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Effects of age on the distortion product otoacoustic emission growth functions

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Abstract

Age-related hearing loss (presbycusis) is thought to result from age-related degeneration (aging) of the cochlea plus the cumulative effects of extrinsic damage (noise and other ototoxic agents) and intrinsic disorders (e.g. systemic diseases). Previous studies have implicated dysfunction of the hair cells (sensory presbycusis) as the principal mechanism of age-related hearing loss. However, recent evidence from quiet-reared gerbils suggests that cochlear aging results primarily from atrophy of the stria vascularis, which is associated with diminished endocochlear potential (EP), spiral ganglion atrophy, and a relatively flat audiometric loss, termed metabolic presbycusis. Because it is not currently possible to measure EP directly in the clinical setting, we wondered if cochlear metabolic dysfunction might be evidenced indirectly from existing clinical tests, specifically, the input–output (IO) growth function of the distortion product (DP) otoacoustic emissions in relation to behavioral hearing threshold levels (HTL). We anticipated finding discordance between the IO functions and HTL with either a greater decline with age in HTL than in IO functions if an age-related metabolic dysfunction of the cochlea was operant, or a greater loss of IO function than HTL if outer hair cell dysfunction was the dominant pathology. To address this supposition we analyzed existing auditory data from a large cohort of adults to determine the change with age in three aspects of the DP IO function: area under the curve, threshold, and slope. The analyses demonstrated a greater effect of age on HTL than on the DP IO measures. This effect supports the hypothesis that strial dysfunction is a substantive factor in cochlear aging. The etiology and mechanisms for this dysfunction are conjectural at present.

Key words: Presbycusis; Strial atrophy; Distortion product otoacoustic emission; Aging

1. Introduction

It is well known that hearing worsens with age (Working Group on Speech Understanding and Aging, 1988). However, the mechanisms that mediate this process are not fully understood. Loss of outer hair cells (OHCs) is commonly observed in association with decreased auditory sensitivity and concomitant elevation of the hearing thresholds in the region of the missing hair cells. These are the classic findings in people with sensory presbycusis (Crowe et al., 1934; Hansen and Reski-Nielsen, 1965; Schuknecht, 1964; Dublin, 1976; Johnsson and Hawkins, 1972; Suga and Lindsay, 1976). However, many people with sensory presbycusis have had substantive lifetime noise exposure, which implicates noise trauma, rather than aging per se, as a major contributor to the OHC loss and associated high-frequency threshold elevations in these cases. Later, Schuknecht et al. (1974) described strial (metabolic) presbycusis in humans based on a relatively flat audiometric pattern with good word recognition ability and histologic evidence of atrophy of the stria vascularis. Strial atrophy, particularly of the middle and upper turns of

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Abbreviations: DP, distortion product; IO, input–output; PTT, pure-tone threshold; HTL, hearing threshold levels; EP, endocochlear potential; OHC, outer hair cells; ABR, auditory brainstem response; OAE, otoacoustic emissions; PTA, pure-tone average

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the human cochlea, was a very common finding in human temporal bone sections (Hawkins and Johnsson, 1985).

More recently, Mills et al. (1990) examined old gerbils raised in quiet and found minimal OHC loss compared to old gerbils raised in noise. Of interest, the range of hearing threshold elevations in the quiet-reared animals was much greater than that of the noise-exposed animals. Direct measures of endocochlear potential (EP) and morphometry of the stria vascularis (the source of the EP) in the quiet-reared gerbils showed age-related declines in EP and strial atrophy (Gratton et al., 1996). This led to the hypothesis that presbycusis due to strial atrophy (i.e. 'metabolic' presbycusis) is the pathophysiological mechanism underlying age-related threshold elevation without hair cell loss and a major factor in human presbycusis. Whether this hypothesis suggests that reduced EP in aging animals impairs the function of the 'cochlear amplifier' (Davis, 1983), or whether the reduced EP impairs inner hair cell function directly, or both, is unclear.

In adult gerbils, a sudden decrease in the EP caused by furosemide injection was shown to raise the auditory threshold (Mills et al., 1993; Rubsamen et al., 1995). There was a very close covariation between the decrease in otoacoustic emission amplitude and the increase in neural thresholds measured in the brainstem. However, the signature of changes caused by an EP decrease was that distortion product (DP) otoacoustic emissions were less affected than the neural threshold. For example, the emission threshold typically increased from 20 to 40 dB SPL as the neural threshold increased from 20 to 80 dB SPL, a 1:3 ratio (Mills et al., 1993). These data suggest that, in the absence of any other factors, a decrease in EP should cause the emissions to decrease much less than pure-tone thresholds (PTTs). In this respect, the effects of acute furosemide administration mirror the results of the quiet-aged gerbil study, in which the DP were indeed found to be less affected than the auditory brainstem response (ABR) thresholds (Mills et al., 1990). One can understand this relationship by noting that a decreased EP causes the input to the inner hair cell to be affected two ways, whereas the OHC is only affected in one. That is, a low EP causes the cochlear amplifier gain to decrease because of lowered drive to the OHC, which causes a lower peak amplitude in the physical input to the inner hair cell at low sound levels. In addition, the voltage across the inner hair cell transduction channel is also decreased.

The greater decline in neural response thresholds compared to DP thresholds contrasts sharply with the typical covariation of emission thresholds and PTTs in a given population. In a young normal population that has been exposed to a variety of noise and ototoxic insults, subjects can have near normal PTTs but elevated emission thresholds. While the two are only modestly correlated in most populations, the emission threshold consistently rises much faster than the PTT (Dancer et al., 1992; Hamernik et al., 1996; Mills, 2001). This signature can be understood by what one would expect if the main variation in the population at a given age is due to direct damage to the OHC functionality, including loss of OHCs. In this case, the cochlear amplifier gain is decreased but this decrease is not caused by a decrease in EP. Rather, because emission amplitude is strongly dependent on the maximum amplitude reached in the basilar membrane motion, in such a case the emission would be expected to drop more sharply than the PTT. In other words, the emission amplitude is a non-linear function of the basilar membrane peak amplitude.

It is not possible to distinguish directly if human presbycusis is due to decreased EP because current clinical technology does not permit direct measures of EP. Because both OHC loss and reduced EP result in elevated hearing threshold levels (HTL), it seemed possible that an indirect measure such as the relative change in hearing sensitivity vs. otoacoustic emissions (OAEs) might permit inferences to be made about the relative contributions of hair cell dysfunction versus reduced EP in human auditory aging.

OAEs measured at low stimulus levels result from active processes that comprise the cochlear amplifier (Kemp, 1978) and robust OAEs are associated with normal auditory thresholds. DPOAE amplitudes at low stimulus levels have been found to indicate normal cochlear function in a wide variety of studies (Brown et al., 1989; Johnstone et al., 1990; Kim, 1980; Martin et al., 1987; Norton et al., 1991; Probst et al., 1991; Rubsamen et al., 1995).

Decreased DP amplitudes at low stimulus levels have been associated with aging independent of hearing loss (Cilento et al., 2001; Gorga et al., 1997). Therefore, we wondered whether other aspects of the DP response might provide additional insight into the effects of aging on cochlear function. The DP input–output (IO) function provides considerable information above and beyond the threshold level (see Fig. 1). Accordingly, we examined the DP IO function using both the slope and the area of the IO function as well as its threshold. We reasoned that the area function, i.e. the sum of all the DP amplitudes above the noise floor, would provide a better estimate of the robustness of the DP IO function than either slope or threshold alone.

There are three theoretical patterns expected for DP responses and HTL abnormality derived from research on animal models. First, with inner hair cell or ganglion losses, the HTL would worsen but the DP would remain normal. Such a finding is typical of people with auditory neuropathy. In the second pattern, with reduced EP the DP and HTL would both worsen but the HTL decline should exceed that of the DP. In the third pattern, with hair cell loss or dysfunction, DP functions should worsen at a faster rate than the HTL (Mills, 2001). To evaluate these issues, we analyzed the results of DPOAE testing in relation to age and audiometric thresholds in a large cohort of adults from the Framingham Offspring Study.

2. Methods

2.1. Subjects

The subjects were volunteer members of the Framingham Offspring Cohort. The Offspring Cohort are the children of the original Framingham Heart Study Cohort who have participated in periodic health assessments principally designed to study the inheritance of cardiovascular disease (Kannel et al., 1979). The present report stems from the first hearing assessment of the Offspring, which was performed during their sixth examination cycle as part of the study of the inheritance of presbycusis (Gates et al., 1999). Of the 3873 members of the Offspring Cohort, 2265 have had routine audiometry during the sixth exam cycle testing. Of these, 519 agreed to return to the study center for additional testing and the 508 who were found to be free of middle ear disease on tympanometry had OAE testing consisting of a DP-gram and, time permitting, a DP IO function. Four-hundred forty-one subjects had one or more DP IO function tests. Nine subjects were excluded because of non-age-related hearing loss (e.g. Meniere's disease, ototoxicity) leaving an total number of 432 for analysis.

2.2. Auditory tests

All subjects had standard pure-tone audiometric assessment with tympanometry and word recognition testing by a qualified audiologist in accordance with ANSI standards for methods and facilities. The audiometric hearing threshold levels in the test ear were summarized as the pure-tone average (PTA) of the three frequencies 0.5, 1.0, and 2.0 kHz.

The DPOAEs were evoked by the EMAV system using a f_2/f_1 ratio of 1.2 and an L_1-L_2 difference of 10 dB. For the DP-gram, the amplitude of the DP was measured at L_1:L_2 of 65:55 dB SPL across the various input frequencies. For the DP IO function, the DP amplitude was measured at fixed input frequencies across varying stimulus intensities. The DP-gram data have been reported previously (Cilento et al., 2001). DP IO data were obtained from the better ear of 431 people. One hundred two subjects have DP IO data for all four test frequencies (f_2 of 0.5, 2, 4, and 8 kHz). The DP IO testing was prioritized for f_2s of 2000, 4000, 8000, and 500 Hz respectively when time or subject compliance was constrained. Only the better hearing ear (i.e. lower PTA) was used for the DP IO testing.

2.3. Analysis variables

The audiometric HTL at the f_2 frequency was used in each comparison of the DP IO with behavioral thresholds.

For each subject, the growth of DP amplitude above the noise floor was plotted in relation to the stimulus level. From this plot, three variables were determined: *area, threshold,* and *slope*.

The 'area' under the DP IO function was calculated as the difference between the amplitude of the noise floor and the DP amplitude at all of the 5 dB stimulus level steps through 60 dB SPL. Only those DP responses above the noise floor were used in the calculation. The cumulative amplitude of the DP responses above the noise floor were multiplied by 5 and reported in dB SPL^2 ($area^2$). To relate $area^2$ to the linear measure of the PTT, the square root of $area^2$ (i.e. *area*) was used in the analyses. We reasoned that large values for *area* would indicate robust DPs and that small values for *area* would indicate diminished DPs. The *area* variable, then, is assumed to provide a measure of the overall strength of the cochlear amplifier. Because DP responses at stimulus levels higher than 60 dB SPL may be due to artifacts of the measurement system, we limited the *area* calculation to stimulus levels at or below this level.

The *threshold* of the DP IO function was designated as the lowest L_2 level associated with a DP amplitude of −5 dB SPL or greater. We reasoned that low *threshold* values would also reflect robust DP and that high *threshold* values would be associated with diminished DP. If the −5 dB SPL threshold was not reached at an L_2 of 60 dB SPL, the threshold was deemed to be absent. The threshold was interpolated if the −5 dB criterion fell between two adjacent L_2 levels.

The *slope* of the raw DP IO function was calculated using ordinary least squares regression methods. The *slope* measure was limited to L_2 stimulus levels of less than 60 dB SPL to eliminate the upper end of the DP IO function, which was often non-monotonic. We reasoned that the *slope* would also indicate robust DP IO responses with the anticipation that large responses would show a steep slope and that diminished responses would show a diminished or flat slope.

2.4. Analysis techniques

Correlations and linear regressions were used to evaluate the associations among the DP IO variables and the corresponding behavioral thresholds (HTL). These analyses were performed separately by gender, because of the known differences in hearing between men and women, and by f_2 frequency. Significance is set at the $P < 0.05$ level.

Analysis of the rate of change of the regression slopes of the DP IO and HTL variables with age was done by comparing their correlation coefficients (Meng et al., 1992). Since the correlation coefficients are equal to the slope of the standardized regression lines, testing the equality of the correlation coefficients is the same as testing the standardized regression slopes (Falk and Well, 1997). Briefly, this method uses the Z-test to evaluate the correlations among each of the three pairs of variables. This analysis uses Fisher' z transformation, which converts the correlation coefficients (Pearson's r) to a normal distribution (the command 'corcor' in Stata v7.0 implements this comparison) (StataCorp, 2001). The command tests the equality of two correlations having one common variable from a dependent sample. Two separate comparisons were made, one using the DP area vs. HTL and the other using DP threshold and HTL (Fig. 2).

Formula for the Z-test:

$$Z = (z_{12} - z_{13}) \sqrt{\frac{(N - \mathrm{df})}{2(1 - r_{23})\left(\frac{(1 - f r_{\mathrm{avg}})}{(1 - r_{\mathrm{avg}})}\right)}}$$

where: $z_{12} = 1/2 \ln (1+r_{12})/(1-r_{12})$, Fisher's z transformation of the correlation of age with DP; $z_{13} = 1/2 \ln (1+r_{13})/(1-r_{13})$, Fisher's z transformation of the correlation of age with HTL; N = sample size and df = degrees of freedom; r_{12} = sample correlation of age with DP; r_{13} = sample correlation of age with HTL; r_{23} = sample correlation of DP with HTL; f = minimum of 1 or $(1-r_{23})/2(1-r_{\mathrm{avg}})$; $r_{\mathrm{avg}} = (r_{12}^2 + r_{13}^2)/2$.

3. Results

3.1. Descriptive

There were 432 subjects, 250 women and 181 men with an age range of 31–79 years. Of these subjects, 100 were tested at $f_2 = 0.5$ kHz, 432 at $f_2 = 2$ kHz, 274

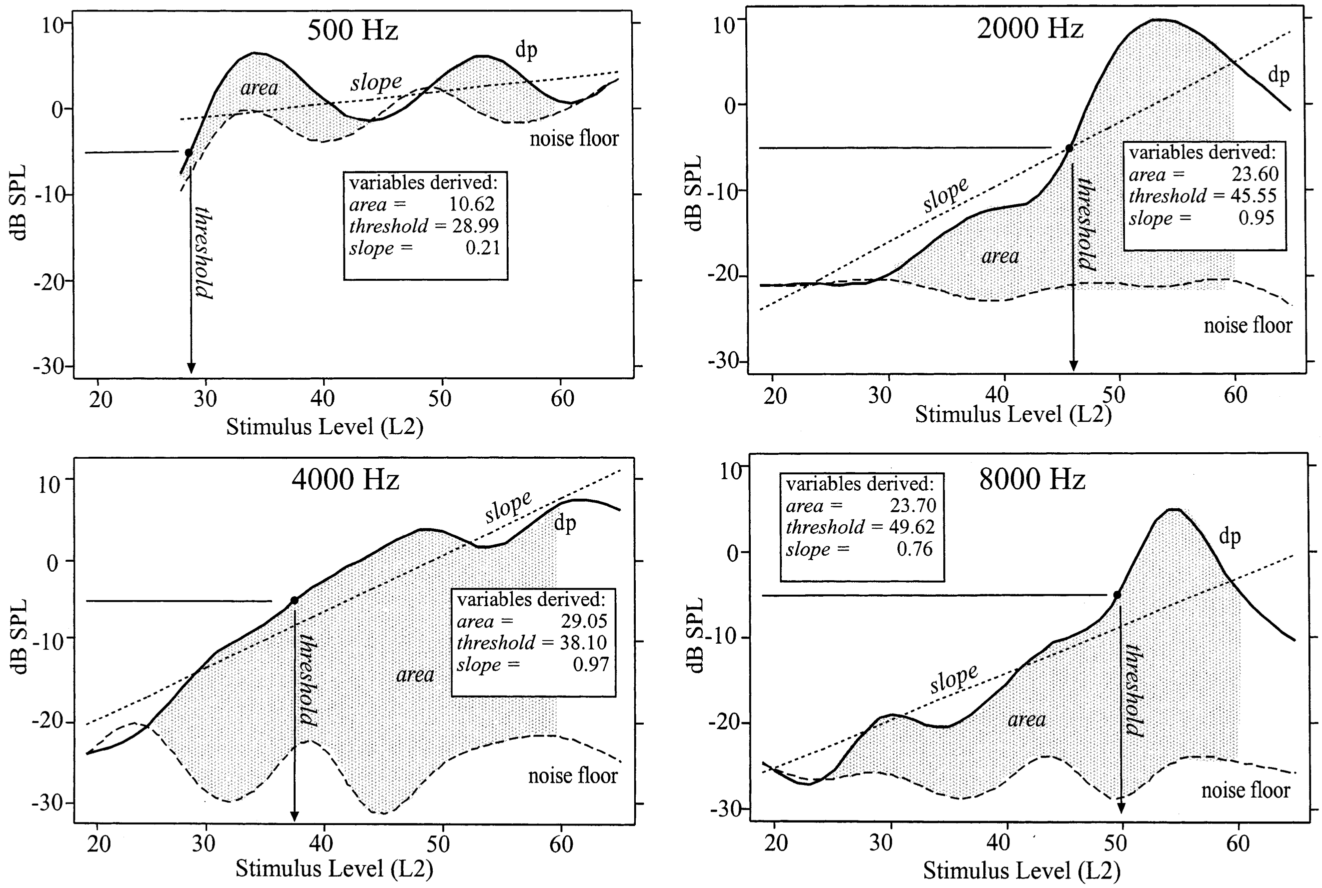

Fig. 1. An example of the DP IO function for a typical younger subject and the schema for the estimation of these three variables: area, threshold, and slope.

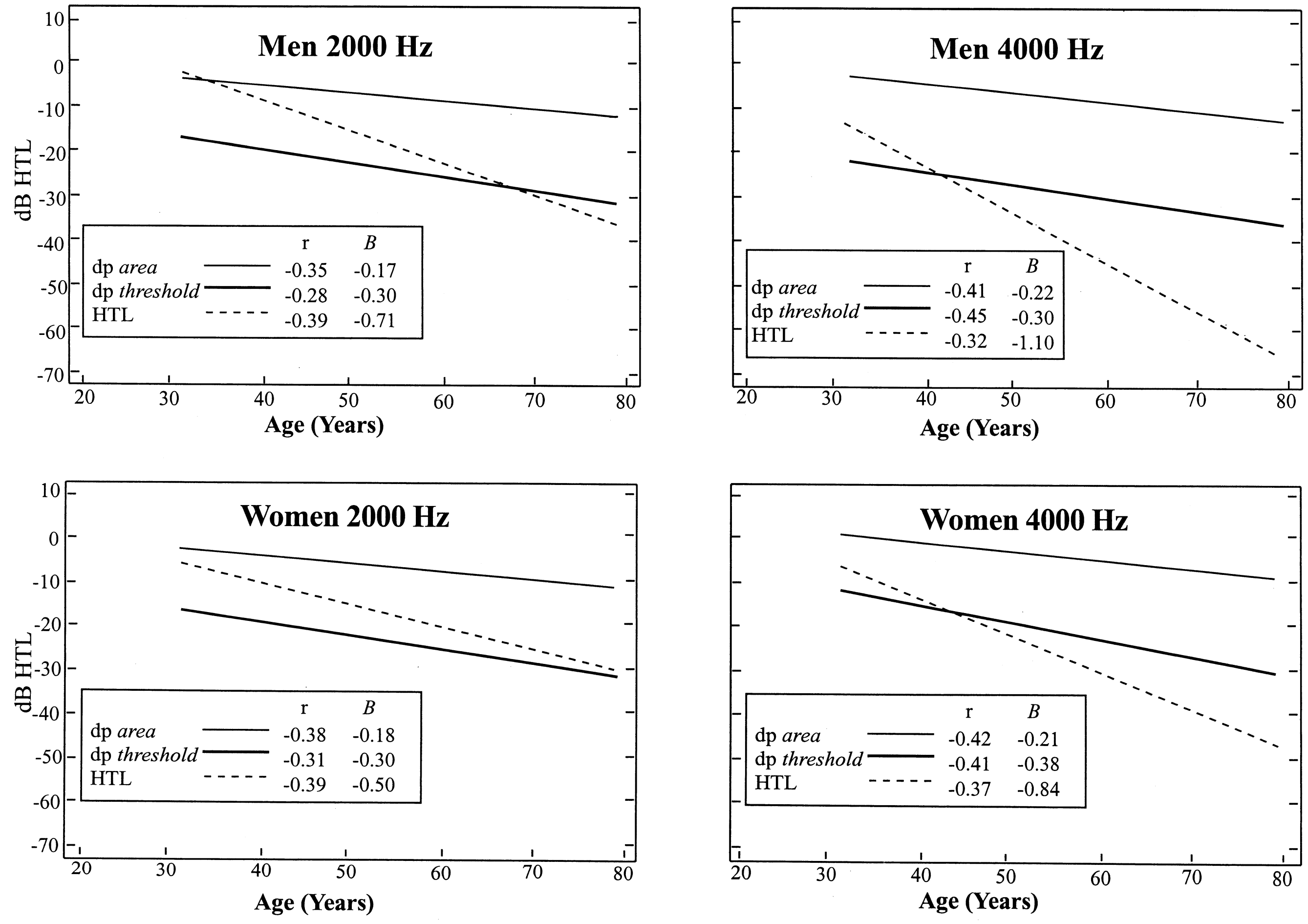

Fig. 2. The linear regression slopes of DP *area* on age and DP *threshold* on age in relation to the linear regression slope of the PTT (HTL) on age. The left hand y (ordinate) scale is marked in dB HTL. The right hand scale is in dB SPL but is left unmarked because the y positions of the slopes of the DP variables have been adjusted vertically for better visualization of the relative slope angles. The legend includes the Pearson correlation (r) with age and the linear regression coefficient (β) or the slope of the regression line.

at $f_2 = 4$ kHz, 117 at 8 kHz. The mean hearing threshold levels (±S.D.) were not different across genders (PTA women vs. men = 13.4 ± 9.2 vs. 13.6 ± 7.7 dB HTL, $P = 0.607$) even though the women were slightly but not significantly older (58.2 ± 9.6 vs. 57.1 ± 9.0 years ($P = 0.115$).

The mean values for the three DP IO variables are displayed by gender and f_2 frequency in Table 1. *Area* was significantly greater for the women in the $f_2 = 2$ kHz and $f_2 = 4$ kHz test frequencies; *area* did not differ by gender for the other two test frequencies. PTTs (HTL) did not differ by gender for any of the test frequencies.

3.2. Correlations

As expected, the DP IO variables showed significant intercorrelations (Table 2): *area* and *threshold* were significantly correlated at all test frequencies; and *slope* and *area* and *slope* and *threshold* were significantly correlated for all of the test frequencies except for 4 kHz. Moreover, there were significant correlations between the behavioral thresholds and the DP IO variables: DP *area* and HTL were significantly correlated for all of the test frequencies except for 8 kHz, DP *threshold* and HTL were significantly correlated at test frequencies 2 and 4 kHz, and DP *slope* and HTL were significantly correlated at all of the test frequencies except for 4 kHz (Table 2). *Slope* showed lower correlations and fewer significant correlations with HTL than did *area* and *threshold.* Therefore, *slope* is not considered further.

Because of the small number of cases at f_2s of 0.5 kHz and 8 kHz, only the $f_2 = 2$ kHz and $f_2 = 4$ kHz test results will be considered further.

3.3. Age regressions

The relationships of age to the DP IO functions and HTL are displayed in Fig. 2. Fig. 2 shows the change in

Table 1
Mean values ± S.D. for the DP variables *area, threshold*, and *slope* along with HTL and sample size (*N*) by frequency (f_2) and gender

f_2 (Hz)	500	2000	4000	8000
Men				
N	37	181	112	43
Area	9.3 ± 3.5[a]	20.9 ± 4.0[b]	21.7 ± 4.0[b]	18.8 ± 1.3[a]
Threshold	40.1 ± 10.2[a]	44.2 ± 8.9[a]	47.8 ± 7.81[b]	55.3 ± 4.7[a]
Slope	0.163 ± 0.269[a]	0.535 ± 0.270[a]	0.581 ± 0.279[b]	0.455 ± 0.269[a]
HTL	10.3 ± 5.0[a]	12.0 ± 7.2[a]	11.5 ± 6.9[a]	11.4 ± 7.4[a]
Women				
N	65	250	164	75
Area	9.1 ± 3.9[a]	22.4 ± 4.41[b]	24.7 ± 4.1[b]	19.8 ± 4.0[a]
Threshold	40.4 ± 10.0[a]	42.6 ± 9.1[a]	42.2 ± 8.2[b]	53.0 ± 7.3[a]
Slope	0.186 ± 0.299[a]	0.575 ± 0.243[a]	0.671 ± 0.243[b]	0.480 ± 0.309[a]
HTL	10.9 ± 8.3[a]	11.7 ± 7.7[a]	11.0 ± 7.4[a]	10.7 ± 7.8[a]

[a] Not significantly different comparing values for men and women for each f_2.

[b] $P < 0.001$ comparing values for men and women for each f_2.

area with age and the change of DP *threshold* with age compared to the change in HTL with age separately by DP f_2 frequency for men and women.

There was a clear decline of *area* and an increase in the HTL with age. The rate of change of HTL with age was significantly greater than the change in *area* with age ($P < 0.001$ for all comparisons). Similarly, the rate of change in HTL with age was greater than the change in DP threshold with age, this difference was only significant at 2 kHz for both men and women (Table 3). There was a trend toward a similar difference in DP threshold vs. HTL thresholds at 4 kHz.

4. Discussion

The prevalence of presbycusis is increasing due to the growing numbers of older people in society. An effective preventive or therapeutic method has yet to be found. Recent findings that strial atrophy is a substantive factor in presbycusis (Mills et al., 1990) and that strial presbycusis is strongly inherited (Gates et al., 1999) provide new insights into age-related hearing loss that may stimulate new directions of research into possible modification strategies.

The present analysis adds to these understandings by supporting the hypothesis of strial atrophy in cochlear aging. We interpret the finding in this study of a significantly greater change with age in the pure-tone HTL than in the DP IO functions as compatible with an age-related fall in EP. This interpretation is based on the knowledge that reduced EP has been shown to affect auditory thresholds more than the DP, and the hypothesis that inner hair cell output will be more severely disrupted by reduced EP than outer hair cell output alone. Reduced EP affects the inner hair cell responses in two ways: first as a result of the reduced voltage across the transduction channels and secondly from

Table 2
Correlation matrices for the DP variables and HTL by frequency

f_2 (Hz)		*Area*	*Threshold*	*Slope*	HTL
500	*Area*	1.00			
	Threshold	−0.26*	1.00		
	Slope	0.30*	0.32*	1.00	
	HTL	−0.41*	0.07	−0.21*	1.00
2000	*Area*	1.00			
	Threshold	−0.76*	1.00		
	Slope	0.22*	−0.13*	1.00	
	HTL	−0.30*	0.22*	−0.17*	1.00
4000	*Area*	1.00			
	Threshold	−0.88*	1.00		
	Slope	0.10	−0.09	1.00	
	HTL	−0.31*	0.33*	−0.09	1.00
8000	*Area*	1.00			
	Threshold	−0.84*	1.00		
	Slope	0.58*	−0.59*	1.00	
	HTL	−0.23	0.12	−0.21*	1.00

Statistically significant, $P < 0.05$.

Table 3
Z-Statistic from two comparisons of correlations by gender and frequency

f_2	Gender	Comparison 1 *Z* (*P* value)	Comparison 2 *Z* (*P* value)
2000	Men	5.84 (0.000)	2.10 (0.018)
	Women	6.85 (0.000)	2.31 (0.011)
4000	Men	4.98 (0.000)	1.76 (0.039)
	Women	5.93 (0.000)	−0.16 (0.439)

Comparison 1: Corr(*area*, age) vs. Corr(HTL, age); Comparison 2: Corr(*threshold*, age) vs. Corr(HTL, age).

the reduced output of the cochlear amplifier. Further support of this interpretation follows from the realization that if dysfunction of the outer hair cells were the principal age-related change in the cochlea, we would have seen an opposite effect wherein the DP IO would be impaired more than the behavioral thresholds as a function of age.

The area function appears to be a more robust measure of the systematic change in the DP IO output than either DP threshold or the slope of the DP IO function. The reason appears to be that noise floor variability, which was evident in these subjects, is accounted for by the area calculation, whereas both threshold and slope of the DP measures give erratic values when the noise floor is high. The rise in behavioral thresholds at 2 kHz was significantly greater than the rise in the DP threshold at 2 kHz, with a similar trend at 4 kHz.

This report is derived from a population-based group of subjects of wide range in age and hearing ability. This fact reduces the likelihood of selection bias and increases the generalizability of the results. The auditory testing was done in a ‘real-world’ setting by one audiologist. While time constraints prevented complete and detailed DP IO assessment in every case, the consistency of technique and equipment contributes to the accuracy of the results.

5. Uncited references

Mills, 2000

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