LUND UNIVERSITY

Pitch, loudness and frequency selectivity in low-frequency hearing loss

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2009

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1

Pitch, loudness, and frequency selectivity in low-frequency hearing loss

Jonas Brännström

Ars artis gratia,
scientia scientiae gratia.

To my family

TABLE OF CONTENTS

ABBREVIATIONS AND DEFINITIONS

2AFC   Two-alternative forced choice
daPa   DecaPascal
ERB   Equivalent rectangular bandwidth
FFT   Fast Fourier transform
FLFHL   Fluctuating low-frequency hearing loss
HL   Hearing level
JND   Just-noticeable difference
Loudness "That attribute of auditory sensation in terms of which sounds may be ordered on a scale extending from soft to loud." [10]
MLSP   Maximum likelihood sequential procedure
Pitch   "That attribute of auditory sensation in terms of which sounds may be ordered on a scale extending from low to high. Pitch depends mainly upon the frequency content of the sound stimulus, but it also depends upon the sound pressure and the waveform of the stimulus." [10]
PSE   Point of subjective equality
PTC   Psychophysical tuning curve
PTA   Pure tone average hearing threshold
RMLSP   Randomised maximum likelihood sequential procedure
SAM   Sine wave amplitude-modulated
SD   Standard deviation
SL   Sensation level
SPL   Sound pressure level
SRS   Speech recognition score
TEOAE   Transient evoked otoacoustic emission
VAS   Visual analogue scale

LIST OF PUBLICATIONS

This thesis is based on the studies reported in the following papers, referred to in the text by their respective Roman numerals.

I. Brännström, K.J. & Grenner J. 2008. Long-term measurement of binaural intensity and pitch matches. I. Normal hearing. Int J Audiol 47:59-66.

II. Brännström, K.J. & Grenner J. 2008. Clinical application of long-term intensity and pitch matches in fluctuating low-frequency hearing loss. Int J Audiol 47:412-419.

III. Brännström, K.J. & Grenner J. 2008. Long-term measurement of binaural intensity and pitch matches. II. Fluctuating low-frequency hearing loss. Int J Audiol 47:675-687.

IV. Brännström, K.J. & Grenner J. 2009. Effects on cochlear frequency selectivity after hypobaric pressure exposure in fluctuating low-frequency hearing loss. J Laryngol Otol. E-publication ahead of print.

V. Brännström, K.J. 2009. Monaural and binaural pitch matches in low-frequency hearing loss using sine wave amplitude-modulated noise. Manuscript.

THESIS AT A GLANCE

	Questions	Methods	Results	Conclusions
I	Can normal-hearing subjects measure long-term measurements of their hearing reliably using portable equipment?	Development of the RMLSP-method. Long-term measurements of binaural loudness and pitch matches during one to several weeks in 10 normal-hearing subjects. Measurements were made by the subjects themselfs in their own homes. Comparison between monaural and binaural pitch-matching ability at the laboratory.	The RMLSP was a reliable method to use in home testing, but the recordings of the normal-hearing subjects varied in stability.	The long-term recordings of binaural loudness matches are reliable in most subjects. Binaural pitch matches could be measured reliably only if the subjects are able to define pitch precisely.
II	Does the method work in fluctuating low-frequency hearing loss?	Long-term home measurements of binaural loudness and pitch matches in one subject with monaural fluctuating low-frequency hearing loss (FLFHL) during one period with and one without symptoms.	More pronounced hearing fluctuations was recorded with symptoms than without symptoms, but the recordings indicated hearing fluctuations during both test periods. The results of both test periods were different from the normal-hearing references in (I).	The long-term measurements seem to provide useful diagnostic information on hearing fluctuations.
III	Are there differences in hearing fluctuations comparing patients with monaural fluctuating low-frequency hearing loss (FLFHL) with vertigo (Ménière's disease) and those without (cochlear hydrops)? Is there a relation between hearing measurements and ratings of subjective symptoms?	Long-term home measurements of binaural loudness, pitch matches, and symptom ratings of hearing, tinnitus/aural fullness, and vertigo in 13 patients with monaural FLFHL.	The patients recorded binaural loudness and pitch matching fluctuations not seen in normal-hearing subjects. Patients with Ménière's disease had higher average day-to-day difference than patients with cochlear hydrops. Subjective symptoms were, on group level, poorly associated with the loudness and pitch matches, although obvious covariations were observed in some subjects.	It seems possible to separate disease subgroups using long-term measurements of loudness and pitch matches. This could prove to be an essential feature in clinical treatment trials.
IV	What effects have pressure exposure on hearing physiology in patients monaural fluctuating low-frequency hearing loss (FLFHL)?	At the laboratory, hearing thresholds, frequency selectivity, outer hair cell function, and speech recognition in noise were measured in 10 patients with monaural FLFHL before and after pressure exposure in the hypobaric pressure chamber.	The pressure chamber exposure may improve, deteriorate, or not affect the inner ear physiology. The observed effects were generally small and specific for individual subjects. Improvements in frequency selectivity were not accompanied by improvements in audiometric hearing thresholds.	The results indicate that the pure tone audiogram may be a too blunt measure of inner ear physiology when monitoring effects of pressure exposures.
V	Does pitch matching precision improve in subjects with monaural fluctuating low-frequency hearing loss (FLFHL) presenting signals with only timing pitch information to the affected ear?	Two normal-hearing subjects, two with monaural FLFHL, and one with high-frequency hearing loss executed monaural and binaural pitch matches at the laboratory using the developed RMLSP-method, pure tones, and band-passed sine wave amplitude-modulated noise (SAM-noise).	Pure tone pitch differences were seen between ears in the subjects with FLFHL subjects, but only when the reference signal was presented to the unaffected ear. Binaural pitch matches made with SAM-noise as reference signal in the affected ear improved the precision in subjects with monaural low-frequency hearing loss, but the precision deteriorated when the variable test tone is presented to the affected ear.	The findings suggest possible detrimental effect of conflicting timing and place cues on pitch matches in subjects with FLFHL.

INTRODUCTION

The problem
Patients with monaural sensorineural fluctuating low-frequency hearing loss (FLFHL) most commonly suffer from cochlear hydrops (tinnitus and aural fullness) or Ménière's disease (tinnitus, aural fullness and recurrent vertigo). These patients often report fluctuations in hearing from one day or week to another, but clinicians still mainly rely on single audiograms and the reported subjective symptoms to obtain a diagnosis. This is also true for the evaluation of therapeutic treatment. In clinical practice, we encounter patients with FLFHL that report variations in hearing and that these changes may occur from one day to the next. These hearing fluctuations do not necessarily represent only changes in hearing sensitivity, since the patients also report changes in quality and clarity. To measure these changes over a longer period of time, we started to develop portable equipment that would make it possible to measure hearing changes in both these different domains.

FLFHL seems to be related to excessive fluid in the inner ear and this kind of patients are often treated with diuretics, salt reduction, or local pressure application [194, 151, 193, 45, 201, 114, 48, 112, 214, 184, 129, 159, 187, 41, 85, 162]. The insertion of a tympanostomy tube is known clinically to relieve symptoms although the underlying mechanism for this is not known [188]. Patients may improve from one or more of these treatments or they may not respond. It cannot be predicted which patients that will respond to which treatment and, in treatment studies, improvement may not be established above the level of chance [129, 187, 41, 162]. This heterogeneity in response to treatment might suggest that the symptoms observed may be generated by different underlying causes, i.e. it might be different diseases presenting with similar symptoms.

Today, the evaluation of treatment is mainly based on a measurement of pure tone audiometry, speech audiometry, and scaling of subjective symptoms before and after using a certain treatment. Improvements are often obscured by the natural course of the disease and it is well known that these patients respond very well to psychosocial support [55, 43, 200], which further complicates the evaluation of the treatment. Long-term monitoring of the disease may provide further information on the hearing fluctuations and may also provide a possibility to quantify disease activity. If disease activity could be categorised, there is a possibility that subtypes of the disease can be discerned.

Pitch coding in the peripheral auditory system
There are basically three theories about how pitch is coded in the peripheral auditory system. They are the place, timing and place/timing theories. The place theory states that a sound excites a certain area on the basilar membrane of the cochlea and that the place of excitation is mainly dependent on the frequency content of the sound (sound pressure level is also known to affect the place). It is said that the cochlea is tonotopically organised. Due to the inherent mass and stiffness properties of the

membrane, lower frequencies are placed at the apical part of the cochlea and higher frequencies at the basal part [44, 155]. In its basic form, the theory proposes a complete passive mechanism [15], but both psychoacoustical [158, 71, 143, 130, 39, 40, 212] and physiological findings suggests the need of an active biomechanical manipulation of the membrane during stimulation, most likely provided by the outer hair cells [e.g. 102, 103, 23, 22, 100, 104, 21, 155, 72]. Accordingly, this theory has been revised to fit these findings.

The theory of timing states that the firing pattern of the neural responses provides information of the pitch of a sound. Evidence suggests that most neurons on the basilar membrane are tuned to their own characteristic frequency; a phase-locking between intrinsic and extrinsic frequencies can be measured in the cochlear nerve using an animal model (at least for lower frequencies) [e.g. 24, 116, 97, 93].

Evidence suggests that lower frequencies (<4-5 kHz and especially below 1 kHz) are more dependent on timing than place dependent and that higher frequencies are place dependent [24, 136, 210, 116, 140, 172, 141, 144, 52, 209] - hence, the timing and place theory. However, all contemporary scientific evidence suggests that the the function of the cochlea and the peripheral hearing system do not rely on a single channel input but rather on many channels providing redundancy in signal information. This means that both place and timing information are used (in varying extent depending on the task) by the auditory system in interpreting and coding the pitch of a sound.

Reported effects in Ménières disease on pitch perception

Fluid volume changes or elasticity changes of the cochlear membranes are the likely cause of increased hearing thresholds characteristically first observed at lower frequencies in patients with cochlear hydrops and Ménière's disease [168, 195, 5, 169, 152, 1, 107, 122]. These changes in hearing threshold sensitivity seen in the patients with monaural FLFHL are often accompanied by changes in pitch perception in the affected ear [175, 176, 203, 179, 177, 2, 3, 4, 195, 60, 147, 151, 20, 81, 149]. This does often mean that the sound in the affected ear is perceived as distorted or that there is a pure tone pitch difference between the ears.

The pitch perception changes seen in patients have been attributed to these fluid volume or elasticity changes [195, 147, 196, 189, 81]. Pitch differences between the ears can easily be measured through binaural pitch matches. This means that the patient adjusts the frequency of a variable tone in the affected ear until the patient indicates that it matches a tone of fixed frequency presented to the unaffected ear. In the literature, most patients with FLFHL judge the pitch of a pure tone presented in the affected ear as higher compared to how it is heard in the unaffected ear, although some patients perceive it as lower or, in some cases, equal in pitch [147, 20]. Based on such findings it may be hypothesised that the degree of pitch difference between the ears might constitute a measure of the disease and that long-term measurements of pitch together with an estimate of hearing sensitivity provide more comprehensive information on the hearing fluctuations than the occasional audiogram at the clinic.

Effects of increased inner ear pressure on cochlear frequency selectivity

A relatively increased pressure in the middle ear during exposure in hypobaric pressure chamber has previously been used to impose positive pressure gradients to the inner ear to affect the cochlear physiology in patients with Ménière's disease [194, 201, 108, 112] or by application of pulsated pressure locally in the ear canal [47, 45, 46, 214, 49, 213, 188, 85]. In most of these studies, the effects on the inner ear have been assessed through measurements of hearing thresholds, speech recognition scores (SRS) and in some cases otoacoustic emissions (i.e. the outer hair cell function). Improvements in the measured parameters have been observed in some, but not all, patients, a finding often explained by different disease activity [194, 193, 201, 108, 112]. SRS have increased after pressure exposure [45, 112]. Since it is known that cochlear frequency selectivity affects SRS [181], it may be hypothesised that pressure exposure in a hypobaric pressure chamber might affect among other things frequency selectivity, increase outer hair cell motility, or decrease pressure on the habenula perforata. This latter relation has not yet been demonstrated experimentally, however.

Conflicting place and timing cues

Pure tone monaural and binaural pitch matches made by patients with low-frequency hearing loss show large variability [59, 197, 149, 86, 109]. For these patients, the increased variability has been attributed to conflicting place and timing information in the affected ear [59, 197, 68] or to low-frequency regions on the basilar membrane without functioning inner hair cells or inner hair cells with reduced function [86, 109]. One way to theoretically remove place cues is to use sine wave amplitude-modulated noise (SAM-noise).

SAM-noise has a long-term average spectrum that is flat and featureless, but it can be used to elicit pitch sensation that may be changed with modulation frequency [127, 148, 75, 156, 28, 153, 154, 83, 29, 163, 61, 199]. These previous studies on normal-hearing subjects, using SAM-noise, have mostly been conducted using amplitude-modulated white noise or other kinds of wideband noises. The overall finding has been that SAM-noise with modulation rates below at least 0.3 kHz do elicit pitch sensation in most subjects and it has also been noted that greater modulation depths are required to elicit pitch sensation at higher modulation rates. For the listener, the pitch may be hard to perceive and it is not as clear as the ones heard listening to pure tones [146].

It has been suggested that tonotopic place cues do not generate this SAM-pitch [156, 28, 153, 83, 29, 77] and evidence supports the notion that it is derived from the neural firing rate pattern present in the auditory nerve [24, 116, 97, 163, 79, 93]. Previous studies also suggest that the frequency coding in the inner ear depends on both place and timing information and that higher frequencies seem to be more place dependent while lower frequencies are more timing dependent [137, 139, 138, 171, 170, 140, 142, 172, 77, 141, 37, 124, 145].

It may thus be hypothesised that patients with sensorineural low-frequency hearing loss may actually perform more precisely in their pitch matches when place

information is eliminated by using for example SAM-noise. There is some evidence for this assumption in previous literature: It has been shown that the monaural difference limens for amplitude-modulation in the affected ear of patients with monaural Ménière's disease are very close to those of normal-hearing controls, while the pure-tone frequency discrimination is impaired [61, 62]. This finding supports the notion that the increased variability may be attributed to conflicting place and timing cues [59, 197].

AIMS

- To determine the stability in daily long-term measurements of binaural intensity and pitch matches during one to several weeks in normal-hearing subjects using RMLSP and also, to compare monaural pitch-matching ability with binaural (I).

- To measure changes in binaural loudness and pitch matches in a single patient with FLFHL in order to assess disease activity during one period with and one without symptoms (II).

- To determine the relation between long-term measurements of binaural intensity matches and pitch matches, and ratings of subjective symptoms in patients with monaural FLFHL without vertigo and in patients with monaural Ménière's disease (i.e. FLFHL with vertigo). To compare patients with normal-hearing references (III).

- To determine the effects of hypobaric pressure chamber exposure, i.e. relatively increased middle ear pressure, on cochlear frequency selectivity in patients with monaural FLFHL (IV).

- To test the pitch matching precision in patients with monaural low-frequency hearing loss by using stimuli containing only temporal information and to compare it with both temporal and place information (V).

METHODS, PROCEDURES AND EQUIPMENT

Description of a version of the randomised maximum likelihood sequential procedure; algorithms and statistical considerations

This section describes the developed version of the randomised maximum likelihood sequential procedure (RMLSP). It presents the algorithms that are used to calculate the next test tone. In the description, it is assumed that loudness balance between the ears is tested, but the procedure can be used for any parameter.

The basic test paradigm presents one tone first to the reference ear (the reference tone) and a second tone to the test ear (the test tone). The reference tone is fixed in frequency and in sound pressure level. A reference tone and a test tone constitute a tone pair. The task for the subject is to judge whether the test tone is softer or louder than the reference tone. If the test tone has a low sound pressure level compared to the reference tone, we might expect the response to be "softer", and the opposite, "louder". Between these "extreme" values, we expect an area of uncertainty containing variable responses. The algorithm that finds the value for the next test tone during the test, should ideally explore the areas of interest (i.e. the area where variable responses are most likely to occur), with a minimum number of observations. The point of subjective equality (PSE) constitutes the midpoint (or average) response, where the likelihoods of responding "softer" or "louder" are equal (that is 50 %). PSE corresponds to the midpoint of any given slope of the psychometric function.

In the first paired tones to be presented, the test tone has always considerably higher sound pressure level than the reference tone. As an example, if the reference tone was 60 dB SPL and the test tone was 70 dB SPL. In this case, the most likely response in a normal-hearing subject is that the test tone is louder than the reference tone. If not, the test tone will be increased further by for example 10 dB. In the second tone pair, the test tone is presented at a much lower level than the first reference tone, e.g. 50 dB. As for the first set of paired tones, the test tone will be decreased in level by e.g. 10 dB) in case of a "louder" response until the subject responds that it is "softer" than the reference tone. In this manner, the initial range is established. Outside this range, it can be assumed that no response of other value will be recorded. Thus,

(1)   initial range $= testtone_1 - testtone_2$.

The value of the third test tone is calculated,

(2) $testtone_3 = (testtone_1 + testtone_2)/2 \pm (testtone_1 + testtone_2)*0.25*rand$

Rand means a random value between 0 and 1. The following test tones (no. 4 and forward) are calculated;

(3) $testtones_{>3} = PSE_{prel} \pm x\ (dB_{rand})$.

PSE_{prel} indicates a preliminary PSE (i.e. mean) calculated through probit analysis [58]. dB_{rand} denotes a specified range from which a random factor is selected. The probit analysis (c.f. the section *Post-test analysis* below) generates a midpoint (PSE) and a slope of the psychometric function. Using the normally distributed slope of the interpolation, the variable dB_{rand} becomes a random value selected from the range 0.3 to 1.2 SD of the regression fit. In pre-test Monte Carlo simulations, test points between 0.3 and 1.2 SD away from the PSE provided the most information regarding the SD of the psychometric function. Theoretically, if the slope becomes very steep, the dB_{rand} may become smaller than the smallest difference that is possible for the human ear to detect. To avoid this, the use of a minimum range was required.

(4)   minimum range$= \pm$ x (dB).

Thus, the minimum range defines the smallest range allowed, e.g. 12 dB ($\pm$ 6 dB), from which we select the random number and dB_{rand} may not have a lower value.

To verify that the initially established range (1) was not too narrow, the program tests - after 2/3 of a sequence - that the four lowest levels used are judged as "softer". The responses to the lowest levels are tested against each of the following sequences, where the numbers signify response button number. If the criteria are still not met, new test points will be added, first within the test range, and if criteria still not are met, a new extended test range (e.g. -7 dB) is used.

(5)   low endpoint matrix = (11111, 121111, 112111, 1112111, 1111211)

The procedure in (5) is repeated at the loudest levels using a corresponding matrix. It should be noted that in the case of frequency, we defined the minimum range as a fraction (0.33 - 0.5) of the frequency-dependent variable equivalent rectangular bandwidth (ERB). ERB is related to the critical bandwidth of the ear and is defined as the bandwidth of a perfect rectangular filter that passes the same amount of energy that passes through the filter that is being specified using white noise [133, 51, 69, 135, 174, 208]. It is related to the critical bandwidth in human hearing, and may be estimated using the formula according to Glasberg and Moore [69]:

(6)   ERB=24.7(4.37f+1),

where ERB means frequency in Hertz and f means centre frequency in kHz. Moore has adopted this formula from the original suggested by Greenwood [71]. Thus, the ERB reflects the bandwidth of a healthy ear as a function of frequency. By using the ERB, the same criterion can be used regardless of test frequency.

(7)   minimum frequency range = ERB(PSE_{prel})* 0.33.
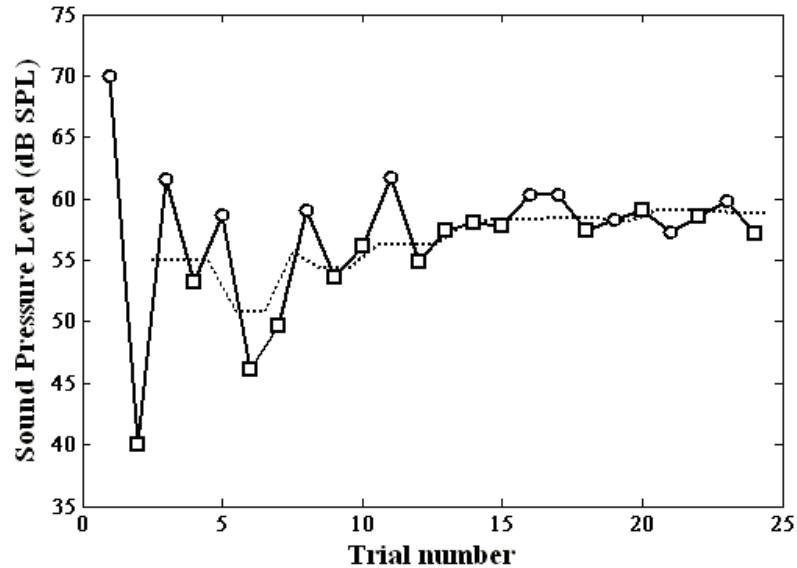
Figure 1. An example of raw data showing the measurement of loudness balance at 0.25 kHz in a normal-hearing subject. The figure shows the progress of the RMLSP. Squares indicate response "softer" and circles response "louder" than the reference tone. The dashed line denotes the preliminary PSE based on probit analysis (see text for more details).

Post-test analysis and Monte Carlo simulations

By using the errors observed in the measurements, the least squares fit can be used to calculate a linear estimation of the "true" underlying PSE; this means that an interpolation line is fitted to the results that generate the smallest sum of the squared distances from the line to each data point (observation) [8]. The point of 50 % probability of response of this interpolation provides the PSE and the slope of the curve the SD. However, if the response curve follows a normal probability distribution, the probit analysis can be used since it assumes that responses to test tones judged at threshold follows the cumulative normal distribution [58]. This differs from the logit transformation only in that the logit assumes that the underlying threshold distribution is the logistic probability distribution. Thus, the probit analysis is also an interpolation of the recorded observation points that provides a PSE at the 50% probability point of response and SD derived from the slope.

Monte Carlo simulations were made using least squares fit and probit analysis to decide which provided the best estimate of the PSE and SD. In brief, Monte Carlo simulation may be used to make experiments with random numbers to evaluate mathematical expressions [67, 66]. Data points may be described by a distribution, which can be e.g. a normalized probability distribution. This means that
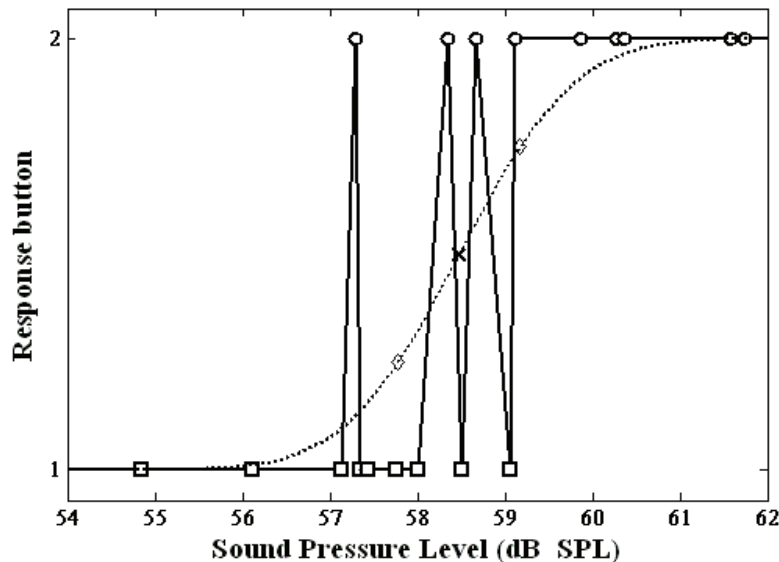
Figure 2. An example of the final probit analysis (post-test) that provides the final PSE (the same data as shown in Figure 1). Squares indicate response "softer" (button 1) and circles response "louder" (button 2) than the reference tone. The dashed line denotes the interpolation of the probit analysis. The cross indicates the PSE and the diamonds ±1SD. The PSE in this example was 58.5 dB SPL and the SD 1 dB.

one can use these simulations to estimate the probability distribution of, for example, the midrange of the data points collected from a subject and one can randomly change any given variable in this data, e.g. PSE and SD. The results of these simulations showed that probit analysis provides a better fit to the model than the least squares fit. Figure 1 shows an example of how the test points gradually come closer to the preliminary PSE during the progression of the test and Figure 2 is an example of the final analysis with probit regression (the dotted line is a cumulative normal distribution function).

Test applications using the randomised maximum likelihood sequential procedure

Loudness matches

Binaural loudness matches were measured at one frequency, 0.25 kHz (V), or two frequencies, 0.25 and 1 kHz (I, II, and III), using a 2AFC paradigm. The unaffected ear was selected as reference ear and the affected as the test ear for the patients with hearing loss, while ear positions were randomly selected in normal-hearing subjects. Pairs of pure tones were presented for binaural matching. Twenty-five pairs of pure tones were presented, the first in the reference ear at 60 dB SPL, and the second tone of variable intensity in the test ear. The length of each tone was 740 ms (including 20 ms rise and fall) and two tones in a tone pair were separated by a 500 ms silent

interval. Tone pairs were separated by a 2020 ms silent interval. When both frequencies were tested, measurements were made first at 1 kHz and then at 0.25 kHz. This test was done to achieve equal loudness between ears in the binaural pitch matching test.

The subject was instructed to decide whether the second (variable) tone was "softer" or "louder" than the reference tone. The intensities of the test tones were selected during the test by using our version of the RMLSP (c.f. the section above). The first and second test tones had the level 70 dB SPL and 40 dB SPL. The minimum range allowed was ±6 dB, even if the subject's precision was better than 5 dB.

Binaural pure tone pitch matches
Binaural loudness matches were always made before the binaural pure tone pitch matches (studies I, II, III, and V). The same RMLSP as for the loudness matches was used for the binaural pitch matches, with responses now labelled "lower" and "higher". Thirty pairs of pure tones were used. Testing with the 1 kHz reference tone, the first and second test tones were 1.33 kHz and 0.667 kHz, respectively. The minimum range allowed was ±22 Hz. Measuring at 0.25 kHz, the two initial test frequencies were 0.333 kHz and 0.167 kHz. The minimum range allowed was ±13 Hz. The binaural pitch matching tests were presented at equal loudness for each ear: The presentation level in the reference ear was 60 dB SPL and the level in the test ear was identical to the final PSE-value recorded in the preceding loudness-matching test for each frequency. This latter level was automatically imported into the binaural pitch-matching test.

Monaural pure tone pitch matches
The same RMLSP procedure as for the binaural pure tone pitch matches were used for the monaural pure tone pitch matches (I, II, III, and V). Monaural pitch matches were used to estimate the reliability of the binaural pitch matches (I, II, and III). Both reference and test tones were presented in the same ear. All other aspects of the testing were identical to the binaural pitch matching procedures. The presentation level was 60 dB SPL for both tones in a tone pair.

Selection of level and frequencies for loudness and pitch matches
The reference level 60 dB SPL was selected to obtain more reliable recordings by avoiding possible contamination of environmental noise in the subjects' homes (I, II, and III), to avoid possible distortion at higher presentation levels (I, II, III, and V), and to avoid the levels where recruitment makes loudness balance less informative (I, II, III, and V). To further reduce the risk of contaminating environmental noise, the subjects were instructed to conduct the tests in the most quiet spots of their homes (I, II, and III).

The use of the frequency 0.25 kHz was based on clinical experience of testing binaural pitch differences with a simple tuning fork on patients with Ménière's disease or FLFHL and it is also in the range where fluctuations are generally observed [147, 20]. The frequency 1 kHz was arbitrarily selected as a frequency at which hearing is known

to fluctuate less. Lower frequencies than 0.25 kHz were considered more difficult for pitch matching. Furthermore, lower frequencies were also regarded as unsuitable due to the limited maximum output of the equipment used.

Pitch matches using sine wave amplitude-modulated noise
The same RMLSP procedure as for the binaural pure tone pitch matches was used for the SAM pitch matches (study V). Monaural and binaural pitch matches were made at equal loudness using two different reference tones; one was a pure tone of 0.25 kHz and the other a high-frequency SAM-noise with a modulation rate of 0.25 kHz (specified below). Each stimulus had a duration of 1000 ms (including 20 ms rise and fall) and the two stimuli in a tone pair were separated by a 500 ms silent interval. Stimuli pairs were separated by a 2020 ms silent interval. The SAM noise was generated in the following manner. First, a narrowband noise was made by applying a digital band pass filter (9 to 11 kHz) to white noise. This narrowband noise was then sine wave amplitude-modulated with a 0.25 kHz modulation rate and a 100% modulation depth. No sign of any spectral component at 0.25 kHz or at any of its harmonics could be seen in a FFT of the acoustical output and the FFT verified that the slopes of the generated narrowband noise were steeper than 45 dB/octave. A Digital Fourier Transform (DFT) of the SAM noise and its waveform is presented in Figure 3; the amplitude modulation can be seen as the envelope of the waveform in Figure 3c.

For monaural SAM pitch matches, both reference and test tones were presented in the same ear. The level of the reference tone was set to 60 dB SPL for normal-hearing subjects and in the unaffected ear for the patients with monaural low-frequency hearing loss. The sound pressure level of the reference tone presented in the affected ear was the same as the level of equal loudness obtained in the SAM binaural loudness-matching test (i.e. reference ear = unaffected ear; test ear = affected). The levels used for the variable test tone were loudness matched to compensate for possible discrepancies in loudness between these two different kinds of sounds (pure tones and SAM-noise).

For binaural SAM pitch matches, the reference and test tones were presented in different ears. The level of the reference tone was set to 60 dB SPL for the normal-hearing subjects and in the unaffected ear for the patients with monaural low-frequency hearing loss. The sound pressure levels of the reference tone presented in the affected ear were the same as the level of equal loudness obtained in the binaural loudness-matching.

Equipment and other methods
Equipment set-up for loudness matches, pitch matches, PTA and PTCs
Binaural loudness and binaural pitch matches that were made in the subject's homes (Figure 4) were measured using a portable PC with a Realtek AC97 soundcard (16 bits/44.1 kHz) and sound shielded circumaural Sennheiser HDA 200 earphones (I, II, and III). Monaural pitch matches were made in the laboratory using the same equipment (I, II, and III).
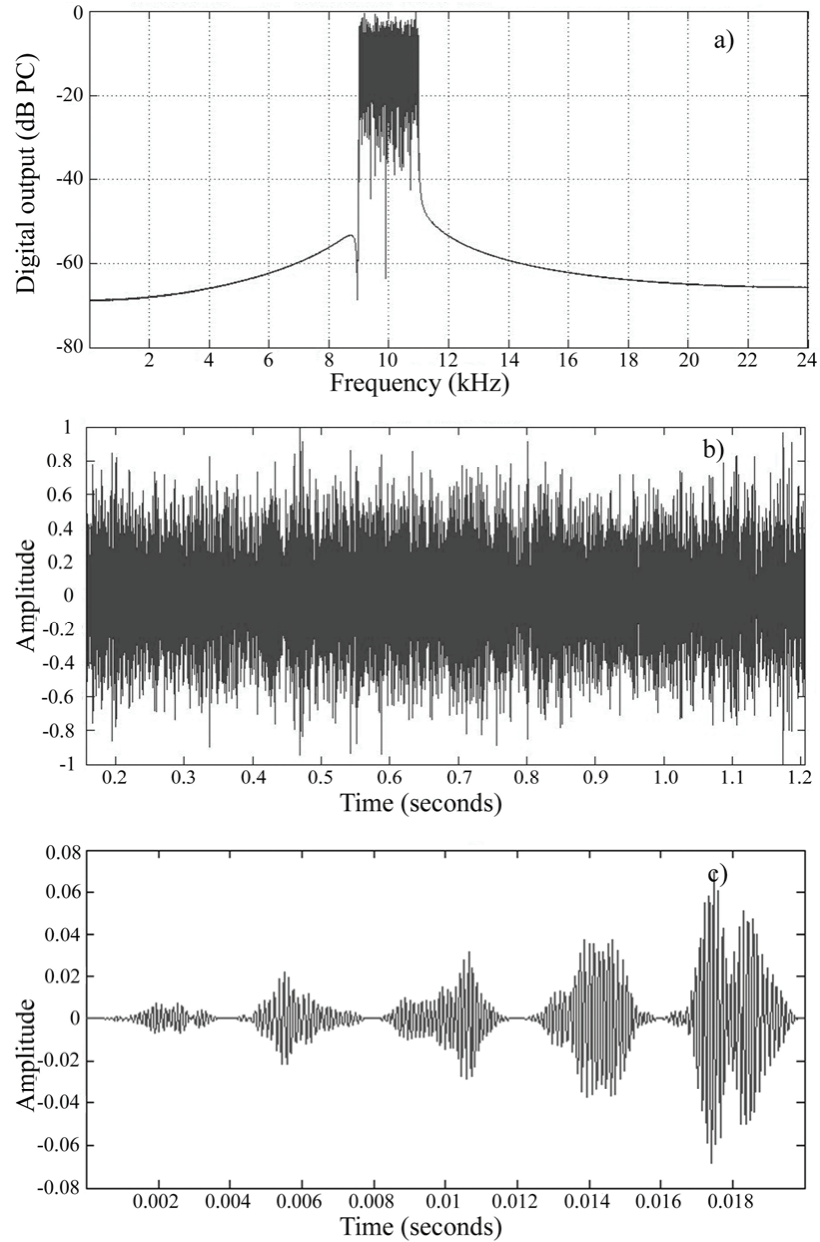
Figure 3. Graphical representation of the sine wave amplitude-modulated narrowband noise used in study V. **a)** A digital Fourier transform of the narrowband noise. **b)** A wide selection (1.2 seconds) of the waveform. **c)** A narrow selection of the rise time in the waveform (20 ms). The envelope of the amplitude modulation (0.25 kHz) can be seen as the undulation of the waveform.

Binaural loudness and binaural pitch matches (pure tones and SAM-noise) in the laboratory were made using the same set-up but with an external sound card, M-Audio Audiophile (24 bits/48 kHz) (V). This equipment set-up was used in Békésy-audiometry and PTCs (I, II, III, IV, and V).

All stimuli generation and equipment calibration were made in accordance with ISO 389-8 [91]. The different complete equipment set-ups were calibrated using a Brüel and Kjaer 2231 sound level meter with a 4134 pressure microphone in a 4153 coupler according to IEC 60318-1 [87] and IEC 60318-2 [88]. A custom-made computer program (created in Matlab 6.5 by Jan Grenner) was used for the generation and presentation of the stimuli; it also recorded the subjects' responses. The total harmonic distortion of the acoustical output from the whole system (i.e. for pure tones) was found to be less than 1% using FFT.

Psychophysical tuning curves
Psychophysical tuning curves (PTC) were measured to assess the sharpness of the auditory filter (i.e. frequency selectivity) in the affected ear of patients with monaural FLFHL (II, III, and IV) [131]. PTC is most likely the psychoacoustical correlate to neural tuning curves, which measures the frequency specificity of single nerve fibres in the auditory nerve [24, 116, 97, 93]. PTCs were made with simultaneous narrowband noise masking either only at 0.25 kHz (IV) or at 0.25 and 1 kHz (II and III). The centre frequencies of the narrowband noise were 0.24, 0.43, 0.78, 0.92, 1.00, 1.08, and 1.23 times the probe tone [132]. The width of the filters was either 1/3 equivalent rectangular bandwidth (ERB) [132] (III; 10 patients) or 20% or a maximum of 320 Hz of the centre frequencies (II, III; 3 patients, and all patients in IV). The three patients in studies II and III who had the wider maskers were the last ones to be tested and the width was increased after methodological discussions with Professor Brian C. J. Moore to minimise the risk of interference (beats) between the maskers and the probe tones. An FFT of the acoustical signal verified that the slopes of each narrowband masker were all steeper than 28 dB/octave. The duration of the narrowband maskers were 3500 ms (including 20 ms rise and fall times) and they were followed by 2400 ms silence. Two pure tones, both 500 ms long (including 20 ms rise and fall times), were used as probe tones. These tones were presented in the narrowband noise separated by 500 ms of silence. The levels of the narrowband maskers were regulated using either a 5 dB "two up and one down" method (II and III) or a 3 dB "two up and one down" method (IV) [32, 89, 11, 115]. Probe tones were presented at 10 dB Sensation Level (SL).

Oral instructions were first given before this supervised test. Written instructions were also given on the computer screen prior to and during the test. The patients were instructed to press a response button if they could detect both probe tones during a noise presentation. A response initiated a new presentation with the level of the masker increased by 10 dB (II and III) or 6 dB (IV). An absence of a response lowered the level of the masker by 5 dB (II and III) or 3 dB (IV) until a response was recorded. One test for a specific masker was concluded when two threshold passages were recorded.

Assessment of hearing thresholds

Pure tone hearing thresholds were assessed by means of fixed frequency Békésy-audiometry (I-V) [14, 164]. Békésy audiometry was performed by the subjects under supervision. Stimuli were pulsed pure tones of octave frequencies 0.125 kHz to 8 kHz. The pure tones, 75 per frequency, were 240 ms long (including 20 ms rise and fall times) and there was a 160 ms silent interval between presentations. The sound pressure level rate change was 2.5 dB per second. After excluding the highest and the lowest values, the mean of the remaining reversals was used to calculate the hearing threshold for each frequency. Subjects were instructed orally and on a computer screen before and during the test to press down a button as long as the stimuli was audible, release the button when the tones could not be heard and press the button when the stimuli were heard again.

Speech recognition scores in noise

SRS in noise was performed in a soundproof booth in the laboratory according to Magnusson [118, 119, 120] (IV). Fifty phonemically balanced monosyllabic words (i.e. one wordlist) were presented at the end of a carrier sentence [166, 90]. Sentences were presented with competing wideband noise at a +4dB signal-to-noise ratio. Wordlists were randomly assigned. Patients were instructed to repeat the last word in each sentence and to guess in case of uncertainty.

The sentences were presented through a Madsen Electronics Orbiter 922 and pair of TDH39-P earphones. This equipment was calibrated according to ISO 389-1 and 8253-3 [90]. In clinical practice in Sweden, this means that the calibration signal (preceding the wordlists) gives 22 dB SPL for TDH39-P on the acoustic coupler with the attenuator set to 0 dB Hearing Level (HL) [180]. This procedure ensure that the attenuator indicates speech level in dB HL.

Transient evoked otoacoustic emissions

Transient evoked otoacoustic emissions (TEOAE) were made to test the integrity of the outer hair cells in the cochlea [102, 103, 104, 157, 155, 73, 72]. TEOAE measurements were performed using default set-up in the non-linear mode using either an ILO88 Otodynamics OAE analyser (software version 5.60Y) or an ILOv6 Otodynamics OAE analyser. The stimuli were 80 µs clicks. The stimulus level range was found to be between 83 to 85 dB peak equivalent SPL. The noise rejection level used was set to $\leq$ 51 dB peak equivalent SPL and the noise input level range was between 34 and 45 dB peak equivalent SPL.

Hypobaric pressure chamber

A hypobaric pressure chamber was used to apply a relative underpressure in the ear canal to impose positive pressure gradients (i.e. relative overpressure) to the inner ear (IV) [35, 36, 111]. The pressure chamber used was located at the ENT-department at Malmö University Hospital, Sweden, at the same elevation as the test booth used. It has previously been used in studies by among others Konrádsson and colleagues [112, 113]. In the pressure chamber, the patient was placed in an upright sitting position. A probe presenting a 0.226 kHz tone was placed in the outer ear canal of the affected ear

where it was used to monitor the middle ear pressure during the whole exposure. In the beginning of the pressure session, the patient was instructed not to swallow and the pressure in the chamber decreased relatively fast (>10 daPa/second) until the middle ear pressure exceeded the individual pressure opening level of the Eustachian tube. After this opening level was established, the following pressure exposures – during which the patients also were instructed not to swallow - were close to this level, but below, to avoid spontaneous opening of the Eustachian tube. This pressure level was maintained during five minutes or until spontaneous opening of the Eustachian tube ocurred. The pressure in the hypobaric pressure chamber was normalised to the prevailing ambient pressure again slowly (3-5 daPa/second). After the normalisation, the patients were instructed to swallow and then the middle ear pressure was measured again; if the patient's Eustachian tube opened spontaneously, the pressure in the chamber was normalised in the same manner (c.f. Figure 4). This procedure was repeated 4 to 7 times.
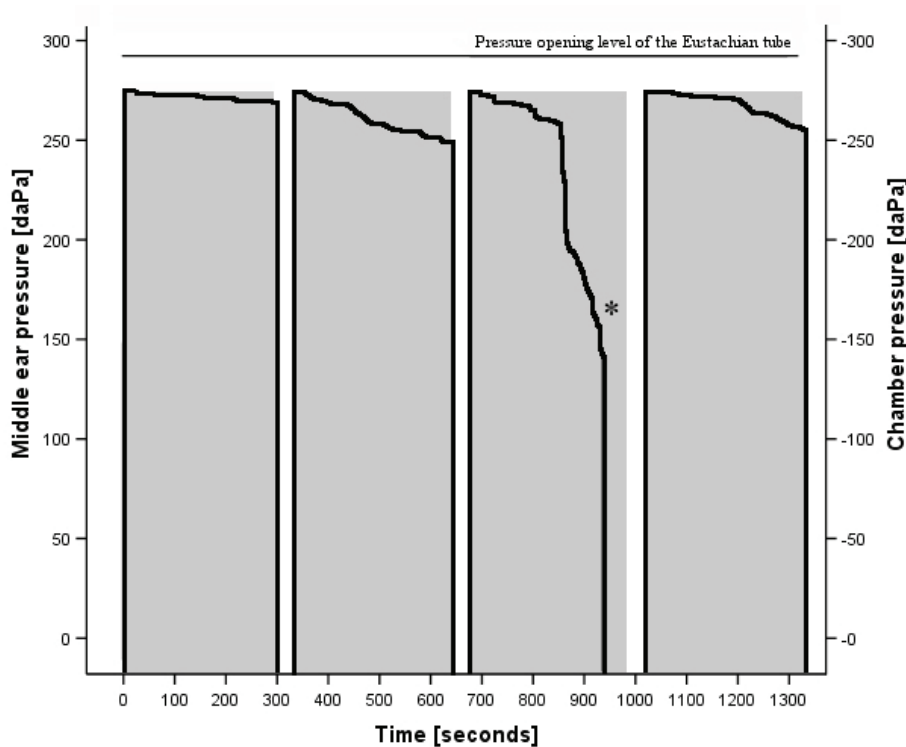

Figure 4. Schematic drawing of a treatment with four hypobaric pressure exposures. The shaded area represents the underpressure in the pressure chamber (right axis). The black curve represents the induced relative tympanic overpressure obtained trough the exposure (left axis). The asterisk noted in exposure 3 indicates a spontaneous opening of the Eustachian tube. Adopted from [53].

Tympanometry

Tympanometry was made using either a GSI 33 Middle Ear Analyser or a GSI Tympstar Middle Ear Analyser to assess the status and function of the tympanic membrane and the middle ear (IV). A 0.226 kHz probe tone was used and the pressure range was –300 to 200 daPa starting at the lower pressure [92, 121].

Subjective symptom ratings

In study III, subjective symptom ratings were made by the patients with FLFHL each day during the long-term measurements of binaural loudness and pitch matches. All patients did this, except patient 3. The patients recorded estimated hearing loss, vertigo, tinnitus and/or pressure in the affected ear using 100 mm visual analogue scales (VAS) ranging from 0 = "best possible …" to 100 = "worst possible …" [123, 206].

In study IV, about 6 weeks after their pressure exposure, all patients received an evaluation protocol. This evaluation asked about subjective changes in hearing, tinnitus, aural fullness and vertigo after the pressure exposure [53].

Statistical analysis of results

All statistical calculations were made according to Altman [8] using the SPSS version 14.0, software for statistical analysis.

Studies I, II, and III

Binaural intensity matches and the pitch matches are reported as PSE $\pm$SD (I, II, and III). Pitch matches are shown as relative frequency shift (%). This relative frequency shift was calculated as,

$$\text{relative frequency shift \%} = [(f_t\text{-}f_r)/f_r]*100.$$

where f_r means the frequency of the reference tone and f_t indicates the frequency of the calculated final PSE. This means perceptually that a negative relative frequency is perceived as an increase in pitch by the listener in the test/affected ear and a positive relative frequency difference thus as a decrease in pitch. Median and inter-quartile range, IQR (range between the 25th and 75th percentiles), of the PSE-values over a test period are also used (I, II, and III). "Group median" and "group IQR" is also reported and indicates the median and IQR of the individual medians of the patient groups (III). Spearman's rank correlation coefficient (rho) was calculated between tests for each subject and an alpha value of $p<0.05$ was considered to be statistically significant (I, II, and III). Differences between groups of subjects (i.e. normal-hearing subjects, patients with FLFHL without vertigo and Ménière's disease) were tested using Kruskal-Wallis test for multiple independent samples and here alpha values ≤ 0.05 were considered statistically significant (III). Significant differences seen in the Kruskal-Wallis test were further explored using Mann-Whitney test for two independent samples, adjusted for multiple comparisons using the Bonferroni correction [8].

For PTCs, Q_{10} was calculated as a measure of frequency selectivity (III). This was done by dividing the probe tone frequency with the bandwidth (in Hz) of the curve 10 dB above the "tip" of the tuning curve (van den Abeele et al., 1992). In the analysis of the results, a separate clinical reference material (n=9) was used with normal Q_{10} at 0.25 kHz above 5.3 and above 5.8 at 1 kHz. The measure of Q_{10} requires a certain amount of steepness in the auditory filter. This means that it cannot be calculated in cases where the filter is too shallow. That is the reason why we did not calculate Q_{10} from the PTC measurements in study IV. To solve this problem in future studies additional high-frequency narrowband maskers can be used.

Study IV
Spearman's rank correlation coefficient (rho) was calculated between tests for each patient. Significant differences were calculated between before and after pressure exposure using the paired-sample T-test. In both these tests, alpha values ≤ 0.05 were considered statistically significant.

Study V
In this study, all subjects made five repetitions for each of the different test conditions used. All pitch matches are reported as the mean $\pm$1SD of the PSEs of these five repetitions (i.e. the mean relative frequency difference, cf. I, II, and III).

THE INVESTIGATIONS

Long-term measurement of binaural intensity and pitch matches. I. Normal hearing (I)

The aim was to determine the stability in daily long-term measurements of binaural intensity and pitch matches during one to several weeks in normal-hearing subjects using RMLSP and to compare binaural pitch-matching ability with monaural.

Subjects

Tests were performed on 10 normal-hearing subjects (5 men and 5 women; median age 35 years, range 25 to 53 years).

Study design

The experiment consisted of two tests of binaural loudness and two of binaural pitch matches that were made daily at home during a period of 9-22 consecutive days at two reference frequencies, 0.25 and 1 kHz. Monaural pitch matches for the same frequencies were made once in the laboratory to assess the reliability of the binaural

Figure 5. Home audiometry performed by a subject.

matches. The RMLSP was used to calculate sound pressure levels and frequencies of the test ear.

Results

The RMLSP was found to be a reliable method to use in home audiometry, but there were varying degrees of stability among normal subjects.

The individual medians for loudness balance showed a significant association with the test ear at 0.25 kHz (p<0.05). This means that subjects with left ear as test ear showed lower medians than those with right ear as test ear. This finding suggests some methodological bias, a preference for pressing the response button opposite to the test ear. Subjects showed relatively high precision with IQRs that ranged between 0.8 to 5.4 dB. For binaural pitch matches, the test results were more variable among subjects and it was found that the medians were significantly associated with the IQRs (p<0.05); this means that subjects with smaller median deviations from the reference frequency also showed higher precision. The precision of the subjects, measured as IQRs, was compared to musical training and it was found that precision could be explained by reported musical ability. That is, the subjects with poor precision also reported poor musical ability. Monaural pitch matches were measured to estimate the reliability in matching and a pattern similar to that for the binaural pitch matches was observed, showing an association between monaural and binaural pitch matches. Furthermore, the PSE-values were significantly associated with their SDs (p<0.01); subjects with smaller deviations in PSE from the reference frequency also showed higher precision.

Conclusions

The findings suggest that long-term recordings of binaural loudness matches could be made reliably in most subjects. The precision and stability of the binaural pitch matches recorded was not comparable to that of highly trained, selected subjects in the laboratory described in the literature. Binaural pitch matches could be measured reliably only if the subjects are able to define pitch precisely.

Clinical application of long-term intensity and pitch matches in fluctuating low-frequency hearing loss (II)

The purpose of this study was to measure changes in binaural loudness and pitch matches in a patient with FLFHL in order to assess disease activity during one period with and one without symptoms.

Patient

The patient was a 51-year-old woman with a mild high-frequency cochlear hearing loss, who suffered episodically from left-sided FLFHL without vertigo. Measurements of binaural loudness and pitch matches were first made during a period with no symptoms (22 days) and were repeated three months later during a period when the patient reported symptoms of hearing loss, aural fullness, and tinnitus (14 days).

Study design

Long-term measurements of binaural pitch and binaural loudness matches at two frequencies, 0.25 and 1 kHz, were made once daily at the patient's home using the RMLSP. Tests were made during a period when the patient demonstrated no symptoms and a period when the patient reported hearing loss, aural pressure, and tinnitus. Békésy audiometry was made at three occasions during the latter test period (days 1, 10 and 12) and PTCs were made to assess the cochlear frequency selectivity using 0.25 and 1kHz probe tones after the conclusion of the second test period.

Results

Generally, the long-term measurements showed more pronounced hearing fluctuations during the test period with symptoms than without symptoms, but the recordings indicated hearing fluctuations during both test periods. The results of both test periods were different from the results of the normal-hearing references (I).

During the test period without symptoms, large fluctuations in relative frequency difference were seen for the binaural pitch matches at 1 kHz on five isolated days (days 4, 8, 14, 18, and 21). These fluctuations were not associated with larger SDs than those seen on non-fluctuating days. The median and IQR-results of the patient were quite similar those of the normal-hearing subjects.

During the test period with symptoms, large fluctuations were observed at 0.25 kHz for both binaural loudness balance and binaural pitch matches. The Békésy audiometry revealed a low-frequency hearing loss on day 10. SDs for the loudness and pitch matches were similar to those seen during the period without symptoms. As during the test period without symptoms, the pitch-matching medians were marginally different from the group medians and group IQRs of the normal-hearing subjects, but loudness matches were seen to be slightly increased in level. The IQR-values were larger for loudness matches at both frequencies and for pitch matches at 0.25 kHz than seen in the results of the test period without symptoms. However, the IQR were smaller for the pitch matches made at 1 kHz during this test period. The loudness matches at 0.25 kHz showed that the patient required higher and higher levels in the affected ear during the first ten days to achieve loudness balance. During the last four days, the level

decreased, but without reaching the lower levels observed without symptoms. Similar results were seen for the pitch matches. On days 8 to 10, when the highest levels were required for equal loudness, the pitch matches at 0.25 kHz decreased to a normal value on day 8 and continued to decrease to a large negative value on day 9. However, this value instantly returned to the highest positive value recorded on day 10. As the levels needed to obtain equal loudness decreased during the last four days of the test period, the pitch match at 0.25 kHz still showed an elevated positive value continuing through to day 12 and it reached normal values on days 13 and 14. PTCs were measured in the affected ear after the second test period and they showed normal tip and tail configurations.

Conclusions
The patient with FLFHL showed long-term measurements of binaural loudness and pitch matches during periods with and without symptoms that were different from those of normal-hearing subjects. The findings indicated that long-term measurements seem to provide useful information on disease activity.

Long-term measurement of binaural intensity and pitch matches. II. Fluctuating low-frequency hearing loss (III)

The aim of this study was to determine the relation between long-term measurements of binaural intensity matches and pitch matches, and ratings of subjective symptoms in patients with monaural FLFHL without vertigo and in patients with monaural Ménière's disease (i.e. FLFHL with vertigo) and to compare their results to those of normal-hearing subjects.

Patients

Thirteen patients participated, all suffering from monaural FLFHL (7 women and 6 men, mean age 51.4 years ± 13.5). The patients were separated into two groups; one with monaural fluctuating low-frequency hearing loss (FLFHL) without vertigo (n=4) and one with monaural Ménière's disease (i.e. FLFHL with vertigo) (n=9).

Study design

Using the RMLSP, the patients themselves measured consecutive binaural pitch matches using both a 0.25- and a 1-kHz reference tones presented at 60 dB SPL to one ear, and a loudness-matched test tone of adjustable frequency presented to the other ear during a period of one to several weeks in order to assess hearing fluctuations. The results were compared to those of normal-hearing subjects (I). During the period of the measurements, the patients with hearing losses also consecutively rated their amount of hearing loss, tinnitus and vertigo using 100 mm VAS.

Results

The long-term results showed that both groups of patients with hearing losses (FLFHL with and without vertigo) showed fluctuations in binaural loudness and pitch matches not seen in the normal-hearing group.

On an individual basis, three types of long-term binaural loudness matches were seen. First, four patients recorded stable matches at both reference frequencies. Second, two patients had gradually changing matches and, third, seven patients showed either large fluctuations over the test period and/or rapidly changing matches on some occasions. Both frequencies were often affected though not in all patients. Patients with highly deviant median matches did not necessarily show more fluctuations during the test period. Changes in loudness matches were significantly associated with reported changes in one or more subjective symptoms in about half of the patients (i.e. seven patients with p<0.05). For the long-term binaural pitch matches, two overall types were seen in the results. First, two patients showed gradually changing pitch matches and, second, eleven patients showed large daily pitch matching changes on more than one occasion or had other intervals of rapid changes. One of these types were generally observed for both tested frequencies for most of the patients, but sometimes a less pronounced change was seen at 1 kHz. Furthermore, the patients sometimes seemed to match the reference tone either predominantly with a higher frequency (about 30 %), a lower frequency (almost 40 %) or variably (about 30 %). Perceptually, a pitch match that has a positive relative frequency difference means that the patient have perceived the test tone as lower in pitch than the reference tone and vice versa.

The individual measurements suggested few associations between pitch matches and VAS.

In the median loudness matches for each patient group (FLFHL without vertigo and FLFHL with vertigo = Ménière's disease), it was observed that at 0.25 kHz both groups of patients required significantly higher sound pressure levels to obtain equal loudness than the normal-hearing subjects ($p<0.05$ and $p<0.01$ respectively). There were no significant differences between the groups with FLFHL without vertigo and with Ménière's disease. At 1 kHz, the results were similar to those of the normal-hearing subjects. In the median relative frequency differences of the groups, the results showed no difference from the results of the normal-hearing subjects. Furthermore, no difference as found between the results of the group with FLFHL without vertigo and the group with Ménière's disease.

For the loudness matches, the average day-to-day difference was calculated for each individual's long-term measurements to capture changes over time in a simplified manner. At group level, a trend could be observed at both reference frequencies using this measure. It showed that the lowest values were observed for subjects with normal hearing, higher values for patients with FLFHL without vertigo and the highest values for those with Ménière's disease. The latter result was significantly higher than the value observed for normal-hearing subjects ($p<0.05$). On a group level, the average day-to-day difference for the binaural pitch matches indicated that large differences with similar distributions could be seen for both groups of patients compared to the normal-hearing subjects at 0.25 kHz. At 1 kHz, lower values were seen for subjects with normal hearing, higher values for patients with FLFHL without vertigo and even higher values for patients with Ménière's disease. Thus, the same trend as for the loudness matches seems to hold. These findings were significantly higher only for the group with Ménière's disease as compared to the normal-hearing group ($p<0.05$). The different results observed in average day-to-day difference suggested that, as a group, the patients with Ménière's disease show more active disease when measured as binaural loudness and pitch matches than patients with FLFHL without vertigo. However, it should be kept in mind that the number of patients in the group without vertigo were fewer (n=4) than the number in the Ménière's disease group (n=9) and that the overall number of patients in the study was relatively small.

The results of the PTC-tests showed that all patients had broader and shallower PTCs at 0.25 kHz than at 1 kHz. This finding suggested poorer frequency selectivity at 0.25 kHz as compared to normal-hearing references.

Conclusions
Fluctuations in binaural loudness and pitch matches could be observed during consecutive long-term measurements in patients with monaural FLFHL, fluctuations that were not seen among normal-hearing subjects. Defining disease activity as an average day-to-day difference suggested that patients with Ménière's disease had a higher hearing related disease activity than observed among patients with FLFHL without vertigo. The findings also suggested that reported subjective symptoms, on a

group level, were poorly associated with the psychoacoustically measured parameters (loudness and pitch matches). However, covariations between symptoms and pitch matches were observed in some patients, and between symptoms and loudness matches in other patients. The results imply that it is possible to separate disease subgroups using long-term measurements of loudness and pitch matches. This could prove to be an essential feature in clinical treatment trials.

Effects on cochlear frequency selectivity after hypobaric pressure exposure in fluctuating low-frequency hearing loss (IV)

The aim was to determine the effects of hypobaric pressure chamber exposure, i.e. relatively increased middle ear pressure, on cochlear frequency selectivity in patients with monaural FLFHL.

Patients

Ten patients (4 women and 6 men, mean age 59 years SD 13) diagnosed with monaural FLFHL participated in the study.

Study design

The hypobaric pressure chamber was used to create a relative underpressure in the ear canal to impose positive pressure gradients to the inner ear. PTA, tympanometry, PTC, TEOAE, and SRS in noise were measured before and after pressure exposure.

Results

After the pressure exposures, tympanometry showed middle ear pressures within normal range in the affected ear for all patients (range -30 to 0 daPa). On average, PTA showed no improvement after the exposure. Individual results showed improved SRS in noise, increased TEOAE strength and increased steepness for PTCs. Deteriorations were also seen among patients, mainly in PTCs. No association between the different tests could be established and measured parameters could not predict subjective improvement.

The individual PTC-results suggested generally poor frequency selectivity among most patients before and after the pressure exposure. Test-retest values for each narrowband masker condition were calculated before and after exposure [165]. Significant deviations ($p<0.05$) from these test-retest values were seen in most patients and the PTCs could be classified according to their configurations observed after pressure exposure. These configurations were (i) changes in relative level but no change in the shape in the tuning curve (two patients), (ii) improved shape (i.e. higher levels were seen at most narrowband maskers except at the one overlapping the frequency of the probe tone; two patients certainly improved and two might have improved), and (iii) deteriorated shape (two patients certainly deteriorated and two might have deteriorated). The sound pressure levels of the maskers of the individual patients were equalised to the level of the probe tone (10 dB SL) and the mean results were calculated. The results suggested slightly, but significantly, improved PTCs after pressure exposure ($p<0.05$).

Conclusions

The findings suggested that hypobaric pressure chamber exposure may improve, deteriorate, or not affect cochlear frequency selectivity measured as SRS in noise, TEOAEs, and PTCs. The observed effects were generally small and specific for individual patients. The results were inconclusive, but they might indicate that the pure tone audiogram may be too blunt measure of inner ear physiology when monitoring

effects of hypobaric pressure exposure, since improvements in frequency selectivity were not accompanied by improvements in audiometric hearing thresholds.

Monaural and binaural pitch matches in low-frequency hearing loss using sine wave amplitude-modulated noise (V)

The purpose of this study was to test the effect on the pitch matching precision in patients with monaural low-frequency hearing loss by using stimuli containing only temporal information as contrasted to both temporal and place information.

Subjects

The participants were two normal-hearing subjects (1 woman and 1 man), two male patients with low-frequency hearing loss, and one man with monaural high-frequency hearing loss.

Study design

Two experiments were made. In experiment I, all subjects executed monaural and binaural pitch matches in the laboratory using RMLSP, pure tones, and band-passed SAM-noise. The reference signal was a 0.25 kHz pure tone or SAM-noise (rate 0.25 kHz, 9 to 11 kHz wide). The variable test signals were pure tones. Five repetitions were made.

In experiment II, the two normal-hearing subjects made additional monaural pitch matches using different modulation rates of the SAM-noise, 0.2 kHz and 0.15 kHz, in one ear only. Three repetitions were made. One normal-hearing subject also made monaural pitch matches, as for the other cases in one ear only, using a SAM-noise with a modulation rate of 0.25 kHz as reference tone before and after listening to repeated presentations of a single pure tone in the left ear with the frequency 0.25 kHz. Five consecutive repetitions were made each separated by approximately 5 minutes.

Results: Experiment I

As seen in Figure 6, the normal-hearing subjects (subjects NH1 and NH2) and the subject with high-frequency hearing loss (subject HF) made monaural pure tone pitch matches that were close to the reference tone with a minimum of variability between matches. These subjects also showed similar results for their binaural pure tone matches. The patients with monaural low-frequency hearing loss (patient LF1 and LF2) performed monaural pure tone pitch matches with poorer precision when the reference tone was presented to the affected ear than when they were presented to their unaffected ears. Their binaural pure tone matches showed poorer precision when the reference tone was presented to the affected ear, but the average result was close to the reference frequency. When the reference tone was presented to the unaffected ear in the binaural matches, the PSE-precision improved in both patients, but they had, on average, significantly larger negative relative frequency differences.

The SAM-noise matches for the normal-hearing subjects showed larger variability than those observed for their pure tone matches, as seen in Figure 6. Subject NH1 showed average matches that were close to the amplitude-modulation rate of the reference signal (0.25 kHz) in all the monaural and binaural test conditions. Subject NH2 showed average matches that were significantly lower in relative frequency than

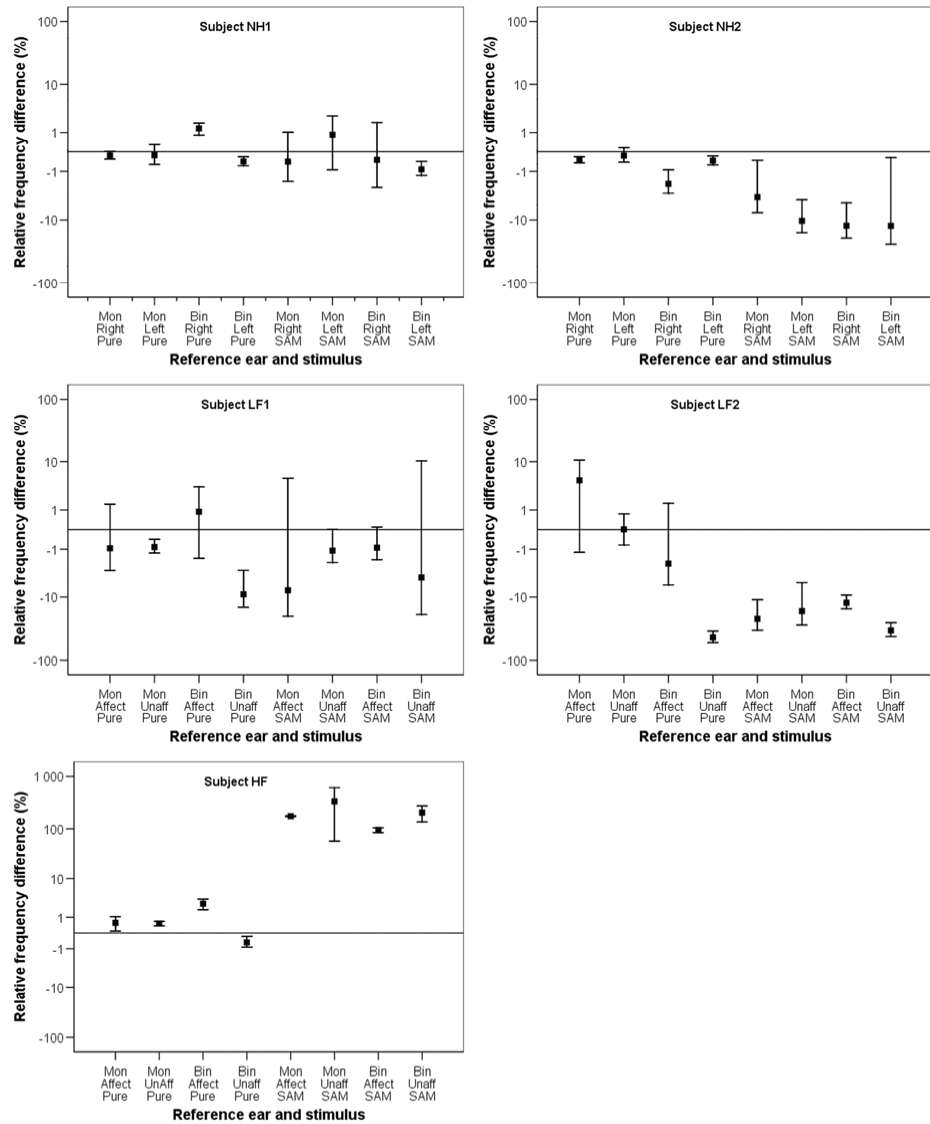**Figure 6.** Monaural and binaural pitch matches presented as reference ear and stimulus used as reference signal (pure = pure tone; SAM = SAM-noise) for all subjects (study V). Results are given as the average relative frequency difference in percent (%) of the PSE. Error bars indicate the 95 % confidence interval.

the frequency of the reference stimuli, irrespective of which ear the reference stimulus was presented to.

Pitch matches made with SAM-noise as reference signal in the affected ear improved the precision in patients with monaural low-frequency hearing loss (Figure 6), but the precision may have deteriorated when the variable test tone was presented to the affected ear.

For patient LF1, when the SAM-noise was presented to the affected ear, the monaural PSE-results showed large variability and also a large average deviation from the amplitude-modulation rate of the reference stimulus. For this patient, both the monaural and binaural SAM conditions showed less variability in the PSEs, when the variable test tones were presented to the unaffected ear. The average binaural match was close to the reference modulation when the SAM-noise was presented to the affected ear. The results of patient LF2 obtained using SAM-noise as reference stimulus were quite similar to those of subject NH2 with large negative relative frequency differences on average from the modulation rate. Variability in PSEs was larger for the monaural test conditions than the binaural. When using the SAM-noise as reference signal in the affected ear (in both the monaural and the binaural condition), the variability was lower than when using a pure tone as reference.
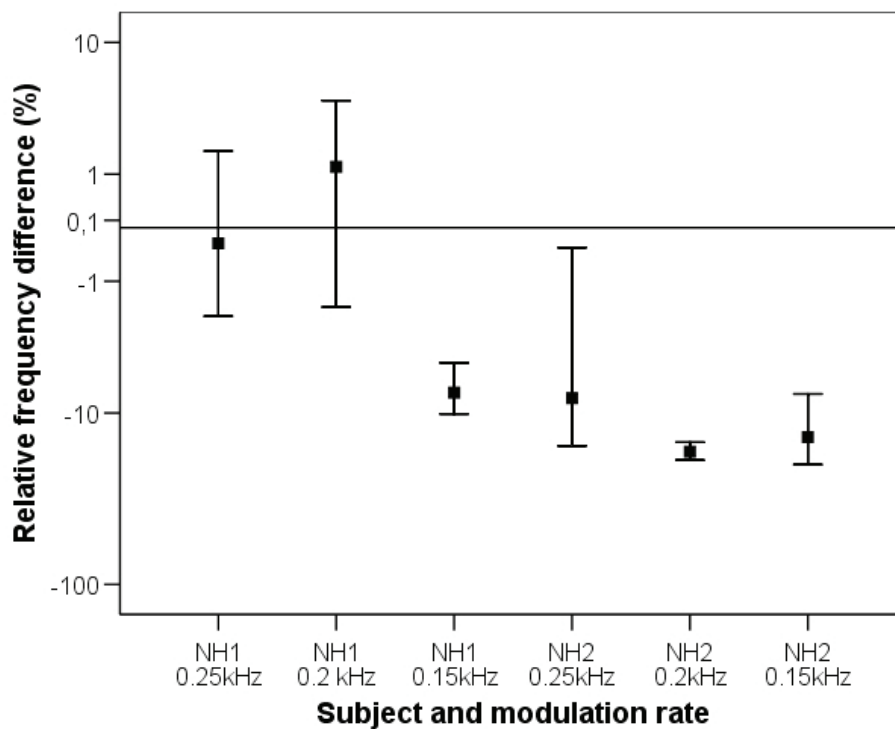
Figure 7. The average pitch matches of three repetitions for different modulation rates (0.15, 0.2, and 0.25 kHz) for the two normal-hearing subjects, NH1 and NH2 (study V). The last three repetitions were used for 0.25 kHz. Results are given as the average relative frequency difference in percent (%) of the PSE. Error bars indicate the 95 % confidence interval.
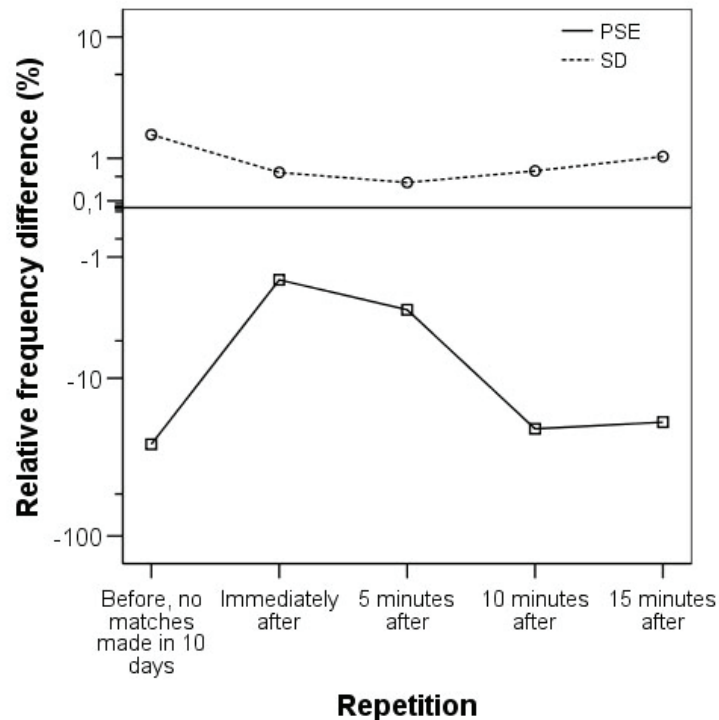
Figure 8. The long-term effect on the SAM-noise pitch matches of the pitch of a repeated pure tone presentation (0.25 kHz) at different moments in time for one normal-hearing subject (NH2) (study V). The PSE-results are presented as squares with a solid line and SD-results as circles with dashed line.

The results of the subject with monaural high-frequency hearing loss were deemed as unreliable. The subject reported that he actually did not hear the pitch of the amplitude-modulation at all in any of the ears, not even after extensive training

Results: Experiment II
As seen in Figure 7, the results of experiment II showed that pitch matches made to the modulation rate (e.g. 0.25 kHz) of a noise carrier as reference signal was lower in some cases than the pure tone pitch matches made with a pure tone reference of the same frequency (e.g. 0.25 kHz). The results also indicated that there seemed to be differences between subjects and also within a single subject depending on the modulation rates/frequencies. The results also indicated that the pitch memory of a pure tone can affect pitch matches using a SAM-noise as reference (Figure 8).

Conclusions
The pure tone pitch matches of the patients with low-frequency hearing loss suggested that to assess pitch differences between ears in these patients the reference signal should be presented to the unaffected ear. Binaural pitch matches made with SAM-

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noise as a reference stimulus in the affected ear may improve the precision in patients with monaural low-frequency hearing loss, but the precision may deteriorate when the variable test tone is presented to the affected ear. This finding suggests a possible detrimental effect of conflicting cues on the matches provided by pure tones. Pitch matches made to the modulation rate (e.g. 0.25 kHz) of a noise carrier as a reference signal may be lower than pure tone pitch matches made with a pure tone reference of the same frequency (e.g. 0.25 kHz) also in normal-hearing subjects. Furthermore, there seems to be differences between subjects and within a single subject depending on the modulation rates/frequencies used.

GENERAL DISCUSSION

Patients with FLFHL often report changes in hearing from day to day and sometimes even during a single day, but they are mainly given 'snapshot diagnostics' based on single audiograms and vestibular examinations. These are valid only for the time of the specific measurement but form the basis for the diagnosis along with the patient's statement of typical symptoms [1]. Continuous or repeated long-term measurements are used in many applications in the field of medicine to characterise changes and fluctuations in e.g. blood pressure, heart rhythm, or middle ear pressure [125, 56, 192, 191, 190, 16]. This approach provides more information on how these biological systems work in real life rather than at a single occasion during a visit to the clinic. One aim of the present thesis was to introduce long-term recordings of 'home audiometry' to monitor hearing changes in patients with FLFHL.

Methodological considerations

As the choice of method in psychoacoustic measurements will affect the results, the choice is important. The RMLSP has been used to assess equal loudness contours [185]. It has also been used, once previously, for binaural pitch matches in the laboratory [149]. No previous study reports repeated long-term measurements of hearing, made in the subjects' homes.

Three different test methods were considered: self-adjustment, constant stimuli, and RMLSP. They all use a paradigm where a fixed reference tone is first presented and then a variable test tone. In self-adjustment, the subjects are required to adjust the variable test tone by pressing an up- or down button (or by turning a potentiometer) to obtain, e.g., a perceived equal pitch between ears. This method is reliable and relatively fast in musically gifted subjects or in highly trained listeners [82, 149, 9, 126]. Deteriorated inner ear function influences the reliability of this paradigm [e.g. 144, 209]. This method was rejected after preliminary testing that showed high correlation between the initial position of the potentiometer and its final position in such subjects.

Constant stimuli means that lists of tones are generated, prior to the test, that are randomised or semi-randomised within e.g. a certain frequency range. Stimuli are then presented according to the list and subjects respond using a two-alterative forced choice (2AFC) paradigm. An example of how this works is presented in Figure 9. The downside of this procedure is that individual subjects might show large changes in range between tests (as expected to be seen in patients with FLFHL), which requires very long lists. Lengthy measurements are acceptable perhaps a few days in a row but they are inconvenient for a subject during 20 consecutive test days or more.

The maximum likelihood sequential procedure (MLSP) is an interactive method that adjusts itself from the subject's previous responses. In its simplest form, the range of the test is defined by selecting the two first test tones. The values of the following test tones are the average of the previous tones and the responses. An example of MLSP is
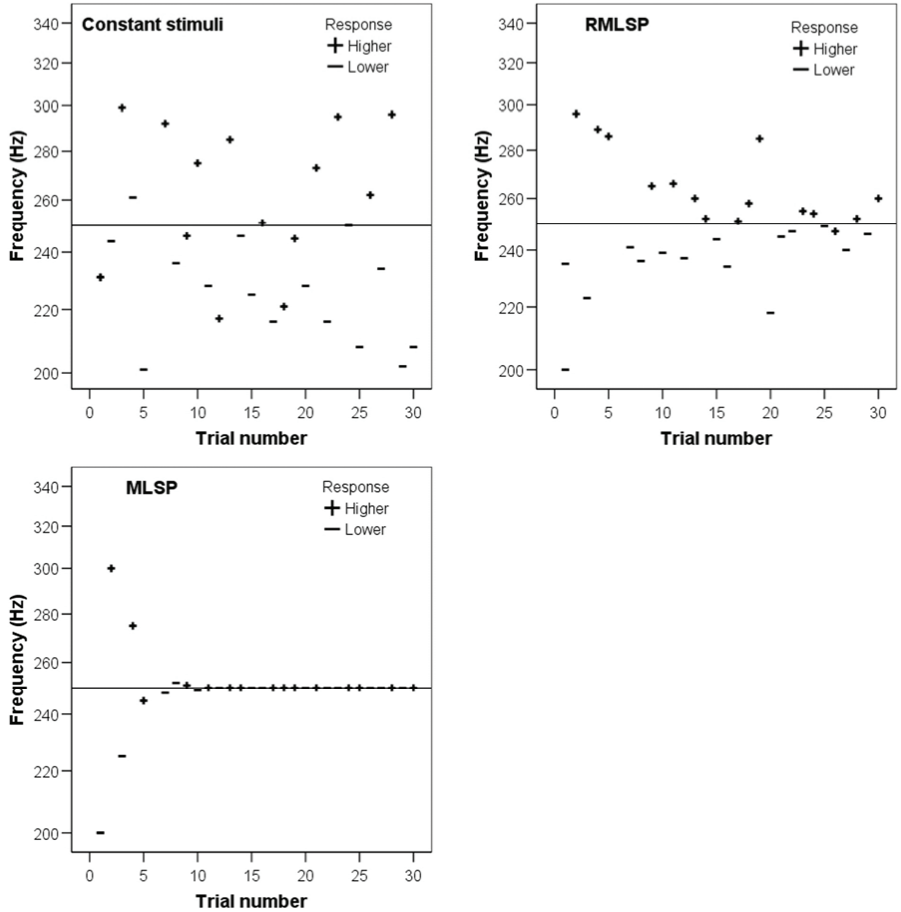
Figure 9. Examples of the methods of constant stimuli, MLSP, and RMLSP (simulated data). "+"-signs mean that the subject has judged the test tone as "higher" and "-"-signs that the subject has judged the test tone as "lower" in pitch than the 0.25kHz reference tone used marked by the line originating from 0.25 kHz. Adopted from [185].

also presented in Figure 9. The problem with this method is that the range often becomes very narrow and that early mistakes made by the subjects have a unproportional impact on the final result. However, by incorporing a random factor into the MLSP, the method can compensate for early mistakes and will thereby never allow a too narrow range, whereby the MLSP becomes a more robust method - RMLSP. The effect of the randomising factor on the MLSP can be seen in Figure 9. After preliminary evaluation, the RMLSP was selected.

Factors affecting long-term measurements

The precision of the long-term measurements (I, II, and III) was probably affected by the measurements being conducted in the subjects' homes; there was no realistic possibility to control ambient noise beyond the use of the sound shielding HDA 200 earphones. However, to minimise the influence of noise, suprathreshold tests were used rather than threshold tests. Also, there seems to be a methodological bias present in the loudness balance data, as the normal-hearing subjects showed a preference to push the preference of response button opposite to the test ear. This bias was not found for the pitch matches. Bias depending on response button can easily be detected or cancelled by a crossover design, but we chose not to do so for the long-term measurements. However, a crossover design was used in study V to test this effect. The binaural pure tone results (shown in the left part of each panel in Figure 6) showed that there was a quite small effect of test ear in normal-hearing subjects (about 1 %). Thus, the bias of test ear seems to be negligible for pitch matches in normal-hearing subjects. For patients with monaural low-frequency hearing loss, a quite substantial effect could be observed: To record a pitch difference between the ears, the reference tone must be presented in the unaffected ear and the variable test tone in the affected. When the reference tone was presented to the affected ear large variability was observed, but only a minor average deviation from the frequency of the reference tone. This finding is not a bias but rather the effect of reduced frequency selectivity and, possibly, long-term integration of a fixed tone in the affected ear.

The results from the normal-hearing subjects in study I suggest that some subjects seem to have a poor pitch matching ability in both monaural and binaural tests. This suggests that there might be another bias in the method used or that old truths regarding pure tone pitch matching ability, pertain only to musical and trained subjects.

Monaural and binaural pitch matches in normal-hearing subjects have been thoroughly studied in the laboratory using pure tones [e.g. 183, 203, 42, 202, 186, 18, 17, 204, 19, 26, 134, 149]. These studies have shown monaural pitch matches less than a few percent of the reference frequency and binaural pitch matches less than 5 % of the reference frequency. The slight differences described by other authors for binaural pitch matches between ears, have been attributed to small irregularities in the individual cochleae [18, 17, 26, 84, 77]. The median binaural results observed for the normal-hearing subjects in the study (I) were similar to those of previous studies, but it is also clear that large individual differences can be observed.

The binaural pitch matches of the normal-hearing subjects of study I are presented in Figure 10 for comparison with pitch matching data from some of the previous studies [17, 26, 64, 149]. The variability seen in the figure suggests individual differences in pitch matching ability among our subjects. The proposal of individual differences finds
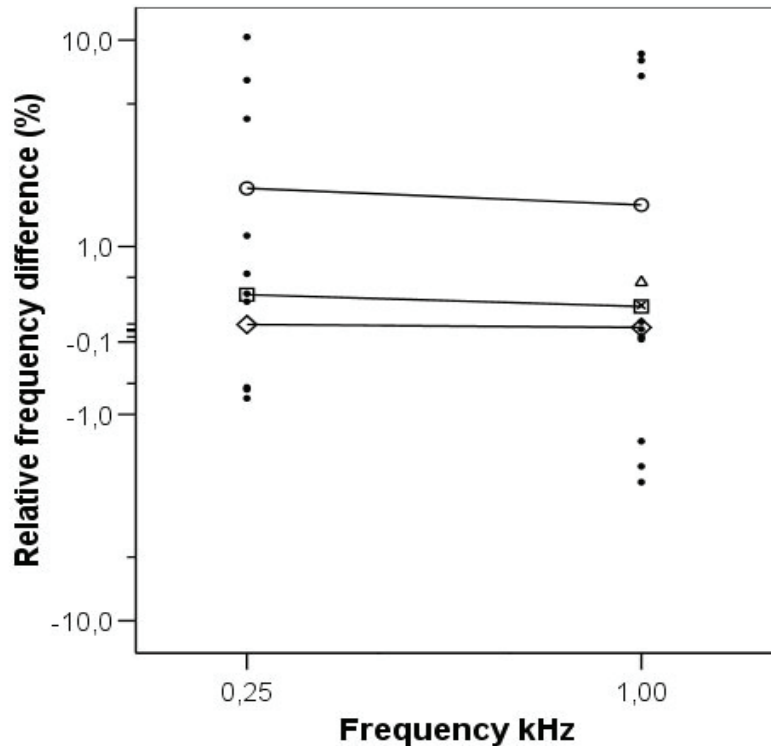
Figure 10. The median binaural pitch matches (circles) and the individual median results (dots) of the normal-hearing subjects made using portable equipment (study I) compared to average results obtained in the laboratory for four previous studies. The cross represents data from [17] (only 1 kHz), the diamonds [26], the triangle [64] (only 1 kHz), and the squares denote [149].

support in previous studies and in order to be able to compare previous results with the present ones, our pitch matches need to be related to the frequency discrimination of the subjects. Just-noticeable differences (JND) in frequency represent the smallest frequency change that can be reliably detected by subjects [76, 78, 209]. The literature on monaural pitch matches in normal-hearing subjects suggests an ability to detect JNDs in frequency of less than 1 Hz at 0.25 kHz and less than 2 Hz at 1 kHz [e.g. 167, 143, 95, 205, 209, 12]. There is a methodological discrepancy between the assessment of pitch matches with PSE as the measure and with JND, since the ideal PSE represents the point where the two stimuli sound the same, but the JND the point where two stimuli start to differ. However, if we assume that the SD of any psychometric function equals the JND [33], we might compare them. JND is often taken as a point where the subject responds correctly in about 70 % of the cases; this corresponds roughly to the probability to record a value outside one SD from the PSE (i.e. about 30 % of the cases) [8]. The SDs of the monaural pitch matches - for the normal-hearing subjects of study I - are presented in Figure 11 for comparison with
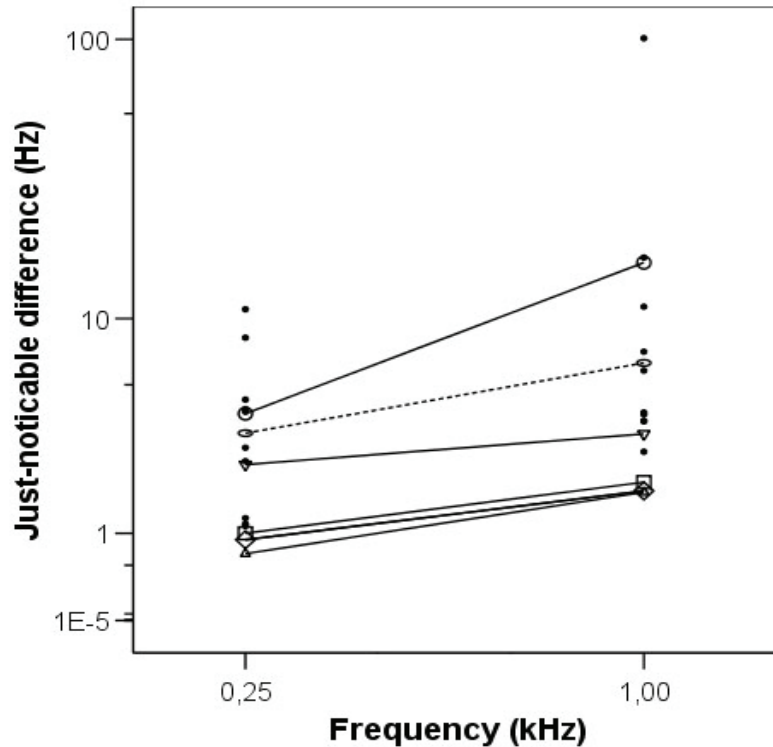
Figure 11. The individual (dots) and the average SDs (circles) the normal-hearing subjects (study I) compared to just noticeable differences (JND) obtained in the laboratory for four previous studies. Two averages are presented; one with (circles and drawn line, n=10) and one without a possible outlier (ovals and dashed line, n=9). The downward triangles represent average JND-results from [178], the diamonds [95], and the upward triangle [143]. The squares represent JND-model proposed by [209].

JND data from some previous literature [178, 143, 95, 209]. As seen, there is a quite large range not observed for the average results in the other studies. However, the performance of our subjects can be compared to those of 338 subjects that did JNDs (70 % correct was set as threshold) using a 250 ms 1 kHz reference tone at 75 dB SPL [106]. In that study, the poorest 10th percentile of the subjects recorded JNDs that were on average 36.27 Hz. No subject in our study showed that poor precision at 1 kHz. One of our subjects showed results that were within the 20th percentile but the other nine showed results that were better than the mean of the 80th percentile. There is further support in the literature for individual differences in auditory abilities [e.g. 98, 38, 101] and, notably, it has been reported that about 15 % of 68 subjects were less efficient in identifying pitch direction than in detecting a frequency difference [173] – a task perhaps more similar to the pitch matching tests used in this thesis. The same arguments can be used regarding the binaural pitch matches; the present variability seen among the normal-hearing subjects in study (I) are most likely the effect of

individual auditory abilities rather than methodological limitations and precise monaural pitch matches are required to perform precisely binaurally.

All normal-hearing subjects in study I performed with stable binaural loudness matches that were within approximately 5 dB from the reference level during the whole test period. Reports on normal-hearing subjects using the present procedure of alternate binaural loudness balance seem to be rather scarce and only one study has been identified [63]. There are on the other hand many studies concerning monaurally hearing impaired patients [see e.g. 94, 74, 25, 65]. However, the reported average SDs for binaural loudness matches were 0.978 dB (right ear as reference) and 1.268 dB (left ear as reference) [63]. The average SDs for our normal-hearing subjects were 1.1 dB at 0.25 kHz and 1.2 dB at 1 kHz (I). There are also numerous reports on intensity discrimination for normal-hearing subjects and sometimes for hearing-impaired too [e.g. 160, 117, 94, 15, 128, 54, 80, 50, 57, 95, 96, 30, 74, 70, 211, 198, 99, 150]. These studies report JNDs that are mostly frequency independent and have a value between 0.3 and 5.5 dB. Binaural loudness matches within 5 dB seen in study I thus seem quite reasonable and accurate in comparison.

Finally, the benefit of the method used for the long-term measurements (studies I, II, and III) is that it is relatively fast, but on the other hand it seems to be slightly more difficult to handle for the subjects than the JND-task. Furthermore, subjects had no training in the method other than the one single supervised session at the beginning of the test period. Methodology and reliability can always be improved, but within the limitations of the present settings the results show that the method for long-term measurements provides quite reliable information on the hearing fluctuations of these patients.

Main findings and their significance

Long-term measurements

The measurements of binaural loudness and pitch matches reported in studies I, II and III demonstrate the daily changes in hearing reported by patients with monaural FLFHL. The measurements provide comprehensive information on the hearing fluctuations not provided with the techniques used in the clinic today. Some patients showed rapid fluctuations, others slow. It was also possible to separate patients with cochlear hydrops from those with Ménière's disease using the average day-to-day change as a measure of disease activity. The number of patients in the groups was small, but both groups showed significant differences from the normal-hearing subjects. This suggests that this method can be used to distinguish different subgroups among patients with FLFHL. The method used here could possibly set a new standard for treatment evaluation of hearing; today this is mainly done through scaling of subjective symptoms and pre- and post treatment PTA.

All patients with FLFHL recorded hearing fluctuations at least once during some part of the test period (III). Some patients showed hearing fluctuations at both test frequencies, some only at one. Patients often showed less pronounced fluctuations at 1 kHz. The individual long-term measurements of pitch matches suggest that the

observed fluctuations could be obscured to some extent by large SD-values. These SDs could have been the effect of undetected bilateral disease, but this seems unlikely since none of the patients has developed bilateral disease at least one year after concluded testing. A more likely explanation, previously proposed, is that binaural pitch matching ability in patients with low-frequency hearing loss is deteriorated and less precise due to conflicting timing and place information in the inner ear [59, 197, 62] or due to low-frequency regions on the basilar membrane without and/or poorly functioning inner hair cells [86]. The PTC-results in studies II and III suggest the possible presence of conflicting cues in most patients at 0.25 kHz (shown as poor Q_{10}), but all patients except one show normal results at 1 kHz.

The individual long-term measurements in study III suggest some associations between loudness matches and subjective symptom ratings, reported as VAS-ratings. However, only a few individual correlations were seen between pitch matches and VAS-ratings. This finding is easily explained by assuming that pitch matches are less related to both pure tone hearing thresholds and audibility, than loudness matches are. This assumption has some support in previous research [110]. Since the average subjective symptoms showed little if any association with the psychoacoustic tests, the results in the present study suggest that our patients' well-being seems to be dependent on other factors, possibly psychological. On the other hand, and on an individual basis, a few patients showed some intricate associations between measurements and symptoms, where a change in one parameter seems to be delayed in time compared to another. Further research is required to elucidate this matter.

Previous studies have suggested that the direction of the pitch matches (i.e. if it is perceived as higher or lower than the actual tone) reveals the stage of the disease [147, 20]. The medians for binaural pitch matches using the 0.25 kHz reference tone indicate three groups of patients with FLFHL (II and III). Close to 40 % of the patients showed overall long-term pitch matches with a lower relative frequency than the reference tone, about 30 % with a higher and about 30 % with a tone almost equal to it. Perceptually, the patients with a lower relative frequency will perceive a fixed tone in the affected ear as being higher in pitch. The patients with a higher relative frequency will perceive it as lower in pitch. Morrison [147] showed that in 60 % of the cases his patients reported lower pitch in the affected ear, higher in 25 % and equal in 15 %. Brookes & Parikh [20] found that their patients reported lower pitch in 77.2 % of cases, higher in 3.6% and equal in 19.1% (n=342). It should be noted that these studies report subjective pitch judgements made by the patients on a fixed pure tone stimulus, while our patients recorded pitch matches across ears.

Both these previous studies [147, 20] have put forward the explanation, based on Tonndorf's suggestion [195], that the pitch direction signifies different stages of the disease. They reason that in the early stages of the disease a volume increment increases the tension of the basilar membrane in the apical parts. This tension causes the patient to perceive subjectively lower pitches in the affected ear, but, in the later stages of the disease subjectively higher pitches are heard in the affected ear due to changed mass and resistance in the cochlear duct [195, 147, 20]. This explanation is

unsatisfying since it poorly accounts for any effects that distension and, more so, possible ruptures of Reissner's membrane and shrivelling of the tectorial membrane have on the hair cells [168, 169, 107, 122, 207]. It seems reasonable to assume that these deformations would affect both hearing sensitivity and pitch judgements. The present findings (II and III) support no relation between disease stage and pitch matches in the affected ear (although the studies were not designed to examine disease stage). However, stages or different causes of symptoms such as fluid volume increment, fluid mixing, elasticity changes, mass alterations, distensions, and/or ruptures could be possible explanations for this observation.

Frequency coding in the hydropic ear
It is a well established notion that Ménière's disease and most likely other forms of FLFHL, is closely related to increased fluid volume (increased pressure) in the inner ear [e.g. 168, 169, 152, 31, 107, 207]. Hearing thresholds (PTA) have been shown to improve in about 50 % of the patients after different types of pressure exposures (hypobaric pressure chamber or local application of pulsated overpressure in the ear canal) in patients with Ménière's disease [194, 47, 193, 45, 201, 114, 108, 112, 46, 214, 49, 188, 85]. In study IV, we found that most patients did not show any change in PTA after pressure exposure in the hypobaric pressure chamber. Nor did our results show any increasing PTA improvement with increasing maximum relative overpressure applied in the middle ear as previously reported by Konrádsson and colleagues [112].

On the other hand, effects on frequency selectivity were observed after the pressure exposures. Half of the patients showed improvements in SRS in noise. SRS have previously been shown to be associated with frequency selectivity [182]. Previous evidence suggests that the outer hair cells of the inner ear affect the frequency selectivity of the cochlea by their active tuning of the basilar membrane [6, 7, 155, 73, 105, 161]. Increased TEOAE emission strength was observed after the pressure exposure in the majority of patients. This may indicate improved outer hair cell motility, which in turn may enhance frequency selectivity. This is in line with previous studies that have shown that pressure exposure change the hydrodynamic properties of the inner ear [34, 45, 214]. The pressure exposure induces an increased fluid transportation that decreases pressure and possibly ionic content of the endolymphatic fluid. Most likely, these two things affect outer hair cell motility. If the middle ear pressure exposure reduces the cochlear fluid volume and leads to an increase in motility of the basilar membrane and the outer hair cells, it should manifest itself as increased emission strength, a relation indeed seen in our results. However, if there is a close relationship between outer hair cell motility and frequency selectivity one would expect PTCs to improve in a similar manner in patients with increased emission strength after exposure. No such general association was found. However, small, but significant, changes in the tuning of the PTCs were observed in most of the patients. These changes were both improvements and deteriorations, a finding that is difficult to explain from the present data. Hence, further research is needed in order to elucidate these findings.

To test the effect of conflicting timing and place cues on pitch matches, study (V) was conducted by assuming that both timing and place information contributes to the pure tone pitch-matching ability at low frequencies. The pure tone pitch matches of the patients with low-frequency hearing loss suggested that to assess any relative frequency difference between ears at all in these patients, the reference signal should be presented to the unaffected ear. The results resemble those reported in previous studies on patients with low-frequency hearing loss [59, 197, 27, 149]. When only timing information was used (presenting the SAM-noise to the affected ear), the patients with monaural low-frequency hearing loss showed improved precision in their binaural pitch matches. This finding suggests a possible detrimental effect on the matches of conflicting cues (provided by pure tones). Previously, it has also been shown that patients with monaural Ménière's disease performed a discrimination task less precisely in the affected ear using pure tones, but using SAM-noise they performed similar to their unaffected ear and normal-hearing subjects [61, 62]. However, the present finding could be affected by individual upper limits of perceiving rate pitch [28, 154, 29, 13]. Further research is required to underlying mechanisms of the present findings.

Clinical implications

The main features of Ménière's disease and cochlear hydrops are their varying symptoms over time. In the clinic, the occasional audiogram or electrocochleography collected together with the patient's symptom and a vestibular examination provides 'snapshot diagnostics' that only reports the disease state at that specific moment in time. In contrast, the consecutive long-term measurements made in the present thesis provide more comprehensive information on hearing fluctuations in these patients. The home audiometry is an easy and feasible method to monitor disease activity in these patients. The course of the individual patient's fluctuations reveals diagnostic information not available today.

The quantifications of the hearing fluctuations indicate that separate disease subgroups can be indentified. Long-term measurements during periods with and without treatment in a larger group of patients could set a new standard for treatment evaluation for these diseases.

The occasional audiogram serves as the golden standard in hearing evaluation in the clinic today. The present findings suggest the need of more advanced measurements of hearing physiology. Especially, in disorders where function varies over time, these variations may, per se, be important for the diagnosis and the choice of treatment.

CONCLUSIONS

- Long-term recordings of binaural loudness matches could be made reliably in most subjects using RMLSP in a portable audiometer. The precision and stability of the binaural pitch matches recorded was not comparable to that of highly trained, selected subjects at the laboratory previously described in the literature. Binaural pitch matches could be measured reliably only if the subjects were able to define pitch precisely (I).

- Long-term measurements of binaural pitch and loudness matches seem to provide information on disease activity. One patient with FLFHL showed long-term measurements of binaural loudness and pitch matches during periods both with and without symptoms that were different from those of normal-hearing subjects' (II).

- Fluctuations in binaural loudness and pitch matches could be observed during consecutive long-term measurements in patients with monaural FLFHL that were not seen among normal-hearing subjects. Defining disease activity as average day-to-day difference showed that patients with Ménière's disease had a higher hearing related disease activity than seen among patients with FLFHL without vertigo. It was shown that reported subjective symptoms, at the group level, were poorly associated with the psychoacoustically measured parameters (loudness and pitch matches), but covariations between symptoms and pitch matches were observed in some patients, and between symptoms and loudness matches in other patients. The results imply that it is possible to separate disease subgroups using long-term measurements of loudness and pitch matches. This could prove to be an essential feature in clinical treatment trials. (III).

- The hypobaric pressure chamber exposure may improve, deteriorate, or not affect cochlear frequency selectivity measured as SRS in noise, TEOAEs, and PTCs. The observed effects were generally small. The results indicated that the pure tone audiogram may be too blunt a measure of inner ear physiology when monitoring effects of hypobaric pressure exposure, since improvements in frequency selectivity were not accompanied by improvements in audiometric hearing thresholds (IV).

- The pure tone pitch matches of the patients with low-frequency hearing loss suggested that to assess pitch differences between the ears in these patients the reference signal should be presented to the unaffected ear. Binaural pitch matches made with SAM-noise as reference stimulus in the affected ear may improve the precision in patients with monaural low-frequency hearing loss, but the precision may deteriorate when the variable test tone is presented to the affected ear. This finding suggests a possible detrimental effect of conflicting cues on the matches provided by pure tones. Pitch matches made to the modulation rate (e.g. 0.25 kHz) of a noise carrier as a reference signal may be lower than pure tone pitch matches made with a pure tone reference of the same frequency (e.g. 0.25 kHz) also in normal-hearing subjects. Furthermore, there seems to be differences between subjects and within a single subject depending on the modulation rates/frequencies used (V).

SWEDISH SUMMARY

Personer med fluktuerande hörselnedsättning lider oftast av s.k. cochleär hydrops (hörselnedsättning, tinnitus lockkänsla i det drabbade örat) eller Ménières sjukdom (hörselnedsättning, tinnitus, lockkänsla och yrselanfall). Dessa personer rapporterar ofta variationer i sin hörsel över tid, men man använder fortfarande enstaka hörselprov och subjektiva symptom för att ställa diagnoserna. Deras hörselnedsättning tycks vara orsakad av att de har vätskeförändringar i innerörat, vilket generellt sett brukar drabbar ett öra i taget. Kanske upp till 50 % av patienterna får sjukdomen i båda öronen. Enstaka hörselprov och symptomskattningar används vid utvärdering av behandling, som oftast består av olika typer av vätskedrivande mediciner men även tryckbehandling, minskat intag av salt eller att sätta ett rör genom trumhinnan som luftar mellanörat. Vi kan inte förutsäga vilken patient som svarar på vilken behandling eller om en förändring i tillståndet är en effekt av spontan återhämtning. Detta får oss att tro att det är olika underliggande orsaker till symptomen. Till detta kommer att sjukdomens övergående karaktär gör det svårt att utvärdera behandlingen. Långtidsmätningar av dessa patienters hörsel bör ge en mycket saknad information om hörselfluktuationerna och framför allt bidra till att kunna kvantifiera deras sjukdomsaktivitet. Om vi skulle kunna kvantifiera sjukdomsaktiviteten, öppnas för möjligheten att särskilja olika undergrupper i sjukdomsgruppen och mer tillförlitligt utvärdera behandling, vilket svårligen görs idag.

I studierna utvecklas och testas metoder för långtidsmätning av hörsel utanför sjukhuset (I-III). Metoderna bygger på uppskattning av olika ljudparametrar, vilka på ett intrikat sätt beskriver innerörats funktion vid ett givet tillfälle. När en och samma ton presenteras först i det ena, sedan det andra örat hos patienter med ensidigt fluktuerande hörselnedsättning, uppfattas den oftast som att den har olika tonhöjd i öronen. Tonhöjdsskillnaden beror troligen på de mekaniska förändringar i innerörats membran som i sin tur beror på tryckförändringen som uppstår vid vätskevolymökningen som orsakas av sjukdomen. Detta tryck tycks variera med tiden och tonhöjdsskillnaden kan utgöra ett mått på tryckförändringen och inte minst sjukdomsaktiviteten. Detta antagande testades i delarbetena II-III.

Långtidsmätningar av binaural hörstyrke- och tonhöjdsbalanseringar genomfördes av 10 normalhörande och 13 patienter med ensidig fluktuerande hörselnedsättning i deras hemmiljö med en specialutvecklad mätmetod (Randomised maximum likelihood sequential procedure, RMLSP) i kombination med s.k. tvingande tvåvalsprocedur (2AFC), d.v.s. den undersökte var tvungen att välja mellan två presenterade toner. Normalhörande uppvisar inte några större fluktuationer, medan patienter med inneröresjukdomarna har stora dagliga variationer. När vi beräknat medelvärdet på den dagliga hörselförändringen som ett mått på sjukdomsaktivitet, såg vi tydligt att patienter med Ménières sjukdom har en mätbart högre variation än patienter med fluktuerande hörselnedsättning utan yrsel, som i sin tur har högre variation än de normalhörande. I flera fall kunde samband ses mellan rapportering av upplevda hörsel- och yrselbesvär och gjorda hörselmätningar. Fluktuationerna kunde vara snabba eller

långsamma, men sambandet kunde inte fångas med enkel korrelationsanalys i vårt material. Slutsatserna för dessa studier är att hemaudiometrin med RMLSP-metoden fungerar som avsett (I), kvantifiering av sjukdomsaktiviteten tycks möjlig (II och III) och metoden tycks kunna användas för att identifiera grupper med olika typ och grad av sjukdomsaktivitet (III).

I delarbete (IV) exponerandes 10 försökspersoner med monaural fluktuerande hörselnedsättning för relativa övertryck i innerörat i en tryckkammare för att testa effekterna. Deras hörtrösklar (PTA), yttre hårcellsfunktion (TEOAE), talförståelse i brus (SRS) och frekvensselektivitetskurvor (PTC) mättes före och efter tryckexponeringen. Vi fann ingen hörtröskelförbättring, men individuella försökspersoner visade dels förbättringar i talförståelse, i yttre hårcellsfunktion och fick skarpare frekvensselektivitetskurvor. Man såg även enstaka försämringar i frekvensselektivitet. Man såg inget generellt samband mellan PTA, OAE, SRS och PTC, och resultaten efter exponeringen kunde inte användas för att förutsäga vem som upplevt hörselförbättringar vid uppföljningen. Tryckkammarexponering kan förbättra, försämra eller inte alls påverka hörselfunktionen i innerörat. Det vanliga hörselprovet är ett alltför trubbigt instrument för att använda vid utvärdering av innerörefysiologin vid tryckkammarexponering i synnerhet och vid Ménière-behandling i allmänhet.

I delarbete (V) prövades om förmågan till precisa tonhöjdsmatchningar mellan öronen hos personer med normal hörsel och ensidig innerörebashörselnedsättning påverkades av att man reducerar informationen till innerörat genom att använda s.k. SAM-brus. SAM-brus är ett periodiskt nivåvarierat brus, som ger en tonhöjdsupplevelse, utan att egentligen innehålla den spektrala informationen (frekvensen) som en ton gör. Överlag visade resultaten att tonhöjdsmatchningar mot SAM-brus varierar mellan försökspersoner och även inom enskilda individer och att detta verkar bero på hastigheten på det periodiska nivåvarierade bruset (modulationshastigheten). Beträffande monaurala matchningar visade personerna med basnedsättning att upprepade presentationer av en ren ton, bestående av en enda frekvens och en ljudtrycksnivå i det sjuka örat, ger tillräcklig information för att göra en adekvat tonhöjdsmatchning. Skillnaden mellan öronen i tonhöjd kan bara uppskattas när den första tonen presenteras i det friska örat. Matchningar mellan öronen blev bättre när endast SAM-brus presenterades i det sjuka örat. Detta betyder att matchningar av rena toner blir mindre precisa hos patienter med bashörselnedsättningar, eftersom det sjukdomspåverkade innerörat lämnar vidare motstridig information om tonhöjden.

Patienter med Ménières sjukdom och cochleär hydrops uppvisar symptom som varierar över tid. Sporadiska hörselprov tagna på kliniken utgör tillsammans med balansundersökning och de symptom som patienten uppger, underlaget som dessa diagnoser oftast vilar på. Dessa undersökningar ger endast en ögonblicksbild av sjukdomarna. De långtidsmätningar som gjorts i denna avhandling ger mer fullständig information om dessa patienters hörselfluktuationer. Hörselmätningar i hemmet är en enkel och lämplig metod att följa sjukdomsaktiviteten hos dessa patienter. Hörselfluktuationernas förlopp för den enskilde individen avslöjar diagnostiskt relevant information som inte finns att tillgå kliniskt idag. Distinkta undergrupper

framträder när man kvantifierar hörselfluktuationerna. Långtidsmätningar med och utan behandling i ett större patientmaterial skulle kunna ge en ny standard för behandlingsutvärdering av dessa sjukdomar.

Idag på kliniken utgör det vanliga hörselprovet (audiogrammet) den gyllene standarden för hörselutredning. Fynden i avhandlingen pekar på behovet av mer avancerade hörselfysiologiska mätningar. Detta är speciellt viktigt i sjukdomar som varierar över tid, där själva variationen sannolikt har betydelse för både diagnos och val av behandling.

ACKNOWLEDGEMENTS

I would like to express my sincere gratitude to everyone who have helped, supported and encouraged me during my work with the present thesis. I would especially like to thank:

My tutor, mentor, and friend, docent Jan Grenner, who with never lasting energy, enthusiasm, and generosity have guided me into the field of audiological research. It has been a privilege to work with him and to be inspired of and share his profound scientific and technical knowledge on hearing and hearing physiology.

My co-tutor professor Måns Magnusson for enthusiastically sharing his great scientific knowledge and for visions, skilful editing, and great discussions on science.

The super troopers, Tina Ibertsson, Johannes Lantz, and Elisabet Thorén for encouragement, discussions on science in general and audiology in particular, and friendship.

Carolina Anderberg, Katarina Billred, Karin Björklund, Katarina Helleberg, Sven Jönsson, Linda Ivarsson, Andreas Sjögren, Ingela Stensman, Ingegerd Wennerström and all the other colleagues at the section of Audiology, ENT-department, Malmö University Hospital. Especially, Åsa Blomberg for generous support and being an excellent head of the section. It is a great place to work and I always travel with light feet to work, thanks to them.

All colleagues at the ENT-department, Malmö University Hospital, especially director dr Bo Tideholm, docent Magnus Jannert, Ann Reutherborg, and Marianne Brattmo.

The colleagues at the Department of logopedics, foniatric and audiology, Lund University. In particular, Anders Jönsson for enthusiasm, inspiration and all discussions on hearing and audiology, and Ingrid Lennart for inspiration and collaboration at the audiology program. Professor Anders Löfqvist for skilful and very generous help with manuscripts. Docent Birgitta Sahlén for sheer inspiration.

The colleagues at section of Audiology, ENT-department, Lund University Hospital. Especially, Pia Skog and Bengt Almqvist.

The Icelandic connection, Einar-Jon Einarsson, for visions, discussion on what is important in life and friendship. Dr Per-Anders Fransson for enlightening discussions and diligent help with manuscripts.

The colleagues in the Research Council of the Swedish Association of Audiologists, Ann-Kristin Espmark (for help with manuscripts), Kim Kähäri, André Sadeghi, Åsa Skjönsberg, and Marie Öberg (for help with manuscripts) for all discussions,

encouragement, and pleasant company. Marie Öberg also for all well-needed phone calls.

My halftime opponents, professor emeritus Stig Arlinger and docent Björn Carlborg, for valuable suggestions on manuscripts and fruitful discussions.

My family and friends who have supported me throughout my studies. My mother, Christine Brännström, for encouragement and good advices. My father, Lauritz Brännström, for encouragement, continuous discussions on science, scientific methods, and diligent help with this manuscript. My sister Jenny Brännström for support and laughter. Jesper Koch for encouragement, discussions on science, and skilful help with presentations. Above all, my partner Lone Koch for love, support and encouragement, and Alfons the dog for well needed breaks.

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ABSTRACT

Patients with Ménière's disease and cochlear hydrops show fluctuating low-frequency hearing loss (FLFHL). At present these changes are followed as patients' subjective reports and occasional measurements. Consecutive long-term measurements should provide more comprehensive information on the hearing fluctuations than the occasional audiogram used today and constitute an approach to quantify the fluctuations. Quantifications could potentially be used to define disease subgroups and to evaluate treatments. This thesis aims to introduce 'home audiometry' to monitor hearing function in monaural FLFHL. The approaches contain assessment of other manifestations of the diseases such as frequency selectivity and frequency coding of the auditory system.

Long-term monitoring of binaural loudness and pitch matches showed that patients had daily fluctuations not present in normal-hearing subjects. The average day-to-day difference was considered as a measure of disease activity. This measure showed that patients with Ménière's disease had more fluctuations than patients with cochlear hydrops, and that both these groups had had more fluctuations than normal-hearing references. There was no simple relation between the measurements and simultaneous symptom ratings, corroborating the importance of the measurements. It seems possible to separate disease subgroups using long-term measurements of loudness and pitch matches. This could prove to be an essential feature in understanding the diseases and in clinical treatment trials.

The deviant pitch matches observed during the long-term measurements suggest changes in inner ear physiology not only related to pure tone hearing. The probable cause is excessive fluid volume in the affected inner ear. Indeed, after pressure exposure in the hypobaric pressure chamber, no average hearing threshold improvements were seen in patients with FLFHL. However, there were improvements in individual subjects regarding speech recognition, outer hair cell function, and frequency selectivity. But deteriorations were also seen, mainly in frequency selectivity. Moreover, after experimentally reducing conflicting frequency information in the affected ear, the pitch matching precision improved to some extent.

It is concluded that the long-term measurements provide more and comprehensive information on the hearing fluctuations than the occasional audiograms used today. More advanced measurements can be done as well, which provide more information than the blunt pure tone audiometry. Separate disease subgroups can be identified by quantifications of the fluctuations. The methods can set a new standard for the hearing evaluation of treatment in FLFHL.