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Research paper

Impaired cochlear function correlates with the presence of tinnitus and its estimated spectral profile

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ABSTRACT

The presence of tinnitus often coincides with hearing loss. It has been argued that reduced peripheral input leads to frequency-specific increase in neuronal gains resulting in tinnitus-related hyper-activity. Following this gain-adaptation hypothesis, impaired cochlear function should be predictive of the presence and spectral characteristics of tinnitus. To assess cochlear function, perceptual thresholds and distortion product otoacoustic emissions (DPOAEs) were measured with high frequency resolution for subjects with tinnitus and non-tinnitus control subjects ($N = 29$ and $N = 18$) with and without hearing loss. Subjects with tinnitus also provided a 'tinnitus likeness spectrum' by rating the similarity of their tinnitus to tones at various frequencies. On average, subjects with tinnitus had elevated thresholds, reduced DPOAE, and increased slope of the DPOAE input-output function in the range from 4 to 10 kHz. These measures were strongly correlated and were equally predictive of the presence of tinnitus. Subjects with a pronounced edge to their hearing loss profile were very likely to have tinnitus. In the group average, the tinnitus likeness spectrum was correlated with perceptual thresholds ($r = 0.98$, $p < 0.01$), confirming previous reports. For 19 of 29 of subjects, perceptual thresholds were correlated with the tinnitus likeness ratings across frequencies and this correlation was significantly improved when low input-level DPOAE were included as an additional variable ($r = 0.83 \pm 0.09$, $N = 19$). Thus, cochlear function is strongly associated with the tinnitus percept and measures of cochlear function using DPOAEs provide additional diagnostic information over perceptual thresholds alone.

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1. Introduction

Tinnitus – the perception of a phantom sound – is often associated with hearing loss. The subjective sound varies across subjects and is often described as a 'buzz', 'ring', 'hiss', or 'hum'. Chronic tinnitus has a prevalence of 6–10% in the adult population (Vesterager, 1997). Severe tinnitus is almost always indicative of hearing loss, with the pitch of the phantom sound generally corresponding to the hearing-loss frequencies and frequently occurring at sharp edges of high-frequency loss (König et al., 2006; Moore et al., 2010). However, tinnitus is not always associated with hearing loss. Some subjects with tinnitus, particularly children, have seemingly normal hearing (Savastano et al., 2009). Also, some individuals with evident hearing loss do not have tinnitus. Therefore, while there is a relationship between peripheral hearing loss and tinnitus, hearing loss is neither a necessary nor sufficient condition for tinnitus. It is generally assumed that tinnitus may be the result of multiple physiological causes (Baguley, 2002). In all but a few rare cases (e.g. objective tinnitus) it is believed that the neural activity associated with tinnitus is generated in the central nervous system (CNS). If hearing loss is not causative for this aberrant central activity, one may ask then, why does it correlate with tinnitus at all?

This work was motivated by our hypothesis that tinnitus is the result of a central gain-adaptation mechanism that, when confronted with reduced peripheral input, increases neural gains to magnify spontaneous activity to a point at which it is perceived as sound (Parra and Pearlmutter, 2007). Gain and contrast adaptation are common strategies of the perceptual system for matching a large dynamic range of natural signals to the limited dynamic range of sensors and neurons (see Rieke et al., 1999, for a review). It may be that in some normal-hearing subjects other mechanisms are at play in generating tinnitus-related neural activity, and that reduced input is a necessary but insufficient condition for the perception of tinnitus (Rauschecker et al., 2010). But it is also possible that the conventional audiogram – a rough measure of

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hearing loss – does not adequately capture peripheral deficits. Thus, the present work aims to accurately assess peripheral hearing, and test whether careful measures of cochlear function are any more predictive of tinnitus than the conventional audiogram.

The data collected here were used to categorize subjects by a number of criteria, each meaningfully segregating the tinnitus population into subgroups for whom their tinnitus is more or less predictable based on high-resolution thresholds and distortion product otoacoustic emissions (DPOAEs). In doing so, the work extends earlier results (Noreña et al., 2002; Roberts et al., 2008; Moffat et al., 2009) by showing that hearing loss is predictive of the tinnitus percept not only on a group level but on an individual subject basis, in particular when including DPOAE as additional measure of peripheral processing. In summary, this paper will argue that careful categorization and assessment of peripheral processing may permit sub-typing of tinnitus subjects, resulting in a subset of subjects for whom treatment with precisely fitted compensatory auditory stimulation holds particular promise.

2. Methods

2.1. Subjects and procedures

29 subjects with tinnitus and 18 control subjects without tinnitus were recruited via advertisements for this study. Subjects with tinnitus (19 male, 10 female) were 47 ± 3 years old and normal-hearing control subjects (9 male, 9 female) were 40 ± 4 (age difference not significant). All subjects were paid $10/hour for participating in the experiment. An institutional review board consent form was signed before the experiment. In their first visit to the laboratory, subjects answered a list of questions related to their tinnitus (comparable to the Tinnitus Reaction Questionnaire, Wilson et al., 1991). There was no exclusion criterion based on hearing loss. For all subjects, peripheral auditory measurements were performed which included perceptual thresholds and DPOAEs. Subjects with tinnitus performed an additional procedure in which subjective ratings of their tinnitus percept were obtained to determine a 'tinnitus likeness spectrum' (Roberts et al., 2008; Noreña et al., 2002). The total experimental time per subject was approximately 4 h.

2.2. Psychoacoustics: thresholds

During the experiment, the subject was seated in a double-wall, sound-attenuating booth. All stimuli were generated digitally and played via an M-audio USB soundcard with 24-bit resolution and 44.1 kHz sampling rate. The stimuli were routed through a headphone buffer (Tucker-Davis Technologies HB7) before being presented to the listeners via Sony MDR-7506 headphones. The specific pair of headphones was equalized to obtain a flat frequency response at the ear drum. Equalization filters were obtained by recording a white noise signal emitted by the headphones with a calibrated microphone (Bruel & Kjaer model 2218) inside a KEMAR head and torso simulator. Filter coefficients were computed from these using linear prediction coefficients of order 20.

Bekesy tracking was used to obtain high-resolution absolute thresholds for both ears in a short period of time (approximately 30 min). The frequency range was from 1 to 10 kHz with 6 points per octave (22 different frequencies). Absolute thresholds were determined with narrow-band noise pulses, which are less influenced by threshold fine structure than pure tone thresholds (see Long and Tubis, 1988). Repeated narrow-band pulses lasted 250 ms with 250 ms silent gaps. Pulses had a bandwidth equal to 20% of the center frequency and amplitude onset and offset ramps followed a 25-ms Hanning half window. The initial level of the pulses was set to 50 dB sound pressure level (SPL), which was audible in most instances. However, subjects were instructed to increase or decrease the starting level of the pulses to an audible and comfortable level. During Bekesy tracking, subjects pressed a button as long as the pulses were audible. Keeping the button pressed reduced the level of the pulses by 2 dB per pulse (4 dB/s). Subjects were instructed to release the button when they no longer heard the pulses. When this occurred, the level of the pulses was increased by 2 dB per pulse. The tracking procedure terminated after 8 reversals. The thresholds reported here are the average level of the last 6 reversals. Subjects were free to take a break after each frequency but mostly chose to complete the procedure without interruption.

2.3. Tinnitus likeness test

An estimate of the spectral profile of the tinnitus percept was determined using the 'tinnitus likeness spectrum' as detailed by Roberts et al. (2008) and based on earlier work of Noreña et al. (2002). This computerized procedure assesses the quality of the tinnitus sensation including perceived location, loudness, temporal properties, quality and frequency spectrum. The following steps were completed in the order indicated. (1) *Localize tinnitus sensation:* Subjects were asked to select one of three options with the keyboard: left, right or both ears. (2) *Bandwidth of tinnitus:* Subjects indicated whether their tinnitus was 'tonal', 'ringing', or 'hissing' (Roberts et al., 2008). Three sounds were played to subjects to illustrate these choices, consisting of a 5 kHz pure tone (tonal), and two types of bandpass noise with a center frequency of 5 kHz differing in bandwidth. The two bandwidths were 5% of the center frequency (ringing) and 15% of the center frequency (hissing). (3) *Temporal properties:* Subjects were asked to indicate if their tinnitus was steady or pulsing. Corresponding audio examples were presented to illustrate these two choices. All subjects reported steady tinnitus. (4) *Tinnitus loudness matching:* Subjects were presented with sounds at various frequencies with bandwidth, modulation, and ear following their choices in steps (1) through (3). The frequency range was from 1 to 10 kHz with 3 points per octave (total of 11 frequencies). Subjects adjusted the volume of each sound to match the perceived loudness of their tinnitus, up to a maximum of 95 dB SPL (safety limit). (5) *Tinnitus likeness rating:* Subjects rated the similarity of each of the sounds presented in step (4) to their tinnitus. Thus, a rating was obtained for each of the 11 frequencies. Subjects were asked 'How much does this tone sound like your tinnitus' and could choose their answer from one of six values: 1 – 'not at all', 2 – 'a little bit', 3 – 'moderately', 4 – 'very similar', 5 – 'identical', and 6 – 'cannot hear it'. The last value ('cannot hear') was included for those subjects whose hearing loss made it impossible to hear the stimulus within the imposed safety limit. Thus a profile across frequency was obtained using the ratings for all 11 frequencies. To determine reliability, these subjective ratings were collected twice ($N = 25$; for 4 subjects only 1 rating was available) at the beginning and end of the entire session, i.e. 2–3 h apart. Whenever available, we used the average of the two repeated measures for analysis. Two examples of the resulting tinnitus likeness spectrum are shown in Fig. 1.

2.4. DPOAE measurement

Several behavioral methods exist for estimating basilar membrane compression, such as the measurement of growth-of-masking (GOM) functions in forward masking or the measurement of temporal masking curves (TMCs) (Rosengard et al., 2005). In this paper, the measurement of DPOAE input/output (I/O) functions was used to provide an objective measure of cochlear function. A technical challenge with DPOAEs is ensuring that one is measuring

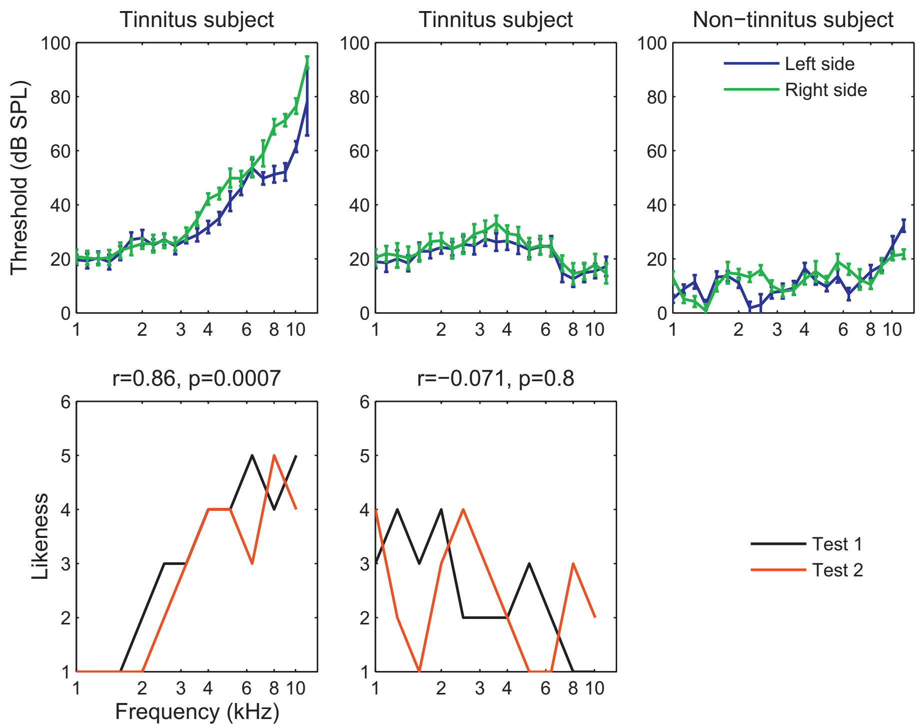

Fig. 1. Examples of absolute thresholds and the tinnitus likeness spectrum obtained using the tinnitus likeness test. Top row: Absolute thresholds for left (blue) and right ear (green). Bottom row: examples of tinnitus likeness ratings, repeated twice to assess reproducibility with correlation coefficient, r, and respective *p*-value, shown for each example. Left column: data for a tinnitus subject with absolute threshold edge and reproducible tinnitus likeness test (significant correlation over two repeats). Center column: this tinnitus subject had no absolute threshold edge and could not provide reproducible tinnitus likeness ratings (no significant correlation between repeats). Right column: Data for non-tinnitus subject. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

the response from just one frequency region in the cochlea. DPOAEs are generated in the cochlea in the region where two nearby primary tone stimuli maximally overlap (reviewed in Shera, 2004). Once the DPOAE is generated, the signal travels both basally towards the oval window and apically to its own characteristic place on the basilar membrane, where it generates an OAE similar to that generated by an external stimulus. The resulting components have the same frequency but originate from two different regions of the cochlea. To evaluate nonlinear growth, more consistent results are obtained when the component from the generator (maximum overlap) region alone is extracted (Mauermann and Kollmeier, 2004). The DPOAE procedure used here follows that of Long et al. (2008). Briefly, DPOAEs were obtained from each ear while subjects were seated in a recliner in a double-walled IAC sound-treated booth. Custom software was used to generate the primaries and to record the ear canal signals. The stimuli used for DPOAE measurement were continuously sweeping primaries with a fixed primary ratio (f2/f1) of 1.22 as described in Long et al. (2008). Sweeps were presented via ER-2 (Etymotic, Elk Grove Village, IL) insert earphones connected to the computer via a MOTU 828 (MOTU, Cambridge, MA) Firewire Interface (24-bit, 44.1 kHz). Ear canal signals were recorded with an ER-10A (Etymotic, Elk Grove Village, IL) microphone/preamplifier system and amplified by an SR560 (Stanford Research Systems, Sunnyvale, CA) low-noise amplifier connected to the same MOTU 828 interface and controlled by the same computer. Primary frequencies were logarithmically swept from an f2 frequency of 1000 − 11314 Hz at a rate of 2 s/octave. Primary tone presentation levels were set based on the scissors level paradigm (Kummer et al., 1998) where $L_1 = 0.4{*}L_2{+}39$ dB SPL, or L_2), whichever is larger. DPOAE levels were measured as a function of input signal level ($L_2 = 25–75$ dB SPL, in 10 dB steps). Several sweeps were obtained for each primary level and averaged to increase the signal-to-noise ratio between the measured DPOAEs and the background noise. The number of sweeps obtained for each level was dependent on the primary level, with the lowest presentation levels requiring more sweeps ($L_2 = 25$ dB SPL, $N = 60$) than the highest presentation levels ($L_2 = 75$ dB SPL, $N = 12$). Spectrograms of the individual sweeps were visually inspected and noisy sweeps eliminated before averaging at each level. An additional average was obtained in which every alternate sound file was inverted in phase. This cancels the DPOAE and permits evaluation of the noise floor at each frequency. A least-squares fit (LSF) procedure was used to extract the level of the DPOAE generator component for each averaged sound file using overlapping analysis windows of 1/2 s and a step size of 1/80 s (see Long et al., 2008, for a review of the LSF procedure), resulting in an estimate of the magnitude and phase of the generator component of the DPOAEs. Examples of DPOAE measures across frequency for one normal-hearing subject and one hearing-impaired subject are shown in Fig. 2, left. Cochlear compression may be estimated as the slope of the DPOAE I/O function (see Fig. 2, right). The noise floor (black line in Fig. 2) was used to determine the levels at which the DPOAE were above the background noise. Only DPOAE levels that were above the background noise level were used to measure compression. Specifically, compression was assessed as the slope of the I/O function by taking the difference between the DPOAEs obtained at 65 and 45 dB SPL input levels divided by 20 dB (compression is best measured in the mid-range of primary levels, see Neely and Kim, 2007). When the DPOAE level for the 45 dB SPL primary level did not exceed the noise floor, the range from 65 to 55 dB SPL was used instead. Slope values of 1.0 correspond to no compression, while normal compression values for a healthy cochlea are in the range from 0.20 to 0.30 (Kummer et al., 1998, see Fig. 4, center).

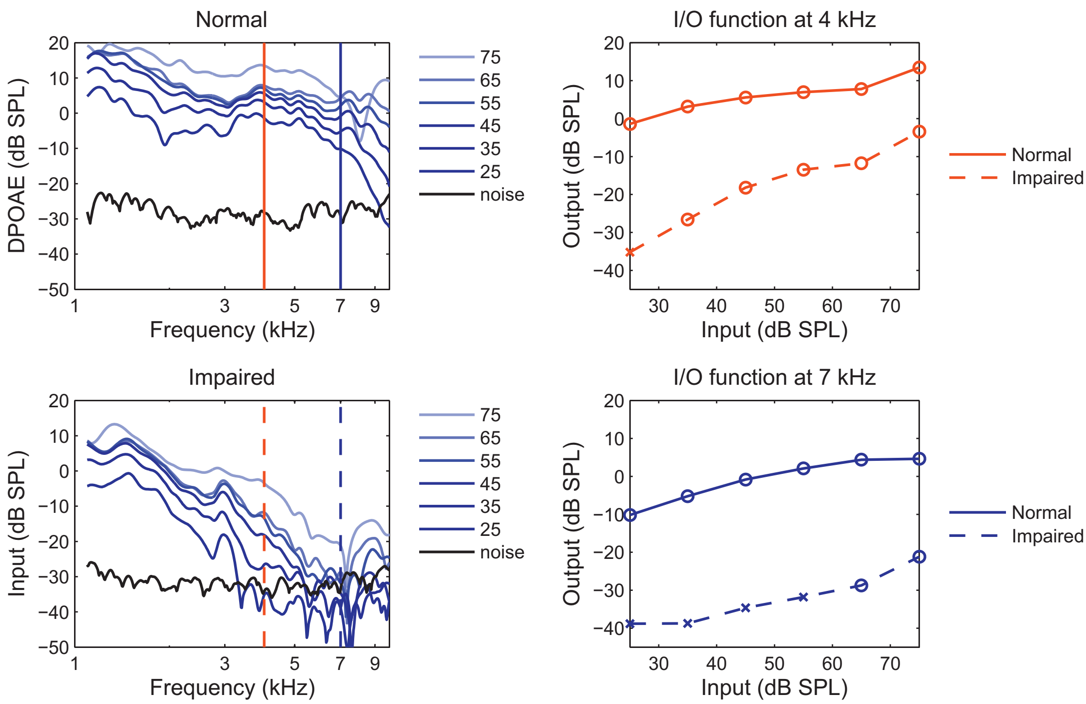

Fig. 2. DPOAE measurements from one normal-hearing (top left panel) and one hearing-impaired (bottom left panel) subject. DPOAEs are shown from 1 to 10 kHz. The vertical lines at two specific frequencies (red – 4 kHz, blue – 7 kHz) are replotted in the right column right as input-output functions. Hearing loss is associated with a decreased DPOAE level, particularly for low primary levels, and an increased slope (loss of compression). Noise floors (black lines) are shown to indicate when DPOAE measures are above the background noise. In the right panel, symbols indicate whether the DPOAE measures were above ('o') or below ('x') estimates of the background noise floor. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

2.5. *Linear prediction of tinnitus*

Three measures were used to predict tinnitus status and tinnitus likeness ratings, namely, absolute thresholds, DPOAE level (average for the 25–45 dB input levels), and DPOAE slope.

2.5.1. *Tinnitus status*

To predict the presence or absence of tinnitus for each subject, these measures were averaged for all frequencies at or above 4 kHz, resulting in 3 single-valued variables for each ear. These values were then averaged across the two ears (see discussion below). The three values obtained were then linearly combined, with coefficients determined using logistic regression (McCullagh and Nelder, 1989). Using a leave-one-out procedure (Duda et al., 2001), tinnitus status was predicted with logistic regression based on data from all subjects (tinnitus and control subjects). Receiver-operating characteristic (ROC) curves were determined from this dataset for binary classification. The area under this ROC curve (AUC) was taken as a measure of prediction (e.g. classification) performance (McClish, 1989, see Fig. 4). An AUC value of 0.5 indicates chance performance whereas an AUC value of 1.0 corresponds to perfect classification. The goal was to predict the presence of tinnitus for a given subject as opposed to predicting tinnitus for each ear. For prediction, one could either select the data from a single ear (for instance, the ear with more hearing loss) or one could base prediction on the average value across ears. We obtained comparable results with the two approaches and report here only the data using the average across the two ears.

2.5.2. *Tinnitus likeness ratings*

To predict the spectral profile of tinnitus for each subject (e.g. the tinnitus likeness spectrum), the three measures were determined for each of the 11 frequencies for which ratings were available (excluding ratings of 6, 'can't hear' and, for 8 cases, excluding frequencies in the range 7.5–10 kHz, for which the DPOAE levels were below the noise floor). The three values for each frequency were combined linearly to compute an estimated likeness rating, with coefficients determined using conventional linear regression (Montgomery et al., 2006). Linear regression was trained and tested using a leave-one-out procedure (Duda et al., 2001) using data from all frequencies and all subjects with tinnitus. Each subject was tested in turn by excluding the subject's data from the training set, and a prediction of their likeness rating was obtained from this trained set based on the coefficients described above. Prediction performance was then measured by comparing the predicted ratings obtained from the leave-one-out procedure to the actual ratings obtained for this subject. The correlation between the predicted and observed likeness ratings was taken as a measure of this prediction performance. As the likeness ratings are subjective and may have a bias and range that changes from subject to subject, a correlation metric is preferable over the conventional r-squared measure of prediction performance, as correlation is insensitive to such cross-subject variability (see Fig. 8).

2.6. *Estimate of high-frequency threshold edge*

Subjects in the tinnitus and non-tinnitus groups had various levels of high-frequency hearing loss, which was characterized here by the absolute thresholds averaged across all frequencies at or above 4 kHz. To more specifically characterize the presence of a pronounced hearing loss edge, i.e. sharp increase in hearing loss with changing frequency, we fitted a sigmoidal function to the perceptual-threshold profile across frequency:

$$I(f) = I_o + \Delta I/(1 + exp(-4(f - f_E)/\Delta f)) \quad (1)$$

where $I(f)$, is the hearing loss as a function of frequency measured in octaves (relative to 1 kHz), I_o, the offset measured in dB SPL, f_E, the edge frequency measured in octaves, ΔI is the magnitude of loss over offset measured in dB SPL, and Δf, the edge bandwidth measured in octaves. The slope of the hearing loss edge is then given by $s = \Delta I/\Delta f$. For the purposes of fitting the sigmoid, we assumed that thresholds at frequencies above the measured values (e.g. >11 kHz) remained constant. Examples of the resulting fit are shown in Fig. 5, left column. Perceptual thresholds were characterized as containing a high-frequency edge if f_E<8.5 kHz and $s > 10$ dB/octave.

3. Results

Based on the gain-adaptation hypothesis, we predicted that: i) one can distinguish between tinnitus and control subjects based on measurements of peripheral processing; ii) Within individual subjects, the spectral characteristic of the tinnitus percept can be predicted from frequency-specific measures of peripheral processing.

3.1. Correlation of perceptual thresholds and DPOAE measurements with tinnitus status

Fig. 3 compares absolute thresholds and DPOAE data for subjects with tinnitus and control subjects. Absolute thresholds above 2.7 kHz differed significantly across groups ($p < 0.05$, two-sample t-test, uncorrected for multiple comparison). This is expected, as subjects with tinnitus usually have elevated high-frequency thresholds (Noreña et al., 2002; König et al., 2006; Roberts et al., 2008). DPOAE level was significantly reduced ($p < 0.05$) in the group mean for subjects with tinnitus for frequencies above 2.8 kHz. This was true for the mean DPOAE level across all levels (25–75 dB SPL) as well as for the mean for low input levels

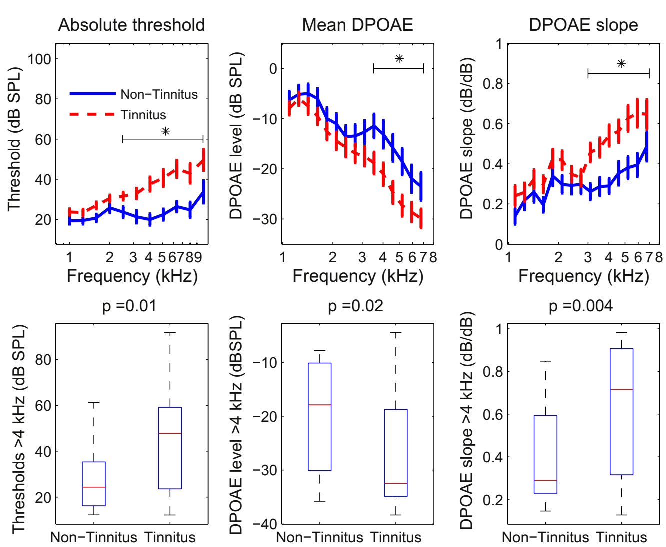

Fig. 3. Results for subjects with tinnitus and non-tinnitus controls. Top row: absolute thresholds, mean DPOAE level for 25–45 dB SPL L2 level and DPOAE input-output slope. All measures are the mean across subjects within each group (red dashed: tinnitus; solid blue: non-tinnitus). Error bars indicate ±1 standard error of the mean (SEM). The horizontal bar with star indicates the frequency range where there was a significant difference between groups ($p < 0.05$). Bottom row: Data averaged across frequencies above 4 kHz for each subject. Box and whiskers indicate median, 25 and 75 percentiles and range across subjects. P-values above each graph (computed with a Wilcoxon rank-sum test) show that subjects with tinnitus have significantly increased thresholds, decreased low-level DPOAE, and increased DPOAE input-output slope. * means $p < 0.05$. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

(25–45 dB SPL). DPOAE I/O slope was higher ($p < 0.05$) for subjects with tinnitus than for control subjects for frequencies above 3 kHz. A single-valued metric for each subject was obtained by averaging across frequencies above 4 kHz (Fig. 3, bottom row). While group median values all differed significantly ($p < 0.02$, Wilcoxon rank-sum test), the populations showed considerable overlap. This means that peripheral loss is not a perfect predictor of whether a subject does or does not report tinnitus.

To quantify how well absolute thresholds and DPOAE measures allow one to distinguish between subjects with tinnitus and control subjects, we performed an ROC analysis with a linear combination of these measures (see Methods). Classification performance was comparable when using thresholds alone (AUC = 0.72) or thresholds and DPOAE measures (AUC = 0.75) (Fig. 4, right). The difference was not statistically significant ($p = 0.12$ using the test of DeLong et al. (1988)). Indeed, high-frequency thresholds and high-frequency DPOAE slopes and low-level DPOAE were highly correlated (Fig. 4, left and center). Thus thresholds and DPOAE measures are equally predictive of tinnitus status.

3.2. Pronounced hearing loss edge is a predictor of tinnitus

Fig. 5 shows an example result for a subject with a pronounced high-frequency threshold edge (top left) and a subject without a high-frequency edge (bottom left). Subjects with an edge frequency less than 8.5 kHz and edge slope of more than 10 dB/octave were characterized as having a ‘high-frequency edge’. The right panel illustrates the number of subjects with and without a high-frequency edge for both the tinnitus and non-tinnitus groups. The same data are given in Table 1. There was a significant association between the presence of a high-frequency edge and tinnitus ($p = 0.02$, Fisher’s exact test). According to the ROC analysis in Fig. 4, high-frequency loss alone is only 66% accurate in predicting the presence of tinnitus. When restricting the analysis to subjects with a high-frequency edge, the presence of an edge was highly indicative of the presence of tinnitus (87% of subjects with the high-frequency edge report tinnitus).

3.3. Subjects with unreliable tinnitus likeness ratings are comparable to control subjects

Of the 29 subjects, 16 could reliably reproduce their tinnitus likeness ratings (significant correlations between the two sets of

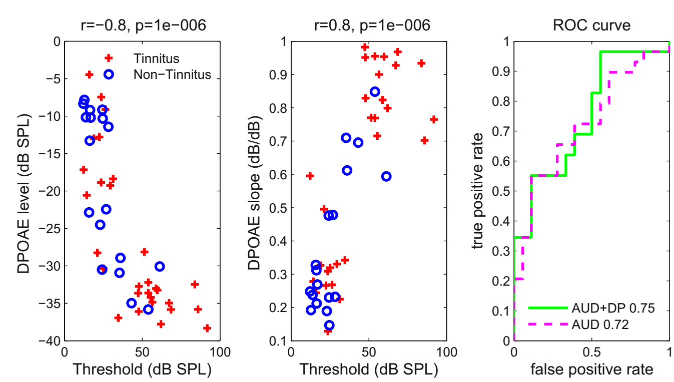

Fig. 4. Relationship between absolute thresholds and DPOAE measures. Left panel: Absolute thresholds and low-level DPOAE levels averaged above 4 kHz for subjects with tinnitus (red +) and control (blue o) subjects. Middle panel: Same thresholds plotted against DPOAE slope. Correlation coefficients, r, between these pairs of variables are highly significant. Right panel: ROC curve of performance obtained using a linear combination of absolute thresholds plus DPOAE measures (solid green line) or absolute thresholds alone (dashed magenta line). (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

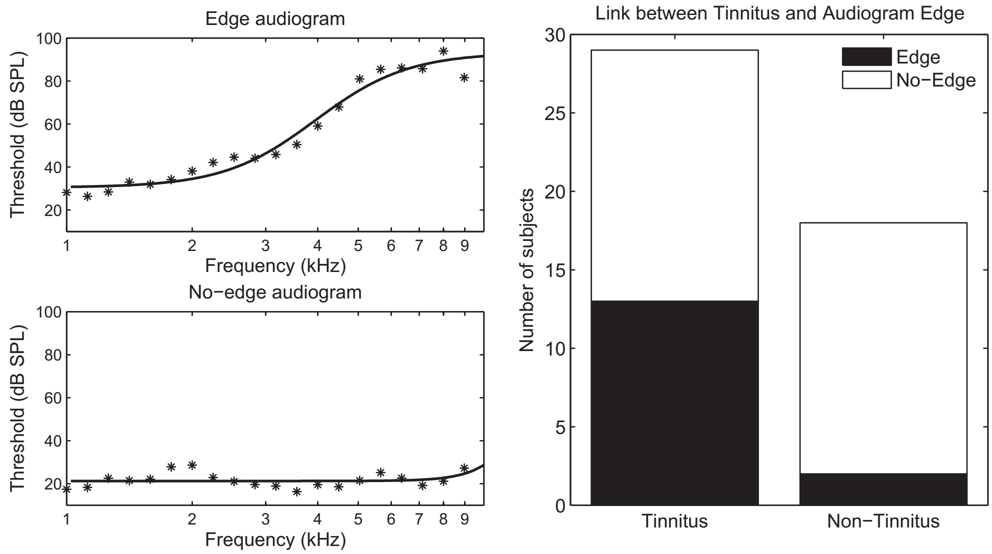

Fig. 5. High-frequency threshold edge is a predictor of tinnitus. Left: Examples of absolute thresholds for subjects with (top) or without (bottom) a pronounced high-frequency edge. Solid line shows sigmoidal fit to the thresholds. Right: Bar graph showing the number of subjects with and without a pronounced edge.

results with $p < 0.05$), 9 subjects could not reliably repeat their subjective ratings, and for the remaining 4 subjects only one set of tinnitus likeness ratings was available. We re-analyzed the high-frequency peripheral hearing measures for the 'reproducible' and 'non-reproducible' tinnitus subjects separately (Fig. 6). Subjects who could reliably rate their tinnitus likeness spectrum had significantly ($p < 0.01$) increased thresholds, decreased mean and low-level DPOAE, and increased DPOAE slope as compared with the control group. The loudness ratings in the likeness procedure did not differ between these two groups, suggesting that tinnitus loudness was comparable for the two groups. Importantly, subjects who were not able to provide a reliable judgment of their tinnitus did not differ from the control group in their peripheral hearing measures. Note that the control group included subjects with and without hearing loss (see Fig. 4).

We used Table 2 to examine if there was an interaction between the presence of a high-frequency edge and the reproducibility of the tinnitus likeness test. A Fisher's exact test showed no significant interaction between these two factors ($p > 0.05$), suggesting that the presence of a pronounced hearing-loss edge and the reproducibility of the tinnitus likeness ratings were not associated, therefore providing distinct diagnostic criteria.

3.4. *Estimated spectral profile of tinnitus can be predicted from high-resolution perceptual thresholds and DPOAE for a subset of subjects*

As reported previously (Noreña et al., 2002; Roberts et al., 2008; Moffat et al., 2009), elevated absolute thresholds coincide with elevated mean likeness ratings across subjects (Fig. 7). The goal of this study was to determine whether the spectral profile of tinnitus could be anticipated from peripheral hearing measures obtained from individual subjects. To this end, a prediction of tinnitus likeness ratings was obtained using a linear combination of thresholds or thresholds plus DPOAE using data from all subjects (both reproducible and non-reproducible) at all frequencies. Prediction performance was assessed using leave-one-out cross-validation (see Methods). The prediction results are shown in Fig. 8. For 19 of 29 subjects with tinnitus, the tinnitus likeness spectrum could indeed be predicted from these physiological measures, i.e. there was a significant correlation between the predicted and observed ratings.

Specifically, estimated likeness ratings, L, are given by the following linear regression function for each frequency:

$$L = +0.007\text{dB}^{-1}I^* - 0.05\text{dB}^{-1}I_{DP} + 0.09\Delta I_{DP} + 1.53 \qquad (2)$$

In this equation, I^* is the absolute threshold in dB SPL, I_{DP} is the low input-level DPOAE level in dB SPL, and I_{DP} is the unitless DPOAE slope, which measures cochlear compression. The coefficients indicate that tinnitus likeness ratings increase with elevated threshold (positive coefficient), reduced DPOAE level (negative coefficient), and increased slope (positive coefficient). The variance of the likeness ratings explained by each term in this sum can be

Table 1
Number of subjects in each group (tinnitus or control) with or without a pronounced high-frequency edge to their hearing loss.

	Threshold (edge)	Threshold (no-edge)
Tinnitus	13	16
Control	2	16

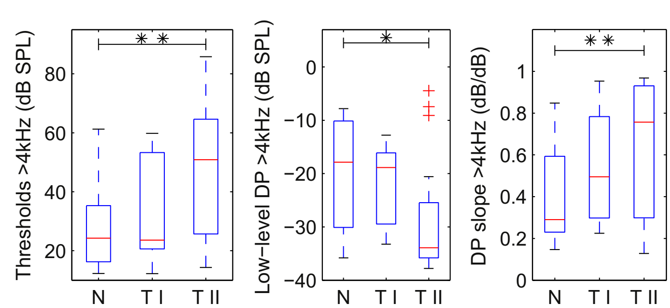

Fig. 6. Peripheral measurements from subjects with tinnitus and non-tinnitus control subjects segregated by the reliability of their subjective tinnitus likeness ratings. N denotes non-tinnitus subjects, T I denotes tinnitus subjects who cannot reliably reproduce their tinnitus likeness ratings and T II denotes those that can. Significant differences in the median values were found between N and T II for all measures ($p < 0.05$, Wilcoxon rank-sum test), but not between N and T I. * means $p < 0.05$, ** means $p < 0.01$.

Table 2
Relationship between high-frequency threshold edge and reproducibility in subjects with tinnitus. Values indicate number of subjects within each category.

	Absolute threshold (edge)	Absolute threshold (no-edge)
Number of reproducible tinnitus likeness tests	8	8
Number of non-reproducible tinnitus likeness tests	3	6

quantified by an r^2 value computed using each term in isolation for predicting L across frequencies and across subjects. The corresponding r^2 values are 0.11 for the perceptual threshold, 0.45 for the low input-level DPOAE level and 0.03 for the DPOAE slope. This suggests that low input-level DPOAE level is the best predictor among the three variables.

To determine accuracy of the prediction, a correlation was used instead of goodness of fit, because the likeness rating was subjective and the scale may be different for each subject. The observed correlation (mean and standard deviation, $r = 0.83 \pm 0.09$, $N = 19$) of the estimated tinnitus likeness spectrum with the observed likeness rating is as good as can be expected given the reliability (correlation across frequency of the two ratings provided by each subject, $r = 0.82 \pm 0.15, N = 16$; for 3 of the 19, repeated measures were not available). The remaining 10 tinnitus subjects tended to give inconsistent likeness ratings ($r = 0.31 \pm 0.31, N = 9$; for 1 of the 10, repeated measures were not available). Fig. 9 shows that the reproducibility of likeness ratings is much lower for the 'non-predictable' subjects, suggesting that ratings could often not be predicted simply because subjects were not able to provide meaningful subjective ratings.

When using absolute thresholds alone, only 13 of 29 tinnitus likeness spectral profiles could be predicted, while including DPOAE measures improved this to 19 of 29. The corresponding p values for the correlation between predicted and observed ratings are indicated in Fig. 8 with 'x' and '*', respectively. This improvement is significant ($p < 0.05$, Wilcoxon rank-sum test on correlation coefficient between perceptual thresholds alone vs. perceptual thresholds plus DPOAE measures). We conclude that, for a subset of individuals (approximately 2/3), the subjective tinnitus percept is linked to objective measurable hearing deficits.

4. Discussion

The premise of this work was that peripheral deficits are a necessary, albeit not sufficient, condition for tinnitus. The notion that reduced peripheral input leads to elevated sensitivity or spontaneous hyper-activity in central structures is well established (for

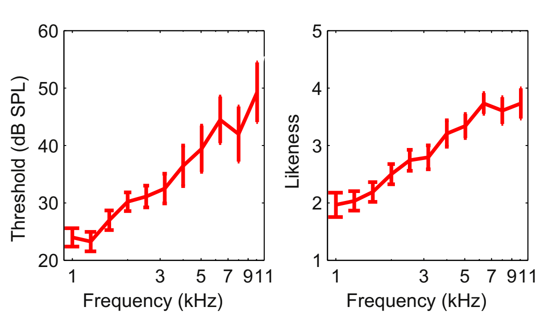

Fig. 7. Left: Group average of absolute thresholds for all subjects with tinnitus. Error bars indicate ±1 SEM. Right: Average tinnitus likeness rating for all subjects with tinnitus. Group average thresholds and likeness ratings are correlated ($r = 0.98$, $p \ll 0.01$).

review see Kaltenbach and Godfrey, 2008). Various mechanisms for this have been hypothesized including reduced feed-forward inhibition (Dominguez et al., 2006), reduced lateral inhibition (König et al., 2006), remapping of de-afferented frequency regions (Eggermont and Roberts, 2004; Roberts et al., 2010; Schaette and Kempter, 2009) and increased neuronal gains. A specific computational model of central adaptation, based on frequency dependent gains, identified three factors influencing such adaptation (Parra and Pearlmutter, 2007): 1) elevated thresholds; 2) loss of dynamic range; and 3) changing sensitivity across frequencies.

The goal of this work was therefore to measure peripheral hearing with high-frequency resolution and from this predict the presence and spectral characteristic of the tinnitus percept for a given subject. Specifically, compression was assessed using DPOAE input-output function slopes, whereas sensitivity was measured using bandpass noise thresholds. The growth of DPOAE amplitude with stimulus level reflects the nonlinear mechanical compression of the basilar membrane with stimulus level (for a review, see Neely and Kim, 2007), and therefore the use of DPOAEs here provides an objective estimate of compression. Both hearing thresholds and DPOAE compression measures have previously been analyzed in the context of tinnitus and have shown that tinnitus is marked by increased thresholds and reduced compression (Janssen et al., 1998; Hesse et al., 2005). In addition, DPOAE amplitude have been shown to be lower in frequency bands that have been matched to the tinnitus percept (Ozimek et al., 2006). The indicator that best correlates with the tinnitus percept is loss of compression (Janssen et al., 1998). This loss of compression is consistent with the co-morbidity of tinnitus and hyperacusis. Indeed, hyperacusis is associated with elevated DPOAE input-output slopes reflecting reduced compression (Bartnik et al., 2009). König et al. (2006) reported that the pitch of the tinnitus percept was correlated with the edge frequency in an audiogram. In subjects with mild-to-moderate hearing loss and bilateral tonal tinnitus, Moore et al. (2010) found a strong relationship between the values of the high-frequency edge and the mean pitch of tinnitus when using an improved definition for the edge frequency. Sztuka et al. (2010) reported that DPOAEs at the 70 dB input level were significantly higher in subjects with tinnitus and normal hearing thresholds as compared with subjects with tinnitus and hearing loss.

To our knowledge, this is the first study where perceptual thresholds and DPOAEs have been measured and analyzed from the same subjects with such high-frequency resolution and in which the distortion product components were separated, resulting in less variable measures of compression (Mauermann and Kollmeier, 2004).

Instead of the use of conventional tinnitus frequency matching (König et al., 2006), we use the tinnitus likeness rating. This technique was developed because the tinnitus percept is often more complex than a single discrete frequency (Noreña et al., 2002). By using ratings across many frequencies, we obtained a spectral profile of the tinnitus percept for each subject, which can be compared to the hearing-loss profile for individual subjects (Roberts et al., 2008). The tinnitus likeness spectrum should not be interpreted as the frequency spectrum of the tinnitus percept itself. Even when subjects are presented with a set of pure tones and asked to provide likeness ratings, one can expect a broad distribution of ratings (Penner, 1995). When we compared the tinnitus likeness spectrum across frequency with the audiogram and DPOAE measures, we found that results followed two patterns; likeness ratings across frequency which could be predicted from the peripheral measures (approximately two thirds in our sample) and likeness ratings which could not be predicted based on peripheral measures. It is noteworthy that the later group differed from the first group in that their likeness ratings were also unreliable, making them hard to predict.

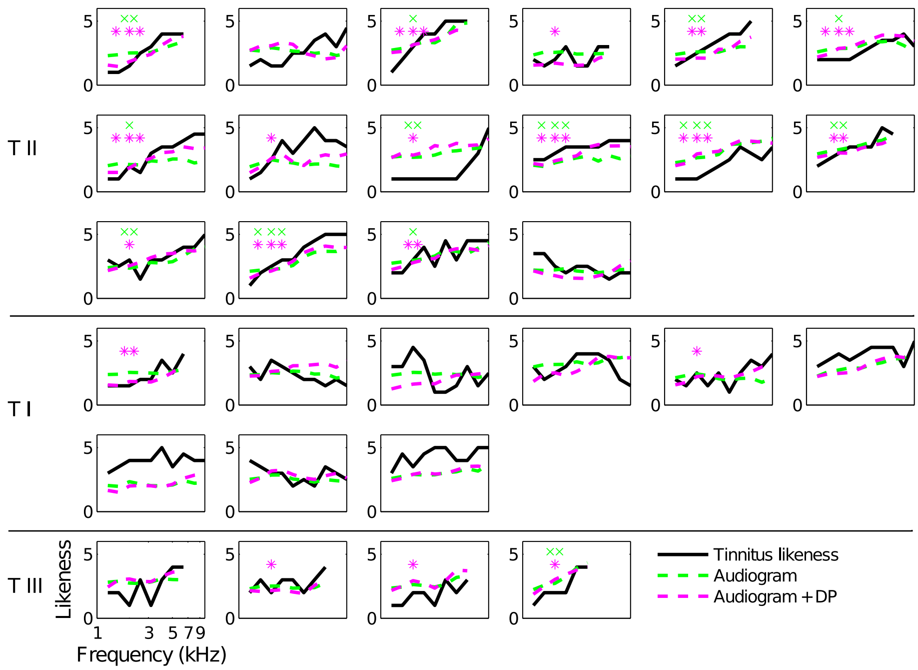

Fig. 8. Predicted and measured tinnitus likeness spectrum for individual subjects. For 19 of 29 tinnitus subjects the predicted tinnitus likeness spectrum is correlated across frequency with the measured likeness ratings ($p < 0.05$). Prediction is either based on absolute thresholds alone or on a linear combination of absolute thresholds and DPOAE measures (lower level and slope). Subjects are grouped based on repeatability of their 'tinnitus likeness rating'; T II are subjects with tinnitus who can reliably reproduce their tinnitus likeness ratings, T I are those that cannot reliably reproduce their tinnitus likeness ratings, and T III are subjects for which no second likeness rating was obtained (see results section). x and * represent significant results using Audiogram and Audiogram+DP, respectively. * means p < 0.05, ** means p < 0.01 and *** means p < 0.001.

The tight link between tinnitus and peripheral hearing in the 'predictable' group suggests that their tinnitus is indeed causally linked to their hearing loss. If so, auditory stimulation designed to compensate for the specific hearing-loss profile and characteristics may be able to reduce the tinnitus percept, provided the adaptive gain mechanism remains active. In addition, the reproducibility of the 'likeness test', and the subsequent ability to predict the likeness rating in these subjects, may indicate its diagnostic potential for sub-typing subjects with tinnitus of differing physiological origins.

Consistent with previous reports (König et al., 2006), we found that subjects with a clear high-frequency edge are likely to have tinnitus (87%). High-frequency loss and the presence of an edge were correlated, but loss alone was less predictive of tinnitus in this sample (66%). Thus, as expected (Parra and Pearlmutter, 2007), the sharpness of the hearing-loss edge represents a predictive factor. Moffat et al. (2009) reached a similar conclusion after analyzing the difference in hearing threshold between neighboring frequency regions. Consistent with previous findings (Noreña et al., 2002; Roberts et al., 2008; Schaette et al., 2010; Moore et al., 2010) and theoretical models (Parra and Pearlmutter, 2007; Schaette and Kempter, 2009), we note that the tinnitus likeness ratings were highest in the middle of the region of hearing loss and not at the edge of hearing loss as some theories based on loss of feed-forward inhibition would predict (for review see Eggermont and Roberts, 2004; Roberts et al., 2010).

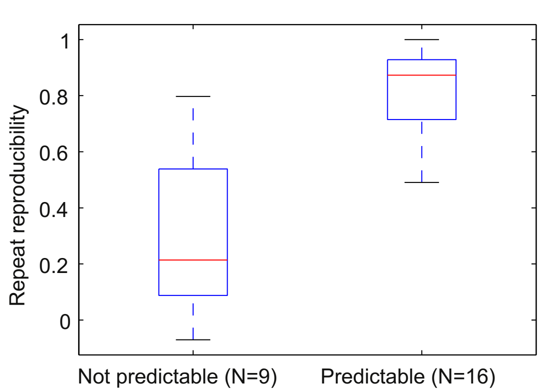

Fig. 9. Box and whiskers plot showing repeat reproducibility of the tinnitus likeness test for non-predictable versus predictable subjects with tinnitus.

The present study identified low input-level DPOAE levels as an important additional predictive variable over absolute thresholds alone. This is consistent with the correlation we found previously between a perceptual measure of gain adaptation (sensitization following notched noise) and low input-level DPOAE (Zhou et al., 2010). In contrast, compression itself may have a lower significance than we previously anticipated (Parra and Pearlmutter, 2007). Low input-level DPOAEs are a sensitive marker of cochlear function while absolute thresholds reflect both inner and outer hair-cell function. Thus, future work to test the hypothesized causal link between peripheral loss and tinnitus will aim to separate changes to inner and outer hair cells.

Another goal of this work was to predict whether a given subject does or does not have tinnitus based on their peripheral hearing measures alone. Here the results were mixed. The present sample contained subjects with or without high-frequency hearing loss in both the tinnitus and control groups. Thus, high-frequency hearing thresholds gave only 66% correct classification. We argue that even mild hearing deficits – not typically considered 'loss' – may lead to tinnitus. As a sensitive objective measure of cochlear mechanics, DPOAEs have the potential to capture such mild deficits. Consistent with previous studies in tinnitus subjects, we found reduced DPOAE levels, in particular for the low input-level DPOAEs, and increased slope, i.e. reduced compression. In the present sample, we did not find the elevated high input-level emissions reported by Sztuka et al. (2010), but note that increased slope is not inconsistent with this finding. DPOAE measures were highly correlated with hearing thresholds. This is not surprising, as the health of the outer hair cells affects both compression and sensitivity (Boege and Janssen, 2002). Inner hair-cell loss is expected to modify thresholds without changing compression. Regardless, the use of multiple measures of peripheral auditory function (e.g. absolute thresholds, DPOAEs) may have the potential to disambiguate some instances of tinnitus without significant hearing loss. While we found an increase in the ability to discriminate between subjects with tinnitus and control subjects when DPOAE measures were added, this increase was not significant. A larger sample of subjects with a precise match in hearing thresholds may be required to address the question of whether compression in itself provides an additional discriminant criterion. Such a study should focus in particular on subjects with 'normal' thresholds.

We have emphasized here that tinnitus results from hearing loss. However, not all hearing loss subjects develop clinically relevant tinnitus. Transient tinnitus is very common and it has been suggested that chronic tinnitus may be a failure to adapt via central feedback mechanisms (cf. Rauschecker et al., 2010). Essentially, those with hearing loss but no tinnitus percept may have learned to 'tune out' the aberrant percept. Indeed, all current clinical treatments emphasize some form of training that teaches patients to ignore or stop attending to the tinnitus percept.

What we propose here is that by compensating for the specific profile and characteristic of hearing loss (e.g. frequency-specific compression) one may reduce the tinnitus percept itself, including tinnitus for subjects with only mild hearing loss. Indeed, treatment with compensatory auditory stimulation has shown some promise (Davis et al., 2008; Hanley and Davis, 2008). In clinical practice, audiologists often find that tinnitus is reduced with the use of an appropriately adjusted hearing aid. However, the results are inconsistent across subjects, and a failure to show improvement may have various explanations (Moffat et al., 2009). A similar theory exists for hyperacusis (cf. Formby et al., 2003), and similar compensatory aids have also shown promising results (Chery-Croze, 2007).

In our view, only a subset of subjects may benefit from auditory stimulation, namely those for whom the tinnitus percept precisely tracks their peripheral deficit. Lack of observable peripheral deficits in other subjects may point to more central origins of their tinnitus percept. Even among those subjects with peripheral deficits, frequency regions with profound hearing loss may preclude effective neuronal stimulation even with high amplitude auditory stimuli. In light of the importance of the audiogram-edge effect, it may be that clinical fitting procedures may not have had the required frequency resolution. Finally, conventional hearing aids are often limited in frequency range, but when they do reach the typically high tinnitus frequencies encouraging results have been obtained (Schaette et al., 2010). We propose that future studies on auditory stimulation focus on the appropriate subject population, a broad coverage of frequencies, and a fine-resolution fitting procedure.

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