TINNITUS AS THE RESULT OF GAIN ADAPTATION

by

XIANG ZHOU

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dissertation requirement for the degree of Doctor of Philosophy.

Professor Lucas Parra

Date — Chair of Examining Committee

Professor Mumtaz Kassir

Date — Executive Officer

Professor Glenis Long

Professor Marom Bikson

Professor Luis Cardoso

Professor Ofer Tchernichovski

Supervisory Committee

THE CITY UNIVERSITY OF NEW YORK

Abstract

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By

Xiang Zhou

Advisor: Professor Lucas C. Parra

Tinnitus is the perception of a phantom sound without peripheral input signal. Usually tinnitus correlates strongly with hearing loss. However, not all subjects with hearing loss have tinnitus and not all tinnitus subjects have significant hearing loss. We hypothesized that tinnitus is the result of a gain-adaptation mechanism that when confronted with degraded peripheral input increases neuronal gains such that spontaneous neuronal activity is perceived as a phantom sound.

Following this hypothesis, the first aim of this study was to find a link between the strength of neuronal gain adaptation and cochlear compression. Compression was assessed using distortion product oto-acoustic emissions (DPOAEs). The neuronal gain adaptation was obtained with indirectly psychoacoustic measurement. The experiment results suggested that short-term dynamic adaptation leading to perceptual sensitization is the result of an active process mediated by the outer hair cells, which are thought to modulate the gain of the cochlear amplifier via efferent feedback.

Then we expected that impaired cochlear function would be predictive of the presence

of tinnitus and of its spectral characteristics. To assess cochlear function, DPOAEs with high frequency resolution as well as thresholds measured using narrow-band noise. For all tinnitus subjects we obtained a "tinnitus likeness spectrum" – a rating of the similarity of the tinnitus percept with tones of varying frequency.

Tinnitus subject had elevated thresholds, reduced DPOAE, and increased DPOAE input-output function slope. Within individual subject we found a correlation of the threshold profile with the likeness-spectrum profile and this correlation was significantly improved when taking low-level DPOAE into account. Thus we conclude that in tinnitus, cochlear function, and in particular outer hair-cell function, as measured by low input-level DPOAE, may provide additional diagnostic information over the threshold alone.

The results suggested that, not for all but for this subset of tinnitus subjects, correcting the specific peripheral deficit may restore the elevated central gains and thus reduce tinnitus. Future work will test the prediction that frequency specific compensation of compression and sensitivity has a causal effect on tinnitus loudness.

DEDICATION

This is dedicated to my parents, Mingsheng Zhou and Xiulan Wu, who love me, believe in me, inspire me and have supported me every step of the way.

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Chapter 1: Research Motivation and Thesis Overview

Tinnitus is often associated with hearing loss. Current evidence suggests that reduced input from the cochlea leads to hyperactivity in adaptive central structures but the precise physiological mechanisms and origins are not well understood. The research approach of this thesis is based on the following hypothesis: Tinnitus is the result of a central gain adaptation mechanism, which, when confronted with reduced or degraded peripheral input elevates neuronal sensitivity to the point of generating spontaneous hyperactivity. A computational model of this mechanism suggests that reduced cochlear compression increases required gain adaptation. That reduced compression also facilitates the tinnitus percept as it increases the gap between loud sounds and silence, thus aggravating the relative depth of hearing loss (Parra and Pearlmutter, 2007).

To capture the strength of gain adaptation, we measured the sensitization to masked tones following notched and band noises. The sensitization observed with this procedure was explained by the model as an instance of gain adaption. To measure compression we measured distortion product otoacoustic emission (DPOAE). To test this neural gain adaptation model, the first aim of this study was to find a link between the strength of neuronal gain adaptation and cochlear compression. However, as reported in Chapter 3 the hypothesized link was not observed. Instead, across subjects, stronger sensitization correlated with stronger DPOAEs evoked by low-level

primaries. In addition, growth of DPOAEs correlated reliably with perceptual thresholds across frequencies within subjects. Together, the data suggested that short-term dynamic adaptation leading to perceptual sensitization is the result of an active process mediated by the outer hair cells, which is thought to modulate the gain of the cochlear amplifier via efferent feedback.

The model further predicted that tinnitus should correlate with cochlear function. To test this prediction, the second aim (Chapter 4) of this study, therefore, was to determine whether impaired cochlear function correlates with presence of tinnitus. In previous research, both elevated hearing threshold and loss of compression have separately been associated with tinnitus. However, these measures have not yet been evaluated jointly as predictors of tinnitus with sufficiently high frequency resolution. The present data in Chapter 4 indicated that elevated hearing threshold, reduced DPOAE and increase slope (loss of compression) strongly correlated with presence of tinnitus. This result is consistent with the neural gain adaptation hypothesis.

The third aim of this thesis was to predict the tinnitus spectral profile from these peripheral measures for each individual subject. Audiograms and distortion product otoacoustic emissions (DPOAE) provided complementary measures of sensitivity and compression and were differentially affected by damage to inner and/or outer hair cells. To access tinnitus spectral profile, tinnitus likeness rating (Roberts et al., 2008) was used in our experiment. In this procedure subjects rated the similarity of their tinnitus percept with sounds at various frequencies rather than just trying to match to a

single best tone. Previous research already identified the correlation between the tinnitus likeness rating and hearing threshold in a group average of tinnitus subjects (Roberts et al., 2008). In our study, we tried to predict the tinnitus likeness rating cross frequency for each subject from the audiogram, DPOAE and DPOAE slope using linear regression. The results in chapter 4 indicate that we can indeed predict tinnitus rating on a subset of subjects. We found that low input-level DPOAE significantly improve the prediction over the audiogram alone.

For this subset of subjects, the results suggest that correcting the specific peripheral deficit may restore the elevated central gains and thus reduce tinnitus. But all of these results only established correlation. Future work will test the prediction that frequency specific compensation of compression and sensitivity has a causal effect on tinnitus loudness.

In summary, the goal of this thesis was to advance the diagnostic criteria and develop potential treatment options for tinnitus, based on careful assessment of peripheral deficits.

Chapter 2: Background on Tinnitus and Gain Adaptation Hypothesis

2.1 Tinnitus

Tinnitus is the perception of a phantom sound without peripheral input signal. When subjects stay in a quiet room for a while, most of them report that they can hear a phantom sound in the brain. This subjective sound varies and is often described as a “buzz”, “ring”, “hiss”, “hum”, or like. These sounds or noises are referred to as tinnitus. Mild tinnitus is common and usually does not disruptive to most subjects, but severe tinnitus usually impairs the quality of life, leading to sleeplessness, anxiety, depression, and even suicide. Chronic tinnitus has a prevalence of 6-10% in the adult population (Vesterager, 1997). For approximately 1% of the subjects, tinnitus symptoms are severe enough to require medical treatment (Leske 1981; Davis and Refaie, 2000).

Duaman and Tyler (1992) suggested that several classification criteria are needed to classify tinnitus. Normal tinnitus is experienced by most people even in the absence clinical hearing loss. In this case, tinnitus lasts less than few minutes and less than once per a week. In contrast, pathological tinnitus the duration lasts for more than five minutes and repeats several times per week. Within pathological tinnitus, Duaman and Tyler (1992) distinguish between acceptable or unacceptable tinnitus conditions as well as temporary or permanent tinnitus.

The acceptability of tinnitus is often evaluated with standard questionnaires, such as the Tinnitus Reaction Questionnaire (TRQ) (Wilson et al., 1991). Short-term temporal tinnitus may result from a temporary dysfunction of the auditory system, such as after noise at work or drug exposure. But permanent tinnitus usually disrupts the patients' daily life.

It is believed that tinnitus is generated in the central nervous system (CNS) but is triggered by peripheral deficits (Schaette and Kempter 2006; Dominguez et al., 2006; Schaette and Kempter, 2008, 2009). Particularly severe tinnitus is often indicative of hearing loss (Hesse et al, 2005; Roberts, 2008) with the pitch of the phantom sound generally corresponding to the frequencies of hearing loss.

Both animal models and functional imaging data in tinnitus patients suggest that tinnitus is associated with increased neuronal activity, increased synchronicity and functional reorganization in the auditory cortex (Giraud et al., 1999; Lockwood et al., 2001; Weisz et al., 2005, 2007; Norena, 2007). Many sites along the auditory pathway have been implicated in tinnitus (Basta and Ernst, 2004; Weisz et al. 2007; Sun et al., 2009; Wei et al., 2010). It is well established that the impaired cochlear leads to the increased spontaneous activity (hyperactivity) in central auditory nuclei. This hyperactivity is believed to be involved in the generation of tinnitus. This has been demonstrated in a wide range of animals models using either mechanically, acoustically, or drug induced cochlear lesions (Kaltenbach et al., 2000; Seki and Eggermont 2003; Kaltenbach et al., 2004; Ma et al., 2006; Brozoski et al., 2007;

Bauer et al., 2008; Dong et al., 2009,2010; Mulders and Robertson, 2009).

In summary, it is believed that the most cases, tinnitus percept does not immediately originate at the cochlear. Instead, it has often been associated with adaptive phenomena in the central nervous system (Hesse et al., 2005). Models of tinnitus have concentrated on a variety of descriptive mechanisms (Eggermont and Roberts, 2004), involving reduction of afferent inhibition, loss of lateral inhibition, spontaneous synchrony of deafferented cortex, or homoeostatic plasticity (Dominguez et al., 2006; Koenig et al., 2006).

2.2 Cochlea

The ear is the anatomical organ that detects sound, which includes outer ear, middle ear and inner ear. The outer ear is the most external portion of the ear that includes the pinna, the ear canal, and the very most superficial layer of the tympanic membrane (ear drum). The main function of outer ear is to collect the sound through the ear canal to the ear drum. The middle ear is the portion of the ear internal to the eardrum, and external to the oval window of the cochlea. The middle ear includes the three ear bones: the malleus, incus, and stapes, which connect with the oval window of the cochlea. The inner ear includes both the organ of hearing (the cochlea) and a sense organ that is attuned to the effects of both gravity and motion (labyrinth or vestibular apparatus). In this thesis, our discussion only focused on the cochlea.

The cochlea is the auditory sensor located the inner ear. The understanding of function

of the cochlea can provide insight into many aspects of auditory perception. Figure 2.1 shows the structure of the cochlea, which is shaped like the spiral shell of a snail.

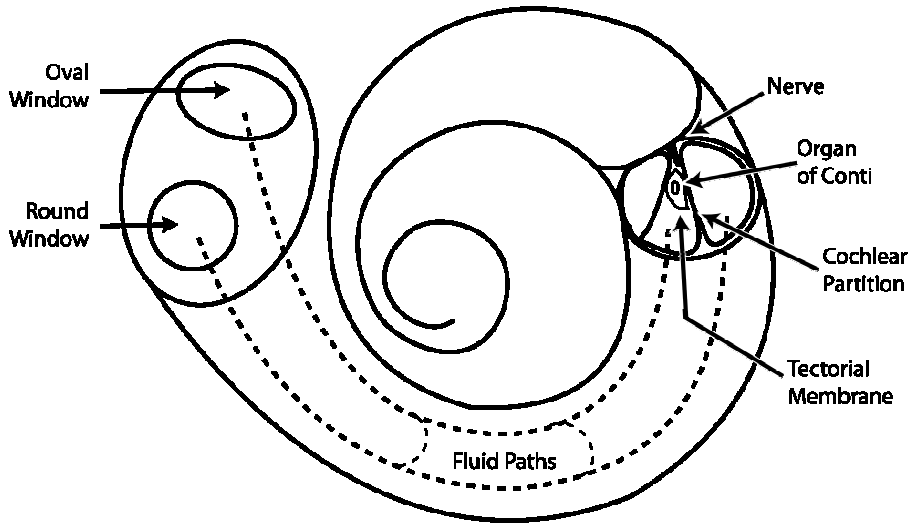

Figure 2.1 Structural diagram of the cochlea: Fluid is pushed at the oval window, deflects the cochlear partition, and bulges back out at the round window (Lyon, 2007).

"The response of basilar membrane to the different frequency sounds is strongly affected by its mechanical properties. The hair cells in the organ of Corti are tuned to certain sound frequencies, being responsive to high frequencies near the oval window and to low frequencies near the apex of the cochlea. The frequency that gives maximum response at a particular point on the basilar membrane is known as the characteristic frequency (CF) for that place. Generally, each point on the basilar membrane can be considered as a band pass filter with a certain center frequency (corresponding to characteristic frequency) and bandwidth, and with slopes outside the pass band (Moore, 2003). Figure 2.2 schematically shows the frequency selectivity of basilar membrane.

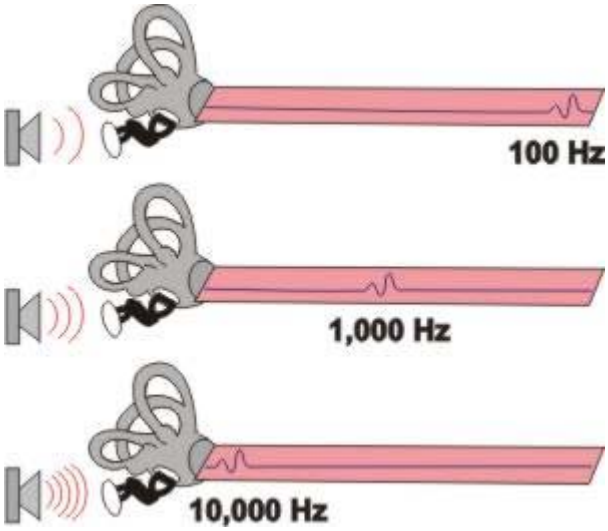

Figure 2.2 Frequency selectivity of basilar membrane (BM): The traveling wave reaches its maximum on the basilar membrane at a distance from the oval window that is characteristic for a given frequency (Zanker, 2009).

For the normal cochlear, the BM motion at the characteristic frequency is almost linear with very low input sound pressure (around 20dB SPL) and at high input sound pressure. However, in the middle input levels it grows at slower rate. This indicates a compressive non-linearity. The large range of input sound levels (around 120 dB) is compressed into a narrow range of neural response on the auditory system. This nonlinear input-output function can be measured directly at the basilar membrane (Robles et al., 1986; Ruggero et al. 1997) or estimated indirectly via psychophysical masking experiments (Oxenham and Plack, 1997; Nelson et al., 2001) or distortion product otoacoustic emission measures (DPOAE; Williams and Bacon 2005; Zhou et al., 2010). Both theoretical model (Eguiluz et al., 2000) and psychophysical experiments (Robles et al., 1986; Ruggero et al. 1997; Oxenham and Plack, 1997; Nelson et al., 2001; Williams and Bacon 2005; Zhou et al., 2010) indicated that this compressive effect is between the 0.2 and 0.5 for normal cochlea. The input-output

function of the cochlea evaluated with DPOAE is shown in Figure 2.4.

The no-linear effect only occurs at the position on the basilar membrane corresponding to the characteristic frequency. In the impaired cochlear, this no-linear growth basilar membrane response with input signal magnitude is not observed. The impaired cochlear loses the ability to provide input-output compression and this typically correlates with hearing loss. There are many potential causes of hearing loss, such as very loud noise that leads to hair cell damage.

Humans have about 15,000 – 20,000 hair cells organized into one row of inner hair cells and three rows of outer hair cells (LeMasurier and Gillespie, 2005). When sound pressure goes through the ear canal and eardrum and then arrives at the middle ear, three small bones vibrate under this pressure. When the oval window of the cochlear is set in motion by this movement, a pressure difference is applied across the Basilar membrane (BM), which causes the BM to move. Cochlea is filled with an incompressible liquid. Between the basilar membrane and the tectorial membrane are hair cells, which form part of a structure, called the organ of Corti. As the fluid in the cochlear moves, thousands of hair cells are set in motion, and convert that motion to electrical signals that are communicated via neurotransmitters to many thousands of nerve cells. These primary auditory neurons transform the signals into electrical impulses known as action potential, which travel along the auditory nerve to structures in the brain for further processing (Moore, 2003).

It is well established that the healthy mammalian cochlea is nonlinear, due to

normally functioning outer hair cells (OHCs; Sellick et al., 1982; Ruggero and Rich 1991). The outer hair cells move in response to the voltage across the membrane of the cell wall. This voltage differences across the cell wall is generated by opening gates at the top the stereocilia due to the relative motion of the basilar membrane and the tectorial membrane. Thus the vibration is converted into electrical potentials. The increased vibration of the basilar membrane leads to more neurotransmitter is released at the base of the hair cell. The release of this neurotransmitter leads to the generation of action potentials in the auditory fibers. Different auditory nerve fibers are differentially sensitive to the neurotransmitter. Some (high spontaneous) only need a litter neurotransmitter but fire a lot even when there is no sound and saturate within 20-40 dB. Others (low spontaneous) need a lot of neurotransmitter before they fire. They only fire very rarely when there is no sound and have wide dynamic ranges. The high spontaneous rate fibers have low thresholds and the BM is linear at low levels so they saturate quickly. The low spontaneous fibers have high threshold and response at levels where the BM is nonlinear. The combination of low and high spontaneous units means the overall auditory nerve response has a wide dynamic range.

Inner hair cells provide the major input to the auditory centers of the central nervous system. In the inner ear, sensory hair cells not only detect but also amplify low amplitude sound. This adaptive amplification is thought to be mediated by the outer hair cells (OHCs), which are in the position to modify basilar membrane mechanics on a cycle-by-cycle basis and is often referred to as the cochlear amplifier (Cooper et al., 2008, as review). The amplification at the low amplitude level is stronger than at

the high amplitude level. This compressive non-linearity provides a reduction in the output range of the incoming sound and an increase in dynamic range required for proper transmission to the auditory nerve. Auditory nerve fibers are active at some rate even when no sound is presented. This is called spontaneous activity, and it is driven by events in the cochlea. The firing rate of auditory nerve fibers, however, increases following the increase of the input sound level. Sachs and Abbas (1974) indicated that the firing rate of auditory-nerve fiber at the fiber's characteristic frequency (CF) increased rapidly over a ranged of 20 to 30 dB above threshold. The rate saturated completely at high sound pressure levels. The firing rate didn't systematically increase when the sound level was increased beyond 30 dB above threshold (see figure 2.3, Yates et al., 1990). Similar results (20 – 50 dB) were reported by others (Smith, 1985; Zwislocki, 1987; Zheng et al., 1999; Dreyer and Delgutte, 2007; Wen et al., 2009).

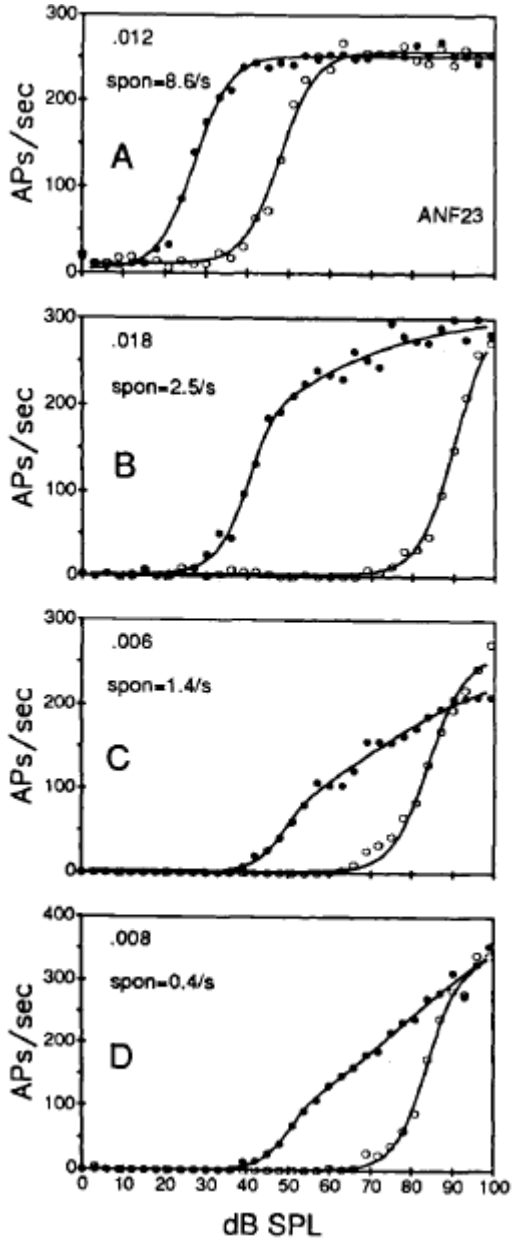

Figure 2.3 Rate-intensity functions recorded from four auditory-nerve fibers at two frequencies (CF and frequency on the tail): A, example of high spontaneous unit; B and C. two examples of medium spontaneous; D, example of low spontaneous unit. (Yates et al., 1990)

2.3 DPOAE provides objective measure of cochlear compression

Measures of non-linear processing in the cochlea can be obtained psychophysically or audiometrically (Williams and Bacon, 2005). Both growth of masking (GOM) and temporal masking (TM) are used to measured cochlea compression. But one problem

of these methods is that takes very long time to estimate the cochlea compression with high frequency resolution. Parra et al. (2010) investigated “the psychophysical pulsation threshold procedure for measuring distortion products (Plack, Oxenham 2000) but found the task difficult to perform. In contrast to a subjective psychophysical metric, distortion product otoacoustic emissions (DPOAE) provide an objective and efficient procedure for evaluating frequency dependent compression (Epstein and Florentine, 2005). A technical challenge for DPOAE is ensuring that one is measuring the response from just one frequency region in the cochlea. DPOAE are generated in the cochlea in the region where two nearby primary tone stimuli maximally overlap (Shera 2004). Once the DPOAE is generated, the signal travels both basally towards the oval window, and also to its own preferred place on the cochlea, 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 from one region alone, one must extract the component from the generator region (Kalluri and Shera, 2001). Long et al. (2004, 2008) developed a procedure in which the primary tones are continuously swept while maintaining a constant frequency ratio. A number of identical sweeps are averaged to reduce noise. The level and phase of the DPOAE are extracted by manipulating the phase and amplitude of the expected components so that RMS error between the predicted waveform and the ear canal signal is minimized. The analysis is then conducted on overlapping windows to provide a detailed picture of DPOAE analysis as a function of frequency. By varying the sweep rate and analysis window,

one can either include both components and evaluate DPOAE's fine structure, or extract the generator component alone. In as little as one hour one can obtain estimates of the DPOAE level as a function of frequency over a range of three octaves (1kHz-8kHz) and a wide range of stimulus levels. In the Figure 2.4, we show the example of the generator component of DPOAE that is measured from both normal and impaired hearing subject with high frequency resolution. The right row of Figure 2.4 indicates the slope of input-output function (compression) of cochlear. In the impaired hearing subject, the loss of compression is observed."

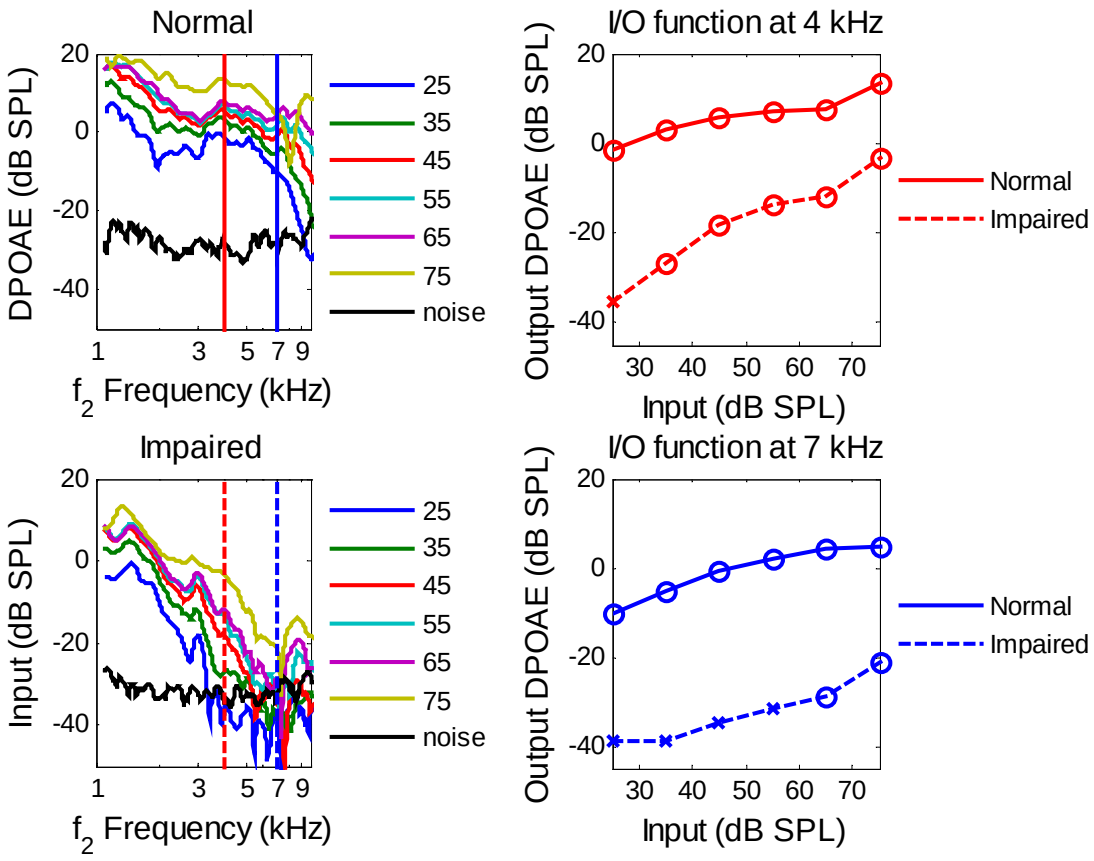

Figure 2.4 DPOAE measurements of normal and impaired hearing subjects: DPOAE is measured from 1k to 10k for both normal (top left) and impaired hearing subject (bottom left). Input-output function of cochlear is plotted at top right panel (4 kHz) and bottom right panel (7 kHz) separately. The loss of slope (compression)

indicates the hearing loss at that frequency.

2.4 Adaptation and Optimality

“It is a common characteristic of the nervous system that the adaptation changes with the different external stimulation conditions. Perhaps the best-known gain adaptation mechanism is the closing of the iris when we step from a dark room into bright sunlight. The recent neurophysiological experiments have indicated that the amplitude of the transfer functions of neurons in the early visual and auditory systems are not static, but are adaptive to the contrast or the variance of time-varying stimuli, which exhibits a contrast gain control phenomenon. This phenomenon is thought to be mediated by a contrast gain mechanism and serves to match a large dynamic range of natural signals to the limited dynamic range of sensors and neurons (Rieke et al., 1996). In particularly, the adaptation to stimulus variance has been observed in both visual neurons (Romero et al., 2003) and auditory neurons (Jenison, 2001) in some animal experiments.” (Parra et al., 2010)

The analogous effect in hearing is the acoustic middle-ear reflex, which mechanically attenuates sound transmission to the cochlea in response to loud sounds (Moller, 2000). Barlow’s efficient coding hypothesis suggests that, given a finite capacity to transmit information, sensor neural system builds an optimally efficient coding strategy to represent the large dynamic range input signal. The most compelling evidence of gain adaptation in the auditory system comes from psychophysical studies, which show increased sensitization in response to reduced input (Formby et

al., 2003; Dean et al., 2005, 2008).

Efferent feedback to outer hair cells is thought to control the gain of cochlear amplification (reviewed in Guinan et al., 2006), while auditory nerve fibers are known to adapt their firing rate at various time scales (Smith and Zwislocki, 1975). In this context it is interesting to note that the efferent inhibition of outer hair-cell function as evidenced by distortion products may be impaired in most tinnitus subjects (Hesse et al., 2005).

A central mechanism is also consistent with the finding that unilateral cochlear implants generally reduce contralateral tinnitus (Quaranta et al., 2004). Gain could also be adjusted through inhibition and/or excitation of primary afferent nerve fibers through lateral olivocochlear (LOC) efferents (Mulders and Robertson, 2005). Finally, the sensitivity (perceptual threshold) will change when the central neuronal gain adjusts with the different external signals. Dean et al., (2005, 2008) indicated that the responses of neurons in the inferior colliculus (IC), the major midbrain nucleus of the auditory pathway, adapt to the statistics of the prevailing distribution of sound levels. Wen et al., (2009) reported that dynamic range adaptation, distinct from classic firing rate adaptation, also occurred in primary auditory neurons.

Note that in the periphery this adaptation is equivalent to changing sensitivity and compression – the two key parameters that we hypothesize to affect the severity of tinnitus. Our neural gain adaptation model is shown in Figure 2.5. Rather than describing the phenomena, this neural gain adaptation model aims to explain why

tinnitus occurs (Parra and Pearlmutter, 2007). Therefore, targeted compensation of peripheral deficit could reduce the hyperactivity of auditory cortex and alleviate the tinnitus symptom.

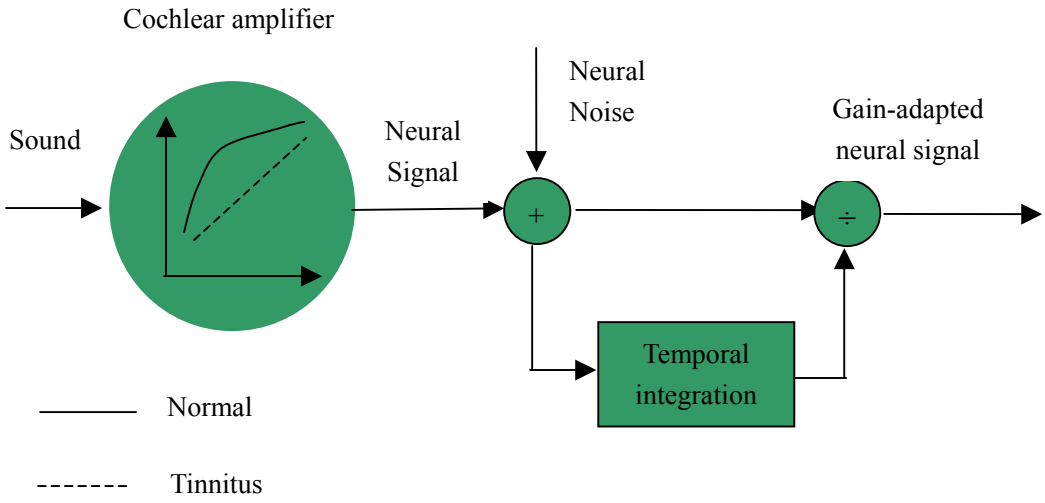

Figure 2.5 Schematic model of gain adaptation explains percepts resembling tinnitus: The model operates independently in each frequency band and assumes a non-linear transduction of sound pressure level (SPL) into a neuronal signal. Normal and tinnitus subjects differ in perception thresholds and non-linear compression of the cochlear amplifier. Neuronal noise adds to this signal in downstream processing. Central gain adaptation integrates signal intensity over time and uses the resulting estimate of power to normalize (divide) signal intensity, i.e. the (inverse) power estimate is used to set the neuronal gain. Hence, if the auditory input in a frequency band is permanently reduced (as with hearing loss) the gain will be elevated only to magnifying internal noise. (Parra and Pearlmutter, 2007)

2.5 Information bottleneck and gain adaptation

"The cochlea transforms acoustic signals into neuronal activity by decomposing the signal into its various frequency components, which are then transmitted by the auditory nerve to the midbrain. The signal intensity in different frequency bands is

encoded in the firing of different auditory nerve fibers. However, the dynamic range of the external stimuli is known to be much larger than the dynamic range of this neuronal activity. Transmitting auditory information through this information bottleneck therefore requires adaptive mechanisms. The nervous system has developed various strategies to cope with this problem including, in particular, gain adaptation. We argue that the main goal of the adaptive mechanism should be to transform the signal in different frequency bands into independent channels with optimally matched dynamic ranges. In this view, gain adaptation accomplishes two functions. First, it adjusts signal variance to the effective dynamic range of each frequency channel, thus optimizing the information capacity in each frequency channel (Rieke et al., 1996). Second, it removes redundancy across channels originating from frequency co-modulation (Parra et al., 2001, the simultaneous variation of amplitude in multiple bands).” (Parra et al., 2010)

2.6 Evidence relating tinnitus and hearing loss

“In the auditory periphery there are at least two mechanisms that are thought to address the problem of dynamic range mismatch between the auditory nerve fibers (20-40dB) and the dynamic range in the auditory input (120dB). First, outer hair cells (OHC) are thought to play a major role in actively amplifying faint sounds, while at high signal intensities the gain is reduced. This nonlinear amplification leads to a compression of dynamic range. Second, inner hair cells (IHC) are contacted by multiple auditory fibers with different response thresholds and gains. Therefore, as

intensity increases an increasing number of fibers is recruited, which effectively increases the available dynamic range of neuronal firing for a group of fibers with a common characteristic frequency. Peripheral hearing loss is associated with elevated thresholds. This results in a reduced diversity of response thresholds required by the recruitment mechanism. In addition, OHC damage leads to a loss of active amplification, reducing the compressive effect of the nonlinear cochlear amplifier (Heinz and Young, 2004). We postulate that, when faced with these challenges, downstream mechanisms in the brain compensate by taking a more active role in coping with the dynamic range of the input. These mechanisms, when confronted with silence in selected frequency bands, increase internal gains, which then amplify neuronal noise to the point that it is perceived as phantom sounds. We note that elevated thresholds are a common correlate of tinnitus (Hesse et al., 2005; Roberts et al., 2008), and abnormal growth of loudness is observed for frequencies matching the tinnitus percept (Penner, 1980). Elevated thresholds are correlated with tinnitus but this is neither a necessary nor sufficient condition for tinnitus. Rather, hearing loss with a sharp edge in the audiogram seems to best correlate with tinnitus (Konig et al., 2006). In addition, distortion products, which are thought to reflect the operation of the nonlinear cochlear amplifier, are selectively altered for frequency bands that have been matched to the tinnitus percept (Ozimek et al., 2006). The indicator that best correlates to the tinnitus percept is loss of compression (Janssen et al., 1998). This loss of compression is consistent with the comorbidity of tinnitus and hyperacusis. Indeed, hyperacusis (with or without tinnitus) coincides with elevated DPOAE

input-output slopes reflecting reduced compression (Bartnik et al., 2005). Finally, release from masking by a secondary masking tone does not occur in tinnitus subjects, indicating once again an alteration of the non-linear cochlear amplifier in tinnitus subjects (Mitchell and Creedon, 1995). All this supports the hypothesis that tinnitus is a result of hearing loss and degraded nonlinear compression. Because of their combined impact it is important to assess both loss of sensitivity and loss of compression. This project will therefore measure both perception thresholds and DPOAE to provide differential information on both IHC and OHC function." (Parra et al., 2010)

2.7 Current treatment options

In summary, tinnitus is associated with increased neuronal activity. This hyperactivity is demonstrated in animal models and human studies. It is believed that this neural hyperactivity is involved in the generation of tinnitus.

This neural hyperactivity is thought to be triggered by an impaired cochlear. The gain adaptation model indicates that the reduced peripheral input signal increases the gain of the auditory nervous system. This increased gain enables neurons to process weak sounds more effectively and makes auditory neuron more sensitive or hyperactive. This hypothesis suggests that increasing peripheral input or restoring sensitivity and hyperactivity could be a therapeutic approach for chronic tinnitus.

To reduce this hyperactivity of auditory neural system, one could use direct current

stimulation (tDCS), transcranial magnetic stimulation (TMS) or compensation of peripheral deficits to modulate dysfunctional brain activity.

Brain stimulation: Targeted modulation of the auditory cortex has been proposed as a new therapeutic approach for chronic tinnitus. Repetitive transcranial magnetic stimulation and direct current stimulation, non-invasive method for modulation of cortical activity, has been applied in different ways in tinnitus patients. Litre et al. (2010) indicated that transcranial magnetic stimulation (rTMS) was placed between the primary and secondary auditory cortices to suppress the auditory nervous firing rates. After this treatment, significant improvement was found in tinnitus patients. Cheung and Larson (2010) applied deep brain stimulation therapy to a locus of caudate nucleus (area LC) showing decreased tinnitus loudness in some patients. Similar results are reported by De Ridder et al. (2006, 2010), Friedland et al. (2007) with direct electrical stimulations and by Kleinjung et al. (2005), Fregni et al. (2006) and Marcodes et al. (2010) with transcranial magnetic stimulations in different areas of the auditory pathway.

In most case, the tinnitus symptom is only temporally alleviated during the TMS and tDCS. More lasting effects are more difficult to obtain. It is not surprising that peripheral deficits are not permanently compensated but that hyperactivity is only temporally modulated with stimulation.

Auditory stimulation: Another common strategy to alleviate tinnitus consists of masking the tinnitus percept with acoustic noise in the corresponding frequency band.

While this method is effective in covering the tinnitus percept for the duration of the noise, patients seldom adopt it long term, as it accomplishes little more than replacing one disturbance by another. Interestingly, residual inhibition of tinnitus is commonly observed following the masking noise and lasting up to minutes (Terry et al., 1983). The inverse is also true: long-term notched-noise stimulation worsens the tinnitus percept. Wilhelmina (2010) reported the efferent pathways modulate hyperactivity in inferior colliculus. The olivercochlear axons were electrically stimulated and effects on cochlear neural output and suppressed spontaneous hyperactivity in inferior colliculus, which is caused by acoustic trauma, are found. Mulders and Robertson (2009) also reported this hyperactivity can be abolished by silencing cochlear activity. All of these experimental results are consistent with a role for the olivocochlear system in residual inhibition. It has also been reported that hearing aids properly fitted to the frequencies of hearing loss can sometimes alleviate tinnitus (Vesterager 1997).

“This is not surprising given the extensive evidence that central adaptation takes place following the use of hearing aids (Philibert et al., 2005; Munro, 2008). Some reports indicate that tinnitus can be alleviated on a longer time scale by delivering variable signals in selected frequency bands (Goldstein 2001). There is evidence from animal models of tinnitus that high frequency tones delivered after noise-induced trauma prevent physiological correlates associated with tinnitus (Norena et al., 2002). Perceptual training paradigms aiming at central adaptation mechanisms have also been used (Formby et al., 2002). Norena and Chery-Croze (2007) have shown that auditory stimulation which compensates for reduced peripheral input can ameliorate

hyperacusis. Finally, there exists an assortment of proprietary treatment paradigms, which are hard to evaluate. For instance Viirre et al. (2006) suggest an auditory habituation paradigm with sounds matched to the frequency of the tinnitus percept. Davis et al. (2002; 2002; 2007) proposed a similar approach using intermittent masking stimulation with sounds that are designed to match the audiogram of individual subjects using a gain of ½ of the hearing loss at each frequency. Neuromonics Ltd. is commercializing this specific approach and a number of clinical trials are currently underway to demonstrate its efficacy (Davis et al., 2008; Hanley and Davis, 2008).

Note that the Neuromonics approach does not compensate for loss of compression on an individual frequency basis as we propose here. All this is in good agreement with the hypothesis proposed above, which maintains that the increased gains at the central level can be reduced by delivering signal power to the damaged channel. Moreover, this suggests that a properly fitted compressive hearing aid may alleviate tinnitus for those subjects with loss of compression and/or a partial loss of sensitivity. In our view the goal of stimulation is to reduce central gain in selected frequency bands, thus preventing spontaneous activity. The challenge for this stimulation approach is to find a rational design criterion that tailors synthetic or natural stimuli to match the specific deficit, thus providing tinnitus relief during stimulation and beyond. Developing such rational design criteria is the long-term goal of this project. Once the predictive power of sensitivity and compression's fine structure have been established, these measures can be used for treatment design: When tinnitus is accompanied by a loss of

peripheral compression, the present hypothesis suggests that one should alter the dynamic range of the natural acoustic input to compensate the deficit in the relevant frequency bands. When tinnitus is associated with reduced sensitivity one should stimulate with narrow band transients that are matched to the loss spectrum. These treatments aim to reset neuronal gains to normal levels and thus alleviate or abolish tinnitus. In case of tinnitus which is not associated with hearing loss TMS and tDCS may be necessary to restore dysfunction of auditory neural system." (Parra et al., 2010)

2.8 Summary of existing evidence in support of gain adaptation hypothesis

"The gain adaptation hypothesis is consistent with a wide array of existing physiological and psychophysical data on tinnitus: (1) Tinnitus correlates with loss of sensitivity as measured by the audiogram in particular at the audiogram edge. This is the essence of the hypothesis and the effects of the audiogram edge are explained in the computational model as a result of lateral inhibition. (2) Tinnitus correlates with hyperacusis – an increased sensitivity to loud sounds that can be interpreted as elevated central gains resulting from reduced input, (3) Tinnitus is associated with reduced cochlear compression measured with otoacoustic emissions. This is explicitly introduced in the gain adaptation model of tinnitus. (4) Tinnitus may be associated with reduced suppression of otoacoustic emissions under contralateral auditory stimulation, which can be interpreted as loss of peripheral dynamic gain adaptation,

(5) Auditory stimulation with band-noise and white noise induces residual inhibition of tinnitus (Roberts et al., 2008). According to the present model, residual inhibition is as transient reduction of central gains following increased input in the corresponding frequency bands, (6) Elevated sensitivity in hyperacusis can be ameliorated with carefully designed auditory stimulation (Norena and Chery-Croze, 2007). (7) Tinnitus can be sometimes treated successfully with carefully fitted hearing aids consistent with the notion that compensation of peripheral loss will restore central gain to their normal range, and similarly (8) In some subjects tinnitus is reduced following auditory stimulation that compensates for the hearing loss as measured by the audiogram." (Parra et al., 2010)

Chapter 3: Cochlear function correlates with sensitization

3.1 Abstract

Neuronal gain adaptation has been proposed as the underlying mechanism leading to the perception of phantom sounds such as Zwicker tones and tinnitus. In this gain-adaptation theory, cochlear compression plays a significant role with weaker compression leading to stronger phantom percepts. The specific aim of this study was to find a link between the strength of neuronal gain adaptation and cochlear compression. Compression was assessed using distortion product otoacoustic emissions (DPOAEs). Gain adaptation is hypothesized to manifest itself in the sensitization of the detection of masked tones observed when they are preceded by notched noise. Perceptual thresholds for pure tones in notched noise were measured at multiple frequencies following various priming signals. The observed sensitization was larger than expected from the combined effect of the various maskers. However, there was no link between sensitization and compression. Instead, across subjects, stronger sensitization correlated with stronger DPOAEs evoked by low-level primaries. In addition, growth of DPOAEs correlated reliably with perceptual thresholds across frequencies within subjects. Together, the data suggest that short-term dynamic adaptation leading to perceptual sensitization is the result of an active process mediated by the outer hair cells, which are thought to modulate the gain of the cochlear amplifier via efferent feedback.

3.2 Introduction

The subjective sensation of sound in the absence of a real stimulus is referred to as a phantom percept. Tinnitus and the Zwicker tone are phantom percepts induced in some subjects at frequencies of reduced auditory stimulation. We argued previously that these phantom percepts result from central neuronal gain adaptation, which increases sensitivity to a point where background neuronal activity is perceived as a phantom sound (Parra and Pearlmutter, 2007). The corresponding computational model suggested a link between the strength of the perceived phantom sounds and the compression factor of cochlear dynamics. Indeed, this previous study found empirically that Tinnitus subjects, who as a group have been shown to have reduced compression (Janssen et al., 1998), are significantly more likely to perceive the Zwicker tone.

The basilar membrane responds to sound in a nonlinear fashion, providing an intensity-dependent gain to incoming sounds (see Cooper et al., 2008 and Neely and Kim, 2008 for a review). This adaptive amplification is thought to be mediated by the outer hair cells (OHCs), which are in the position to modify basilar membrane mechanics on a cycle-by-cycle basis and is often referred to as the cochlear amplifier (see Cooper et al., 2008). At lower signal levels amplification is stronger than at high signal levels at which point the basilar membrane is believed to become purely passive. These results in a compressive non-linearity, which provides a reduction in the output range of the incoming sound and an increase in dynamic range required for

proper transmission to the auditory nerve. Adaptive gains have also been documented for central auditory processing stages. For instance, Dean et al., (2005, 2008) showed that rate-response curves of neurons in the inferior colliculus adjust thresholds (sensitivity) and slope (gain) to the auditory stimulus intensity on a time scale of 100 ms.

The specific aim of this study was to find a link between the strength of this central neuronal gain adaptation and the instantaneous cochlear compression. Following the gain-adaptation model, we predict the strength of central neuronal gain adaptation correlates with instantaneous cochlear compression. Previous research indicated that the addition of a long-duration masker, or precursor, can either improve (notched-noise) or reduce (band-noise) the detection thresholds of a stimulus as the stimulus is delayed from the onset of the masker. We hypothesized that this sensitization is the result of neuronal gain adaptation, which increases sensitivity in the missing frequency of the notch but reduces sensitivity in the band frequency.

Cochlear compression was assessed with high frequency resolution using a newly developed method for obtaining distortion product otoacoustic emissions (DPOAEs), which extracts the generator component of the DPOAE (Long et al., 2008). To measure gain adaptation we took an indirect approach. Initial preliminary experiments (not shown here) indicated that following a notched noise, the sensitivity to faint sounds in the notch region should be increased. In the extreme, we hypothesized that this increased sensitivity results in the perception of a tone even in the absence of a

sound, a phantom percept known as the Zwicker tone. However, we did not find an increase in sensitivity for pure tones in quiet, but for tones that were simultaneously masked by notched noise—a phenomenon that had been observed previously (Carlyon, 1989; Strickland, 2004). The surprising observation is that the addition of a long-duration masker, or precursor, can improve detection thresholds of a stimulus as the stimulus is delayed from the onset of the masker. This phenomenon is referred to as overshoot (Zwicker, 1965). Viemeister and Bacon (1982) and Thibodeau (1991) reported a similar effect with the use of an adaptor stimulus on the enhancement of a masker in a forward masking paradigm. When a preceding adaptor stimulus lacked the spectral content of the masker, an increase in masking was observed. In this scenario the enhancement effect was attributed to an increase in gain at the masker frequencies resulting from an adaptation to suppression of the components contained in the adaptor stimulus. Here we hypothesize that this sensitization is the result of neuronal gain adaptation, which increases sensitivity in the missing frequency band of the notch. We therefore use this sensitization as a measure of neuronal gain adaptation. In order to measure this sensitization psychophysically, a paradigm is established here that measures perceptual thresholds of a simultaneously masked pure tone in the presence of a long-duration precursor stimulus. Two experiments were conducted: Experiment I aimed to establish a link between compression and sensitization, and experiment II aimed to confirm that this sensitization is not just a result of a linear process. The results of these experiments suggest that the observed sensitization is the result of an active process mediated by outer hair cell function, but

that cochlear compression by itself does not necessarily affect its strength. The experiments also revealed a reliable correlation of compression with perceptual thresholds across frequency.

3.3 Methods

3.3.1 Subjects and procedures

Eighteen subjects were recruited for this study (11 for experiment I and 7 for experiment II, see below). Initial audiograms were performed to exclude cases of moderate and severe hearing loss. All but two subjects had hearing thresholds of less than 20 dB hearing level (HL) at all audiometric frequencies. Two subjects each had mild hearing losses of less than 30 dB HL at one single frequency. Subjects were between 20 and 45 years of age and were recruited from the main campus of the City University of New York. All subjects were paid $10 an hour for participating in the experiment. An Institutional Review Board consent form was signed before the experiment. The experiment consisted of a psychoacoustic task as well as DPOAE measurement. The total experiment time per subject was approximately 4 hours.

3.3.2 Psychoacoustics: Primed notched-noise masking

Masked-thresholds were measured using a three-interval three-alternative forced-choice (3I3AFC) paradigm with an adaptive threshold-tracking procedure. During the experiment subjects were seated in a Industrial Acoustics Company (IAC) sound-treated booth. For a given trial, the listener pressed one of three keys to indicate

the interval in which the probe tone was perceived. A visual aid marked each interval and feedback was provided after each response to indicate if the response was correct or incorrect.

The stimulus contained the following three components, which are represented schematically in Figure 3.1: (1) a 1000 ms precursor period which can have one of four precursors: notched noise, bandpass noise, white noise, or no precursor ("quiet"). The notched- and bandpass-noise precursors had a 4-ERB bandwidth and the noise was fixed at 50 dB sound pressure level (SPL) overall [ERB(f)=0.108f +24.7 at center frequency f]; (2) a variable-level probe tone (initial level of 50 dB SPL), and (3) a fixed-level (50 dB SPL overall) simultaneous notched-noise masker (4-ERB notch width). In all conditions the total durations (including onset/offset ramps) of the precursor, masker, and signal were 1000, 40, and 40 ms, respectively. The probe tone and simultaneous notched noise masker had 5 ms Hanning window onset and offset ramps. The precursor had 50 ms Hanning window ramps. There was a 250 ms time delay between the offset of the precursor and onset of the simultaneous notched-noise masker.

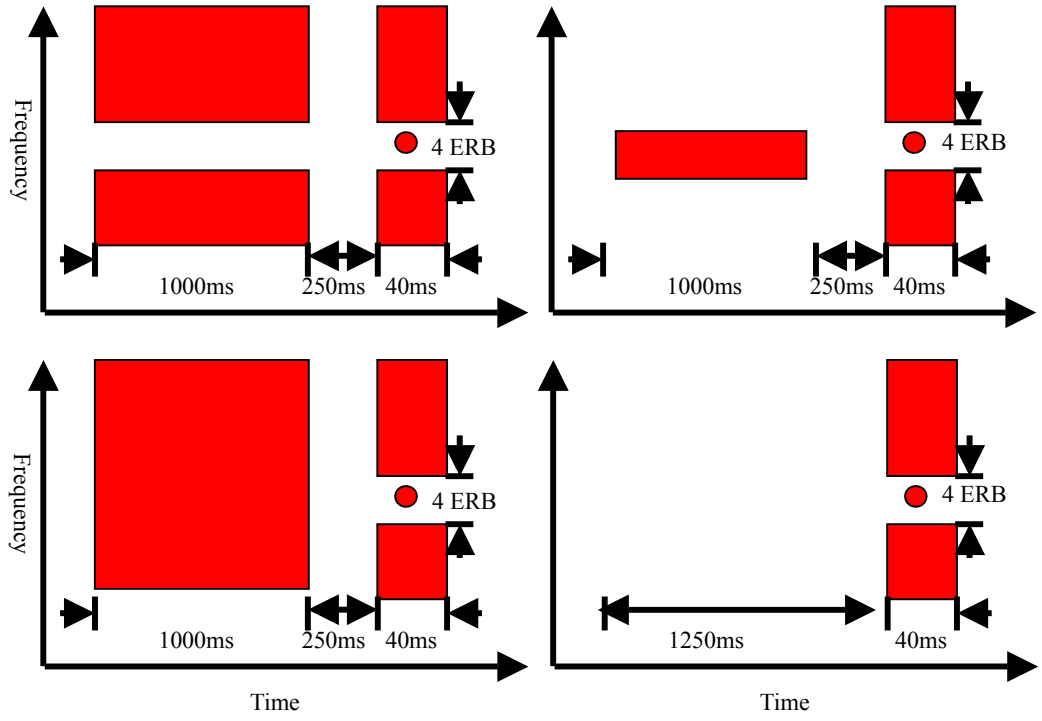

Figure 3.1 Schematic of spectral content in psychoacoustic experiment: Thresholds were obtained for a brief probe tone (indicated by the black dot) simultaneously masked by notched noise (light shaded area). The four panels show the different precursors (dark shaded area) clockwise from the top left: notched-noise, band-pass noise, no precursor/quiet, and white noise.

All stimuli were generated digitally and played via an M-audio USB sound-card with 24-bit resolution at a sampling rate of 44.1 kHz. These stimuli were routed through a headphone buffer (TDT HB7) before being presented to the listeners via Sony headphones MDR-7506. All signals were filtered to equalize the spectrum of the specific pair of headphones. Equalization filters were obtained by recording a white noise signal emitted by the headphones with a calibrated microphone (Brüel & Kjær, Nærum Denmark, model 2218) inside a KEMAR head and torso simulator. Filter coefficients were computed from this using linear prediction coefficients of order 20.

During each experiment, masked thresholds were measured at signal frequencies ranging from 1 to 4 kHz in steps of 250 Hz. Each trial consisted of three observation intervals. The primed precursor and simultaneous masker were presented in all three intervals, and the probe tone was randomly presented in one of three intervals. The threshold was measured using a modified version of the threshold-tracking procedure known as Parameter Estimation by Sequential Testing (PEST) (Taylor and Creelman, 1967), which estimated the threshold level at the 70% correct point on the psychometric function. In this procedure, the initial tone level was set to 50 dB SPL and decremented with a step size of 8 dB. After the first reversal the step size was reduced to 4 dB and after an additional reversal to 2 dB. The threshold estimate was taken as the mean of the last four reversals with a 2 dB step size. Data collection did not begin until a listener had several practice trials with the experimental paradigm. Presentation of a single frequency condition was randomized across subjects. Each threshold reported here represents the mean over two repetitions of this procedure. In experiment I the range of these two measures (max-min) pooled across frequencies and subjects was 2.7 dB SPL. In the first experiment (experiment I), 11 subjects were tested in the band-pass and notched-noise precursor conditions. Two threshold estimates were obtained for each condition and averaged to obtain the final threshold. One subject was excluded from the analysis because a second estimate could not be obtained. An additional seven subjects participated in a second experiment (experiment II) and were tested using all four precursor conditions (band-pass, notched, white, and quiet).

3.3.3 Distortion product otoacoustic emissions

DPOAE input-output functions were obtained from all subjects and were used to estimate the basilar membrane response. There are several ways to estimate basilar membrane input/output (I/O) functions such as measuring a growth of masking (GOM) function or measuring temporal masking curves (TMCs) (e.g., Rosengard et al., 2005). In this paper, DPOAEs provide an objective measure of cochlear compression. A technical challenge for DPOAEs is to ensure that one measures 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 (Shera, 2004). Once the DPOAE is generated, the signal travels both basally toward the oval window and also apically to its own characteristic place on the basilar membrane, where it generates an OAE similar to that generated by the external stimulus. The resulting components have the same frequency but originate from two different regions of the cochlea. To evaluate nonlinear growth, one must extract the component from the generator (maximum overlap) region alone (Mauermann and Kollmeier, 2004).

DPOAEs were obtained from one ear of each subject, who was seated in a recliner in a double-walled IAC soundtreated booth. Custom MAC software (OSX) was used to generate the primaries and to record the ear canal signals. Sweeps were presented via etymotic ER-10A earphones connected to the computer via a MOTU828 firewire

interface (24 bit, 44.1 kHz). Ear canal signals were recorded with an Etymotic ER-10A microphone/preamplifier system and amplified by a Stanford SR560 low-noise amplifier connected to and controlled by the same computer. The stimuli used for DPOAE measurement were continuously sweeping primaries with a fixed primary ratio (f_2/f_1) of 1.22, as described by Long et al. (2008). Primary frequencies f_1 and f_2 ($f_1<f_2$) were logarithmically swept from an f2 frequency of 1000– 4000 Hz at a rate of 2 s/octave. Primary tone presentation levels were set based on the scissors level paradigm (Kummer et al., 1998) according to the equation $L_1=\max(0.4L_2 +39$ dB SPL,$L_2)$. DPOAE levels were measured as a function of input signal level (L_2=25–75 dB SPL, 5 dB step).

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 depended 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 were eliminated before averaging at each level. 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.

3.4 Results

The goal of the first experiment was to establish a link between cochlear compression and threshold sensitization. DPOAEs were obtained at various primary levels (L_2: 25–75 dB SPL in steps of 5 dB) and perceptual thresholds for pure tones masked by notched-noise preceded by one of two precursors (band-pass or notched noise, see Figure 3.1). Figure 3.2 shows the resulting data for one of the ten subjects that participated in this experiment. The top panel of Figure 3.2 shows the DPOAE level in the range from 1 to 4 kHz. The bottom panel shows the perceptual thresholds obtained at 12 frequencies within that same range. One measure of compression can be obtained by measuring the slope of DPOAE level growth as a function of the L_2 level (input/output slope). Low slope values correspond to a more compressive growth function and hence stronger cochlear amplification. In this instance, a compression factor was determined for each frequency as the difference in DPOAE levels between the highest and lowest input L_2 levels (75 and 25 dB SPL)—essentially the spread of the DPOAE curves—divided by 50 dB to obtain an input-output slope. Generally, for various subjects, these compression factors were within 0.25 and 0.5, indicating normal hearing (see Figure 3.4). Compression factors above 0.5 coincided with mild hearing loss in two subjects (e.g., subjects 1 and 9). These values are in agreement with previous literature (Williams and Bacon, 2005). In addition to slope, we evaluated the mean DPOAE level as the average across all input

L_2 levels (mean over all curves in Figure 3.2, top).

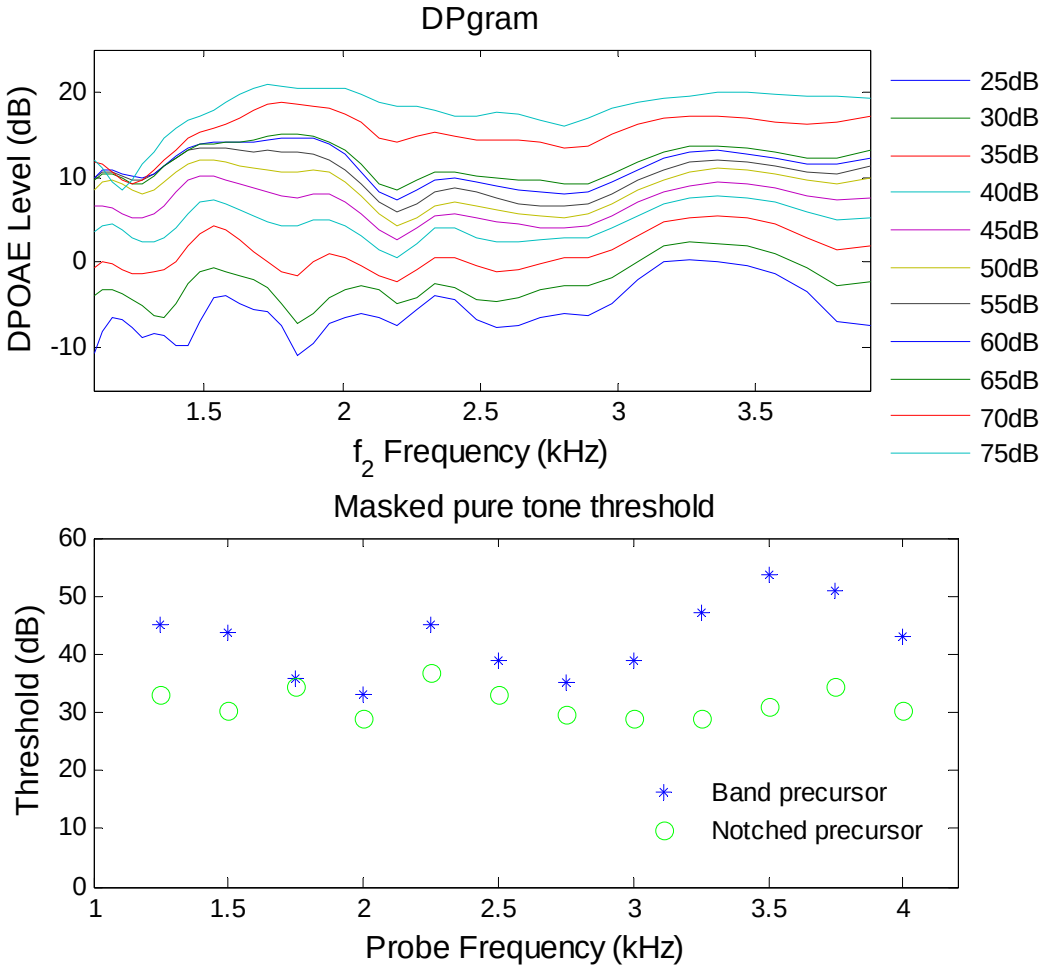

Figure 3.2 Example of measured DPOAE and perceptual thresholds for one subject: Top: Each curve shows DPOAEs for one of 11 primary levels (L_2: 25–75 dB SPL). A larger spread between levels indicates weaker compression. Bottom: Perceptual thresholds for tones under simultaneous notchednoise masking measured with two different precursor conditions (notched and bandpass noises). Distance between the data from two conditions indicates perceptual sensitization.

Estimation of sensitization is based on the difference between perceptual thresholds with the notched- and bandpass-noise precursors. Preliminary unpublished experiments with no precursor established that thresholds are reduced by 5±2 dB ($p<0.0001$, $N=4$) when the masked tone is preceded by a 3 s notched noise. For the

present experiment, with a 1 s precursor duration, thresholds are reduced by 5.5±1.1 dB ($p<0.0001$, N=10) when compared to the bandpass-noise condition. The relationship between the no-precursor and bandpass-noise precursor conditions will be analyzed below. These results are consistent with previously reported results using similar stimuli and precursor durations (Carlyon, 1989; Strickland, 2004).

Various psychoacoustic and DPOAE data were compared across frequency. Figure 3.3 shows these comparisons for subject 2. The heading of each panel gives the correlation coefficient (and the corresponding p-value) across frequency for each pair of measures.

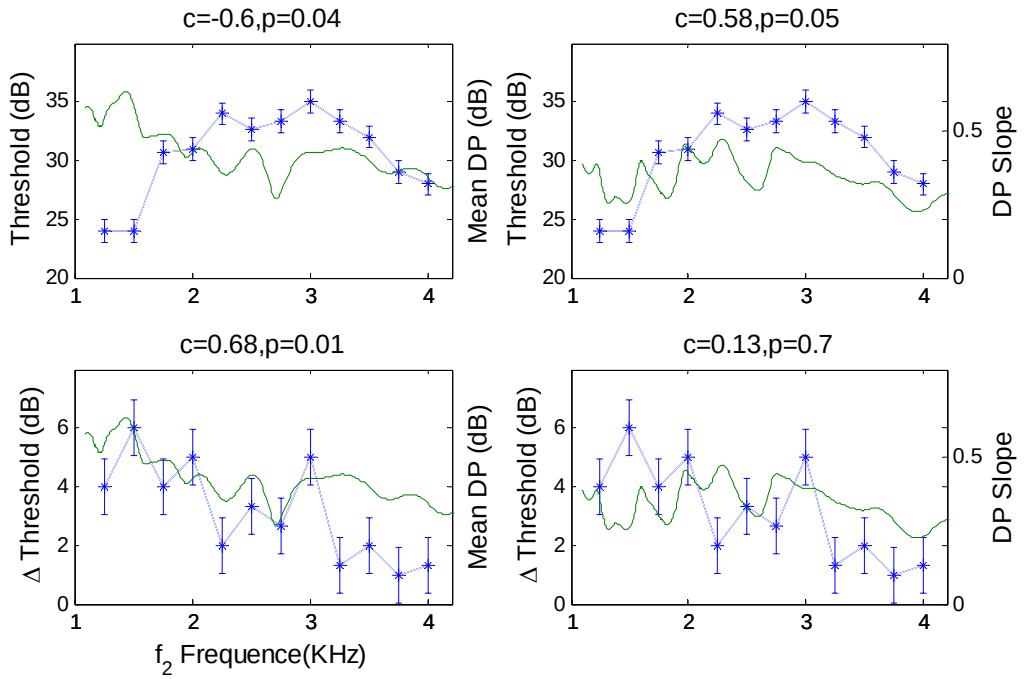

Figure 3.3 Within-subject comparison of DPOAEs and psychoacoustic threshold measures: Top left panel plots correlation between masked threshold and mean DPOAE level (averaged across all L_2 levels) as a function of frequency. The top right panel shows the correlation between the threshold and compression (DPOAE I/O slope) as a function of frequency. The lower left panel shows the correlation between ΔThreshold (the difference between notched- and band-pass noise thresholds) and the

mean DPOAE level. The lower right panel shows the correlation between ΔThreshold and DPOAE compression (symbols represent psychoacoustic results, solid curve represents DPOAE measures and error bars indicate range of two repeated measures pooled over frequencies).

We found that elevated thresholds in the notched-noise condition were significantly correlated with reduced compression for eight of ten subjects (average correlation coefficient c=0.67 for subjects with p<0.05; Figure 3.4).

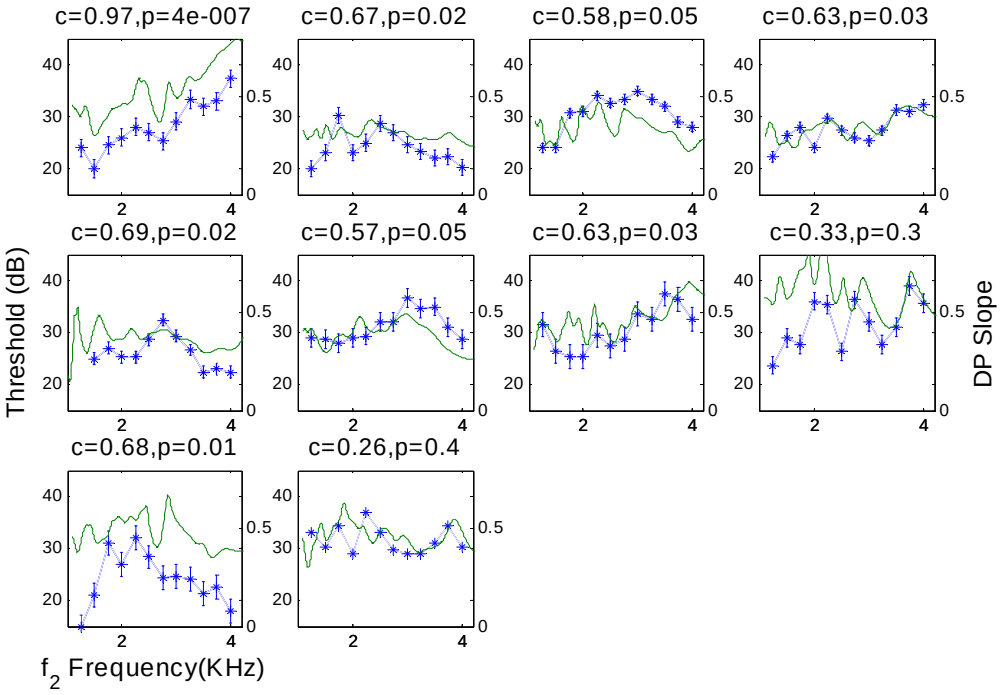

Figure 3.4 within-subject correlations of compression and masked thresholds: Panels show masked thresholds for each subject with notched precursor (symbols) and estimates of DP compression (solid curve). Error bars indicate range of two repeated measures pooled over frequencies. Significant correlations across frequency (p<0.05) were observed for eight of the ten subjects. For these subjects, c=0.67±0.04.

As a group, this correlation is highly significant, as shown in Figure 3.5, top panel. Additionally, as a group, a significant correlation between compression and masked thresholds following the bandpass-noise precursor was found (p <0.01; Figure 3.5, middle panel). However, the correlation between sensitization and compression was

not significant. Instead, stronger sensitization correlated with stronger DPOAEs for the lowest primary level measured (c =0.24, p=0.008, N=10, Figure 3.5, bottom panel).

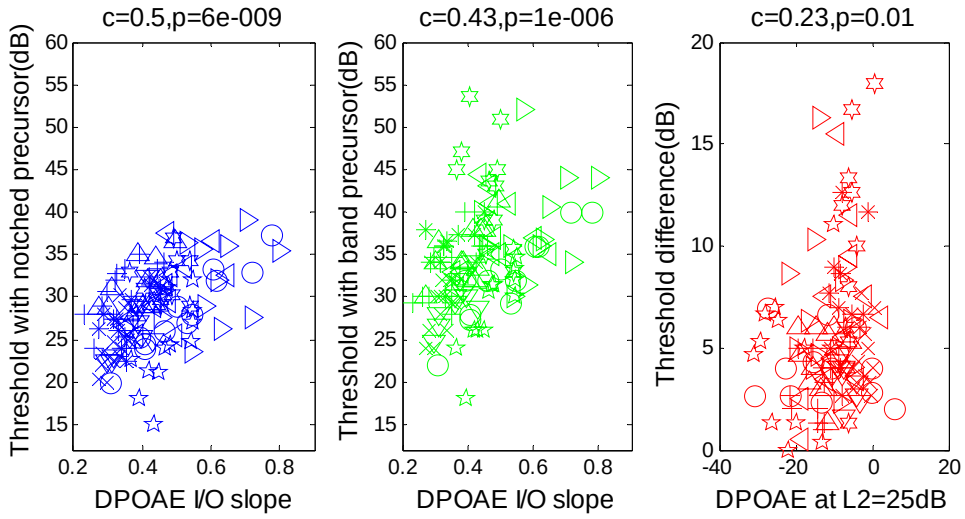

Figure 3.5 Comparison of DPOAEs and masked thresholds for all subjects and all frequencies: The top panel shows the correlation between masked thresholds with notched-noise and estimates of compression for all ten subjects. The middle panel shows that thresholds with the band-pass noise precursor correlate with estimates of compression. The bottom panel shows the correlation for DPOAEs obtained at the lowest primary level and sensitization (band-pass precursor-notched precursor).

The sensitization of masked thresholds 250 ms after a notched-noise precursor is interpreted here as the result of neuronal gain adaptation (see Section 3.5 for more details). To further quantify this sensitization and assess the differential effects of the on- and off-frequency bands in the precursor, an additional two precursor conditions were tested, namely, a quiet and a white noise condition. The top panel of Figure 3.6 shows the results obtained in all four precursor conditions. Indeed these data confirm the preliminary observation that the notched-noise precursor significantly improves detection thresholds as compared to the quiet condition [two-way analysis of variance

(ANOVA) with frequency and condition as factor, p=0.004, N=7, df=1, and F=21.0]. On average the improvement was 3.2 dB.

Can this improvement be explained as the effect of the off-frequency bands alone or does the contrast in the notched-noise precursor matter? The white noise condition has the same off-frequency power as the notched-noise condition, but also contains power in the on-frequency band. Therefore, its effect was compared to the combined effect of the notched- and band-pass noise precursors by examining whether the threshold under the notched- and band-pass noise conditions, I_N+I_B, was equivalent to the thresholds obtained in the white-noise and quiet conditions, I_W+I_Q. In other words, whether the relation $I_N+I_B=I_W+I_Q$ holds (I_Q is included to factor in the effect to the simultaneous notched noise masker). The improvement due to the notch is significantly larger than this combined effect by 2.5 dB (two-way ANOVA with combined thresholds and frequency as factors, p=0.015, N=7, df=1, and F=11.4). Note that this comparison implies that additivity does not hold under these conditions and that the combined effects of these various precursors point to an underlying non-linear mechanism.

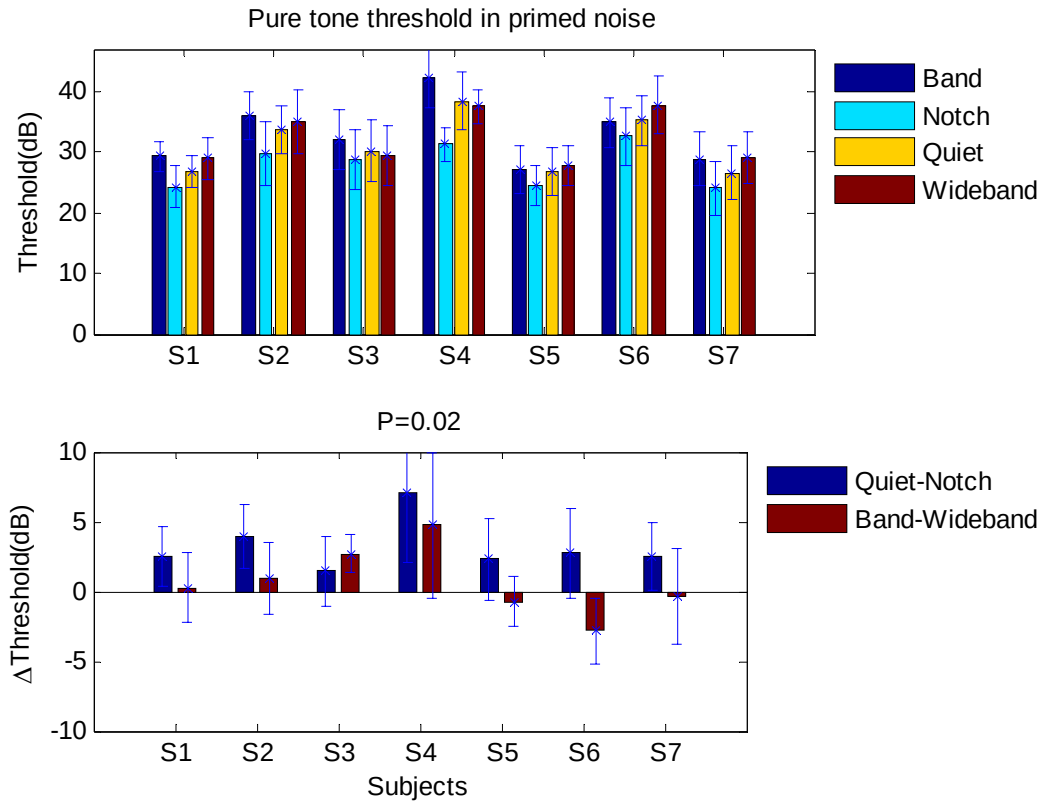

Figure 3.6 Masked pure tone thresholds in each precursor condition for seven subjects: The top panel shows individual subjects thresholds in each condition averaged across frequencies. The bottom panel shows the combined thresholds I_N+I_B and I_W+I_Q for each subject (error bars represent standard deviation across frequency).

3.5 Discussion

The premise of this work was that the perception of a tone is affected by central gain-adaptation mechanisms and that this adaptation would be affected by the amount of cochlear compression: A more compressive cochlea would reduce the intensity difference between a loud and a quiet stimulus, and thus, changes in neuronal gain following changes in signal intensity should be less pronounced. Indeed, neuronal gain adaptation has been demonstrated in the inferior colliculus (Dean et al., 2005) and auditory nerve (Wen et al., 2009). Here, gain adaptation was assessed by the

sensitization observed following a notched-noise precursor, and cochlear compression was assessed using DPOAEs emitted at various primary input levels. Contrary to our expectation, no significant correlation was found between the measure of DPOAE compression and sensitization as measured by the difference between primed narrow-band and primed notched-noise thresholds. However, this sensitization did correlate with the DPOAEs measured with the lowest level primary (see Figure 3.5, bottom panel). This suggests that this sensitization is affected by or depends on the amplification mechanism which depends on outer hair cells.

The sensitization phenomenon, which can be considered a form of release from masking, is unique in that sensitivity is increased when adding a sound to a probe signal—rather than decreased as is typically the case in masking. The interpretation of this effect as the result of a neurally mediated adaptive gain is supported by the nonlinearity of the combined effects of the notched- and band-pass noise precursor conditions, as well as the long time scale over which this effect occurs. Note that sensitization is observed here as late as 250 ms after the precursor signal. This is much longer than the instantaneous effect of cochlear compression, longer than the rate adaptation for single auditory nerve fibers, and still longer than forward masking (Meddis and O'Mard, 2005). Thus, we speculate that sensitization is determined more centrally but mediated to some extent by adjusting OHC amplification gains via an efferent feedback loop. An alternative hypothesis is that the decrease in threshold using a notched-noise precursor may result from a perceptual grouping of the precursor and masker. In this scenario the notched-noise precursor and masker are

grouped together in the auditory system, resulting in the increased detect ability of the target stimulus (Bregman, 1990). To test this hypothesis, a notched-noise precursor with a different spectrum from that of the masker could be used in order to control such effects and will be investigated in a future experiment. Overall, the results show that sensitization occurs after presentation of a notched-noise masker and the strength of this sensitization correlated with DPOAEs elicited by the lowest primary level. Additionally, evidence of cochlear compression based on DPOAE I/O functions correlated strongly with both notched- and band-pass noise psychoacoustic thresholds. In eight of ten subjects these measures correlated significantly across frequency (significance could be established despite a relatively small sample of frequencies).

3.6 Conclusion

In normal hearing subjects, notched noise increases sensitivity to tones embedded in noise. This increased sensitization was found to be a non-linear effect, consistent with our hypothesis of a neurally mediated gain-adaptation mechanism. However, perceptual grouping cannot be ruled as a potential mechanism. The correlation between this sensitization and DPOAEs measured with the lowest primary level is interpreted as a link between outer hair cell function and gain adaptation. Cochlear compression correlated strongly with various perceptual thresholds. This establishes DPOAE compression as a potential candidate for the objective evaluation of hearing.

Chapter 4: Impaired Cochlear Function Correlates with Tinnitus Presence and its Spectrum Profile

4.1 Abstract

Tinnitus correlates strongly with hearing loss. However, not all subjects with hearing loss have tinnitus and not all tinnitus subjects have significant hearing loss. We previously hypothesized that tinnitus is the result of a gain-adaptation mechanism that when confronted with degraded peripheral input increases neuronal gains such that spontaneous neuronal activity is perceived as a phantom sound. Following this hypothesis we expected that impaired cochlear function would be predictive of the presence of tinnitus and of its spectral characteristics. To assess cochlear function, distortion product otoacoustic emissions (DPOAEs) with high frequency resolution (160 points per octave) as well as thresholds measured using narrow-band noise (resolution of 6 points per octave). All measures were obtained in the frequency range of 1 kHz to 8 kHz (N=9), or 11 kHz (N=38) for 29 tinnitus subjects and 18 non-tinnitus subjects with similarly matched hearing loss. For all tinnitus subjects we obtained a "tinnitus likeness spectrum" – a rating of the similarity of the tinnitus percept with tones of varying frequency. Tinnitus subject had elevated thresholds, reduced DPOAE, and increased DPOAE input-output function slope in the range of 4k to 10k Hz. These measures were strongly correlated and seemed to be equally predictive of the presence or absence of tinnitus in a given subject. As previously reported, likeness spectrum coincided with thresholds in the group average. But even

within individual subject we found a correlation of the threshold profile with the likeness-spectrum profile and this correlation was significantly improved when taking low-level DPOAE into account. Thus we conclude that in tinnitus, cochlear function, and in particular outer hair-cell function, as measured by low input-level DPOAE, may provide additional diagnostic information over the threshold alone.

4.2 Introduction

Tinnitus (the perception of a phantom sound) is often associated with hearing loss. The subjective sound varies, it is often described as something like “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 predominantly occurring at sharp edges of high-frequency loss (Koenig et al., 2006; Moore and Vinay, 2010). However, tinnitus is not always associated with hearing loss. Some tinnitus subjects, particularly children, have seemingly normal hearing (Savastano et al., 2009). On the other hand, some individuals with evident hearing loss do not have tinnitus. Therefore, while there is a strong correlation, hearing loss may be neither a necessary nor sufficient condition for tinnitus. It is thus 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 to be generated in the central neural 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?

The hypothesis of this work is 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 Perlmutter, 2007). 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 threshold, a crude measure of 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 threshold.

The data collected here categorizes subjects by a number of criteria, each segregating the tinnitus population into subgroups for whom the tinnitus is more or less predictable based on high-resolutions thresholds and distortion product oto-acoustic emissions (DPOAE). Thus, careful categorization and assessment of peripheral processing may permit sub-typing for the purpose of selecting the most efficacious tinnitus treatment.

4.3 Methods

4.3.1 Subjects and procedures

29 tinnitus subjects and 18 non-tinnitus subjects were recruited for this study. Tinnitus subjects (19 male, 10 female) were 47±3.15 years old and non-tinnitus subjects (9 male, 9 female) were 40±4.22 (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). For all subjects, thresholds and DPOAE measures were obtained. Tinnitus subjects performed an additional procedure to determine the "tinnitus-likeness spectrum", which are subjective ratings of how much a tone sounds like their tinnitus. The total experiment time per subject was approximately 4 hours.

4.3.2 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. These stimuli were routed through a headphone buffer (TDT HB7) before being presented to the listeners via Sony headphones MDR-7506. All signals were filtered to equalize the spectrum of the specific pair of headphones. 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 & torso simulator. Filter coefficients were computed from these using linear prediction coefficients of order 20.

Bekesy-tracking was used to obtain high-resolution perceptual thresholds for both ears in a short period of time (approximately 30 min). The frequency range was from 1 kHz to 10 kHz with 6 points per octave (22 different frequencies). Perceptual thresholds were determined with narrow-band noise pulses, which have proven 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 of intermittent silence. 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 volume of the probe tones was set to 50 dB sound pressure level (SPL), which is audible in most instances. However, subjects were instructed to increase or decrease the starting volume for each tone to an audible and comfortable level. During Bekesy-tracking, subjects press a button as long as they hear the probe tones. Holding the button pressed reduces the volume of the probe tone by 2dB per pulse (4dB/second). Subjects are to release the button when they can no longer hear the probe tones. At this point the volume is increased again by 2dB per pulse. The tracking procedure terminates after 8 reversals. The thresholds reported here is the average volume at the last 6 reversals. Subjects were free to take a break after each frequency but mostly chose to complete the procedure without interruption.

4.3.3 Tinnitus likeness test

The spectral profile of tinnitus was determined using the “tinnitus likeness spectrum” as established by Roberts, et al. (2008). This computerized procedure assessed the quality of the tinnitus sensation including perceived location, loudness, temporal property, 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 by keyboard: left, right or both ears. (2) Bandwidth of tinnitus: Subjects indicated whether their tinnitus was “tonal”, “ringing”, or “hissing”. Three sounds were played to subjects to illustrate choices, consisting of a 5 kHz pure tone (tonal), and two band-pass noise with central frequency of 5 kHz differing in bandwidth. The two bandwidths were 5% of central frequency (ringing) and the 15% of central frequency (hissing). (3) Temporal properties: Subjects were asked to indicate if their tinnitus was steady or pulsing. Corresponding audio examples were presented to subjects to illustrate these two choices. In this study all subjects reported steady tinnitus. (4) Tinnitus loudness matching: Subjects were presented with sounds at various frequencies with bandwidth, modulation and side following their choices in steps (1) through (3). The frequency range was from 1 kHz to 10 kHz with 3 point per octave (total of 11 frequencies). Subject adjusted the volume of each sound to match the perceived loudness of their tinnitus, up to maximum of 95 dB SPL (safety limit). (5) Tinnitus likeness rating: Subjects rated the similarity of each of the sound presented in step (4) to their tinnitus. Thus, a rating is obtained for each of the 11 frequency. Subjects were asked “How much does this tone sound like your tinnitus”

and could choose their answer from six levels: 1 – "not at all", 2 – "a little bit", 3 – "moderately", 4 – "very similar", 5 – "identical" and 6 – "can't hear it". A profile across frequency is obtained using the ratings for all 11 frequencies. To determine reliability, these subjective ratings were collected twice (N=25; for N=4 subjects only 1 rating was available) at the beginning and end of the entire session, i.e. 2-3 hours apart. Whenever available we used the average of the two repeated measures for analysis. Two examples for the resulting tinnitus likeness spectrum are shown in Figure 4.1.

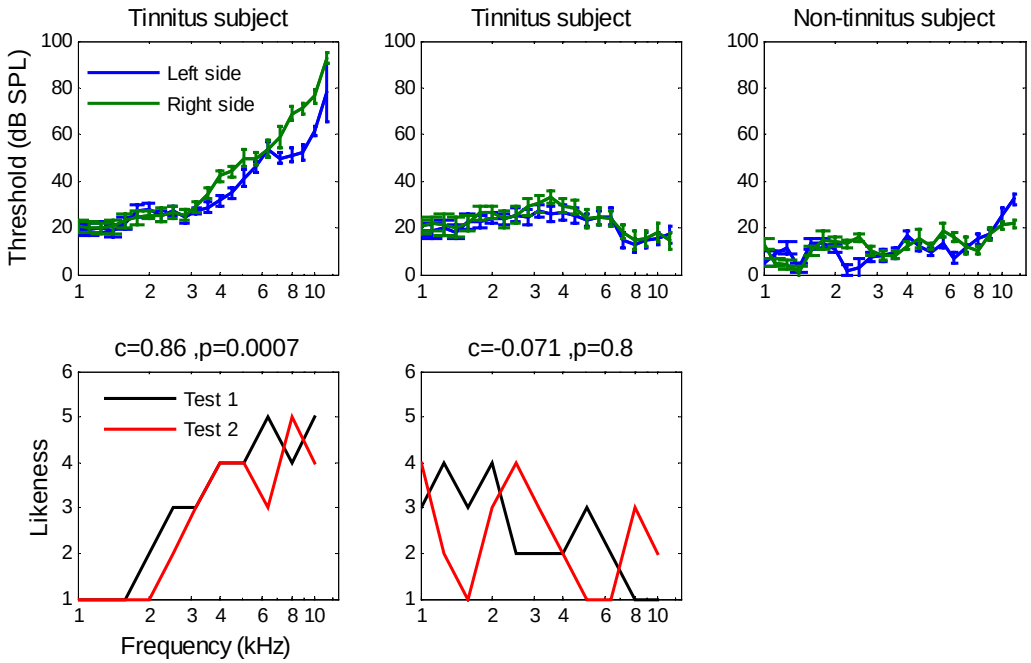

Figure 4.1 Examples of perceptual thresholds, DPOAE and tinnitus likeness test: Top row: perceptual thresholds in the same frequency range for left (blue) and right ear (green). Bottom row: examples of tinnitus likeness measurements repeated twice to assess reproducibility. Left column: data for a tinnitus subject with perceptual-threshold edge and reproducible tinnitus likeness test (significant correlation over two repeats). Center column: this tinnitus subject had no perceptual-threshold edge and could not provide reproducible tinnitus likeness ratings (no significant correlation between repeats). Right column: Data for non-tinnitus subject.

4.3.4 DPOAE measurement

Distortion product oto-acoustic emissions (DPOAE) input-output functions were used to estimate basilar membrane response. There are several ways to estimate basilar membrane I/O functions such as measuring a growth of masking (GOM) function or measuring temporal masking curves (TMCs) (Rosengard et al., 2005). In this paper, DPOAEs provide an objective measure of cochlear function. A technical challenge for DPOAEs is ensuring that one is measuring 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 also apically to its own characteristic place on the basilar membrane, where it generates an OAE similar to that generated by the external stimulus. The resulting components have the same frequency but originate from two different regions of the cochlea. To evaluate nonlinear growth, one obtains more consistent results when one extracts the component from the generator (maximum overlap) region alone (Mauermann and Kollmeier, 2004). DPOAEs were obtained from one ear of each subject, who was seated in a recliner in a double-walled IAC sound-treated booth. Custom Mac software (OSX) was used to generate the primaries and to record the ear canal signals. Sweeps were presented via etymotic ER-2 insert earphones connected to the computer via a MOTU 828 Firewire Interface (24-bit, 44.1 kHz). Ear canal signals were recorded with an Etymotic ER-10A microphone/preamplifier system and amplified by a Stanford SR560 low-noise amplifier connected to the same MOTU 828

interface and controlled by the same computer. The stimuli used for DPOAE measurement were continuously sweeping primaries with a fixed primary ratio (f_2/f_1) of 1.22 as described in Long et al. (2008). Primary frequencies, f_1 and f_2 ($f_1 < f_2$), were logarithmically swept from an f_2 frequency of 1000 Hz to 4000 Hz at a rate of 2 s/octave. Primary tone presentation levels were set based on the scissors level paradigm (Kummer et al., 1998) according to the equation $L_1 = \max(0.4L_2+39 \text{ dB SPL}, L_2)$. DPOAE levels were measured as a function of input signal level (L_2 =25 to 75 dB SPL, 10dB step). 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 depended on the primary level, with the lowest presentation levels requiring more sweeps (L_2=25, N=60) than the highest presentation levels (L_2=75dB SPL, N=12). Spectrograms of the individual sweeps were visually inspected and noisy sweeps eliminated before averaging at each level. In addition to the average to evaluate DPOAE levels, an additional average was obtained in which every alternate sound file was inverted. This cancelled the DPOAE and permitted 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 second and a step size of 1/80 second (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 a normal hearing subjects and a hearing impaired subject are shown in

Figure 4.2, left. Cochlear compression may be estimated as the slope of DPOAEs measured at different primary input-levels, that is, as the slope of the "input-output" functions (see Figure 4.2, right). The noise floor during the experiment (displayed in Figure 4.2) was used to determine the levels at which the DPOAE are meaningfully above the background noise. Only DPOAE data, which is above the background noise level was used to measure compression. Specifically, compression was assessed as the slope of the input-output function by taking the difference between the DP emissions for the 65dB and 45dB input levels and divided by 20dB (compression is best measured in the midrange of primary levels, see Neely and Kim, 2008). If the 45dB primarily level does not fall above the noise floor, then we used the range of 55dB to 65 dB instead. Slope of 1.0 corresponds to no compression, while normal compression values for a health cochlea are in the range of 0.20-0.30 (Kummer et al., 1998; see Figure 4.4, center).

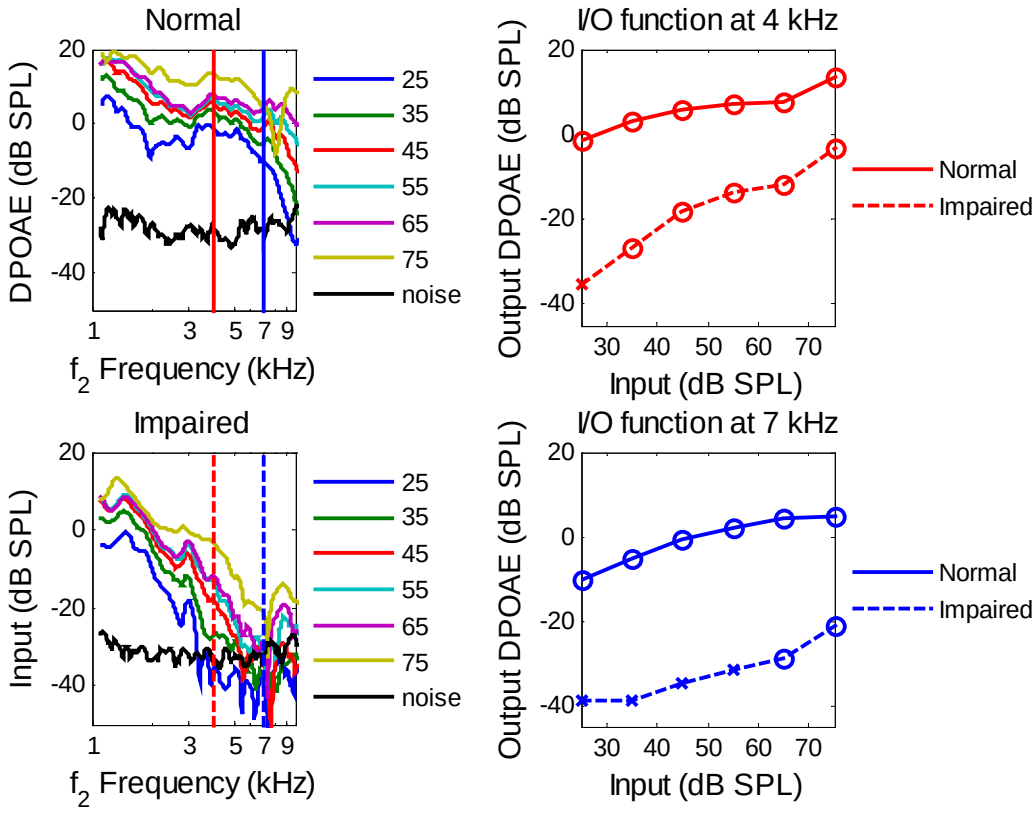

Figure 4.2 DPOAE measurements of normal and impaired hearing subjects: DPOAE is measured from 1k to 10k for both normal (top left) and impaired hearing subject (bottom left). The same data is shown for two specific frequencies (red – 4 kHz, blue – 7 kHz) on the right as input-output function (top and bottom respectively). Hearing-loss is associated with a decreased DPOAE, particularly for low primary-levels and an increased slope (loss of compression). Noise-floor (black) is shown to indicate when DPOAE measures are above background noise. In the right panel symbols indicate whether the DPOAE measures were above ('o') or below ('x') the background noise floor.

4.3.5 Linear prediction of tinnitus

Three peripheral measures were used to predict tinnitus status and tinnitus likeness ratings, namely perceptual thresholds, low input-level DPOAE (average of 25 dB to 45 dB input-levels), and DPOAE slope as described above.

Tinnitus status: To predict the presence or absence of tinnitus for each subject, these variables were averaged for all frequencies at or above 4 kHz, giving 3 features values

for each ear and average these between the two ears (see discussion blow). These three values are combined linearly, with coefficients determined using logistic regression (McCullagh and Nelder, 1989). Logistic regression is trained and tested using a leave-one-out procedure (Duda et al., 2001) using data from all tinnitus and non-tinnitus subjects. Receive-operator characteristic curves were determined on the test-set and area under the ROC (AUC) was taken as a measure of prediction (classification) (McClish 1989; see Figure 4.4). AUC of 0.5 indicates chance performance and AUC=1.0 perfect classification. The goal was to predict the presence of tinnitus for a given subject as opposed to predicting tinnitus for each ear (i.e. lateralization). Thus, for prediction, we can either select the data from one ear (for instance, the ear with more hearing loss) or we could base prediction on the average value between both ears. We obtained comparable results with either approach and report here only the data using the average between both ears.

Tinnitus likeness ratings: To predict the spectral profile of tinnitus within individual subjects the three peripheral hearing measures were determined for each of the 11 frequencies for which ratings were available (excluding ratings of 6, “can't hear” and for N=8 cases excluding frequencies in the range 7.5-10kHz for which the DPOAE were in 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 (Douglas et al., 2001). Linear regression is trained and tested using a leave-one-out procedure (Duda et al., 2001) using data from all frequencies and all tinnitus subjects (Each subject was tested in turn by excluding the

data of this subject from the training set and measuring performance by comparing predicted and actual ratings for this subject). Correlations between the predicted and observed likeness ratings were taken as a measure of prediction performance. Correlation is preferable over the conventional r-square measure of prediction performance because likeness ratings are subjective and may have a bias and range that changes from subject to subject – correlation is insensitive to such cross-subject variability (see Figure 4.9).

4.3.6 Estimate of high-frequency threshold edge

Subjects in the tinnitus and non-tinnitus group had various levels of high-frequency hearing loss, which was characterized here by the perceptual thresholds averaged across all frequencies equal or greater than 4 kHz. To characterize more specifically the presence of a pronounced hearing loss edge, i.e. sharp increase in hearing loss with changing frequency we fit a sigmoid function to the perceptual-threshold profile across frequency, $I(f)=I_o+ I_L/(1+4\exp((f-f_E)/s)$. The following parameters were fit to the threshold data I(f) represented as dB loss over frequency measured in octaves (relative to 1kHz): offset, I_o, measured in dB, edge frequency, f_E, measured in octaves, magnitude of loss over offset, I_L measured in dB, and edge slope, s, as measured in dB per octave. Examples are of the resulting fit are shown in Figure 4.5, left. Perceptual thresholds were characterized as containing a high frequency edge if $f_E < 8.5$ kHz and $s > 10$ dB/octave.

4.4 Results

Based on the gain-adaptation hypothesis we predicted that i) one can distinguish between tinnitus and non-tinnitus 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.

To assess peripheral processing, we measured DPOAE with high resolution (160 points per octave) as well as perceptual thresholds (6 points per octave) for both tinnitus and non-tinnitus subjects (examples in Figure 4.1, top rows and Figure 4.4). The tinnitus spectral profile was assessed for each tinnitus subject using the well-established tinnitus-likeness test (Roberts et al., 2008; examples in Figure 4.1, bottom row). 29 subjects with tinnitus and a control group of 18 non-tinnitus subjects participated in this experiment. Both groups included subjects with normal hearing and subjects with significant hearing loss. All measures were obtained in the frequency range of 1 kHz to 10 kHz (N=39; earlier DPOAE recordings were limited to 7.5 kHz, N=8).

4.4.1 Both perceptual thresholds and DPOAE measures correlate with tinnitus status

Figure 4.3 compares perceptual thresholds and DPOAE data between tinnitus and non-tinnitus subjects. Perceptual thresholds above the 2.7 kHz differed significantly between the non-tinnitus and tinnitus subjects ($p<0.05$, two-sample t-test, uncorrected

for multiple comparison). This is not unexpected as tinnitus subjects usually present with elevated high-frequency thresholds (Konig et al., 2006; Roberts et al., 2008). DPOAE were significantly reduced in the group-mean for tinnitus subjects at frequencies above 2.8 kHz. This was true for the mean DPOAE across all levels (25dB-75dB) as well as for the mean of low input-levels (25dB - 45dB). Compression of the cochlear amplifier can be assessed as the slope of the DPOAE input-output function. Slope was higher for tinnitus subject as compared to non-tinnitus subjects for frequencies above 3 kHz. To compare high-frequency loss between groups, we obtain for each of the 3 types of measures a single value per subject by averaging across frequencies above 4 kHz (Figure 4.3, bottom row). While group-median values all differ significantly ($p<0.02$, Wilcoxon rank-sum test) the populations do show considerable overlap. This means that peripheral loss is not a perfect predictor of whether a subject does or does not report tinnitus.

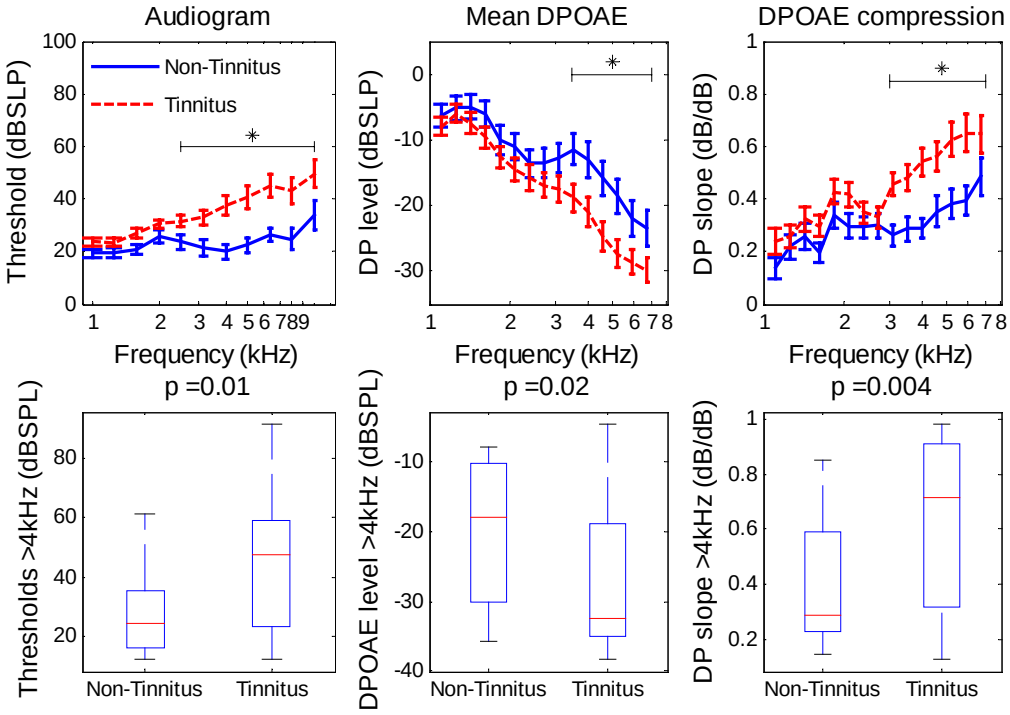

Figure 4.3 Peripheral measurements from normal and tinnitus subjects: Top row: perceptual thresholds, mean DPOAE of 25-45 dB SPL L_2 level and DPOAE compression based on DPOAE input-output slope. All measures given here are the mean across subjects within each group (solid red: tinnitus; solid blue: non-tinnitus). Error-bars indicate standard error of the mean. Horizontal bar with star indicates 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 indicates median, 25 and 75 percentiles and range across subjects. P-values above each graph (computed with a Wilcoxon rank-sum test) show that tinnitus subjects have significantly increased thresholds, decreased low-level DPOAE, and increased DPOAE input-output slope, i.e. reduced compression. In this paper, * means $p<0.05$, ** means $p<0.01$ and *** means $p<0.001$.

To quantify how well perceptual thresholds and DPOAE measures allow one to distinguish between tinnitus and non-tinnitus subjects we performed an ROC analysis linearly combining these measures (see Methods). Classification performance was comparable when using hearing thresholds alone (AUC=0.72) or thresholds and DPOAE measures (AUC=0.75) (Figure 4.4, right). This difference is 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 emissions are highly correlated (Figure 4.4, left and center). Thus, thresholds and DPOAE are equally predictive of tinnitus status.

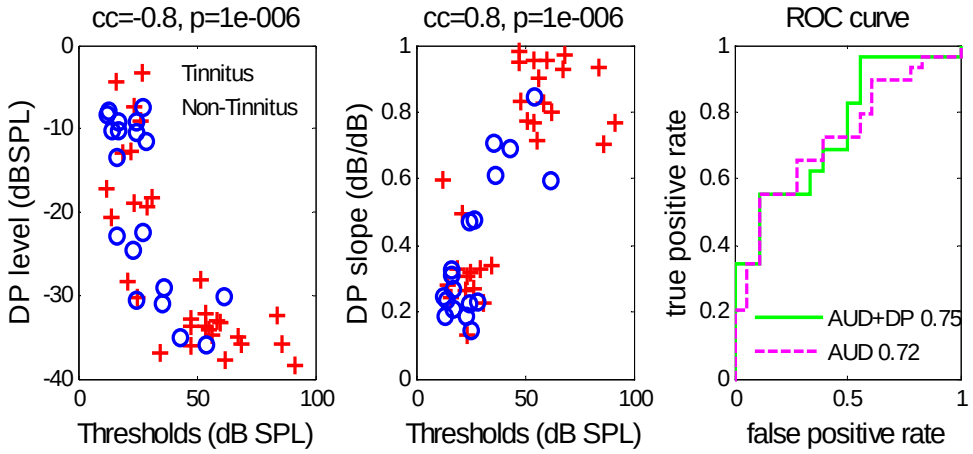

Figure 4.4 Significant correlation between auditory thresholds and DPOAE measures: Left panel: Perceptual thresholds and low-level DP averaged above 4 kHz for tinnitus (red +) and non-tinnitus (blue o) subjects. Middle panel: Same thresholds plotted against DPOAE slope. Correlation coefficients (cc) between these pairs of variables are highly significant. Right panel: ROC curve of test-set performance obtained using a linear combination of audiogram thresholds plus DPOAE measures (solid green line) or audiogram thresholds alone (solid magenta line).

4.4.2 Pronounced hearing loss edge is a predictor of tinnitus

The co-occurrence of elevated thresholds and the presence of tinnitus have previously been established in particular for cases with a sharp hearing loss edge. We analyzed the present data for the presence of a high-frequency threshold edge by fitting a sigmoid curve to plots of thresholds as a function of frequency (see Methods). Figure 4.5 shows an example of a pronounced high-frequency threshold edge (top left) and an example of thresholds without a high-frequency edge (bottom left). Thresholds with a sinusoidal fit with edge frequency of 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 subjects with high-frequency edges and with no high-frequency edge for both the tinnitus and non-tinnitus groups. The same data is given also in table 1, indicating a significant interaction between the presence of a high-frequency edge and tinnitus (p=0.02, Fisher exact test). According to the ROC analysis in Figure 4.4, high-frequency loss alone is only 66% accurate in predicting the presence of tinnitus when including all subjects in this sample. When restricting the analysis to edge-only subjects it becomes evident that the presence of a pronounced high-frequency edge in thresholds is highly indicative of the presence of tinnitus (87% of subjects with the high-frequency edge report tinnitus).

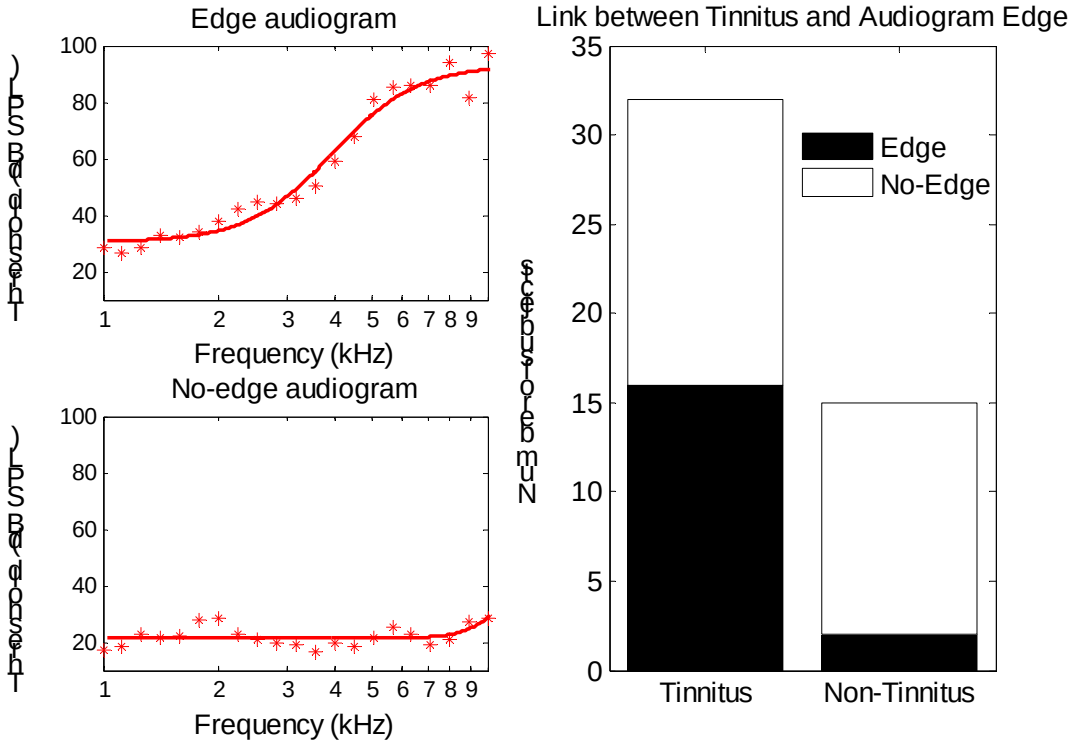

Figure 4.5 High-Frequency threshold edge is a predictor of tinnitus: Left: Examples of subjects with (top) or without (bottom) a pronounced high-frequency edge. Solid line shows sigmoid fit to determine presence of a high-frequency edge

reveals a pronounced hearing-loss edge. Right: Bar graph revealing the number of subjects with a pronounced hearing-loss edge.

	Threshold (edge)	Threshold (no-edge)
Non-tinnitus subjects	2	16
Tinnitus subjects	13	16

Table 4.1 Number of subjects with or without a pronounced high frequency hearing–loss edge.

We didn't have enough data to show that non-tinnitus subjects with elevated thresholds all have a flat audiogram (no edge) (see figure 4.6). The threshold edge criteria, i.e. the presence of a pronounced high-frequency edge in thresholds was only found to be an indicator of the presence of tinnitus.

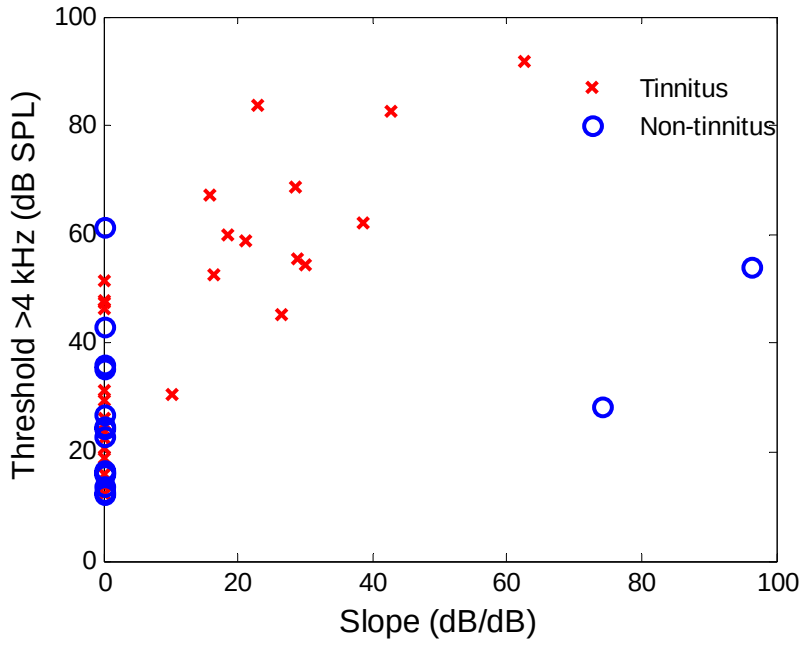

Figure 4.6 Hearing loss edge vs mean hearing threshold above 4 kHz: Scatter plot the hearing threshold edge with the mean hearing threshold in tinnitus subjects (red cross) and non-tinnitus subjects (blue cycle).

4.4.3 Subjects with unreliable tinnitus ratings are not discriminable from non-tinnitus subjects

Tinnitus percept was assessed using the well-established tinnitus-likeness test. In this test, subjects are asked to rate how much their tinnitus resembles a pure tone or tonal noise at various frequencies thus providing a "tinnitus spectrum". All tinnitus subjects participated in this test. For each subject, the same likeness test was repeated twice. A correlation coefficient was obtained between these two results to evaluate reproducibility. Of the 29 subjects 16 could reliably reproduce their likeness ratings (significant correlations between the two repeats with $p<0.05$) and 9 of 29 subjects could not repeat their subjective ratings. The remaining 4 subjects only provided one set of tinnitus likeness ratings. We reanalyzed the high-frequency peripheral hearing measures for the "reproducible" and "non-reproducible" tinnitus subjects separately (Figure 4.5). Subjects who could reliably rate their tinnitus spectrum had significantly ($p<0.01$) increased thresholds, decreased mean and low level DPOAE and increased DPOAE slope. Importantly, subjects who were not able to provide a reliable judgment of their tinnitus did not differ in their peripheral hearing measures from the control group of non-tinnitus subject. Note that this control group does include subjects with and without significant hearing loss (see Figure 4.4). While one may find differences with an increase sample size it remains notable that those subjects with reliable judgments of their tinnitus spectral characteristics tend to have a more pronounced high-frequency loss.

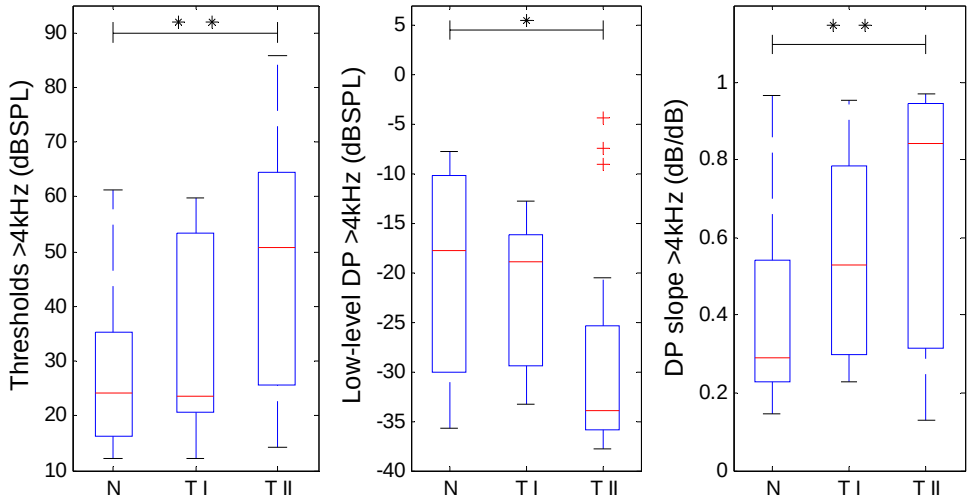

Figure 4.7 Peripheral measurements from non-tinnitus and tinnitus subject segregated by the reliability of their subjective tinnitus likeness ratings: In this figure, N are non-tinnitus subjects, T I are tinnitus subjects who cannot reliably reproduce their tinnitus likeness ratings and T II are those that can. Significant different in the median values was found between N and T II in all measures ($p<0.05$, Wilcoxon rank-sum test), but not between N and T I.

Could this result simply reflect larger likeness ratios at the high-loss frequencies from subjects with a pronounced high-frequency edge? We used table 2 to examine if there is an interaction between the presence of a high-frequency edge in perceptual thresholds and the reproducibility of tinnitus likeness test. A Fisher exact test shows no significant interactions between these two factors ($p>0.05$), suggesting that the presence of pronounce high-frequency hearing-loss edge and the reproducibility of the tinnitus likeness ratings provide distinctive diagnostic criteria.

	Perceptual Thresholds (edge)	Perceptual thresholds (no-edge)
Number of reproducible tinnitus likeness test	8	8
Number of no-reproducible tinnitus likeness test	3	6

Table 4.2 Relationship between High-frequency threshold edge and reproducibility in tinnitus subjects: Values indicate number of subjects within each category.

4.4.4 Spectral profile of tinnitus can be predicted from high-resolution perceptual thresholds and DPOAE for a subset of subjects

As reported previously (Roberts et al., 2008) elevated thresholds coincide with elevated mean likeness ratings across subjects (Figure 4.8). The goal in this study was to determine whether the spectral profile of tinnitus could be anticipated from peripheral hearing measures 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 at all frequencies. Prediction performance was assessed using leave-one-out cross-validation (see Methods). The prediction result is plotted in the Figure 4.9. For a subset of subject (N=19 of 29), the tinnitus spectrum can indeed be predicted purely from these physiological measures,

i.e. there is a significant correlation between the predicted and observed ratings.

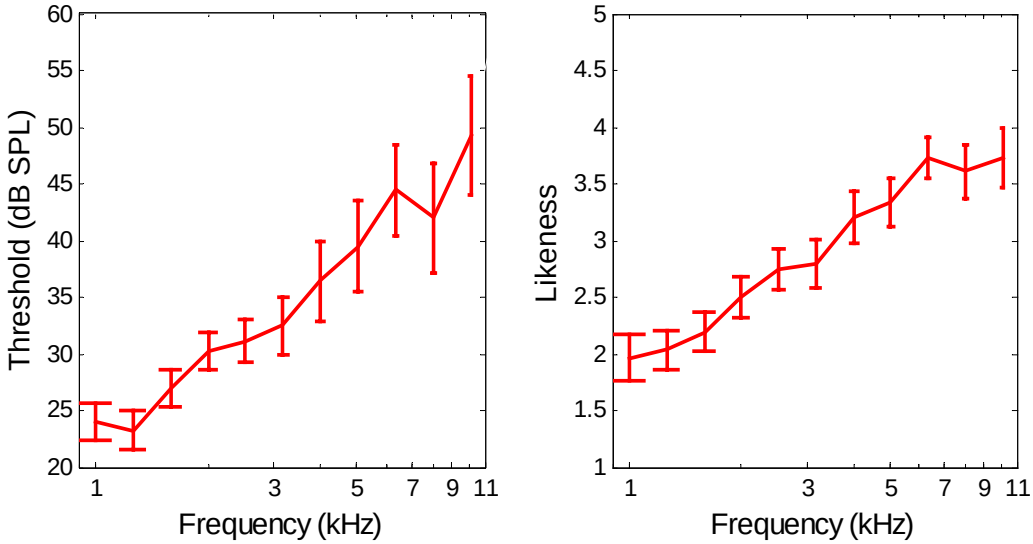

Figure 4.8 Group average thresholds and likeness ratings coincide: Left: Group average of perceptual thresholds for all tinnitus subjects with error bars indicating SEM. Right: Average tinnitus likeness rating for all tinnitus subjects.

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

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

In this equation, I* is the perceptual threshold measured in dB SPL, I_{DP} is the low input-level DPOAE in dB SPL and ΔI_{DP} is the unit-less DPOAE slope which measures cochlear compression. The coefficients in this prediction indicate that tinnitus likeness rating increases with elevated threshold (positive coefficient) reduced DPOAE level (negative coefficient) and increased slope (positive coefficient). The variance of the likeness rating explained by each term in this sum can be 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 and 0.03 for the DPOAE slope, suggesting that low input-level DPOAE is the most predictive variable among the three tested.

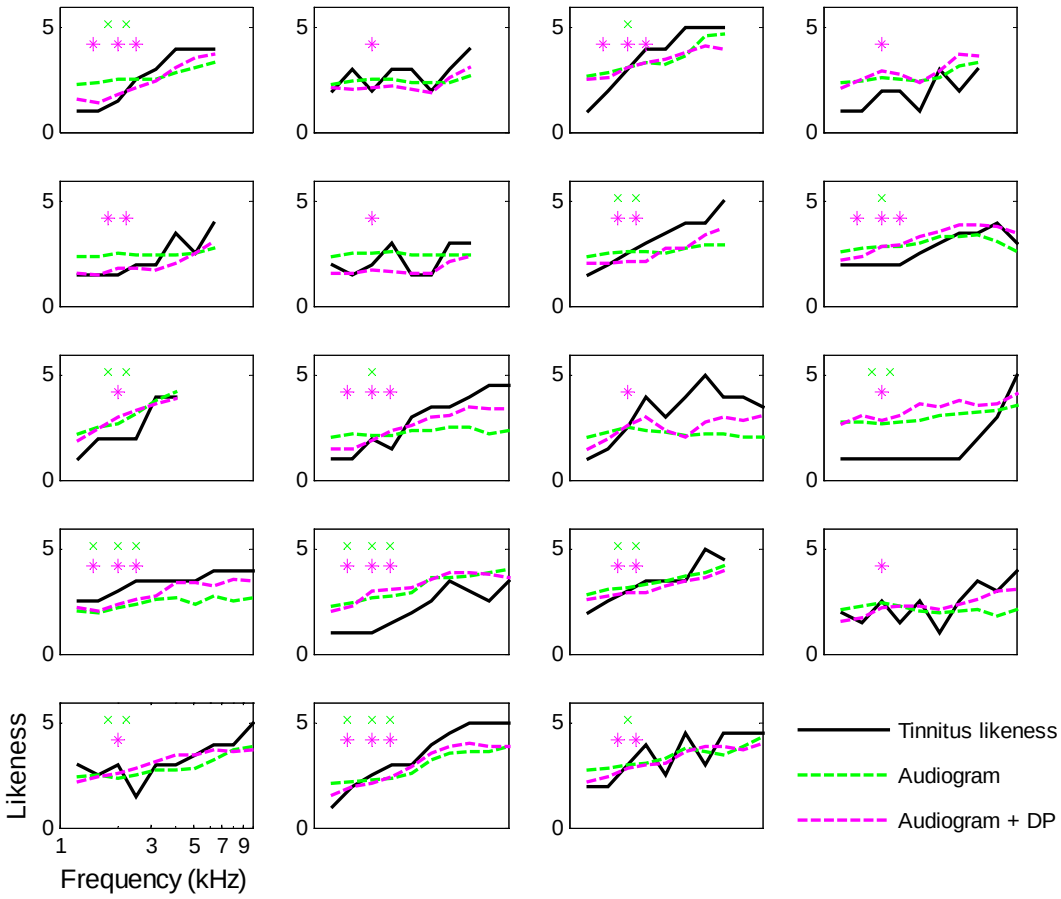

Figure 4.9 Predicted and measured tinnitus likeness spectrum for individual subjects: For 19 of 29 tinnitus subjects the predicted tinnitus spectrum correlates across frequency with the measured likeness ratings ($p<0.05$). Prediction is either based on perceptual thresholds alone or on a linear combination of perceptual thresholds and DPOAE measures (lower level and slope).

To determine accuracy of the prediction, correlation is used instead of goodness fit because the likeness rating was subjective and the scale was probably different for each subject. The observed correlation ($c=0.83\pm0.09$, $N=19$) of the estimated tinnitus

spectrum with the observed likeness rating is as good as can be expected given the subject's repeat-reliability (correlation across frequency of the two ratings provided by each subject, c=0.82±0.15, N=16, for 3 of the 19 repeated measures were not available). The remaining 10 tinnitus subjects contrasted from this predictable group in that they tended to give inconsistent likeness ratings (c=0.31±0.31, N=9). See section 4.4.3 above. Figure 4.10 shows that the reproducibility of likeness ratings is much higher for these "predictable" subjects suggesting that ratings could often not be predicted because subjects were not able to provided meaningful subjective ratings.

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

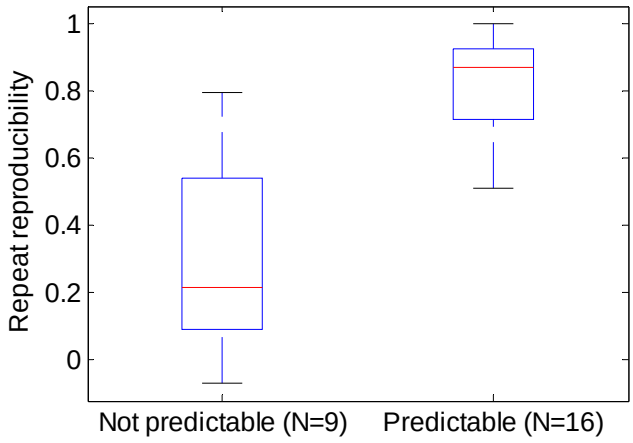

Figure 4.10 Reproducibility of non-predictable tinnitus subjects VS predictable tinnitus subjects: Correlation between two tinnitus likeness tests are significant different for predictable and non-predictable tinnitus subjects

4.5 Discussion

The premise of this work was that hearing loss is a necessary, albeit not sufficient condition for tinnitus. The notion that reduced peripheral input leads to elevated sensitivity and/or spontaneous hyper-activity in central structures is not new (Kaltenbach and Godfrey, 2008). Various mechanisms for this have been hypothesized including reduced feed-forward inhibition (Dominguez et al., 2006), reduced lateral inhibition (Koenig et al., 2006), remapping of de-afferented frequency regions (Eggermont and Roberts, 2004; Roberts et al., 2008; Schaette and Kempter, 2009) and increased neuronal gains (Dean et al., 2005). A specific computational model of central adaptation based on frequency dependent gains identified three critical factors for such adaptation (Parra and Pearlmutter, 2007): 1) elevated peripheral sensitivity; 2) loss of dynamic range; and 3) a contrast across frequencies.

The goals of this work were 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 PDOAE input-output function slope and sensitivity measured with bandpass noise hearing thresholds. Both hearing thresholds and DPOAE compression measures have previously been analyzed in the context of tinnitus showing increased thresholds and reduced compression (Janssen et al., 1998; Hesse et al., 2005). DPOAE are also difference selectively for frequency bands that have been matched to the tinnitus percept (Ozimek et al., 2006). The indicator that best correlates to the tinnitus percept is loss of compression (Janssen et al., 1998). This loss of compression is consistent with the comorbidity of tinnitus and hyperacusis. Indeed, hyperacusis (with or without tinnitus) coincides with elevated DPOAE input-output slopes reflecting reduced compression (Bartnik et al., 2005). Konig et al. (2006) reported that the pitch of the tinnitus percept correlated with the edge-frequency in a high-frequency loss threshold. Moore et al. (2010) found a clear relationship between the values of the high-frequency edge and the mean pitch of the tinnitus with the improved definition of edge-frequency. Moffat et al. (2009) indicated that tinnitus percept was affected only weakly in the conventional amplification group, and was not at all affected in the high-bandwidth group. Sztuka et al. (2010) reported DPOAE at 70dB input level was significant higher in tinnitus subjects with normal hearing thresholds. In our data, we did not find the same result.

However, to our knowledge, this is the first study where perception thresholds and DPOAEs are measured and analyzed from the same subjects and with such high

frequency resolution. In contrast to previous studies we avoid the use of tinnitus frequency matching (Koenig et al., 2006). Matching is at times difficult for subjects as the tinnitus percept is often more complex than a single discrete frequency (Robert et al., 2008). By using ratings across many frequencies instead, we obtain for each subject a spectral profile of the tinnitus percept, which can be compared to the hearing-loss profile for individual subjects. When we do this, we find two groups of subjects; those for which likeness ratings across frequency can indeed be predicted from their peripheral measures (approximately two thirds in our sample) and those for which we can't predict likeness ratios. 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. The tight link between the tinnitus with 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 the specific hearing-loss profile and characteristic may reduce tinnitus, provided the adaptive gain mechanism remains active. The present study identified low input-level DPOAE as an important additional predictive variable over the threshold alone. This is consistent with the correlation we previously found 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 DPOAE is a sensitive marker of cochlear function while perceptual thresholds capture 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 both inner and outer-hair cells.

The second 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 are mixed. The present sample contains subjects with or without high-frequency hearing loss in both the tinnitus and non-tinnitus groups. Thus, high-frequency hearing thresholds give only 66% correct classification. We argue that even mild hearing deficits – not typically considered "loss" – are necessary for tinnitus. As a sensitive objective measure of cochlear mechanics DPOAE have a potential to capture such milder deficits. Consistent with previous studies in tinnitus subjects, we find reduced DPOAEs, in particular for the low input-level DPOAE and increased slope, i.e. reduced compression. In the present sample, we did not find the elevated high-input level emissions reported in Sztuka et al. (2010), but note that increased slope is not inconsistent with this finding, which is also consistent with our preview study (Zhou et al., 2010). In our subject sample the DPOAE measures are highly correlated with hearing thresholds. This is not surprising as the health of outer-hair cell impacts both compression and sensitivity (Boege and Jassen, 2002). Only inner hair-cell loss selectively impacts hearing thresholds. Regardless, the extra measures may have the potential to disambiguate some instances of tinnitus without hearing loss and hearing loss without tinnitus. While we see a increase in the discrimination the ability to discriminate between tinnitus and non-tinnitus subjects when DPOAE measures are added, this increase is not significant in this sample. A larger sample of subjects with

a precise match in hearing thresholds may be required to ultimately address the question as to whether compression in itself provides an additional discriminant criterion. Such a study should focus in particular on subjects with "normal" thresholds.

On the other hand, and consistent with previous reports (Koenig et al., 2006), we found that subjects with strong high-frequency edge are very likely to have tinnitus (83%). Consistent with previous findings (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 ratings are 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).

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 to an otherwise widespread phenomenon (Rauschecker et al., 2010). Essentially, non-tinnitus subjects with hearing loss may have learned to "tune out" the aberrant percept. Indeed, all current clinical treatment emphasizes some form of training that teaches patients to ignore or stop attending to the tinnitus percept.

What we propose here is that by compensating the specific profile and characteristic of hearing loss one may reduce the tinnitus percept itself including cases of mild

hearing loss. Indeed, audiologists often find that tinnitus is reduced with the use of an appropriately adjusted hearing aid (Davis et al., 2008) at least when the hearing aid reaches the typically high tinnitus frequencies that required compensation (Hanley and Davis, 2008).

4.6 Conclusion

Impaired cochlear function correlated with the presence of tinnitus and its spectral profile. The elevated threshold, reduced DPOAE and increased DPOAE slope was obtained in our experiments, which was consistent with neural gain adaptation hypothesis. This result suggested that the compensation of peripheral deficit (both linear gain and non-linear compression) could modulate tinnitus percept.

Chapter 5: Summary and Future Work

5.1 Summary and achievement

Both hearing loss and loss of compression have separately been associated with tinnitus (see Chapter 2 and Chapter 4). Tinnitus is often associated with hearing loss as assessed by single tone perception thresholds. However, an altered threshold is neither a necessary nor sufficient condition for tinnitus. In fact, the threshold may be an insufficiently sensitive indicator of altered peripheral processing in tinnitus subjects (Weisz et al., 2006). Most studies using DPOAE to assess cochlear-processing show an alteration of DP levels (e.g. Bartnik et al., 2005). The most reliable indicator of tinnitus was found to be the growth of the DP I/O function (a measure of compression) (Janssen and Kummer, 1998). However, to our knowledge there were no studies that compare the tinnitus percept to the perception thresholds and compression factors in combination at multiple frequencies. According to our model, lateral inhibition accentuates the gain adaptation effect at edges of hearing loss and so for its prediction it was necessary to measure these parameters with a fine frequency resolution.

We hypothesized that gain adaptation may be assessed psychophysically by the sensitization that a priming signal can induce on the detection of pure tones. We measured perception thresholds of pure tones in notched-noise following various priming signals (band and notched noise, with silence and white-noise as control conditions). Cochlear compression was obtained by extracting the generator

component of DPOAE across frequency. The psychophysical experiment revealed more sensitization than expected by conventional forward masking. This highlights the uniqueness of the observed sensitization effect, which is counter to the more common increase in perceptual thresholds. We did not, however, find a link between sensitization and compression. Instead, stronger sensitization correlated with stronger DPOAE for low primer levels. This result is consistent with the notion that the DPOAE is a sensitive indicator of the healthy of outer-hair cell. Together these data suggest that the short-term dynamic adaptation leading to sensitization is mediated by the amplification mechanism of outer hair cells. Interestingly, compression correlated with perception thresholds across frequencies for individual subjects. This reliable, within-subject correlation of a psychophysical perception threshold with the objective physiological measure of compression establishes our particular DPOAE paradigm as a strong candidate for the assessment of peripheral hearing. This is particularly relevant given the simplicity of the test, making it attractive for use in a clinical setting.

Furthermore, we also found that impaired cochlear function correlates with the presence of tinnitus. To assess cochlear function, we measured DPOAE with high frequency resolution as well as thresholds measured using narrow-band noise for tinnitus and no-tinnitus subjects. We found tinnitus subject had elevated thresholds, reduced DPOAE, and increased DPOAE input-output function slope, which is consistent with previous studies. These measures were strongly correlated and seemed to be equally predictive of the presence or absence of tinnitus in a given subject.

Particularly, subjects with a pronounced hearing-loss edge were almost certainly found to have tinnitus.

We also predicted that the tinnitus percept could be determined for individual subjects from measures of their peripheral processing when obtained with sufficient frequency resolution. The tinnitus percept was assessed using the well-established tinnitus-likeness test. This test asks subjects to rate how much their tinnitus resembles a pure tone or tonal noise at various frequencies thus providing a 'tinnitus spectrum'. For a subset of subjects, the tinnitus spectrum can indeed be predicted purely from thresholds and DPOAE measures (both low input level DPOAE and DPOAE slope). The correlation of the estimated tinnitus spectrum with the observed likeness ratings is as good as can be expected given the subject's repeat-variability. The remaining subjects contrasted this group in that the subjects gave inconsistent likeness ratings so that we could not determine compression. The prediction using DPOAE in addition to thresholds is significantly better than using thresholds only. We concluded that for a subset of individuals, the subjective tinnitus percept could be linked back to objectively measurable hearing deficits. This approach is consistent with current attempts to treat tinnitus using custom-fit auditory stimulation.

In summary, the gain adaptation hypothesis makes a number of testable predictions, and has been tested with the data that is shown in this thesis. Psychophysics experiments confirm the model's prediction that notched noise will improve perception thresholds for tones in the notch band (Chapter 3). The prediction that

cochlear compression and sensitivity measures are predictive of the tinnitus percept at different frequencies is also confirmed with our data, which is presented in the Chapter 4. When including the DPOAE with the threshold the coincidence with the likeness rating is now specific to individual subjects and not just on the group level (as in Roberts et al., 2008). But we did not find that tinnitus status was significantly improved with DPOAE. The compression itself may have a lower significance than previous research (Parra and Pearlmutter, 2007).

All of these experimental results suggest us that, for tinnitus patient, carefully measuring thresholds and DPOAE in combination and with high-frequency resolution are necessary and important. Both compensation of hearing loss (linear gain) and compensation of no-linear compression are the potential treatment to alleviate tinnitus symptom.

5.2 Future work

A causal effect on central processing has been shown following hearing aid use (Philibert et al., 2005; Munro 2008). Prolonged use of hearing aids reduced the perceived loudness of sounds at the aided frequency bands in hearing impaired subjects. Therapeutic high frequency auditory stimulation reduces loudness discomfort in hyperacusis subjects (Norena and Chery-Croze, 2007). Auditory stimulation that compensates for elevated hearing thresholds are used to reduce tinnitus masking levels (Davis et al., 2008, Hanley and Davis, 2008). These data suggest that increased input at the loss-frequencies causally reduces elevated central

gains. However, to date, no effort has been made to compensate for a loss in compression on an individual frequency basis. We note that adaptation in the inferior coliculus responds separately to peripheral change in thresholds (affected by gain) and changes in dynamic range (affected by compression) (Dean et al., 2005). The preliminary experiments show that for a subset of subject peripheral compression and sensitivity correlates with the presence of tinnitus at individual frequencies. For these subjects we will test if the tinnitus percept can be modulated prospectively by compensating for these specific measurable peripheral losses.

We predict that frequency specific compensation of compression and sensitivity has a causal effect on tinnitus loudness. Our experiments show that for a subset of subject peripheral compression and sensitivity correlates with the presence of tinnitus at individual frequencies. Not for all tinnitus subjects, but just for this subset of subject, we will test if the tinnitus percept can be modulated prospectively by compensating for these specific measurable peripheral losses.

5.3 Final words

The ultimate goal of this research is to determine the correlation between the tinnitus symptom and peripheral deficit. Not for all tinnitus patients, but at least for some of them, the hyperactivity of auditory neuronal system, which is believed to correlate with tinnitus, is triggered with this peripheral deficit. Comparing with conventional threshold, our study points out that the careful measure of cochlear function (both threshold and DPOAE) are necessary. As a treatment of tinnitus patients, the

compensation of both linear gain and no-linear compression could reduce the spontaneous firing rate of auditory cortex and improve the quality of life our patients.

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