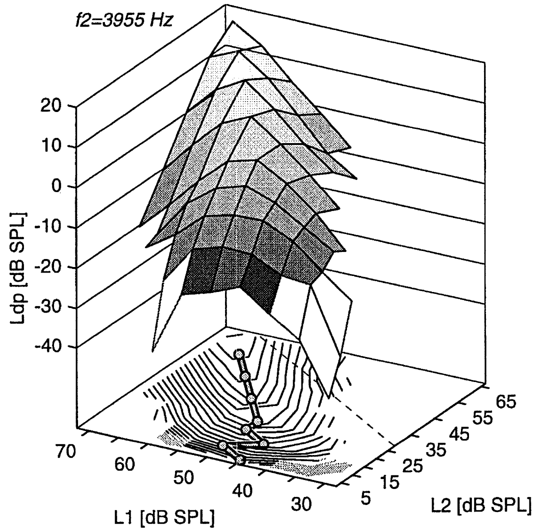

Fig. 1. Typical DP data from one normal-hearing subject at $f_2 = 3955$ Hz, plotting L_{DP} against L_1 and L_2. The shaded area indicates S/N greater than 6 dB. Contours of the data are projected into the L_1,L_2 stimulus level plane. The circles and line indicate optimal L_1 levels, where a local maximum of the DP level was reached at a given L_2. This line continuously deviates with decreasing L_2 from the diagonal dashed line that indicates $L_1 = L_2$.

Contour plots at all f_2 frequencies between 1 and 8 kHz from the same subject as in Fig. 1 and from averaged DP levels ($n = 22$ subjects) are depicted in Fig. 2a,b, respectively. Contours were linearly interpolated from the data in 2-dB steps. The black lines indicate that the DP was at least 6 dB above the noise floor (left column: 2 dB), the gray lines show data with lower S/N ratios. The bold line indicates where $L_{\mathrm{dp}} = 0$ dB SPL, the dashed line is $L_1 = L_2$. The circles and lines point out the optimal L_1 values $L_{1\mathrm{opt}}$ in the individual case (Fig. 2a) and in the mean data (Fig. 2b). In the latter, the error bar show ranges of the mean ± one S.D. of $L_{1\mathrm{opt}}$ from all subjects, for $n > 5$. Table 1 provides the exact numbers.

It can be seen that the pattern described in Fig. 1 is common to all frequency regions, both in the individual case and in the mean data (except a few cases as in Fig. 2a at $f_2 = 1953$ Hz, which will be discussed below). $L_{1\mathrm{opt}}$ is greater than L_2 at all L_2 levels. This optimal $L_1 - L_2$ level separation, which can be read from the vertical distance to the dashed line that indicates $L_1 = L_2$, is small at high L_2 levels but continuously increases with decreasing L_2. At $L_2 = 55$ dB SPL, $L_{1\mathrm{opt}}$ is mostly 65 dB SPL. With decreasing L_2, $L_{1\mathrm{opt}}$ decreases by about 5 dB per 10-dB decrease of L_2. At lower levels, mostly below $L_2 = 25$ dB SPL, $L_{1\mathrm{opt}}$ remains constant at about 50 dB SPL, further increasing the optimal $L_1 - L_2$ primary tone level difference.

The lowest L_2 level where $L_{1\mathrm{opt}}$ could be measured was between 25 and 5 dB SPL, depending on f_2. Both the increasing noise floor at low frequencies and the decreasing DP level at 8 kHz increased the DP detection threshold; at $f_2 = 3955$ Hz, DP were regularly measured down to $L_2 = 5$ dB SPL. At high L_2 levels of about 65 dB SPL, the DP level often monotonically increased with increasing L_1 up to the highest $L_1 = 70$ dB SPL, preventing $L_{1\mathrm{opt}}$ definition, especially at $f_2 = 3$, 4, and 8 kHz (see n in Table 1). The mean $L_{1\mathrm{opt}}$ values (and S.D.s) given in Fig. 2 and Table 1 thus are biased at the highest L_2 levels and the actual values may be higher.

Across frequency, there appear to be no great differences of $L_{1\mathrm{opt}}$. The mean $L_{1\mathrm{opt}}$ values vary by less than

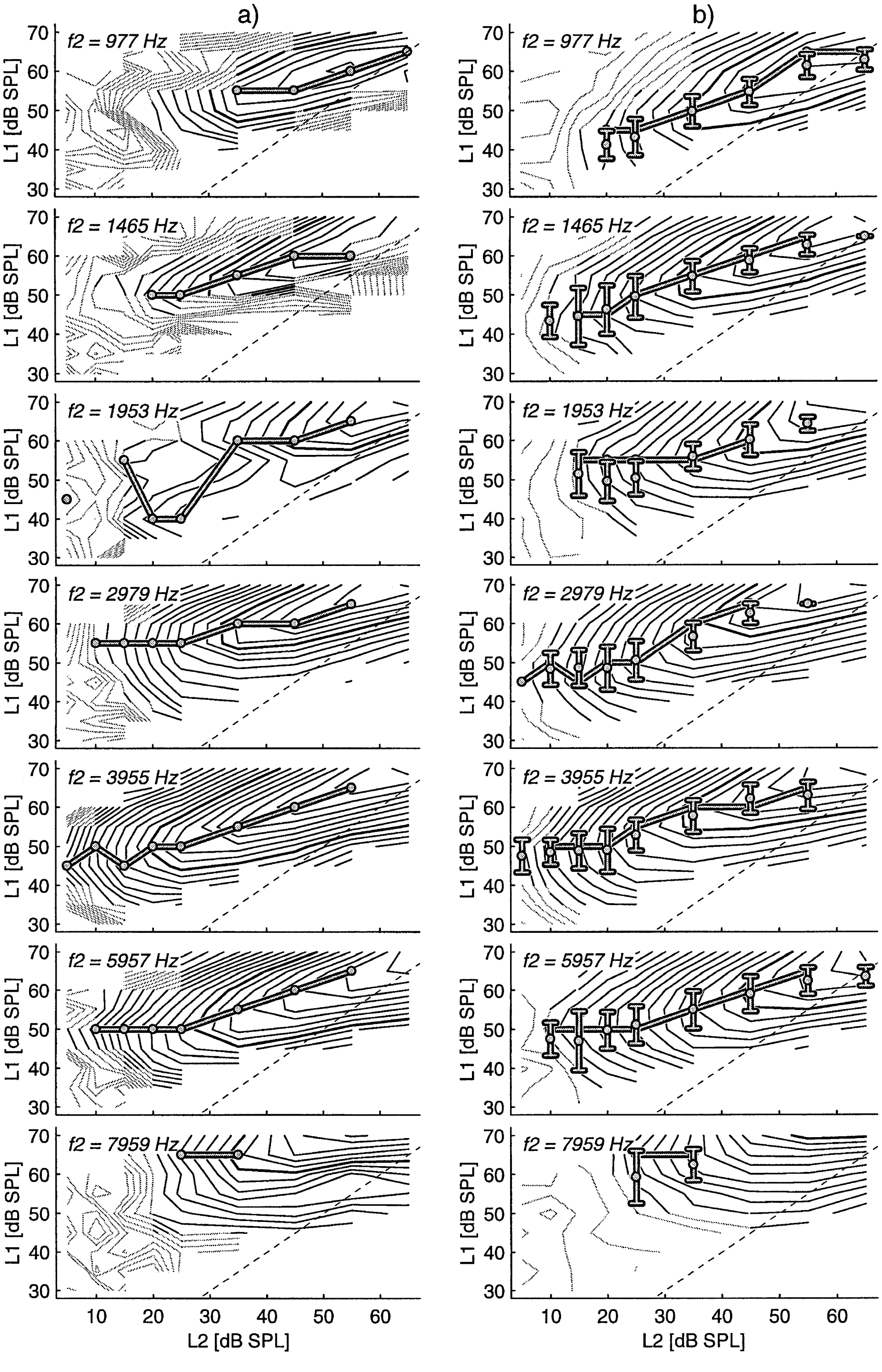

Fig. 2. Contour plots at all f_2 frequencies between $f_2 = 977$ and 7959 Hz from (a) the same subject as in Fig. 1 and (b) the mean DP level, averaged across all subjects ($n = 22$). Contours are linearly interpolated from the data in 2-dB steps. Black lines indicate S/N ratios greater than 6 dB (b: 2 dB), the gray lines lower S/N. Bold contour is 0 dB SPL, the dashed line $L_1 = L_2$. Circles and lines indicate the optimal L_1 values $L_{1\mathrm{opt}}$, where a local maximum was reached at a given L_2. In b, the error bars indicate ranges of the mean ± one S.D. of the individual $L_{1\mathrm{opt}}$ values from all subjects, for $n > 5$ (see also Table 1).

5 dB, i.e., in the order of their standard deviations. Only at 1 and 8 kHz were the $L_{1\mathrm{opt}}$ values somewhat lower and higher, respectively.

Data were therefore averaged across frequency (Fig. 3 and Table 2). Below $L_2 = 55$ dB SPL, $L_{1\mathrm{opt}}$ continuously decreases from 63 dB SPL by about 4 dB per 10-dB decrease of L_2 down to $L_2 = 20$ dB SPL, but by only 2 dB/dB below (Fig. 3a); at those low L_2 levels, $L_{1\mathrm{opt}}$

Table 1
The $L_{1\text{opt}}$ levels that produced maximum DP levels, in dB SPL, for each fixed L_2 in the different frequency regions examined

L_2	f_2 (Hz)						
	977	1465	1953	2979	3955	5957	7959
5		45.0 ± 5.0 (3)	45.0 ± 0.0 (1)	40.0 ± 0.0 (1)	47.5 ± 4.2 (6)	55.0 ± 0.0 (1)	
10	30.0 ± 0.0 (1)	43.3 ± 4.1 (6)	52.5 ± 2.9 (4)	48.3 ± 4.1 (6)	48.5 ± 3.2 (13)	47.5 ± 4.2 (6)	
15	36.7 ± 2.9 (3)	44.5 ± 7.2 (10)	51.4 ± 5.6 (7)	48.6 ± 4.6 (14)	48.8 ± 4.5 (17)	47.0 ± 7.5 (10)	
20	41.3 ± 3.5 (8)	46.3 ± 6.2 (16)	49.5 ± 5.0 (10)	48.5 ± 5.5 (17)	49.0 ± 5.5 (20)	49.7 ± 4.6 (16)	58.0 ± 5.7 (5)
25	43.2 ± 4.6 (11)	49.5 ± 5.4 (20)	50.4 ± 4.3 (13)	50.5 ± 5.0 (19)	52.8 ± 3.9 (22)	51.1 ± 4.7 (18)	59.3 ± 6.7 (7)
35	49.8 ± 3.8 (20)	54.8 ± 3.9 (22)	55.9 ± 3.2 (17)	56.6 ± 3.6 (22)	57.7 ± 4.0 (22)	55.0 ± 4.8 (22)	62.5 ± 4 (12)
45	54.8 ± 3.3 (21)	58.9 ± 3.1 (22)	60.2 ± 3.9 (22)	62.6 ± 2.6 (22)	62.2 ± 3.6 (22)	59.1 ± 4.5 (22)	65.0 ± 0.0 (4)
55	61.5 ± 2.9 (17)	62.9 ± 2.5 (20)	64.3 ± 1.8 (15)	65.0 ± 0.0 (9)	63.0 ± 3.5 (10)	62.5 ± 3.4 (22)	
65	63.0 ± 2.6 (10)	65.0 ± 0.0 (7)	65.0 ± 0.0 (4)		63.3 ± 2.9 (3)	63.6 ± 2.4 (7)	65.0 ± 0.0 (1)

Mean ± S.D. were determined in the number of subjects out of 22 indicated in parentheses where local maxima in the DP level were measured 6 dB above the noise floor.

remains almost constant at about 47 dB SPL. At $L_2 = 65$ dB SPL, the actual $L_{1\text{opt}}$ is probably higher than the value given since the DP level increased monotonically with L_1 in most of the cases and $L_{1\text{opt}}$ was defined in only 20% of the cases (Table 2); the value given is actually close to the maximum $L_{1\text{opt}}$ of 65 dB SPL that could be defined from a true local maximum of the DP level. The optimal primary tone level separation $L_{1\text{opt}} - L_2$ thus increases moderately from 8 to 28 dB between $L_2 = 55$ and 20 dB SPL, but rapidly from 28 to 42 dB between $L_2 = 20$ and 5 dB SPL (Fig. 3b). The ratio by which $L_{1\text{opt}}$ changes with L_2 was defined as $dL_{1\text{opt}}$, differentiating the $L_{1\text{opt}}$ functions (Fig. 3c). Whereas the average $dL_{1\text{opt}}$ is almost constant 0.45 ± 0.44 dB/dB above $L_2 = 20$ dB SPL, it was virtually zero below $L_2 = 20$ dB SPL (0.08 ± 0.74 dB/dB).

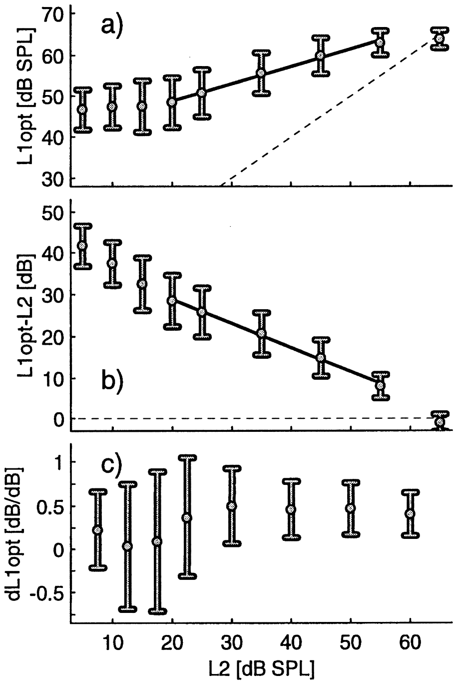

Fig. 3. The optimal L_1 levels $L_{1\text{opt}}$ (a), the optimal stimulus level separations $L_{1\text{opt}} - L_2$ (b), and the slopes of the $L_{1\text{opt}}$ functions $dL_{1\text{opt}}$ (c), averaged from all 22 subjects across frequency ($f_2 = 977$–7959 Hz). The exact numbers are given in Table 2.

A regression line was fitted to the linear, unbiased range of the $L_{1\text{opt}}$ data between $L_2 = 20$ and 55 dB SPL (solid line in Fig. 3b). The parameters of an equation $L_{1\text{opt}} = a\,L_2 + (1-a)\,b$ were $a = 0.41$ and $b = 69.5$ dB SPL. From this equation, the optimal L_1 would equal L_2 at about 70 dB SPL. Given that $dL_{1\text{opt}}$ was virtually constant in this range, this extrapolation seems valid and compensates for the experimental shortcoming of limited data at $L_1 \leq 70$ dB SPL and $L_2 \leq 65$ dB SPL.

Behavior that deviated from the common behavior described above was found in 16/154 data sets, an example of which is displayed in Fig. 2a, at $f_2 = 1953$ Hz. Instead of the common growth pattern with an initial increase to a maximum and an eventual decline, a non-monotonic growth pattern with two maxima, separated by a more or less sharp notch, occurred when L_1 was increased at a given L_2. These notches occurred mostly at L_1 levels of 50 and 55 dB SPL, separating two 'ridges' by a valley (Fig. 2a). As in this example, $L_{1\text{opt}}$ then often skipped between both ridges, here between $L_2 = 35$ and 25 dB SPL (and back again below). How-

Table 2
The $L_{1\text{opt}}$ levels (mean ± S.D.) that produced maximum DP levels, in dB SPL, for each fixed L_2, averaged across all f_2 frequencies examined

L_2	$L_{1\text{opt}}$	n
5	46.7 ± 4.9	12
10	47.4 ± 5.1	36
15	47.5 ± 6.3	61
20	48.4 ± 6.1	92
25	50.7 ± 5.8	110
35	55.7 ± 5.0	137
45	59.9 ± 4.4	135
55	63.0 ± 2.9	93
65	63.9 ± 2.1	32

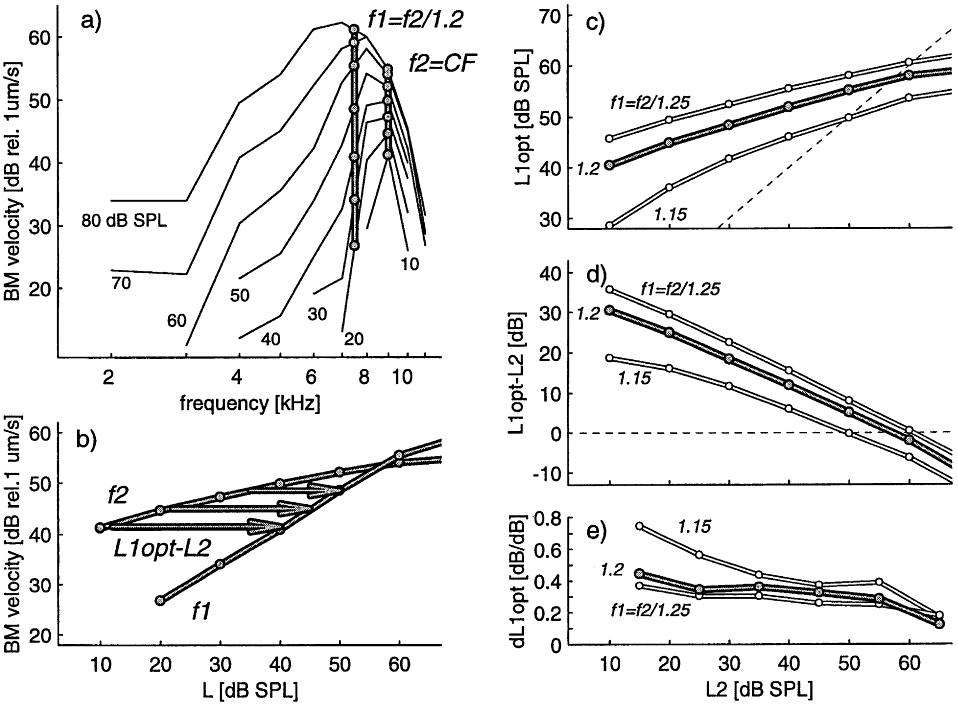

Fig. 4. (a) Analysis of BM velocity data (after Ruggero and Rich, 1991) at a place at the basal end of the chinchilla cochlea (CF = 9 kHz). Assuming consideration of responses at the f_2 place, responses to f_2 and f_1 are set off ($f_2/f_1 = 1.2$). (b) The f_1 and f_2 responses are replotted as I/O functions. The arrows point to the primary tone level differences $L_{1\text{opt}}-L_2$ necessary to achieve equal primary tone responses at the f_2 place. (c,d) $L_{1\text{opt}}$ and $L_{1\text{opt}}-L_2$ are plotted against L_2. For comparison, data are added for $f_2/f_1 = 1.15$ and 1.25. The dashed lines indicate $L_1 = L_2$. (e) Plot of the rate $\mathrm{d}L_{1\text{opt}}$ by which $L_{1\text{opt}}$ changes against L_2, which is the ratio of the primary tone compression rates at the f_2 place.

ever, such behavior was found in only about 10% of the cases, mostly at frequencies below $f_2 = 2$ kHz. In the averaged data (Fig. 2b), these notches made no difference.

3. Analysis of BM data

In this section BM velocity data from Ruggero and Rich (1991) are analyzed addressing the question of optimal stimulus level combinations, following previous notions introduced by Gaskill and Brown (1990) and elaborated by Whitehead et al. (1995a) that optimal stimulus level combinations for DP measurements may be explained in detail on the basis of known characteristics of BM vibration. This analysis is intended to graphically visualize this hypothesizing, to support a more intuitive understanding.

The BM data have been collected in the chinchilla cochlea at a place near the basal end with a characteristic frequency (CF) of 9 kHz and are plotted as a function of frequency at different levels in Fig. 4a. The data shall be considered to represent responses at the f_2 place. It is assumed that this is the place in the region of maximum overlap and nonlinear interaction of both primary tones, where the DP mainly originates. Both primary tone responses are set off for comparison, the CF response (f_2) and the response to f_1, which is about 0.26 octaves lower for $f_2/f_1 = 1.2$. The response growth is most compressive for the CF tone f_2 but distinctly less compressive for lower frequencies as f_1. Analysis of the data is based on the assumption that stimulus conditions may be optimized when both primary tone responses are equal at the f_2 place such that the response modulation is maximal. At least up to medium levels, the f_2 tone produces greatest responses at its characteristic place. No nonlinear interaction of both primary tones is considered.

The I/O functions reconstructed from the BM response data of Fig. 4a at f_1 and f_2 show great differences of both stimulus responses (Fig. 4b). The f_2 response is most compressive and produces distinctly greater responses than f_1 at levels below about 60 dB SPL. Assuming that stimulus conditions are optimal when both primary tone responses are equal at the f_2 place, the optimal levels $L_{1\text{opt}}$ would be those that achieve the respective f_2 responses. For three L_2 levels between 10 and 35 dB SPL, the arrows show that these $L_{1\text{opt}}$ are distinctly greater than L_2. In Fig. 4c, $L_{1\text{opt}}$ is plotted against L_2. With decreasing L_2 from 60 to 10 dB SPL, $L_{1\text{opt}}$ decreases only between about 57 and 40 dB SPL. The optimal stimulus level difference $L_{1\text{opt}}-L_2$ thus increases from about zero to 30 dB in this L_2 range (Fig. 4d). At high levels $L_{1\text{opt}}-L_2$ is negative, since the maximum response shifts from f_2 towards lower frequencies and the f_1 response becomes greater than that of f_2. For comparison to the filled lines, derived from the data for $f_2/f_1 = 1.2$, the open lines indicate the respective L_{1opt} and $L_{1opt}-L_2$ for a f_2/f_1 ratio of 1.25 and 1.15 (Fig. 4c,d). The L_{1opt} and the respective $L_{1opt}-L_2$ systematically increase with increasing f_2/f_1 in this range (Fig. 4c,d), reflecting that the f_1 response decreases at all levels in this range and becomes less compressive (Fig. 4a).

Assuming that L_{1opt} indicates that the f_1 and f_2 responses are equal at the f_2 place, the relative change dL_{1opt} in a given L_2 range is related to the ratio by which both responses are changing. Thus, one may derive the ratio of the primary tone compression rates at the f_2 place from the rate by which L_{1opt} changes (Whitehead et al., 1995a). For $dL_{1opt} = 0.5\ dL_2$, the f_1 response would change twice as much as the f_2 response, for $dL_{1opt} = dL_2$, both responses change at the same rate. In the BM data analyzed (Fig. 4e), dL_{1opt} is on average about 0.3 dB/dB for $f_2/f_1 = 1.2$. It decreases with increasing L_2, reflecting the decreasing growth of f_2 compared to the relatively constant f_1 growth. For the three different f_2/f_1 ratios examined, i.e., 1.25, 1.2, and 1.15, dL_{1opt} systematically increases from an average of 0.28, 0.31, to 0.45 dB/dB, respectively. In other words, the growth rates adapt when f_1 and f_2 responses approach each other.

4. Discussion

4.1. The frequency selectivity of the BM compression accounts for optimal primary tone level separations $L_{1opt}-L_2$

For yielding maximum DP levels with decreasing primary tone levels, an increasing primary tone level separation L_1-L_2 is necessary. Based on data from 22 human ears it was found that the optimal primary tone level separation $L_{1opt}-L_2$ increased linearly with decreasing L_2 from 65 to 20 dB SPL, without great differences at f_2 frequencies between 1 and 8 kHz. In the averaged DP data, the parameters a and b of Eq. 1 (after Whitehead et al., 1995b) were $a = 0.4$ and $b = 70$ dB SPL.

This extends and confirms the findings of previous studies in humans, gerbils, guinea pigs, and rabbits (Gaskill and Brown, 1990; Brown and Gaskill, 1990; Dhar et al., 1998; Mills et al., 1993; Mills and Rubel, 1994; Whitehead et al., 1992a, 1995b). Some studies examined optimal level separations L_1-L_2 only at high primary tone levels (Hauser and Probst, 1991; Rasmussen et al., 1993). Only two studies have provided systematic data of human subjects over a wide primary tone level range. From the Gaskill and Brown (1990) data that were averaged from up to nine data sets from different subjects and frequencies at L_2 levels between 25 and 60 dB SPL one may yield $a \approx 0.5$ dB/dB and $b = 65$–70 dB SPL ($f_2/f_1 = 1.225$). From eight subjects, Whitehead et al. (1995b) reported that for primaries at a geometric mean frequency of 2.98 kHz ($f_2/f_1 = 1.25$), the parameters of Eq. 1 were $a \approx 0.5$ dB/dB and $b \approx 90$ dB SPL. From limited data at other frequencies and f_2/f_1 ratios these authors concluded that a was relatively constant across frequency, but b is at a local maximum at 2.98 kHz and may vary between 65 and 85 dB SPL between 1 and 8 kHz with $f_2/f_1 = 1.21$ (Whitehead et al., 1995a).

Furthermore, previous interpretations of the systematic dependence of L_{1opt} on L_2 in terms of BM response patterns (Gaskill and Brown, 1990; Whitehead et al., 1995a) are extended, providing a quantitative analysis of recent chinchilla BM data (after Ruggero and Rich, 1991). This analysis is based on the assumption that equal primary responses at the f_2 place are optimal for DP generation. It was found that there is a good qualitative and even quantitative correspondence between the optimal primary tone level separations found in our human DP data and those predicted from chinchilla BM data.

Analysis of the frequency-selective BM nonlinearity showed that the less compressive f_1 response compared to the most compressive f_2 response accounts for the fact that the optimal level separation increases with decreasing L_2. For $f_2/f_1 = 1.2$, L_{1opt} almost linearly decreased by about $a = 0.3$ dB/dB with lowering L_2. Due to the basal shift of the BM peak response with increasing level, L_{1opt} equals L_2 at $b = 57$ dB SPL. This close correspondence appears to confirm the model assumption that optimal conditions for the DP generation are equal primary tone responses at the f_2 place and to emphasize the major importance of the f_2 place for the DP generation.

The fact that two-tone suppression between the primary tones was ignored in these considerations apparently did not confound the BM analysis. Although two-tone suppression may be assumed to cause the decrease of the DP level with L_1 increasing beyond L_{1opt}, it may not or not substantially affect the determination of the level where both primary tones have equal responses. In 1990, Kemp et al. reported on simultaneous stimulus frequency emission (SFE) and DP generation and suppression. They found that in certain respects, the ear appeared to behave like a simple saturating nonlinearity, where maximum distortion is generated as a function of L_1-L_2 when both primaries have similar levels. When the stronger primary suppressed the weaker, the generated distortion also decreased. In the human ear, the maximum of $2f_1-f_2$ DPs as a function of L_1-L_2

was found to be close to the level where equal mutual suppression of the primary tone SFEs occurred. With further increasing L_1-L_2, the DP level decreased together with the SFE of the lower level primary tone.

Part of the quantitative differences between the $L_{1\mathrm{opt}}$ predicted from chinchilla BM data and the $L_{1\mathrm{opt}}$ measured in human ears may be due to differences in cochlear tuning. From the analysis of the BM data, it may be easily understood that, e.g., factor a in Eq. 1 depends on cochlear mechanical tuning. The analysis showed that a reflects the ratio of the primary tone compression rates. At a given cochlear place, this ratio depends on the primary tone frequency ratio. As the f_2/f_1 ratio decreases and the primary tone responses approach each other at a given place, the ratio of the compression rates approaches unity. Experimental data confirm this prediction in rabbits and gerbils (Whitehead et al., 1992a; Mills and Rubel, 1994). On the other hand, frequency- or species-dependent variations of factor a in the DP data point to frequency- or species-dependent differences in cochlear tuning. In our data, the $L_{1\mathrm{opt}}$ values appeared almost constant between $f_2=1.5$ and 6 kHz, but were smallest at 1 kHz and greatest at 8 kHz, for $f_2/f_1=\mathrm{constant}$; both are consistent with increased cochlear tuning sharpness with increasing frequency between 1 and 8 kHz. Species-specific differences may be accounted for with the same reasoning.

However, limits of the agreement between BM-based predictions and measured $L_{1\mathrm{opt}}$ appear to reflect also the limits of the model assumptions. In particular, at high levels, the DP generation site may no longer be at the f_2 place, but rather follow the basal movement of the f_2 peak excitation with increasing level. Assuming that primary tone responses should be equal at this site of peak excitation, parameter b in Eq. 1 would increase considerably, reducing the gap between model prediction of 57 dB SPL and the measured 70 dB SPL; also, no negative L_1-L_2 would be predicted. On the other hand, when response patterns maintain some tuning, $L_{1\mathrm{opt}}=L_2$ would never be reached, since any other response will be lower compared to the peak response. Also, at very low levels of L_2, the behavior of the measured $L_{1\mathrm{opt}}$ could hardly be predicted by the BM data. In fact, $L_{1\mathrm{opt}}$ was almost constant at about 47 dB SPL below $L_2=20$ dB SPL. Similar behavior has not been reported before in humans, but was also found in rabbits and gerbils (Whitehead et al., 1995b; Mills and Rubel, 1994).

Nonmonotonic DP growth in normal hearing was frequently (10%) found with $L_1=L_2$ in this study as in the literature (Popelka et al., 1993; He and Schmiedt, 1993), but is comparatively rarely observed (3%) with optimized L_1 levels (Kummer et al., 1998). He and Schmiedt (1993, 1997) found that nonmonotonic and highly variable DP growth at closely neighboring frequencies may be due to systematic frequency shifts of the DP fine structure. These frequency shifts were explained as being due to systematically changing cochlear generation sites of the DP with changing the primary tone levels under the $L_1=L_2$ condition. The analysis of the BM data in this study supports this idea. With optimized L_1, it appears that the DP generation site can be held constant at the f_2 place in the cochlea. It may be expected that the DP growth is therefore more reliably predictable and may be used as a useful parameter for the assessment of cochlear function. The rarely found nonmonotonic DP growth may point to the limits of a fixed primary tone level setting that need not match individual optimal L_1-L_2 conditions. On the other hand, it may also be due to interactions between DP sources at the primary DP generation site at the f_2 place and at a place of reemission from the DP place (Kemp and Brown, 1983; Kummer et al., 1995; Heitmann et al., 1997).

4.2. Implications for clinical applications

Laboratory animal studies have shown that optimal L_1 not only maximizes the DP level for a given L_2 but also represents specific L_1-L_2 combinations where changes of the DP level following OHC trauma are maximal (Whitehead et al., 1995b; Mills and Rubel, 1994). Thus, optimizing the L_1 level is not a trivial DP level maximization but rather appropriate for maximizing the sensitivity of DP measurements. This may be understood by taking into account that the L_2 level may be considerably decreased with optimal L_1. Since the role of OHC is thought to be maximal at low levels, low L_2 level may increase the sensitivity of DP measurements to OHC damage. Indeed, Whitehead et al. (1995b) have shown that the decrease of the DP level caused by trauma continuously increases with decreasing L_2, the measurable decrease only being limited by the noise floor.

Also in humans, predominant DP losses occurred at lowest L_2 levels when DP I/O functions were measured between $L_2=20$ and 65 dB SPL in moderately hearing-impaired humans, according to $L_1=0.4L_2+39$ dB SPL ($a=0.4$, $b=65$ dB SPL in Eq. 1), i.e., with level combinations virtually identical to the optimal level combinations described in this study (Kummer et al., 1998; Janssen et al., 1998). It was found that the correlation of the DP level with the hearing threshold increases with decreasing L_2 and approaches a one-by-one correlation. The best correlations occurred at $L_2=35$ dB SPL. Only at the lowest L_2 levels used in these studies did this correlation decrease, obviously for the noise floor.

Further, it was shown (Kummer et al., 1998) that with such a paradigm DPs may be measurable above about 1.5 kHz on average within 10 dB of the pure tone threshold, both in normal and in moderately impaired hearing. Optimized L_1 levels, which are thought to equalize f_1 responses to those of the f_2 primary tone (see above), obviously make it possible to detect mechanical responses to f_2 at stimulus levels close to the hearing threshold. Although this paradigm is based on data from normal-hearing subjects, its application also appeared effective in impaired hearing. In fact, animal experimental data of Whitehead et al. (1995b) show that even in cochlear trauma an asymmetry in L_1,L_2 space persists similar to that in normal hearing. This may, at least in part, be expected from the above analysis of cochlear mechanical responses, since parameter b of Eq. 1 is related to high-level cochlear response characteristics, which are thought to be passive and less susceptible to trauma, and parameter a reflects the ratio of both primary tone compression rates, which need not change with trauma in contrast to their absolute values.

For a clinical application of DPs and especially their I/O functions it is therefore recommended that L_1-L_2 not be used as a constant as it has been – to our knowledge – exclusively applied so far in clinical studies. It is recommended rather to use optimized L_1-L_2 over the whole L_2 range examined, as has previously been reported from our laboratory (Janssen et al., 1995) and suggested by Whitehead et al. (1995b). According to the present data, one single $L_{1\text{opt}}$ function, i.e., $L_1=0.4\ L_2+41$ dB SPL, appears adequate for clinical applications, at L_2 levels between 20 and 65 dB SPL and for f_2 frequencies between 1 and 8 kHz, with restrictions only at the boundaries of this frequency range. To account for individual variations it appears desirable that for any L_2, the individually optimal L_1 is searched.

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