A Distortion Product Otoacoustic Emissions (DPOAE) Assessment of Cochlear Function in Tinnitus Subjects with Normal Hearing Sensitivity

by

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Abstract

Tinnitus, the perception of sound in the absence of an external acoustic source, disrupts the daily life of 1 out of every 200 adults, yet its physiological basis remains largely a mystery. While tinnitus and hearing loss (i.e., elevated pure tone thresholds) commonly co-occur, many people without hearing loss experience tinnitus, raising the question of whether cochlear pathology is always a prerequisite for this percept. This study used distortion product otoacoustic emissions (DPOAEs) to evaluate the cochlear amplifier of 13 tinnitus subjects and 13 non-tinnitus subjects (matched by age, sex, and audiogram) across a broad range of frequencies and intensities. DPOAE magnitudes were measured for at least 52 frequencies (500 Hz $\leq f_2 \leq$ 8 kHz, with f_2/f_1=1.2) and nine intensities (20 dB $\leq L_2 \leq$ 60 dB, with $L_1 = 39 + 0.4L_2$) in each ear. Further, this study only considered ears with normal audiograms and unremarkable history so that any abnormal findings could not be attributed large-scale hair cell damage within the cochlea. Consistent differences in the shape of the DP-gram (DPOAE magnitude as a function of presentation frequency, f_2) were found in tinnitus subjects. A quantitative method for assessing DP-gram shape was developed, and statistical analyses were performed to determine whether tinnitus or other patient characteristics correlated with the abnormal DP-gram shape. The data collected in this study suggest peripheral auditory malfunction in tinnitus subjects with normal audiograms.

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Chapter 1

Introduction

Tinnitus is the perception of sound that lacks an acoustic source. While most adults have experienced brief tinnitus at some point during their lives (Dobie, 2004), as many as 1 in 200 people experience constant tinnitus so distressing that they cannot lead a normal life (Coles, 1984; Leske, 1981). Sometimes tinnitus directly results from a known pathology (e.g., Meinere's disease, salicylate toxicity, temporomandibular syndrome, otoscelerosis, acoustic neuroma), but often tinnitus has no obvious cause. This study systematically examines cochlear function in those with chronic, idiopathic tinnitus.

1.1 Motivation

At present, it is not clear whether peripheral auditory abnormality is a prerequisite for tinnitus. Most persons with tinnitus have elevated hearing thresholds, but the correspondence between tinnitus and hearing loss is far from perfect (Fowler, 1944, 1965; Heller and Bergman, 1953). Persons with normal thresholds can suffer from tinnitus, and persons with unilateral tinnitus may have identical thresholds in each ear. This raises a question of whether some forms of tinnitus arise from peripheral auditory abnormality that does not affect the threshold of hearing.

Distortion product otoacoustic emissions (DPOAEs) provide a means to assess peripheral auditory function. DPOAEs result from non-linearities in cochlear micromechanics, which occur when electromotile outer hair cells (OHCs) generate feedback forces that modify the motion of the basilar membrane (Dallos, 1992). Two presentation stimuli at frequencies f_1 and f_2 produce traveling waves along the cochlear basilar membrane, which then yield the cubic distortion product $(2f_1 - f_2)$. One can evaluate different cochlear regions by systematically altering the presentation stimuli.

1.2 Background

Previous studies have used DPOAEs to probe cochlear function in tinnitus patients; however, they have presented results inconsistent with one another. Some groups (e.g., Janssen et al., 1998) have focused on tinnitus subjects with hearing loss, as most tinnitus patients have elevated hearing thresholds. However, in the presence of multiple auditory pathologies (i.e., tinnitus and hearing loss), it is difficult to link a single pathology to any observed DPOAE abnormality. Other groups (e.g., Nottet et al., 2006; Gouveris et al., 2005; Riga et al, 2007; Janssen et al., 2000) have focused on DPOAE testing in subjects with acute tinnitus, which may have a different etiology than chronic tinnitus. Even though age and sex impact DPOAE level (Lonsbury-Martin et al., 1991; Lonsbury-Martin and Martin, 2007; Stover and Norton, 1993), most studies do not carefully match non-tinnitus and tinnitus subjects based on age and sex.

A handful of groups have reported decreased DPOAE magnitudes in tinnitus sufferers in certain frequency regions (Shiomi et al., 1997; Job et al., 2007; Ozimek et al., 2006). This observation is consistent with classical OHC damage. When damage occurs within a population of OHCs, there is reduced basilar-membrane feedback, which in turn decreases the generation of distortion products. However, other groups have reported elevated DPOAE magnitudes in tinnitus sufferers in certain frequency regions (e.g., Mitchell et al., 1995; Janssen et al., 1998; Gouveris et al., 2005). Sometimes referred to as cochlear "hyperactivity," this observation is not consistent with traditional OHC damage. Rather, Janssen et al. (1998) suggest a more complex pathology. In addition to seemingly contradictory results in the literature regarding whether DP magnitude increases or decreases with tinnitus, the frequency regions specified for decreased and elevated DP magnitude are inconsistent across studies.

Though several studies have evoked DPOAEs in tinnitus subjects, the studies have used different primary levels. Janssen et al. (1998) suggest that DPOAEs grow abnormally with primary intensity in some tinnitus subject. Thus, the same tinnitus sufferer may have either elevated or decreased DPOAEs relative to the non-tinnitus population depending on the level of the primary tones. Not only is a study across many primary levels needed, but, given the individual variability of DPOAE magnitude, it also makes sense to consider individual DP-grams along with the mean DPOAE data for subject populations.

1.3 Overview

This study sought to determine what results in the aforementioned literature, if any, could be reproduced with a more careful study. Because hyperacusis (decreased sound tolerance) so frequently coexists with tinnitus, this study also considered this previously neglected factor. This study includes subjects with chronic, idiopathic tinnitus and normal thresholds of hearing. Because the critical factors for DP-grams are age, sex, and audiogram, the tinnitus population is matched subject-by-subject to an age, sex, and audiometrically similar non-tinnitus population.

This study contrasts previous work in its careful matching of tinnitus and non-tinnitus subjects and in its consideration of individual data as well as group data. Considering individuals led to a possible tinnitus subclassification, which eventually may contribute to more effective tinnitus management.

Following the first chapter, which introduced the problem, reviewed relevant background information, and detailed the motivation for this work, the structure of this thesis will be as follows: Chapter 2 will discuss subject selection, the experimental design, and a novel method of DP-gram analysis. Chapter 3 will present composite results among the non-tinnitus and tinnitus populations as well as results pertaining to individual subjects. Chapter 4 will discuss trends suggested by the results, physiological connections, and other implications of this work.

Chapter 2

Methods

In this study, a carefully screened tinnitus population and matched non-tinnitus population underwent behavioral and DPOAE testing. After collecting DPOAE measurements, a novel analysis method was applied to the DP-grams.

2.1 Subjects

Twenty-six subjects participated in this study. Thirteen had chronic tinnitus (11 men; 9 right-handed; mean age 42.0 +/- 9.8 years). Thirteen had no tinnitus (11 men; 10 right-handed; mean age 43.3 +/- 9.5 years). All of the non-tinnitus subjects, and 11 of the tinnitus subjects had normal pure tone thresholds (<= 25 dB HL) in both ears at octave intervals from 250 through 8000 Hz. The remaining two subjects had normal thresholds in one ear and a mild high-frequency loss in the other (threshold between 30 and 35 dB HL at 8000 Hz). In these subjects, only the normal ear underwent DPOAE testing. One non-tinnitus subject also had DPOAE testing in only one ear to avoid disrupting what appeared to be a small laceration in ear canal. In total, 24 ears were tested in tinnitus subjects, and 25 ears were tested in non-tinnitus subjects. Subjects were systematically asked about any prior overexposure to acoustic noise. Two reported having had such exposures on a regular basis (subject 109, a tinnitus subject, and his non-tinnitus match, subject 46).

Subjects were tested according to protocols approved by the Massachusetts Eye and Ear Infirmary (MEEI) and the Massachusetts Institute of Technology. Written informed consent was obtained prior to testing.

The tinnitus subjects were recruited through the MEEI tinnitus clinic (11 subjects), the MEEI Audiology Department (1 subject), or personal contacts (1 subject). Table 1 summarizes the characteristics of these subjects. All but one subject had tinnitus in both ears or "in the head." In the subject with unilateral tinnitus, both ears were tested.

All subjects reported chronic tinnitus for at least six months prior to testing. Three subjects reported having tinnitus for as long as they could remember (tinnitus duration = "lifelong" in Table 1). Two subjects reported that they experienced some form of tinnitus throughout their lives, but that it changed in quality (subject 85) or from intermittent to constant (subject 91).

The non-tinnitus subjects were recruited through advertisements in local newspapers (6 subjects) and through personal contacts. Each non-tinnitus subject was matched to a tinnitus subject by sex and age (maximum age difference: 5 years; average age difference: 1.7 years). Table 2 summarizes the characteristics of non-tinnitus subjects. The subject order of Table 2 is such that pair-wise matched tinnitus and non-tinnitus subjects appear in the same row of Tables 1 and 2.

2.2 Behavioral testing

The Contour Test of loudness (Cox et al., 1997) was used to determine the highest tolerable level of monaural broadband noise, or loudness discomfort level (LDL). The test involved presenting the noise briefly (~2 s) at progressively higher levels that increased in 5 dB steps from 35 dB SPL until the highest level produced by the audiometer (114 - 119 dB SPL) or until the subject indicated that the stimulus was uncomfortably loud. The test was repeated in each ear. The LDL for an ear was designated as the more intense of the two sound levels that the subject deemed "uncomfortable."

Tinnitus pitch, tinnitus loudness, minimum masking level (MML), and residual inhibition (RI) were assessed in tinnitus subjects. The pitch of the tinnitus was the pure tone frequency between 250 and 8000 Hz (inclusive, half-octave resolution) deemed most similar in pitch to the tinnitus. Tinnitus loudness was determined by adjusting the level of a broadband noise to match the loudness of the tinnitus to within 5 dB for each ear separately (stimulating the tested ear). MML is the lowest level of binaurally-presented broadband noise needed to completely mask the tinnitus. Tinnitus loudness and MML were expressed relative to the detection threshold of the broadband noise (i.e., in dB sensation level (dB SL)). The test for residual inhibition established whether one minute of binaurally-presented broadband noise at 10 dB above MML resulted in complete tinnitus suppression for any length of time after the noise was turned off. In Table 1, where subject tinnitus characteristics are summarized, the "residual inhibition" column indicates whether complete tinnitus suppression occurred.

All subjects completed a handedness questionnaire (Oldfield, 1971), inventories of depression and anxiety (Beck et al., 1988; Beck et al., 1961), and a questionnaire assessing sound tolerance (Tyler et al., 2003). The latter questionnaire consisted of a 0 – 100 rating in response to each of the following three statements: (1) Many everyday sounds are unbearably loud to me. (2) Sounds that others believe

TABLE 1
Tinnitus subjects and characteristics

Subject	Age	Sex	Handedness	Tinnitus duration	Tinnitus quality	Tinnitus frequency match (left, right)	Tinnitus loudness (dB SL) (left, right)	LDL (db SPL) (left, right)	MML (db SL)	RI	ST score	TRQ	Depression score	Anxiety score
22	38	F	Right	1.4 years	Ringing	(1.5 kHz, N/A)	(20, N/A)	(100, 94)	(50, N/A)	No	0.07	4	0	0
23	33	M	Mostly right	~10 years	Ringing	(8 kHz, >8kHz)	(25, 40)	(95, 99)	(70, 70)	No	0.33	47	3	5
28	23	M	Right	8 years	Ringing	(1.5 - 2 kHz, 2kHz)	(25, 35)	(90, 89)	(45, 45)	No	0.40	34	21	1
72	46	M	Mostly left	13 years	Ringing	(8 kHz, 8kHz)	(15, 20)	(LOSS, 114)	(30, 30)	No	0.30	43	9	7
84	48	M	Right	5 years	Ringing	(>8kHz, >8kHz)	(15, 15)	(>115, >114)	(65, 70)	No	0.30	29	5	8
85	53	M	Left	lifelong	Hissing, pulsing tone	(6kHz, 6kHz)	(20, 30-35)	(>115, LOSS)	(70, 70)	No	0.05	19	0	2
87	47	M	Right	~20 years	Ringing	(>3 kHz, >3kHz)	(7, 7)	(85, 84)	(60, 60)	No	0.47	13	12	0
91	31	M	Right	lifelong	Pure tone ringing	(2kHz, 2kHz)	(30, 30)	(100, 94)	(35, 35)	No	Unavailable	Unavailable	Unavailable	Unavailable
109	46	M	Right	lifelong	High pitched ringing	(6-8 kHz, >6-8 kHz)	(35-40, 40-45)	(>115, >114)	(65, 65)	No	0.07	37	22	21
110	41	M	Right	2 years	Ringing, buzzing, hissing	(1.5 kHz, 1.5 kHz)	(20, 15)	(85, 79)	(20, 20)	Yes	0.53	67	13	13
111	37	M	Right	3 years	Tonal, high frequency pitch	(3kHz, 3kHz)	(25, 25)	(104, 105)	(20, 20)	No	0.00	14.5	21	6
112	60	F	Right	8 years	Tonal, several tones	(2kHz, 1.5 kHz)	(20, 20)	(108, 109)	(50, 50)	No	0.73	10	5	15
116	43	M	Mostly right	>20 years	Tonal, ringing	(6kHz, 6kHz)	(10, 10)	(>118, >119)	(30, 30)	No	0.00	53	13	10

are moderately loud are too loud to me. (3) I hear very soft sounds that others with normal hearing do not hear (taken from the Hyperacusis Intake questionnaire of Tyler et al., 2003). A sound tolerance (ST) score was calculated as the sum of these responses, normalized to the maximum total of 300. Subjects with tinnitus also completed a questionnaire asking about the characteristics of their tinnitus (e.g., quality of percept, location) and an inventory of the effects of tinnitus on quality of life (the Tinnitus Reaction Questionnaire (TRQ) of Wilson and colleagues, 1991). Tables 1 and 2 include questionnaire data for each subject.

TABLE 2
Data summary for non-tinnitus subjects. LDL data is in the form (left, right)

Subject	Age	Sex	Handedness	LDL (dB SPL) (left, right)	Sound tolerance	Depression score	Anxiety score
49	43	F	R	(>115,>114)	0.23	12	9
124	33	M	R	(108, 114)	0.00	0	1
121	24	M	R	(103, 104)	0.10	1	0
55	46	M	Mostly R	(>115, >114)	0.00	0	2
9	51	M	R	(85, 89)	0.25	0	0
122	55	M	R	(118, 119)	0.00	0	3
125	48	M	R	(88, 89)	0.10	0	0
118	32	M	Mostly L	(Unavailable, 119)	Unavailable	Unavailable	Unavailable
46	46	M	Mostly R	(>118, >119)	0.00	0	0
8	46	M	R	(110, 109)	0.00	1	0
120	38	M	R	(>118, 119)	0.03	0	4
53	58	F	R	(>115, >114)	0.17	2	1
119	43	M	R	(118, 119)	Unavailable	Unavailable	Unavailable

2.3 DPOAE measurements

DPOAEs were measured using an Etymotic Research probe (ER10C) and a commercial otoacoustic emissions system (Mimosa Acoustics, version 3.2) that includes a PC card and software running on a laptop. During testing, the laptop ran on battery power to avoid introducing line noise into the DPOAE measurements.

Testing began after the subject had been in the quiet conditions of the test booth for at least 10 minutes. A foam ear tip housing the Etymotic probe was inserted snugly into the subject's ear canal to a standard insertion depth (as per Berger et al., 2003). To minimize slippage, the probe was taped to the subject's outer ear. Prior to DPOAE testing, the measurement system was calibrated by driving each of the measurement probe's two independent acoustic sources with chirp stimuli and measuring the ear canal sound pressure from the probe microphone. During testing, the level of the primary tones in the ear canal was monitored and the system was recalibrated if, at any point during the test session, the level of either primary tone drifted by more than 3 dB. Slippage due to subject movement was suspected in only a handful of ears and always was detected early (within the first two or three minutes of a 45 minute experiment). After any recalibration, all testing was repeated on the ear and previous data was discarded. Subjects typically read quietly during the experiment, remaining awake and still during DPOAE measurement.

The distortion product $2f_1 - f_2$ ($0.5 \text{ kHz} \leq f_2 \leq 8 \text{ kHz}$; $f_2 / f_1 = 1.2$) was measured at either 14 or 28 points per octave (52 or 83 points total, respectively). The intensity of the primary tones had the following relationship: $L_1 = 0.4L_2 + 39$ dB, where L_2 ranged from 60 dB SPL to 20 dB SPL in decreasing 5 dB steps. This L_1-L_2 relationship, initially proposed by Kummer et al. (1998) was compared against other L_1-L_2 relationships (including Neely et al., 2005) in pilot measurements of five tinnitus and six non-tinnitus subjects. While the L_1-L_2 relationship that produced the largest DP levels varied among subjects (regardless of tinnitus status), none of the alternatives considered provided, on average, larger DP magnitude for a given L_2 level than the Kummer relationship.

The Mimosa software guaranteed that 1) the absolute noise floor at the DP frequency, which was measured immediately before DP measurement, never exceeded 10 dB SPL; and 2) the noise level in the given time sample never exceeded the noise floor measured at the DP frequency during calibration by more than 10 dB (artifact rejection). The maximum duration of data taking varied with primary level: 4 seconds at the lowest intensities (25 or 20 dB SPL), 3 seconds for L_2 = 35 or 30 dB SPL, and 2 seconds for L_2 > 35 dB SPL. Post-experiment analysis imposed an inclusion criterion on each data point taken (SNR > 6 dB).

2.4 Quantitative measure of DP-gram shape

After noticing that a mid-frequency "dip" in DP magnitude appeared to be more prevalent among tinnitus subjects than non-tinnitus subjects (e.g., see Figure 4), the "dip index" was developed to determine whether the DP-grams of the two subject types could be quantitatively and objectively distinguished on the basis of shape . The shape qualitatively recognized as a dip is both deep and broad. Separate indices quantify depth and breadth. The first, *d*, reflects depth by measuring the difference in DP magnitude between the dip (m_{Dip}) and regions of peak magnitude at lower and higher frequencies

($m_{LowPeak}$ and $m_{HighPeak}$).

$$d = \min[(m_{LowPeak} - m_{Dip}), (m_{HighPeak} - m_{Dip})] \qquad \text{(Eq. 1)}$$

The second, *b*, reflects breadth by assessing the DP-gram based on the frequency location of the dip (f_{Dip}) relative to the frequency locations of the magnitude peaks at lower and higher frequencies ($f_{lowPeak}$, $f_{highPeak}$).

$$b = \min[\log_2(f_{Dip} / f_{LowPeak}), \log_2(f_{HighPeak} / f_{Dip})] \qquad \text{(Eq. 2)}$$

These measures use minima to ensure a baseline level of dip. Considering the shallowest, narrowest aspects of each DP-gram regarding dip shape gives a minimum level of match to an ideal dip.

To determine m_{Dip}, $m_{LowPeak}$, and $m_{HighPeak}$, a moving average of DP level across frequency was calculated between the low frequency extreme (the lowest frequency data point to meet the SNR criterion, $f_2 \geq$ 1 kHz) and the high frequency extreme (the highest frequency data point to meet the SNR criterion, $f_2 \leq$ 8 kHz). Each averaging window spanned at least a third of an octave (either 5 or 11 consecutive frequency points depending on the frequency resolution of the data—14 or 28 pts/octave, respectively) and allowed for no more than two (three at higher resolution) rejected points in a given window. The frequency of the dip in DP-gram (f_{Dip}) is the center frequency of the averaging window yielding the lowest average across frequency while the average itself is m_{Dip}. To ensure that the "dip" was not assigned to either frequency extreme of the DP-gram, the center of the moving average window used to determine m_{Dip} and m_{Dip} was constrained to lie at least half of an octave from both the low and high frequency extremes of the DP-gram. Specifically, m_{Dip} could not correspond to any of the 8 (in the 14 points per octave case) or 16 (in the 28 points per octave case) frequency data points adjacent to the extremes of the DP-gram as defined above. The peak magnitudes, $m_{HighPeak}$ and $m_{LowPeak}$, were the highest DP magnitudes yielded by any window with center frequency greater than f_{Dip} ($f_{HighPeak}$) and lower than f_{Dip} ($f_{LowPeak}$), respectively.

Figure 1 shows three examples of DP-grams and their respective *d* and *b* measurements. Figure 1a is a typical DP-gram displaying a dip. Figure 1b shows a DP-gram with a dip that has greater breadth on the high frequency side and greater depth on the low-frequency side. Figure 1c shows a DP-gram that lacks a dip (*dip index* = 0). The minimum just above 4 kHz is not detected as a dip because there are too few points on the high-frequency side to justify an upward trend. Because *d* (Eq. (1)) and *b* (Eq. (2)) assess different dimensions of the DP-gram shape, the combined dip index is a weighted average of the two. The constant, *c*, accounts for the scaling differences between *d* and *b* and was adjusted so that the quantitative dip index agreed with the visual impression of a dip in the DP-gram.

$$dip\ index = \begin{cases} \text{sqrt}\,[\,(d / c)^2 + b^2]; & d > 0 \\ 0; & d \leq 0 \end{cases} \quad \text{(Eq. 3)}$$

Here, $c = 25$. In cases of zero or negative d, which indicates the absence of one of the side peaks, the dip index is set to 0, regardless of b value, to reflect an absence of dip in the DP-gram shape.

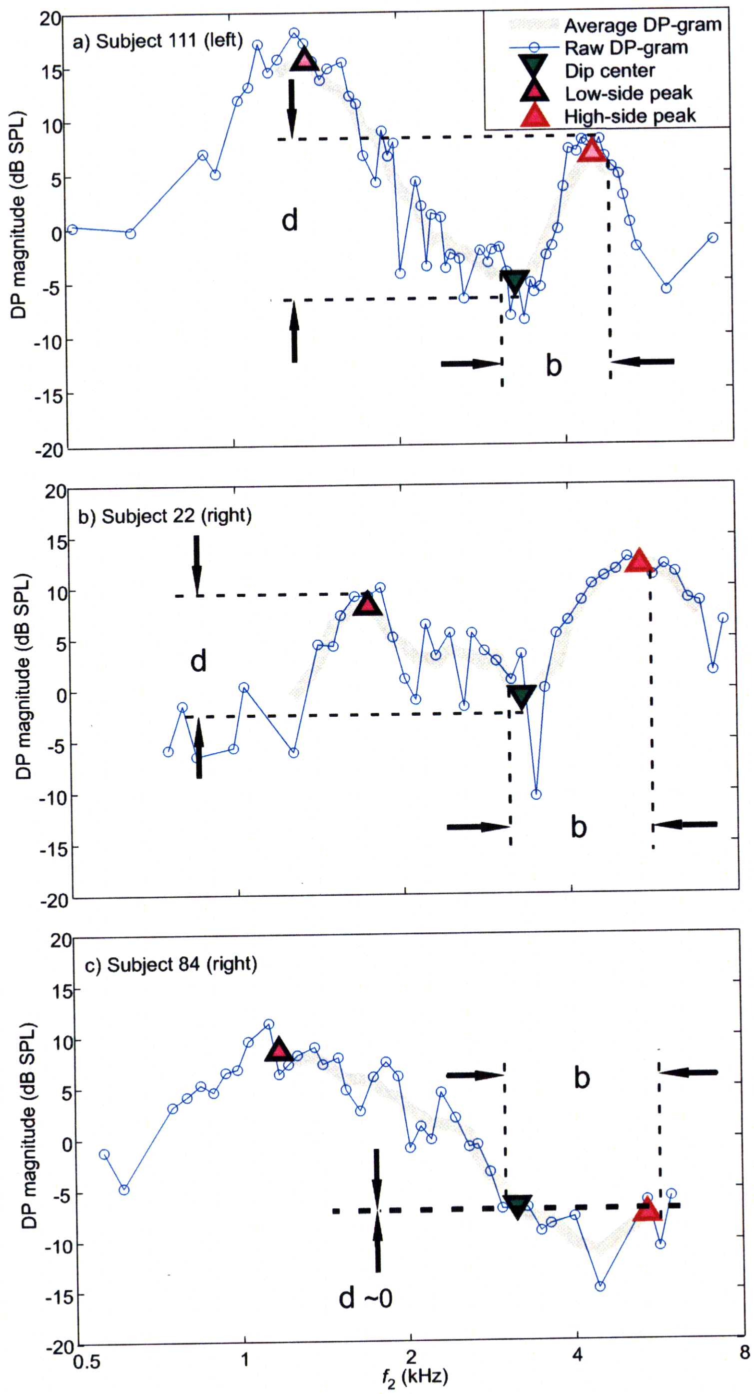


FIGURE 1

DP-grams with peaks and dip noted. The gray line shows the moving average of the DP-gram used to determine the dip (green, inverted triangle) located between two high peaks (pink triangles). The left ear of subject 111 (a) has a conventional dip. Note that the depth, d, and the breadth, b, correspond to the smaller and closer of the two side peaks. The right ear of subject 22 (b) has a smaller dip that is relatively broad, but not particularly deep. The minimum breadth and depth are on opposite sides of the dip. This helps to capture the overall qualitative impression of the DP-gram rather that simply focusing on one of the side peaks. The right ear of subject 84 (c) has a dip index of zero because $d = 0$ (see Figure 3).

Chapter 3

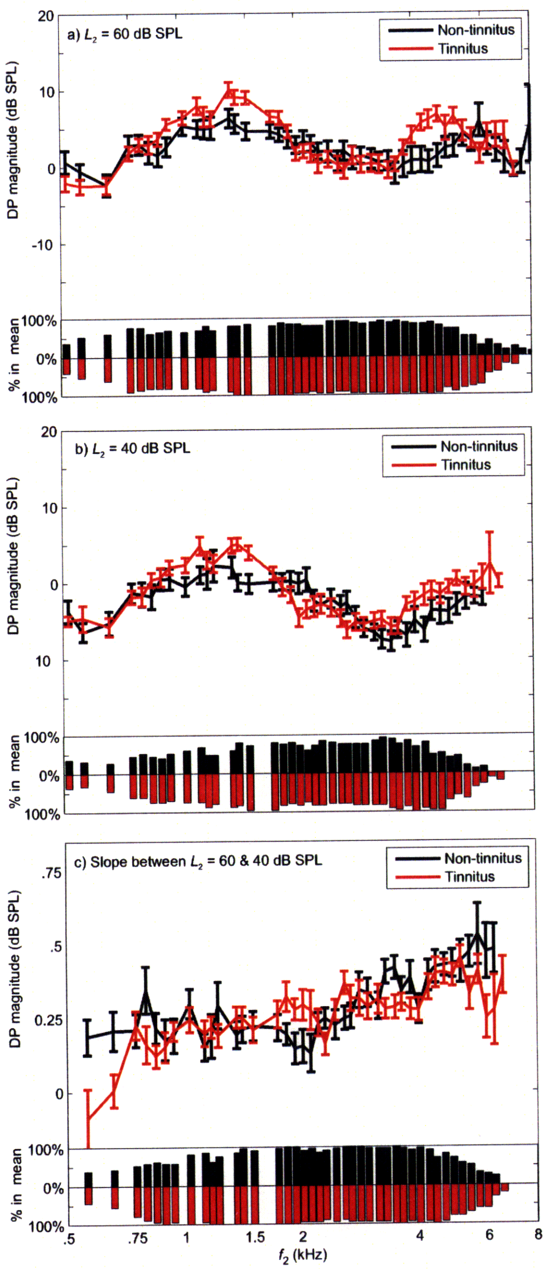
Results

The DPOAE measurements were assessed for the non-tinnitus and tinnitus populations as a whole by considering the mean magnitude at different primary levels as well as the mean growth. Individual analysis were also performed.

3.1 Average differences between tinnitus and non-tinnitus subjects

Figure 2a shows the average DPOAE magnitude vs. f_2 relationship for non-tinnitus and tinnitus subjects at the following primary levels: L_1 = 63 dB SPL, L_2 = 60 dB SPL. The mean for non-tinnitus subjects is comparable to DPOAE magnitude data in the literature for normal-hearing subjects of similar age who were tested at comparable primary levels (Dorn et al, 2005; Kummer et al., 1998). The mean non-tinnitus DP-gram also has a similar shape to those in the literature, showing a decline in magnitude below 1 kHz and a slight dip between 2 kHz and 4 kHz. The mean DP-gram for tinnitus subjects was significantly greater than the mean for non-tinnitus subjects near f_2 =1.5 kHz ($p = 7.5 \times 10^{-3}$; Mann–Whitney–Wilcoxon test) and tended to be greater for 4 kHz $\leq f_2 \leq$ 6 kHz ($p < 0.03$ for each f_2 with at least 75% of data meeting the SNR inclusion criterion; Mann–Whitney–Wilcoxon test). As a result, the tinnitus group showed an accentuation of the normal dip in DPOAE magnitude between 2 and 4 kHz (i.e., a dip of about 10 dB as compared with the few dB dip frequently observed in non-tinnitus subjects).

At the lower primary levels of L_1 = 55 dB SPL and L_2 = 40 dB SPL, DPOAE magnitude also differed significantly between non-tinnitus and tinnitus subjects (Figure 2b). Like those evoked with higher level primaries, DPOAE magnitude for tinnitus subjects was, on average, greater than for non-tinnitus subjects for f_2 = 1.5 kHz ($p = 0.04$) and 4 kHz $\leq f_2 \leq$ 6 kHz ($p < 0.05$). Again, this resulted in a more accentuated "dip" in magnitude for the tinnitus group. In addition, DPOAE magnitude for tinnitus subjects was less than that of non-tinnitus subjects near 2 kHz ($p = 0.017$; Mann-Whitney-Wilcoxon test). This was not observed in the DPOAEs evoked in the L_2 = 60 dB SPL (L_1 = 63 dB SPL) case. The different relationship between non-tinnitus and tinnitus data at L_2 = 40 vs. 60 dB SPL suggests different rates of DPOAE growth with level in the two groups. The difference can be seen in Figure 2c, which plots the slope of a line fit to the DPOAE magnitude values determined at all L_2 primary values from 40 through 60 dB SPL. Near f_2 = 2 kHz, the growth rates for tinnitus and non-tinnitus subjects differ significantly ($p = 0.025$, Mann-Whitney-Wilcoxon test).



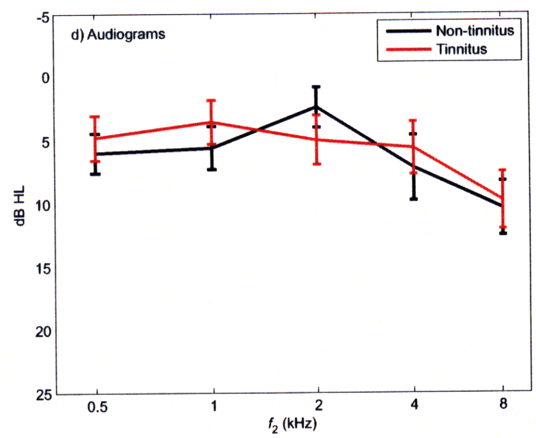
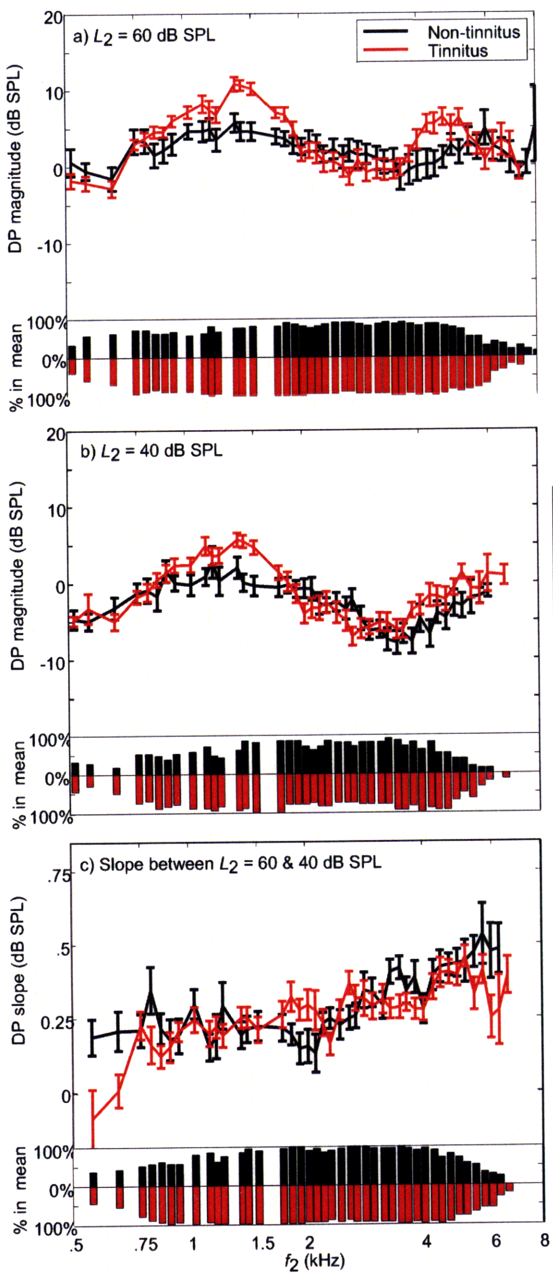


FIGURE 2

Mean DP-grams, DP growth with level, and audiograms for non-tinnitus (black) and tinnitus (red) subjects. DPOAE magnitude v. f_2 for (a) L_1 = 63 dB SPL, L_2 = 60 dB SPL and (b) L_1 = 55 dB SPL, L_2 = 40 dB SPL. (c) Mean slope of DPOAE growth from L_2 = 40 to 60 dB SPL (inclusive). For each ear and f_2, a linear, least mean-square error fit was performed across presentation levels to yield a slope value at each frequency. (d) Mean pure tone threshold. In all panels (a) - (d), each curve is an average of data from 24 (tinnitus) and 25 (non-tinnitus) ears. Bars indicate the standard error. Data for each ear is considered an independent point. Histograms below the plots in (a), (b), and (c) show the percentage of tested ears contributing to the mean DPOAE magnitude (a, b) or mean slope (c) at each f2 value. Data for a given subject and ear contributed to the mean when DPOAE magnitude exceeded the noise floor by 6 dB. The mean audiograms in (d) include all subjects and ears. No smoothing was applied to these data or that of subsequent figures.

These statistically significant differences in DPOAE magnitude and growth rate between tinnitus and non-tinnitus subjects occurred despite close audiometric, sex, and age matching between groups. Mean pure tone thresholds differed by less than 2.6 dB at any given frequency, and this difference was never significant ($p > 0.2$, Mann-Whitney-Wilcoxon test; Figure 2d). The two groups differed in average age by approximately one year and, again, not significantly (tinnitus: 42.0 +/- 9.8 years; non-tinnitus: 43.3 +/- 9.5 years; $p = 0.70$, Mann–Whitney–Wilcoxon test). Both tinnitus and non-tinnitus groups were approximately 80% male. A four-way ANOVA (tinnitus x threshold x age x sex) was conducted on the DP-grams at $L_1 = 63$ dB SPL, $L_2 = 60$ dB SPL in the frequency range where most ears consistently contributed to the DP-gram mean (1 kHz $<= f_2 <=$ 6 kHz). The test showed a significant effect of tinnitus, but no effect of threshold, age, or sex ($p_{tinnitus} = 0.02$; $p_{threshold} = 0.67$; $p_{age} = 0.54$; $p_{sex} = 0.20$).

While the subjects' sex did not appear to affect DPOAE data, low female representation in the subject groups weaken tests for sex effects. Figure 3 shows data for male subjects (11 non-tinnitus (21 ears); mean age: 42 +/- 9.3 years; 10 right-handed and 11 tinnitus (20 ears); mean age: 40.7 +/- 8.9 years, 8 right-handed) separately. The differences between tinnitus and non-tinnitus subjects apparent in Figure 2 are seen in Figure 3 as well. It cannot be stated conclusively whether the same differences hold in female subjects, but qualitative examination of the individual data for female subjects suggests that they may (compare subjects 49 and 53 to subjects 22 and 112 in Figure 4).



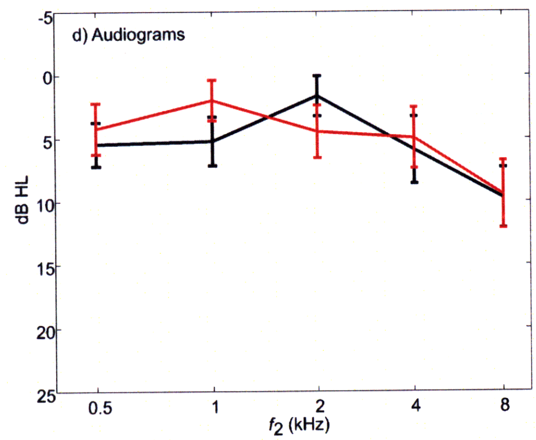


FIGURE 3

Same as Figure 2, but for male subjects only. Each curve is an average over 20 (tinnitus) or 21 (non-tinnitus) ears with histograms (a, b, and c) indicated the percentage of ears included in the mean for a given frequency when the SNR inclusion criterion is applied.

In addition to comparing tinnitus and non-tinnitus subjects as a whole, we also compared the specific tinnitus and non-tinnitus subjects contributing to the mean DP-grams in frequency ranges where DPOAE magnitude differed between tinnitus and non-tinnitus subjects. This comparison is important because 100% of ears did not contribute to the mean value at each f_2, as indicated by the histograms at the bottom of panels a – c in Figure 2. At the f_2 values showing the greatest differences between tinnitus and non-tinnitus subjects, the match was just as close for the contributing subjects as for the groups as a whole.

Data from the 10 non-tinnitus (mean age: 42 +/- 10.5 years; 8 male, 8 right handed) and six tinnitus (mean age: 45.5 +/- 7.9 years; 5 male; 5 right handed) subjects tested at the higher frequency resolution of 28 points per octave enabled an analysis of DP-gram fine structure. These groups were nearly as well age and audiometrically matched as the overall group (Figure A1 in Appendix A gives audiometric data). The largest audiometric difference at any frequency between 500 and 8000 Hz was 4.2 dB. The amount of fine structure was determined by applying a high pass filter to the DP-gram for L_1 = 63 dB SPL, L_2 = 60 dB SPL between f_2 = 1 and 4 kHz. In the frequency region considered, all ears had at least 2/3 of points meet the inclusion criterion, and on average, 92% of points in that region met inclusion criteria for a given ear. The RMS values of the filtered data, a measure of fine structure, did not differ significantly between the non-tinnitus and tinnitus populations ($p > 0.13$, Mann–Whitney–Wilcoxon test, for all cutoff frequencies such that $0 < f_{\text{cutoff}} < f_{\text{Nyquist}}$).

3.2 DPOAE magnitude in individual subjects

To identify differences between non-tinnitus and tinnitus subjects that might not be apparent from group averages, the data for individual subjects also were examined. Figure 4 shows audiograms; DP-grams at L_1 = 63 dB SPL, L_2 = 60 dB SPL; and dip index values determined at L_2 = 60 dB SPL, for each ear. The DP-grams have a range of shapes, some reflecting the dip shape apparent in the group average for tinnitus subjects (Figure 4, top right) and some not (bottom left). Notice how the audiograms do not correlate with the shape of the DP-gram and how tinnitus subjects tend to have a larger dip in their DP-grams.

From Figure 4, tinnitus subjects clearly tend to exhibit a greater dip index than non-tinnitus subjects ($p = 4.4 \times 10^{-4}$, Mann–Whitney–Wilcoxon test), but significant differences between the non-tinnitus and tinnitus populations also exist for both *b*, the breadth measure, alone ($p = 2.6 \times 10^{-4}$, Mann–Whitney–Wilcoxon test) and *d*, the depth measure, alone ($p = 0.01$, Mann–Whitney–Wilcoxon test). In Appendix A, Figure A2 shows a scatter plot of *b* and *d* derived from DP-grams at L_2 = 60 dB SPL (L_1 = 63 dB SPL) with subject number labels, and Figure A3 shows histograms of the dip index, *b*, and *d* distributions among tinnitus and non-tinnitus subjects collectively. Notably, tinnitus pitch did not correlate with dip frequency ($\rho = 0.96$, rank correlation with Spearman's rho).

Neither age, sex, handedness, dip frequency, nor threshold in dip region (i.e., pure-tone threshold taken closest to the individual's dip frequency) correlated with dip index across both subject populations (Table 3). Further, while certain characteristics are known to be more common in those with tinnitus (low LDLs, depression, anxiety, and low sound tolerance), the questionnaire scores associated with those characteristics never correlated significantly with dip index within the individual non-tinnitus and tinnitus populations (Table 4). Among tinnitus subjects, there was no correlation between

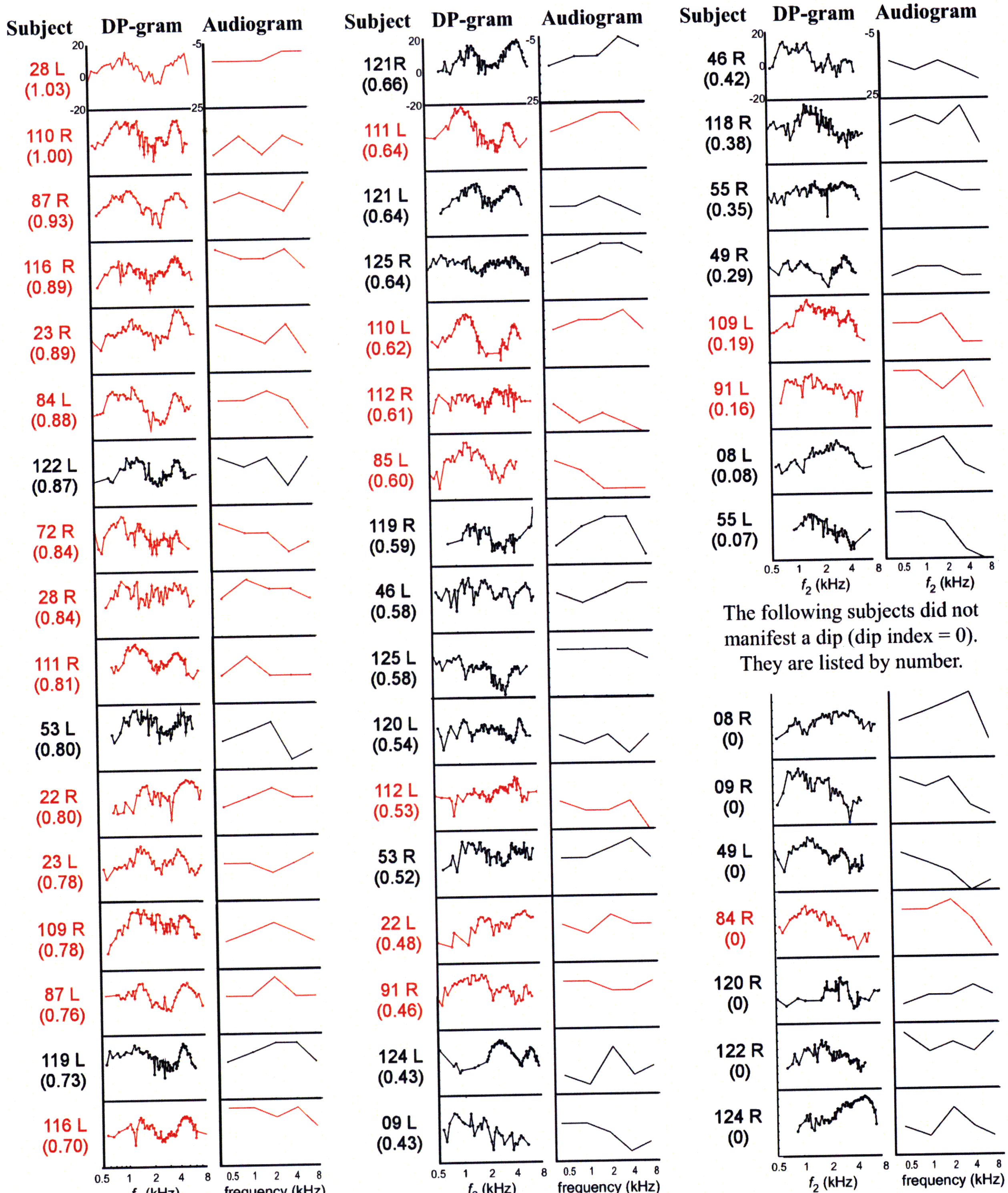


FIGURE 4

Dip index, DP-gram, and audiogram for each ear (left to right, by row). Data for tinnitus and non-tinnitus subjects are plotted in red and black, respectively. Data are ordered by dip index from greatest (top, left) to least (bottom, right). Dip indices appear in parentheses under the subject identifiers. The DP-gram was evoked with primaries L_2 = 60 dB SPL, (L_1 = 63 dB SPL). The verical axis for each DP-gram spans DPOAE magntidues from -20 to 20 dB SPL. The vertical axis for each audiogram spans from 25 to -5 dB HL.

frequency, loudness, minimum masking level (MML), TRQ, or tinnitus duration. In cases of lifelong tinnitus, the subject's age was used as the duration (Table 5). In the subject with unilateral tinnitus, her non-tinnitus ear actually had a larger dip index than her tinnitus ear, but there were not enough subjects with unilateral tinnitus to test for a relationship between tinnitus laterality and DP-gram shape. Notably, there did seem to be a difference in dip index between subjects with "lifelong" tinnitus and those who developed tinnitus later in life (p = 0.033, Mann–Whitney–Wilcoxon test between subpopulations of tinnitus subjects), as they tend to have smaller dip indices than other tinnitus subjects. All analyses shown in Tables 3, 4, and 5 used non-parametric ranking methods: either the Mann–Whitney–Wilcoxon test or rank correlation with Spearman's rho (ρ).

TABLE 3
Comparison between subject characteristics and dip index

Characteristic	Correlation with dip index (p or ρ)
Age	ρ =0.37
Sex	p =0.60
Handedness	p = 0.77
Threshold at dip frequency	ρ = 0.79
Dip frequency	ρ = 0.08

TABLE 4
Comparison between dip index questionnaire responses and LDL

Characteristic	Tinnitus vs. non-tinnitus subjects	Correlation with dip index (p or ρ)		
		All subjects	Non-tinnitus	Tinnitus
LDL	$p = 0.08$	ρ = 0.19	ρ = 0.64	ρ = 0.19
Depression	$p = 1.2 \times 10^{-5}$	$\rho = 1.6 \times 10^{-3}$	ρ = 0.83	ρ = 0.40
Anxiety	$p = 1.5 \times 10^{-3}$	ρ = 0.40	ρ = 0.23	ρ = 0.23
Sound tolerance	$p = 3.2 \times 10^{-3}$	ρ = 0.02	ρ = 0.62	ρ = 0.63

TABLE 5 Comparison between dip index and tinnitus characteristics	
Characteristic	**Correlation with dip index (ρ)**
Tinnitus frequency	ρ = 0.69
Tinnitus loudness	ρ = 0.39
Minimum masking level	ρ = 0.44
TRQ	ρ = 0.13
Tinnitus duration	ρ = 0.73

Further, differences between subjects cannot be explained by individual differences in earplug placement and size. There was little change in the DP-gram when these factors were systematically varied (Figure 5a). While the literature contains many studies that defend the consistency of DPOAE measurements across time (e.g., Gorga, 1994), we nonetheless conducted repeated measurements, months apart, in 4 subjects. The variability observed between measurements (Figure 5b-d) was not enough to account for the extreme differences in Figure 4. Thus, the range of DP-gram shapes exceed what can be explained by within-subject variability or variability in measurement technique. Only a few of the ears were retested at some or all of the primary levels. Figures 5b and 5c show DP-grams at L_2 = 40 dB SPL in two female control subjects. Figure 5d and 5e show DP-grams at L_2 = 60 dB SPL for two control subjects, a female and a male respectively.

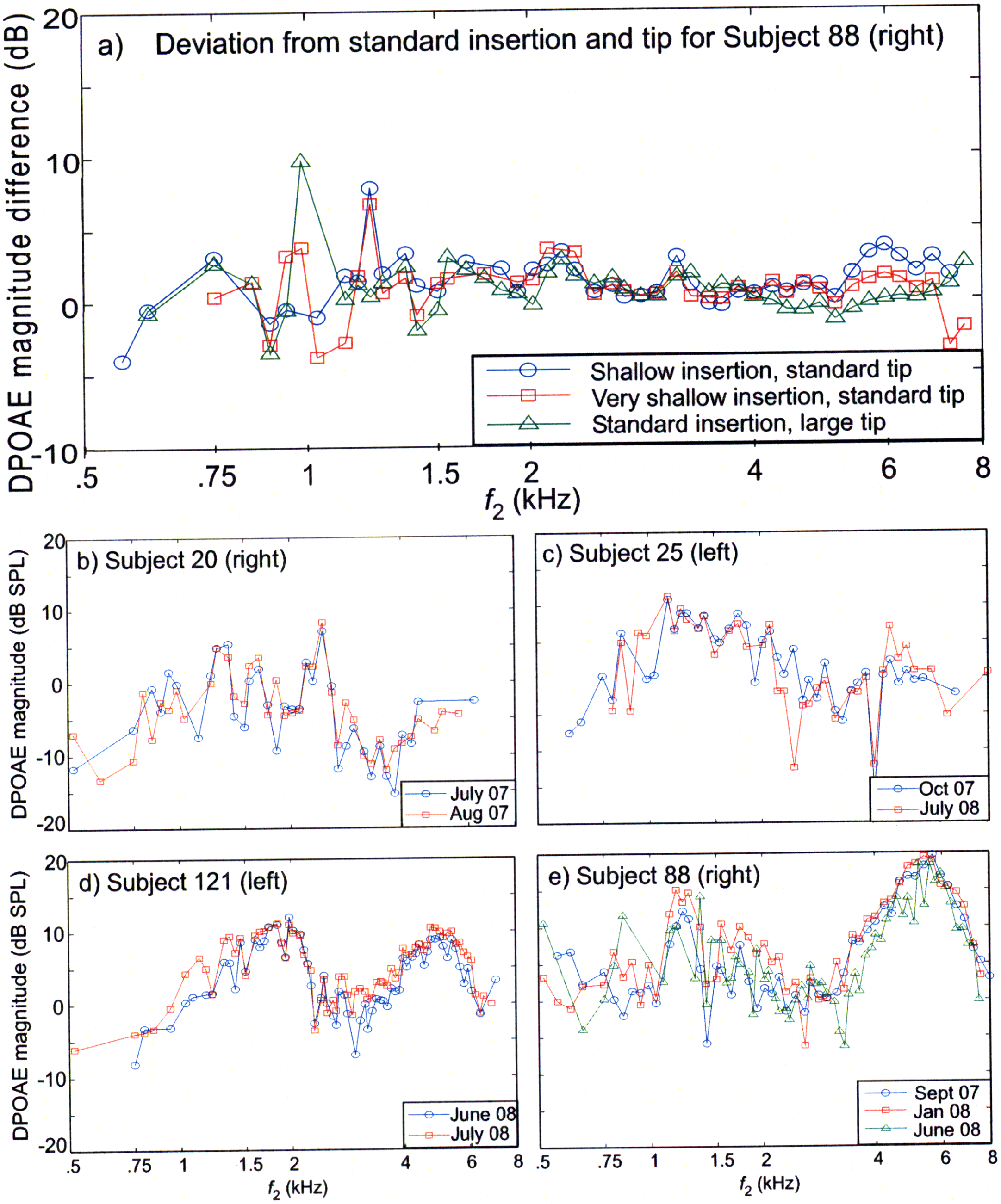


FIGURE 5

DP-grams were insensitive to probe size or placement (a) and were stable across measurement sessions (b-e). (a) A DP-gram taken with standard insertion and ear tip was subtracted from DP-grams measured during the same session using a shallower insertion (blue), a much shallower insertion (red), and larger tip than reasonably fit the subject (green), all at $L_2 = 60$ dB SPL ($L_1 = 63$ dB SPL). Superposition of DP-grams measured at $L_2 = 40$ dB SPL ($L_1 = 55$ dB SPL) taken (b) a month apart in the same setting and (c) 11 months apart in different settings (quiet rooms, sound-attenuating chambers); and DP-grams measured at $L_2 = 60$ dB SPL (L1 = 63 dB SPL) taken (d) 1 month apart in the same setting and (e) 3, 6, and 9 months apart twice in the same setting at lower resolution and once in a different location at higher resolution (June 08). The same ear is shown in both a) and e), but all data in e) were taken with a standard ear tip and insertion.

Chapter 4

Discussion

Compared with the average of their non-tinnitus counterparts, the mean DP-grams for tinnitus subjects show larger magnitude in lower and higher frequency regions (i.e., f_2 near 1.5 kHz and 4 kHz $\leq f_2 \leq$ 6 kHz, respectively). Tinnitus subjects also showed lower mean DP magnitude in the middle frequency region, forming a "dip" shape. Although non-tinnitus subjects had a slight dip, the dip observed in the tinnitus population was substantially deeper. While the literature has not previously considered DP-gram shape related to tinnitus, the exaggerated dip can be observed in previously published DP-grams of tinnitus subjects with normal audiograms (Ozimek et al., 2006; Mitchell et al., 1995; Shiomi et al., 1997). The literature also presents a DP-gram dip in tinnitus patients with notched hearing loss (Shiomi et al., 1997) and in a patient with salicylate-induced tinnitus whose dip became shallower after recovery (Janssen et al., 2000). Although this study carefully accounted for noise exposure and only considered subjects without hearing loss or a history of auditory pathology, the findings regarding the DP-gram dip may extend to other populations of tinnitus sufferers.

4.1 A possible peripheral auditory correlate to tinnitus

The DP-gram differences observed between non-tinnitus and tinnitus subjects imply a peripheral auditory difference between the subject populations that does not affect pure-tone thresholds. At the low-to-moderate levels used in this study, DPOAEs reflect the behavior of the cochlear amplifier (Brown, 1989). Within the cochlear amplifier, electromotile cochlear outer hair cells, which are innverated by efferent neurons from the medial olivocochlear (MOC) bundle, provide stimulus-dependent feedback to the basilar membrane (Geisler, 1998). Several studies in the literature suggest dysfunctions in the cochlear amplifier may contribute to some forms of tinnitus (e.g., Ceranic et al., 1998; Chery-Croze et al., 1994; Job et al., 2007; Nottet et al., 2005; Shiomi et al., 1997; Zenner and Ernst, 1993). Outer hair cell damage may contribute directly to certain kinds of tinnitus. On the other hand, outer hair cell malfunctions may not have a causal role in tinnitus, but may simply coincide with other pathologies, such as the loss of high-threshold spiral ganglion neurons or the malfunction of MOC feedback. Looking to potential MOC involvement, guinea pig studies have suggested that weaker efferent feedback from the MOC correlates with in increased vulnerability to acoustic injury (Maison and Liberman, 2000). Linking acoustic injury to tinnitus, Nottet et al. (2005) showed that the duration of tinnitus after acute acoustic trauma (AAT) correlated with DP levels, and that DP differences persisted in those with tinnitus following AAT even after pure-tone thresholds returned to their previous level. Even though all subjects in this study deny acute acoustic trauma, the acoustic intensities encountered in daily life may be enough to cause non-threshold shifting damage and induce tinnitus in those with cochlear amplifier dysfunction. Alternately, abnormalities in the cochlea amplifier may induce basilar-membrane resonances (i.e., spontaneous emissions) and lead to the perception of sound at all times. Finally, it is possible that when OHCs unevenly feedback on the basilar membrane, the difference between cochlear amplification in different frequency regions leads to central compensatory mechanisms and, thus, tinnitus perception.

4.2 Predictive potential of DP-grams regarding tinnitus

It is not clear whether the tinnitus subjects in this study manifested a DP-gram dip before developing tinnitus. In a study of fighter pilots, Job et al. (2007) reported bilaterally lower DPOAEs in the 1.5 kHz $\leq f_2 \leq$ 2.8 kHz range among those who occasionally experience tinnitus after flights compared with those who never experience tinnitus. While DP-gram abnormality may predict a person's likelihood of experiencing temporary, noise-induced tinnitus (as Job et al., 2007, contend), it is not as clear whether DP-grams predict tinnitus vulnerability. A predictive DP-gram dip that precedes tinnitus onset may explain why some subjects who currently do not experience tinnitus manifest rather large DP-gram dips; however, it is also possible that some individuals have a DP-gram dip related to tinnitus. Within the tinnitus population, DP-grams may change to manifest the dip at the onset of tinnitus.

4.3 Relationships between subject characteristics and DP-gram shape

Although all tinnitus subjects in this study had idiopathic tinnitus, there was no correlation between subject characteristics, tinnitus characteristics, or questionnaire responses and dip index in individual tinnitus subjects. The subjects with lifelong tinnitus typically did not manifest the dip shape observed in other tinnitus sufferers. In particular, subject 109, who cannot remember a time without tinnitus, and subject 91, who has always had intermittent tinnitus that slowly evolved into constant tinnitus, have very low dip indices. Another lifelong, bilateral tinnitus subject, 10, who was not included in the presented cohort because a suitable control match could not be found, also has bilaterally low dip indices. These three male tinnitus subjects may indicate that lifelong tinnitus has a different etiology than other forms of tinnitus. The other lifelong tinnitus subject in this study raises further questions. Until two years before testing, subject 85 had experienced low-level chronic tinnitus for as long as he could remember. Then, his percept changed dramatically and became more intense. Unlike other life-long tinnitus suffers, his DP-gram manifests a dip in his normal-hearing ear. This does not disprove the lifelong tinnitus/dip relationship; rather, it raises the question of whether some changes in tinnitus percept may have the same origin as idiopathic tinnitus that begins later in life. Regardless, this work seems to confirm Levine's suggestion (2006) that examining individual data in any physiological investigation of tinnitus (OAE, imaging, evoked potentials) may be crucial for identifying different physiological forms of tinnitus to the extent they exist.

Acknowledgements

I would like to thank my advisers, Jennifer Melcher and Christopher Shera, for their guidance, insight, and support. I am fortunate to have advisers who asked a lot of me. The standards that I set for my work now are higher than they were 18 months ago. I also am grateful that Jennifer and Chris have encouraged me to pursue my interests and passions regardless of where they lead.

I also want to thank Dr. Robert Levine for the many hours he allowed me to observe in his tinnitus clinic. I am also grateful to Dr. Christopher Halpin for his assistance in all aspects of audiology, to Barbara Norris for her logistical help, and to Wendy Gu for her friendship and collaboration.

I want to thank my husband, Jared, for daily encouragement and constant support.

Finally, I would like to thank my parents for putting family first and for showing me, by example, the joy of learning and the satisfaction of hard work.

Appendix A

Additional Figures

Figure A1 shows the mean audiograms for tinnitus and non-tinnitus subjects tested at higher resolution. Like Figures 2d and 3d, there is no significant difference between the subject populations at any of the frequencies tested.

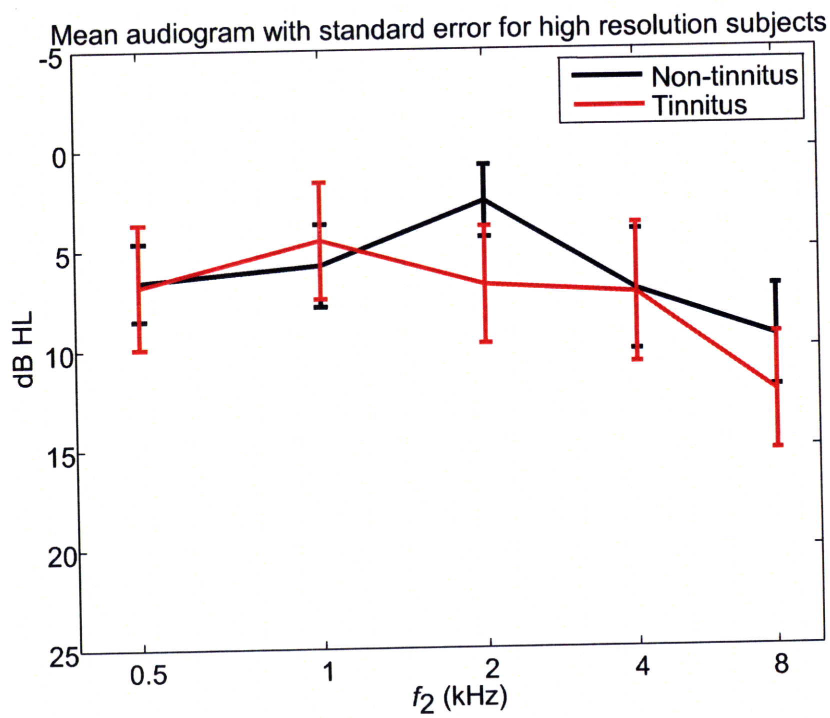


FIGURE A1

The mean audiograms of subjects tested at higher resolution (28 points per octave) in the non-tinnitus and tinnitus populations.

Figure A2 is a scatter plot showing the individual breadth (*b*) and depth (*d*) values for all subjects by ear. The dip indices, which take both breadth and depth into account, are shown in Figure 4.

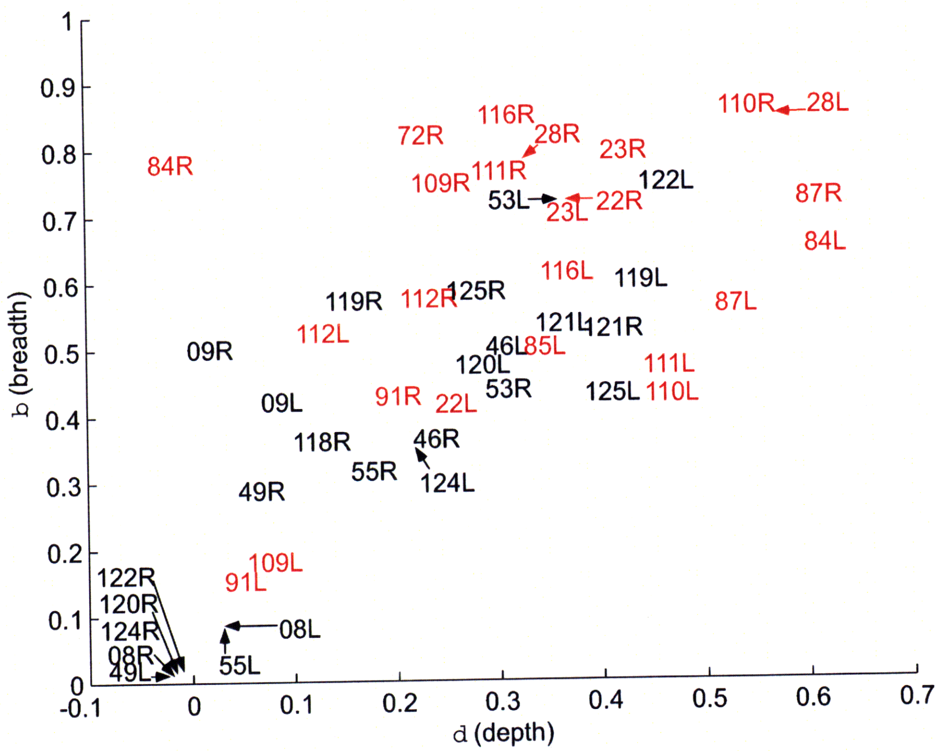


FIGURE A2

A scatter plot of tinnitus (red) and non-tinnitus subjects (black) showing the b and d values for individual subjects generated from the subject's DP-grams at L_2 = 60 dB SPL (L_1 = 63 dB SPL). Note the general trend for tinnitus subjects to show larger b and d values than their non-tinnitus counter parts. When an arrow is not present, the b and d values correspond to the lower left corner of the label. Here the depth is normalized by the maximum possible depth (i.e. the range between the largest and smallest DP magnitudes observed for all subjects). The normalization value was the same for all subjects.

While the scatter plot in Figure A2 provides information about individual subjects, Figure A3 presents histograms of the dip index, *b*, and *d* distributions among tinnitus and non-tinnitus subjects collectively. Again, we see group differences between tinnitus and non-tinnitus subjects for these measures of DP-gram shape.

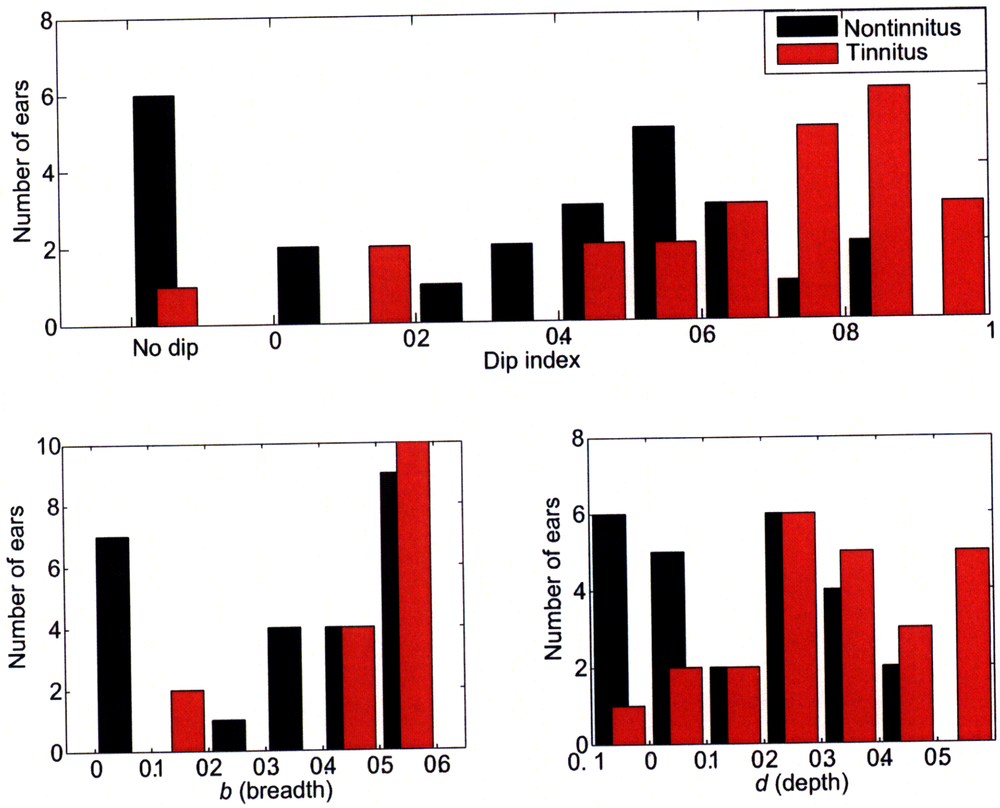


FIGURE A3

Histograms showing the dip index, *b*, and *d* values for tinnitus and non-tinnitus subjects based on their DP-grams at $L_2 = 60$ dB SPL ($L_1 = 63$ dB SPL). The dip index (a) is zero for subjects without peaks on both frequency sides of the dip. Thus, the negative values shown in the d histogram (c) correspond to the "no dip" subjects in (a).

Appendix B

Selected MATLAB Code

While this section shows only a tiny fraction of the code generated and used in this work, the functions here illustrate a few of the more important calculations. The first subsection shows how the means were determined for different subpopulations. The second subsection concisely illustrates slope calculation. The third subsection fleshes out the dip index in two parts. All code was run in MATLAB v.7.4.0 on a PC.

B.1 Mean calculation

The same methodology was used to calculate mean DP magnitude for several populations (e.g., all male tinnitus subjects, all non-tinnitus subjects, all tinnitus subjects whose DPOAEs were evoked at higher resolution, etc.). Code Example 1 shows how the average DP magnitude was calculated. Code Example 2 shows how the average audiogram was calculated.

CODE EXAMPLE 1
Mean DP magnitude calculation

```
function [avg, includedDataPts] = getAvgDPOAE(lev, possibleFreq, fractPresent,
varargin)

%Purpose:
%Calculates the average DP magnitude for a group of subjects
%Inputs:
% lev: identifies the L2 level used to evoke data (lev = 1 corresponds
%      to L2 = 60 dB SPL)
% possibleFreq: f2 values at which averages should be determined
% fractPresent: the percentage of ears which must have a "good" point
%      at the given frequency for a mean to be calculated
% varargin:  a cell array of identifiers for ear DP data interspersed with
%      the total number of data points at each level (either 52 or 83)
%Outputs:
% avg: a matrix with columns corresponding to f2, the mean DP magnitude
%    and the standard error
%includedDataPts: DP values averaged at a given f2 value

%Gets the data for each ear at the specified "possible frequencies"
%Only uses points that meet the SNR criterion
for count = 1:2:length(varargin)
    a = extractData(varargin{count}, 1, 1, 1, 6, varargin{count+1});
    counter = 1;
    buildingUp = [];
    for count2 = 1:length(possibleFreq)
        while length(a{lev}) > counter && a{lev}(counter, 2) >
possibleFreq(count2)
            counter = counter + 1;
        end
        if a{lev}(counter,2) == possibleFreq(count2)
            buildingUp = [buildingUp; a{lev}(counter,:)];
        end
    end
    plotThis(ceil(count/2)) = {buildingUp};
end

%This part gets the average value for each frequency point
ptsIncluded = 0;
counter = ones(length(plotThis), 1);
includedFreqs = [];
%Loops through, one frequency at a time
for count2 = 1:length(possibleFreq)
    ptsToAvg = [];
    %Collects data from all subjects with good points at that frequency
    for count3 = 1:length(plotThis)
        if plotThis{count3}(counter(count3),2) == possibleFreq(count2)
            ptsToAvg = [ptsToAvg; plotThis{count3}(counter(count3),5)];
            if counter(count3) ~= length(plotThis{count3})
                counter(count3) = counter(count3) + 1;
            end
        end
```

```
    end
    %This finds the average at the current frequency
    %At least 3 ears must be present for averaging to be valid
    if length(ptsToAvg) >= 3 && length(ptsToAvg) >= ...
       ceil((length(varargin) - 4*Con121Present)*fractPresent/2)
        ptsIncluded = ptsIncluded + 1;
        avg(ptsIncluded,1) = possibleFreq(count2);
        avg(ptsIncluded,2) = mean(ptsToAvg);
        avg(ptsIncluded,3) = std(ptsToAvg) / sqrt(length(ptsToAvg));
        includedFreqs = [includedFreqs; possibleFreq(count2)];
        includedDataPts(ptsIncluded) = {ptsToAvg};
    end
end
```

CODE EXAMPLE 2
Mean audiogram calculation

```
function meanAud = getAveAudiogram(audiograms)

%Purpose:
%Calculates the mean audiogram at specified frequencies given a set of input
%audiograms

%Inputs:
% audiograms: a cell array of subject audiograms (frequency, threshold)

%Outputs:
% meanAud: a column array with the frequency, the average threshold
%          among the input audiograms, and the standard error

%The possible frequencies for averaging are defined as follows
possibleFreq = [500, 1000, 2000, 4000, 8000];

for count = 1:length(possibleFreq)
    include = [];
    %Loop through each audiogram input
    for count1 = 1:length(audiograms)
      %Loop through each audiogram until you find the desired frequency
      %(note some audiograms contain addition frequency points)
        for count2 = 1:length(audiograms{count1})
            if audiograms{count1}(count2, 1) == possibleFreq(count)
                include = [include; audiograms{count1}(count2, :)];
                break;
            end
        end
    end
    meanAud(count, :) = [possibleFreq(count), mean(include(:,2)), ...
        std(include(:,2))/sqrt(length(audiograms))];
end
```

B.2 Slope calculation

While most of the analysis considered DP-grams, DPOAE magnitude as a function of stimulus frequency at a single stimulus level (i.e., a single L_2 value and corresponding L_1 value), the slope calculation allowed for direct comparison across levels. From the slope, we can determine how increasing and decreasing stimulus levels affect a specific point along the cochlea, corresponding to a particular frequency. Code Example 3 provides some insight into this calculation.

CODE EXAMPLE 3
Slope calculation

```
function [lineFit] = getSlope(growthPoints)

%Purpose:
%Calculates the slope across presentation levels

%Input:
% growthPoints: a cell array with one cell per frequency. Each cell contains %
all the points that met the inclusion criterion and the L2 value used
%      to evoke each point for that frequency.

%Output:
% lineFit: the result of a linear curve fit at each frequency level between
%       DPOAE and the L2 levels (from 40 dB to 55 dB).

%Defining empty vectors to fill with the appropriate slope values
lineFit = [];

%Loop passes through the growthPoints array frequency-wise.
for count1 = 1:length(growthPoints)
    poi = [];    %points of interest

    %This part extracts the data from each level L2 >= 40 dB SPL (allowing
    %for a 2.5 dB fudge factor)
    for count2 = 1:size(growthPoints{count1},1)
        if growthPoints{count1}(count2, 1) > 37.5
            poi = [poi; growthPoints{count1}(count2,:)];
        end
    end
    %This section finds the slope of a fitted line through points with
    %L2 = 40 to 60 dB SPL at a certain frequency
    if size(poi, 1) >= 3 %minimum necessary for calculation
        tempSlope = polyfit(poi(:,1), poi(:,2),1);
        lineFit = [lineFit; [growthPoints{count1}(1, 3), tempSlope(1)]];
    end
end
```

B.3 Dip index calculation

Two functions are included in this section. The first shows how the peak information and the dip information are determined (Code Example 4). The second calls the function shown in Code Example 4 to get the information needed to determine the dip index (Code Example 5).

CODE EXAMPLE 4
Extracting peak and dip frequency and magnitude information

```
function [dhp, dlp, dt, fhp, flp, ft] = getTroughAndPeaks(data, ptsInData, lev)

%Purpose:
%Determines the frequency and magnitude of the dip (or trough, as it is
%called here) and the peaks

%Inputs:
% data: pre-extracted subject data
% pts: the number of total points per L2 level for the subject
%(52 or 83)
% lev: identifies the L2 level used to evoke data (lev = 1 corresponds %
to L2 = 60 dB SPL)

%Outputs:
% dhp: DP mag at high frequency peak
% dlp: DP mag at low frequency peak
% dt:  DP mag at trough (dip)
% fhp: frequency of high side peak
% flp: frequency of low side peak
% ft:  frequency of trough (dip)

earAve = [];
flag = -10000; %identifies points that don't meet SNR criterion
gdPts = length(data{lev});
    if ptsInData == 83
       buffer = 16;
       %half window length (i.e. how many points must be present on
     %each side of a point to form the average)
     %In this case there are 9 consecutive frequency points averaged
       hwl = 5;
    else
       buffer = 8;
       %In this case there are 5 consecutive frequency points averaged
     hwl = 2;
    end

    %This loop finds the first good point
    firstGoodPoint = 1;
    while data{lev}(firstGoodPoint, 5) == flag
        firstGoodPoint = firstGoodPoint + 1;
```

```
    end

    %This loop finds the last good point
    lastGoodPoint = 1;
    for count2 = 1:length(data{lev})
        if data{lev}(count2, 5) ~= flag
            lastGoodPoint = count2;
        end
      %Data for f2 < 1 kHz is not considered
        if data{lev}(count2, 2) < 1000
            break;
        end
    end

    %This loop finds the moving average
    for count2 = hwl+firstGoodPoint:lastGoodPoint-hwl
        if data{lev}(count2, 5) ~= flag
            total = 0;
            ptsInc = 0;
           for count3 = count2-hwl:count2+hwl
             if data{lev}(count3, 5) ~= flag
                 total = total + data{lev}(count3, 5);
                 ptsInc = ptsInc + 1;
             end
           end
           if ptsInc >= 2*hwl - 1 - ceil(hwl/5)
            earAve = [earAve; data{lev}(count2, 2), total / ptsInc, ptsInc];
           end
        end
    end

   %Finds the trough
    [dt, index] = min(earAve((buffer-hwl)+1:length(earAve)-(buffer-hwl), 2));
    %Use buffer-hwl so the buffer starts with the first good data point
    %not the first good data point + hwl
    indexT = index + buffer - hwl;
    ft = earAve(indexT, 1);

    %Find the high side peak
    [dhp, indexH] = max(earAve((1:indexT-1), 2));
    fhp = earAve(indexH, 1);

    %Find the low side peak
    [dlp, index] = max(earAve(1+indexT:length(earAve), 2));
    indexL = index + indexT;
    flp = earAve(indexL, 1);
end
```

CODE EXAMPLE 5
Dip index calculation

```
function dipIndex = getDipIndex(subj, pts, lev)

%Purpose:
%Calculates the dip index for a given subject

%Inputs:
% subj: indentifies the subject
% pts: the number of total points per L2 level for the given subject
%(52 or 83)
% lev: identifies the L2 level used to evoke data (lev = 1 corresponds        %
to L2 = 60 dB SPL)

%Outputs:
% dipIndex: the index assigned to the subject at the specified level

%Extracts needed data
[throwAway, data] = extractData(subj, 1, 1, 1, 6, pts);

%Finds trough and peak information
[dhp, dlp, dt, fhp, flp, ft] = getTroughAndPeaks(data, pts, lev);

%Breadth
b  = [min([log2(ft'./flp'); log2(fhp'./ft')])]';

%Depth
d = [min([(dhp-dt)'; (dlp - dt)'])]';

%Scaling constant
c = 25;

%Calculates the dip index
    dipIndex = sqrt((d/c)^2 + b^2);
    %When the DP-gram only has one side peak, d will be negative.
    if d < 0
       dipIndex = 0;
    end
end
```

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