High-Frequency Hearing Influences Lower-Frequency Distortion-Product Otoacoustic Emissions

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Objectives: The primary goal of this study was to test the ability of $2f_1-f_2$ distortion-product otoacoustic emissions (DPOAEs) to detect reduced cochlear function in the presence of normal behavioral sensitivity.

Design: A prospective study was performed in normal-hearing young adults using simple and complex regression analyses to clarify the relationship between ultra-high frequency (UHF) hearing and DPOAE levels at lower frequencies, as well as the influence of hearing levels for frequencies within the conventional test range and subject age on this association.

Methods: Average DPOAE levels between 4 to 8 kHz, which were elicited by equilevel primary tones of low to moderate levels, were measured as level-frequency functions, or distortion-product (DP) grams, and related to the mean UHF hearing levels from 11.2 to 20 kHz. The median hearing level for the UHF hearing was used to separate subjects into good and poor UHF hearers. This distinction was then used to compare DPOAE levels from 4 to 8 kHz for the 2 groups to determine if UHF hearing status influenced DPOAE levels at lower frequencies.

Results: Simple regression analysis revealed that the 4- to 8-kHz DPOAE levels were significantly correlated with the pure-tone average (PTA) from 11.2 to 20 kHz. However, the PTA for 4 and 8 kHz was also significantly correlated with the PTA for UHF hearing. Further multiple regression analyses revealed that UHF hearing significantly and uniquely accounted for approximately 14% of the variance in DPOAE levels from 4 to 8 kHz for most of the primary-tone level combinations. In contrast, neither the PTA for the conventional hearing range nor subject age contributed significantly to the DPOAE variance.

Conclusions: The findings suggest that UHF hearing influences DPOAEs at significantly lower frequencies because emissions are sensitive to subtle changes in outer hair cells not yet detected by pure-tone thresholds in this region or because alterations in the basal cochlea affect the generation of lower-frequency DPOAEs originating from more apical cochlear regions.


The cochlear sounds discovered by Kemp and referred to as otoacoustic emissions (OAEs) presumably represent a population-based response in which OAE amplitude indicates the summed activity of a substantial number of outer hair cells (OHCs). In contrast, it is likely that normal behavioral sensitivity to pure tones in quiet can, in many circumstances, depend on the optimal responsiveness of only a few OHCs and inner hair cells and their associated eighth-nerve fibers. These notions are consistent with the earlier experimental findings of noise and ototoxicity studies in which a 30% to 50% loss of OHCs in the apical cochlea went undetected by well-controlled, pure-tone behavioral audiometry. Thus, in contrast to behavioral measures, the summed nature of OAEs suggests that normal-evoked emissions probably require the collective responses from many more related OHCs. Based on this premise, it could be hypothesized that, as scattered OHC loss accumulates, OAE amplitude decreases prior to any detectable change in behaviorally measured pure-tone thresholds.

Supporting the notion that OAEs act as “early detectors” of imminent cochlear dysfunction are clinical observations in humans of reduced OAEs in normal-hearing patients, who have typically been exposed to impulse noise, or to potentially ototoxic drugs, and who complain of hearing difficulties. An example of this paradox is illustrated in Figure 1 for a 41-year-old female patient. The patient, a right-handed recreational gun shooter, who admitted to the intermittent use of hearing protectors, complained of hearing difficulties (ie, hearing loss, tinnitus, and difficulty in understanding speech in background noise) in the presence of the normal pattern of clini-
MATERIALS AND METHODS

SUBJECTS

Fifty normal-hearing subjects (29 [58%] male and 21 [42%] female), with a mean age of 27 years (SD, 5 years; range, 17-37 years), were recruited to the study. These subjects, who were screened through verbal questioning for the absence of an ear-disease history, familial-based hearing loss, and exposure to excessive sound or ototoxic drugs, satisfied the criterion of normal audiometric hearing, as determined with a computer-based audiometer (Model 310; Virtual Corp, Portland, Ore). That is, they had sensitivities of less than 20-dB hearing levels (HL) at the octave frequencies between 0.25 and 8 kHz. An additional inclusion criterion was normal middle ear function, as measured with a digital aural-immittance testing system (Model 310; Virtual Corp). That is, it was necessary for tympanometric findings to include a middle ear pressure of −100 to +100 daPa, a static admittance of 0.3 to 1.9 mohms, and acoustic-reflex thresholds for ipsilateral (1-2 kHz) and contralateral (1-4 kHz) acoustic stimulation of 100 dB HL or less.

Hearing levels were measured with the subject seated comfortably inside a double-walled, sound-treated chamber, whereas immittance testing was performed in a quiet area, adjacent to the soundproofed booth. Subject permission as required by the local institutional review board for research on human subjects was obtained from each study participant in the form of a signed “informed consent” document.

EXPERIMENTAL PROTOCOL

After satisfying the above inclusion criteria of normal hearing and middle ear function, one ear from each subject was selected randomly as the test ear using a coin-toss method. For each test ear, the UHF hearing of the subject was examined using the extended-frequency software available for the microcomputer-based audiometer and its associated special earphones (Koss 4XPLUS; Koss Corp, Milwaukee, Wis), which basal noise damage reduced low-frequency TEOAEs. Similarly, in humans, these same investigators also found that poorer ultrahigh frequency (UHF) hearing (8-16 kHz) correlated with reduced TEOAE amplitudes evoked at much lower frequencies (1-5 kHz). However, in this latter study, age and UHF hearing levels were also correlated and, therefore, it was not possible to exclude aging as the primary cause of the relationship between TEOAEs and UHF hearing. Finally, using multiple-regression techniques in an earlier study, Avan et al showed that the amplitude of TEOAE frequency components significantly correlated with auditory thresholds as higher frequencies, with the strongest correlation occurring approximately 1 octave above TEOAE frequencies.

During the past few years, primarily due to their ability to measure frequencies above 4 kHz, DPOAEs have received considerable attention as a clinical test of the functional status of the cochlear for the purposes of the differential diagnosis of hearing problems, serial monitoring of potentially progressive hearing disorders, and
signal processor board's analog-to-digital converter. Specifically, the levels of the DPOAEs elicited by the 92-millisecond tone bursts and their related noise floors were calculated using a 4906-point (bin width = 10.8 Hz) fast Fourier transform. Noise floors were computed as the mean amplitude of 10 fast Fourier transform bins, using 5 sequential frequency intervals above and below the DPOAE–frequency bin, i.e., ±54 Hz around the DPOAE frequency. A DPOAE was considered to be present if its level was 3 dB or more above that of the related noise floor range.

**DATA PROCESSING AND STATISTICAL TESTS**

Due to the relatively small numbers of subjects in the study, it was not expected that the assumed influence of UHF hearing on DPOAE levels at the higher-frequency end of the conventional test range (i.e., 4-8 kHz) would be powerful enough to significantly affect individual DPOAE test frequencies. Indeed, this expectation was borne out by a set of preliminary analyses that yielded spurious correlations between individual DPOAE test frequencies and various combinations of the UHF hearing-test frequencies. Consequently, to reduce the variance in the emissions' data, DPOAE amplitudes were averaged for test frequencies from 4 to 8 kHz so that these 12 frequencies produced a single DPOAE score for each of the 3 primary-tone levels. Thus, for DPOAEs elicited by 75-dB SPL primaries, this entity became DP grams at 75-dB SPL (4-8 kHz), whereas for emissions evoked by 65-dB SPL primaries, the value was DP grams at 65-dB SPL (4-8 kHz), and for the 55-dB SPL primary tones, it was DP grams at 55-dB SPL (4-8 kHz).

Following this computation, individual correlations were performed between each of these average values and all pure-tone thresholds from 0.25 to 20 kHz. These tests showed that the DP grams at 75-dB SPL (4-8 kHz), for example, that DPOAEs from 4 to 8 kHz were significantly correlated with only the traditional pure-tone test thresholds at 2 kHz. For the UHF-hearing range, however, significant correlations were also obtained for all thresholds from 11.2 to 20 kHz. The lack of significant findings at 9 and 10 kHz suggests that the statistically consequential correlations for many of the UHFs were not related to the different earphones, or to unknown aspects of the UHF-test procedure, but, rather, reflect the fact that hearing levels at 9 and 10 kHz were much closer to those of the conventional test range. Based on this analysis, a pure-tone average (PTA) score for the 4- and 8-kHz audiometric frequencies (i.e., PTA [4 and 8 kHz]) was calculated to match the DPOAE scores. In addition, an average UHF score for the analysis of high-frequency hearing (i.e., PTA [11.2-20 kHz]), was computed based on the thresholds determined from 11.2 to 20 kHz.

Following these data-processing steps, for each test ear, all data were either entered manually (i.e., demographic facts including sex, age, ear sidedness) or transferred electronically (conventional- and UHF-hearing sensitivity, levels of DPOAEs, and related noise floor ranges) from the computer-based collection systems to a commercially available spreadsheet (Microsoft Excel version 5.0; Microsoft Corp, Redmond, Wash). For statistical testing, a commercially available software package (Statview v 4.3; Abacus Concepts Inc, Berkeley, Calif) was used to calculate both simple and multiple regressions in the form of simple (r) and multiple (R) correlation coefficients, as well as repeated-measures analyses of variance (ANOVA). Semipartial correlation coefficients (sr) and their significance were also computed according to Cohen and Cohen using formulas implemented in the spreadsheet.

The sr and its square (sr²) were computed rather than the more commonly used partial correlation coefficient, because sr can isolate the unique contribution of the relevant independent variable (IV) to R² the variance of the dependent variable (DV) accounted for by all IVs. Thus, sr² provides the increase in R² when this IV is included over the R² that encompasses the other IVs, but excludes the IV of interest. Specifically, sr² represents the unique contribution of a given IV expressed as a proportion of the total variance of the DV, whereas the partial correlation coefficient expresses this contribution as a proportion of that part of the DV variance not accounted for by the other IVs.

screening the hearing of newborns. At the same time, DPOAEs have been used successfully in experimental studies to detect the beginning stages of noise-induced hearing loss.14,15 Moreover, the results of other experimental studies using tolar overexposures indicate that DPOAEs have the ability to detect the dysfunction of restricted populations of OHCs.8-17 Together, both the practical observations of the detection of preclinical abnormalities in patients exposed to potentially damaging agents, and the experimentally induced findings in animal models of the sensitivity of emissions to ongoing cochlear dysfunction suggest the possibility that DPOAEs have the ability to indicate OHC damage, before it becomes functionally significant as a hearing loss. However, to our knowledge, unlike the TEOAE studies mentioned above, no experiments have been performed to evaluate the influence of UHF hearing on DPOAEs recorded at lower frequencies.

The primary purpose of the present study was to provide more systematic evidence to support the hypothesis that DPOAEs can serve as “early detectors” of OHC abnormality prior to clinically measurable changes in hearing level. Because many of the factors causing high-frequency hearing loss, such as noise and ototoxic drug exposure, operate in an orderly manner from high to low frequencies, it seemed reasonable to assume that, as UHF hearing becomes poorer, the corresponding cochlear impairment also progresses systematically in a basal to apical direction.18 This supposition was used to test the above notion by assuming that poor UHF hearing would be associated with a reduced number of functioning OHCs. Thus, increasingly poorer UHF hearing should be accompanied by regions of dysfunctioning OHCs that proceed progressively toward the cochlear regions encoding lower frequencies, so that they eventually affect the conventional 4- to 8-kHz test range. Consequently, even in the presence of clinically normal hearing levels at 4 and 8 kHz, if DPOAEs can subtly detect OHC abnormalities, it would be expected that the variance of DPOAE amplitude in this region would be significantly influenced by UHF hearing, and this effect would be revealed by appropri-
ate correlational techniques. Portions of these results have been reported elsewhere.19

RESULTS

To demonstrate the relation between PTA (11.2-20 kHz) and the levels of lower-frequency DPOAEs, aside from the traditional scatterplots, the overall group of subjects was sorted into good and poor UHF hearers based on their median high-frequency PTA (11.2-20 kHz) scores. If DPOAEs at lower frequencies were unrelated to high-frequency thresholds, then this categorizing procedure would not be expected to result in differentiated groups sorted on this basis. In other words, DPOAE levels would be randomly distributed and equal between the 2 groups. The results of this sorting procedure are shown for the entire group of subjects in Figure 2 for the UHF audiograms (Figure 2, A) and for DP grams at 75-, 65-, and 55- dB SPL (4-8 kHz) (Figure 2, B-D, respectively). Repeated-measures ANOVAs demonstrated that DPOAEs at 75-dB SPL (4-8 kHz) (n = 31, DP grams at 65-dB SPL, P < .06; n = 31, DP grams at 55-dB SPL, P < .06), respectively, probably due to the reduced number of subjects tested at the lower levels. As would be expected, the ANOVA tests performed on PTA (11.2-20 kHz) were highly significant (P < .001), but also resulted in significant differences in PTA (4 and 8 kHz) between the 2 groups of good and poor UHF hearers (P < .005).

Figure 3 shows individual examples that resulted from this sorting procedure for both good and poor UHF hearing. In this example, the significant differences in DPOAE levels that occurred between the 2 groups can be appreciated, even though the hearing levels at 11.2 kHz and below were virtually identical. Overall, these data suggest that UHF hearing affects DPOAEs measured at lower frequencies.

The more traditional approach to the problem of establishing the relationship between 2 variables is shown in the scatterplots of Figure 4 for DPOAEs (4-8 kHz), at all primary-tone levels (A, 75-; B, 65-; and C, 55-dB SPL), as a function of PTA (11.2-20 kHz). It can be seen that, regardless of primary-tone level, DPOAEs in the conventional 4- to 8-kHz hearing range were significantly...
and negatively correlated with UHF hearing in that larger DPOAE amplitudes were associated with lower UHF thresholds. From the $r^2$ values shown in each plot, it is clear that across primary-tone levels PTA (11.2-20 kHz) accounted for approximately 16% to 18% of the DPOAE (4-8 kHz) variance.

It was noted above that sorting on UHF thresholds also resulted in significant differences between HLs for the conventional 4- to 8-kHz test frequencies, which suggested a correlation between PTA (4 and 8 kHz) and PTA (11.2-20 kHz). A simple regression analysis performed on these 2 variables revealed that, in fact, PTA (4 and 8 kHz) was significantly correlated with PTA (11.2-20 kHz). This relationship of the 2 hearing ranges is illustrated in the scatterplot of Figure 5. Thus, poorer UHF also tended to be associated with poorer hearing at the traditional 4- and 8-kHz test frequencies. Consequently, the effect of UHF hearing on DPOAEs at lower frequencies may be due in part to the fact that UHF is also associated with poorer hearing in this range, thus leading to reduced DPOAE amplitudes.

One approach toward controlling the above problem of an association between 2 IVs (ie, conventional and UHF hearing) is to use multiple regression analyses so that the variance of the DV accounted for by the various IVs can be partialled out. This process is conceptually illustrated in Figure 6, which shows that the variance in DPOAE amplitude is shared by the 2 IVs, in this case, PTA (4 and 8 kHz) and PTA (11.2-20 kHz). The overall $R^2$ of the multiple regression analysis provides the variance accounted for by the optimal combination of the 2 IVs, while computation of $sr^2$ allows the determination of the unique contribution of each IV to the variance in DPOAE amplitude.22 The results of performing multiple regression analyses with DPOAE amplitudes for the 3 primary-tone levels as the DVs, and with PTA (4 and 8 kHz) and PTA (11.2-20 kHz) as the IVs, are shown in the Table. From this analysis, a significant overall $R^2 (0.404; P < .05)$, shown at the top left of the Table, was obtained only for DPOAEs at 75-dB SPL (4-8 kHz). Subsequent computation of $sr^2$ indicated that only the PTA (11.2-20 kHz) contributed significantly to the variance of the DPOAEs at 75-dB SPL (4-8 kHz). Thus, in this instance, UHF hearing uniquely accounted for approximately 14% of the variance in DPOAE levels in the 4- to 8-kHz range. For the other primary-tone levels, similar

![Figure 2](image-url)
trends were noted. However, only for DPOAEs at 55-dB SPL (4-8 kHz) did the PTA (11.2-20 kHz) significantly contribute to the observed variance in emission levels. Nevertheless, this latter outcome should be viewed with caution, because the overall $R$ did not reach statistical significance, again, presumably because of the reduced number of subjects in the 2 groups of hearers, ie, poorer vs better UHF hearers, tested at 55-dB SPL.

It was also noted that subject age correlated with UHF hearing. However, when age was included in the multiple regression analysis, none of the IVs reached statistical significance. In these analyses, age and PTA (4 and 8 kHz) each accounted for less than 1% of the variance of DPOAEs at 75-dB SPL (4-8 kHz), whereas PTA (11.2-20 kHz) still accounted for approximately 6% of the variance in DPOAE amplitude, which is consistent with the significant results obtained for the 2 hearing-range IVs.

Anecdotal observations in human clinical situations suggest that instances occur in which evoked OAEs appear to be more sensitive to cochlear insult than the traditional pure-tone audiogram. This notion is bolstered by the findings from animal studies, in which substantial numbers of OHCs can be missing but go undetected by behavioral audiometry. However, in humans, the hypothesis that OAEs can be more sensitive to subtle cochlear damage than traditional audiometry can only be investigated by correlational techniques from either normally hearing individuals or patients with hearing loss. The present study used individuals with normal hearing for the traditional audiometric frequencies to investigate the influence of UHF hearing on DPOAEs at the lower frequencies. By sorting individuals based on their UHF hearing ability, DPOAEs from 4 to 8 kHz were sepa-
rated into 2 distinct groups of larger and smaller emissions, thus suggesting that UHF can influence DPOAEs at lower frequencies. The results of these sorting procedures were further substantiated by multiple regression analyses demonstrating that UHF contributed uniquely and significantly to the variance of DPOAE levels from 4 to 8 kHz.

Recently, a similar study was performed by Avan and colleagues for TEOAEs in which UHF hearing, defined as the frequencies from 8 to 16 kHz, significantly influenced TEOAEs evoked at much lower frequencies. In that study, aging was also found to be correlated with UHF hearing, but multiple regression statistical techniques were not used to determine the unique contribution aging made to TEOAE-amplitude variance. The present study also noted the effects of aging on UHF hearing, but the subject pool was too small to significantly partial out the effects of this IV on DPOAE levels. However, in the absence of statistically reliable findings with age, UHF hearing still tended to account for the largest proportion of DPOAE amplitude (4-8 kHz) variance.

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The multiple regression analyses demonstrated that UHF contributed to the variance of DPOAE levels from 4 to 8 kHz.

In the Avan et al study, the remote influences on TEOAEs were confined to low-level clicks. In contrast to the TEOAE findings, in the present study, significant effects were observed for DPOAEs elicited by moderate (75-dB SPL) and low-level (55-dB SPL) primaries (Table). Exactly why intermediate-level (65-dB SPL) primaries did not reach statistical significance is not clear, other than the possibility that this outcome was due to the effects of the reduced number of subjects in the groups stimulated with lower primary-tone levels. Overall, the findings that lower-level stimuli were influenced by remote hearing levels could be used to argue that low-level emissions are acting as early detectors of local damage. That is, low-level stimuli would result in restricted regions of DPOAE generation, which would be confined largely to the stimulus place on the basilar membrane. Then, as stimulus level is increased, more basally located basilar-membrane sites would be expected to be involved in the emission-generation process. Thus, contrary to the above outcomes, the correlation between UHF hearing and DPOAE levels might be expected to increase at higher stimulus levels.

### Table: Multiple Regression Analyses With DPOAE Amplitudes for Primary-Tone Levels

<table>
<thead>
<tr>
<th>Primary-Tone Level</th>
<th>TPA (4 and 8 kHz)</th>
<th>PTA (11.2-20 kHz)</th>
<th>r</th>
<th>r²</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>DP Grams at 75-dB SPL (4-8 kHz)</td>
<td>0.043</td>
<td>-0.369</td>
<td>0.002</td>
<td>0.140</td>
<td>.008*</td>
</tr>
<tr>
<td>R = 0.404*</td>
<td>0.163*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DP Grams at 65-dB SPL (4-8 kHz)</td>
<td>-0.158</td>
<td>-0.315</td>
<td>0.025</td>
<td>0.099</td>
<td>.08</td>
</tr>
<tr>
<td>R = 0.435*</td>
<td>0.190</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>DP Grams at 55-dB SPL (4-8 kHz)</td>
<td>-0.049</td>
<td>-0.371</td>
<td>0.002</td>
<td>0.138</td>
<td>.04*</td>
</tr>
<tr>
<td>R = 0.425</td>
<td>0.181</td>
<td></td>
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</tbody>
</table>

*DPOAE indicates distortion-product otoacoustic emissions; DP, distortion product; sr, semipartial correlation coefficient; and PTA, pure-tone average. P< .05.
The above results suggest that, clinically, a substantial amount of OAE variance can be attributed to changes in hearing remote from the OAE-test frequencies. These relations may often be missed in clinical situations especially for TEOAEs, because the influences are small (approximately 4.5 dB), noise levels are high, and low-level clicks are needed to observe the effects. Like TEOAEs, it is difficult to determine in individual cases if, in fact, decreased DPOAE levels are indicators of early damage. Clearly, as shown in Figure 3, various individual subjects may show large reductions in DPOAEs when their UHF hearing is poor. At this time, whether these abnormally low-amplitude DPOAEs, in cases such as that shown in Figure 1, are signaling “early detection” of cochlear abnormalities must be based largely on clinical history. However, experimental studies are in agreement that both TEOAEs and DPOAEs appear to be affected by remote changes in hearing level, but the exact interpretation of these decrements in evoked-emission levels remains unclear.

The outcome of the present study for DPOAEs and the recent findings for TEOAEs in humans can be accounted for by 2 alternative hypotheses. First, some minute abnormalities to the cochlea and/or its OHCs may have been present at places tuned to the lower frequencies, and the OAEs were more sensitive to these functional deficits than clinical tests of hearing sensitivity. Second, it is possible that significant contributions to the generation of lower-frequency OAEs may have come from higher-frequency sites in the basal cochlea that exhibited damage due, for example, to age-related hearing loss or presbycusis. Neither of the above studies could determine the basis for the influence of the basal cochlea on more apically generated OAEs. However, the fact that cochlear damage typically progresses from a basal to apical direction suggests that, in some individuals, this systematic progression has begun to significantly encroach on the more apically generated OAEs. It also must be remembered that these 2 hypotheses are not mutually exclusive. In other words, the basal cochlea may to some extent contribute to more apically generated OAEs, and OAEs may also in some instances be more sensitive to OHC dysfunction than traditional behavioral measures. The sensitivity of OAEs may depend to a large extent, for example, on the magnitude and pattern of OHC loss. Thus, for OAEs to be more sensitive than behavior, there may need to be small regions of normal OHCs that can mediate the behavioral task interspersed throughout regions of significant OHC loss.

Whatever the underlying cause of the ability of OAEs in the conventional frequency-test range to detect progressive functional deficits, it appears that these response measures may be useful in instances in which it is beneficial to detect early abnormalities. As such, evoked OAEs may provide a measure of “cochlear reserve” in that decreased emissions in the presence of normal behavioral hearing may indicate an underlying pathologic condition, for example, following noise or drug exposure, that, if continued, might soon result in a significant hearing loss.