Aus dem Fachbereich Medizin
der Johann Wolfgang Goethe-Universität
Frankfurt am Main

betreut in der
Klinik für Hals-Nasen-Ohrenheilkunde
Direktor: Prof. Dr. Timo Stöver

Tinnitus bei Normalgehör: Untersuchung von Hörschwellenfeinstruktur, otoakustischen Emissionen und Hörnervenpotenzialen

Dissertation
zur Erlangung des Doktorgrades der Medizin
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vorgelegt von
Felix Kirchfeld

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Schriftliche Erklärung

Ich erkläre ehrenwörtlich, dass ich die dem Fachbereich Medizin der Johann Wolfgang Goethe-Universität Frankfurt am Main zur Promotionsprüfung eingereichte Dissertation mit dem Titel

Tinnitus bei Normalgehör: Untersuchung von Hörschwellenfeinstruktur, otoakustischen Emissionen und Hörnervenpotenzialen

in der Klinik für Hals-Nasen-Ohrenheilkunde unter Betreuung und Anleitung von Prof. Dr. Uwe Baumann ohne sonstige Hilfe selbst durchgeführt und bei der Abfassung der Arbeit keine anderen als die in der Dissertation angeführten Hilfsmittel benutzt habe. Darüber hinaus versichere ich, nicht die Hilfe einer kommerziellen Promotionsvermittlung in Anspruch genommen zu haben.

Ich habe bisher an keiner in- oder ausländischen Universität ein Gesuch um Zulassung zur Promotion eingereicht*. Die vorliegende Arbeit wurde bisher nicht als Dissertation eingereicht.

Vorliegende Ergebnisse der Arbeit wurden (oder werden) in folgendem Publikationsorgan veröffentlicht:

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*) im Falle des Nichtzutreffens entfernen

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List of abbreviations

ABR	Auditory brainstem response
ARC	Activity-regulated cytoskeleton-associated protein
CG	Control group
DCN	Dorsal cochlear nucleus
DFL	Differential limen for frequency
Fos	Fos-like immunoreactivity
IC	Inferior Colliculus
IHC	Inner hair cell
LN	Lateral nucleus
NIHL	Noise induced hearing loss
OHC	Outer hair cell
PTA11	Pure tone audiometry with 11 test frequencies
SFR	Spontaneous firing rates
SOC	Superior olivary complex
SR	Stochastic resonance
TCD	Thalamocortical dysrhythmia
TG	Tinnitus group
TTS	Temporary threshold shifts
VAS	Visual analog scale
VCN	Ventral cochlear nucleus

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Zusammenfassung (Deutsch)

Tinnitus ist ein Symptom, welches von den meisten Menschen mindestens einmal im Leben verspürt wird. In den meisten dokumentierten Fällen kann ein neu aufgetretener, chronischer Tinnitus mit einem Hörverlust in einen zeitlichen Zusammenhang gebracht werden. Ein Tinnitus kann aber auch bei (scheinbar) normalhörenden Menschen auftreten und verbleibt ohne nachzuvollziehende vorhergegangene Ursache. Trotz der Häufigkeit des Auftretens von Tinnitus sind die pathophysiologischen Zusammenhänge immer noch nicht vollends erforscht. Eine aktuelle Hypothese stellt einen „versteckten“ Hörverlust genannt *Synaptopathie* als Pathomechanismus des Tinnitus bei Normalhörenden in den Fokus. In der vorliegenden Arbeit sollte geprüft werden, ob eine Feinstrukturaudiometrie oder die Messung otoakustischer Emissionen eventuell übersehene Hörschäden bei vermeintlich Normalhörenden mit chronischem Tinnitus demaskieren kann. Somit würde ein mit den üblichen Methoden audiologisch nicht nachweisbarer Hörverlust in Ergänzung oder an die Stelle des vermuteten Synaptopathie-Pathomechanismus treten. Ein weiteres Ziel lag in dem Versuch der Replikation von bereits vorliegenden Ergebnissen einer anderen Arbeitsgruppe zur Synapthopathie bei Tinnitus. Schaette und McAlpine (2011) konnten mittels der Ableitung von klick-evozierten akustischen Hirnstammpotenzialen einen signifikanten Unterschied zwischen Gruppen von Normalhörenden mit und ohne chronischem Tinnitus in den Amplituden der Welle I nachweisen, und damit die Hypothese der Synaptopathie erhärten[18].

Für die vorliegende Studie wurde eine Studienkohorte aus normalhörenden Probanden bestehend aus einer Gruppe von Tinnitusprobanden (N = 15) und einer Kontrollgruppe (N = 14) untersucht. Zur Bestimmung der Hörleistung wurde eine manuelle Reintonaudiometrie mit 11 Testfrequenzen durchgeführt. Aufnahmekriterium waren Luftleitungs-Tonhörschwellen von 10 dB HL oder geringer. Eine Abweichung bei einer Prüffrequenz von maximal 15 dB HL wurde hierbei toleriert. Die Daten der Tinnitus-Charakteristika, wie Tonhöhe und Intensität wurden durch Vergleichsdarbietungen, die Qualität und die subjektive Belästigung per Fragebogen erhoben. Des Weiteren wurden bei beiden Testgruppen Daten mittels Békésy-Gleitfrequenzaudiometrie erhoben (794 Prüffrequenzen), sowie eine DPOAE Messung (36 Prüffrequenzen) und eine Hirnstammaudiometrie (Ab-

leitung früher akustisch evozierter Potenziale, FAEP) durchgeführt. Die Ergebnisse zeigten eine Korrelation der ermittelten Tinnitus-Vergleichstonhöhe mit der Frequenzlage der größten Abweichung (Verschlechterung) von der normalen Hörkurve in der Békésy-Gleitfrequenzaudiometrie ($p = 0{,}032$). Alle weiteren Analysen der Feinstruktur-Hörkurve (Steilheit der Hörverlust-Absenkung, Anzahl der Hörverlust-Senken) zeigten keinen statistisch signifikanten Zusammenhang zwischen der Morphologie der Feinstruktur-Hörkurve und den Tinnitus-Charakteristika. Die Feinstrukturmessung deckte Hörverlustbereiche auf, die in der manuellen Reintonaudiometrie nicht abgebildet wurden. Diese „unentdeckten“ Hörverluste hätten zum Ausschluss von 12 von 29 Testpersonen (41,4 %) geführt, wenn die Feinstruktur-Hörkurve als Inklusionskriterium verwendet worden wäre. Im direkten Vergleich der mittleren Feinstruktur-Hörkurven beider Testgruppen zeigte sich eine mit etwa maximal 4 dB statistisch signifikant bessere mittlere Hörleistung der Tinnitusgruppe ($p < 0{,}05$) in 3 unterschiedlichen Prüffrequenzbereichen (1,5 kHz, 3 kHz, 7 kHz). Die Analyse der mittleren Amplituden der Welle I der FAEP zeigte entgegen der Erwartung einen schwachen Trend zu höheren Amplituden in der Tinnitusgruppe ($p = 0{,}06$). Nach Schaette und McAlpine (2011) hätte sich der Synaptopathie-Pathogenese zu Folge ein gegenläufiger Trend, also eine Verringerung der Amplitude der Welle I in der Tinnitusgruppe ergeben sollen. Nebenbefundlich konnte ein schwacher Trend zwischen der Amplitude der Welle I und der subjektiv empfundenen Belästigung des Tinnitus nachgewiesen werden ($p = 0{,}06$). Die statistische Analyse der aus den DPOAE-Messungen ermittelten Parameter erbrachte keinen signifikanten Unterschied zwischen der Tinnitus- und Kontrollgruppe. Im direkten Vergleich der DPOAE und Feinstruktur-Hörkurven wurde ein signifikanter Unterschied in den Differenzen der frequenzspezifischen Messungen um 2,4 kHz gefunden ($p = 0{,}007$).

Die Ergebnisse der Arbeit legen die Schlussfolgerung nahe, dass in bisherigen Studien mit vermeintlich normalhörenden Tinnitusprobanden ein unerkannter Hörverlust vorlag, der entweder durch das Raster der Prüffrequenzen der manuellen Reintonaudiometrie fiel, oder Probanden mit vormals überdurchschnittlichem Gehör eine dezente spontane Absenkung ihres Hörvermögens als Tinnitus-Pathogenese erfahren haben. Für diese Vermutung spricht auch, dass zwischen dem Frequenzbereich des größten Hörverlustes in den Feinstruktur-Hörkurven und der Tinnitusfrequenz eine signifikante Korrelation besteht.

Der vermutete Pathomechanismus der Synaptopathie bei „Normalhörenden“ mit Tinnitus konnte nicht bestätigt werden. Der Zusammenhang zwischen der Amplitude der Welle I

und der subjektiv wahrgenommenen Belästigung durch den Tinnitus, auf den die Datendieser Studie hinweisen, sollte in zukünftigen Studien genauer untersucht werden. Weitere Forschungsarbeiten mit genaueren Messmethoden und größeren Probandengruppen sind zur Klärung der Hypothese „Genese des chronischen subjektiven Tinnitus ohne Hörminderung“ erforderlich.

Abstract (English)

Tinnitus is a symptom experienced by most people at least once in their lifetime. In most documented cases, a new onset of chronic tinnitus can be chronologically correlated with hearing loss. However, tinnitus can also occur in people with (apparently) normal hearing and remains without a traceable preceding cause. Despite the frequency of occurrence of tinnitus, the pathophysiological mechanisms are still not fully understood. A currently proposed hypothesis focuses on a "hidden" hearing loss called synaptopathy as a pathomechanism of tinnitus in normal hearing subjects. In the present study, the objective was to test whether fine-structure audiometry or measurement of otoacoustic emissions can reveal possibly overlooked hearing impairment in presumed normal-hearing individuals with chronic tinnitus. Thus, a hearing loss not audiologically detectable by the usual methods would supplement or replace the presumed synaptopathic pathomechanism. Another objective was to attempt to replicate the existing findings of another research group on synaptopathy as cause for tinnitus in normal hearing people. Schaette and McAlpine (2011) were able to demonstrate a significant difference in wave I amplitudes between groups of normal hearing subjects with and without chronic tinnitus by deriving click-evoked auditory brainstem potentials, thus supporting the hypothesis of synaptopathy[18].

For the present study, a cohort of normal-hearing subjects consisting of a group of tinnitus subjects ($N = 15$) and a control group ($N = 14$) was tested. Manual pure-tone audiometry with 11 test frequencies was conducted to determine hearing performance. Inclusion criteria were defined as air conducted hearing thresholds of 10 dB HL or lower. A deviation at a test frequency of 15 dB HL or less was tolerated. Data of tinnitus characteristics, such as pitch and intensity, were collected by presentation and matching of comparative tones, quality and subjective disturbance by questionnaire. Furthermore, data was obtained from both test groups by Békésy gliding frequency audiometry (794 test frequencies), as well as DPOAE measurement (36 test frequencies) and auditory brainstem response (ABR) audiometry (derivation of early auditory evoked potentials). The results showed a correlation of the determined tinnitus comparison pitch with the frequency location of the largest deviation (impairment) from the normal hearing curve in the Békésy gliding frequency audiometry ($p = 0.032$). All further analyses of the fine-structure hearing curve (steepness of hearing loss, slope, number of hearing loss dips) showed no statistically significant

relationship between the morphology of the fine-structure hearing curve and tinnitus characteristics. Fine-structure measurement revealed areas of hearing loss that were not mapped in manual pure-tone audiometry. These "undetected" hearing losses would have led to the exclusion of 12 of 29 subjects (41.4 %) if the fine-structure hearing curve had been used as an inclusion criterion. A direct comparison of the mean fine-structure hearing curves of both test groups showed a statistically significant better mean hearing performance of the tinnitus group ($p < 0.05$) in 3 different test frequency ranges (1.5 kHz, 3 kHz, 7 kHz) with a maximum of 4 dB HL. Analysis of the mean amplitudes of wave I of the ABRs showed, contrary to expectation, a weak trend toward higher amplitudes in the tinnitus group ($p = 0.06$). According to Schaette and McAlpine (2011), synaptopathy pathogenesis should have resulted in an opposite trend, i.e., a decrease in wave I amplitude in the tinnitus group. As a secondary finding, a weak trend between wave I amplitude and subjectively perceived disturbance of tinnitus was demonstrated ($p = 0.06$). Statistical analysis of the parameters determined from the DPOAE measurements did not reveal any significant differences between the tinnitus group and control group. Direct comparison of the DPOAE and fine-structure hearing curves, revealed a significant difference in the differences of the frequency-specific measurements around 2.4 kHz ($p = 0.007$).

The results of the study suggest that in previous studies with supposedly normal hearing tinnitus subjects there were unrecognized hearing losses that either went unrecognized by the screening by manual pure-tone audiometry, or subjects with previously above-average hearing experienced a subtle spontaneous decrease in their hearing as tinnitus pathogenesis. This assumption is also supported by the fact that there is a significant correlation between the frequency range of the greatest hearing loss in the fine-structure hearing curves and the tinnitus frequency.

The suspected pathomechanism of synaptopathy in "normal hearing" subjects with tinnitus could not be confirmed. The correlation between wave I amplitudes and subjectively perceived disturbance by tinnitus, indicated by the data of this study, should be investigated in more detail in future studies. Further research with more accurate measurement methods and larger subject groups is needed to clarify the hypothesis "Genesis of chronic subjective tinnitus without hearing loss".

1 Introduction

1.1 Definition of tinnitus

Tinnitus, from the Latin word "tinnire" which means "ringing", is an acoustic phenomenon that the majority of people have experienced at some point in their life. Usually it is temporary and harmless, but between 10 and 15 percent of those affected suffer from a persistent tinnitus with the need for medical attention[2]. The perceived feeling can encompass a multitude of different qualities, from soft to loud, from high to low pitch, and usually presents itself as ringing, but can also be perceived as humming, swirling, roaring and many others[3].

It is still controversial when the earliest historic reference of tinnitus occurred, but whether it was written in the Papyrus Ebers of the ancient Egyptians or been recorded by Hippocrates itself, it remains certain, that the tinnitus phenomenon was a known symptom to humans since the earliest days of our civilization[4].

Despite the wide spread of the tinnitus phenomenon, the understanding of the causal pathophysiology was rudimentary until recently. Only in the last 20 years, when humans began to explore the living brain using indirect measurement methods and were given the opportunity to create brain images, have scientist been able to get an idea of the sheer complexity of the neurobiochemical relationships that probably underlie tinnitus.

The roughest distinction between tinnitus can be made by distinguishing objective from subjective tinnitus. Objective tinnitus is defined as the perception of a sound without external stimuli that can be perceived by both the person affected and the examiner. Objective tinnitus occurs when there is a normal perception of an abnormal sound or an abnormal perception of a normal sound in the ear. Since objective tinnitus usually has an identifiable cause, it is curable in most cases. The causes include disturbances of the vascular system such as pulse-synchronous sounds of the large cervical vessels when the laminar flow gives way to a turbulent flow, arteriovenous malformations, aneurisms, vascular stenosis and intracranial hypertension. Other possible causes include abnormal muscle contraction of the palatal or middle ear muscles and a malformation of the Eustachian tube, which can lead to a sound synchronous with respiration[5].

Whereas objective tinnitus can be related to actual sound, created within our body[6], the majority of tinnitus patients suffer from subjective tinnitus , which is defined as a perception of a sound without a corresponding physical correlate[7,8]. Most humans have experienced short term tinnitus repeatedly in their lifetime[1]. Usually the sensation of tinnitus is of limited duration and linked to a reversible cause such as exposure to harmful levels of noise, certain pharmaceuticals like aspirin or fever[9]. Even though it proves to be harmless most of the times in between 1-3 percent of the population the tinnitus sensation is loud enough to be affect negatively the quality of life[9]. Symptoms include distress, sleep impairment and reduction of productivity[8].

1.2 Central tinnitus models

Ever since surgical procedures have been performed that have led to a complete severing of the cochlear nerve, it has been observed that it causes changes in the volume or quality of chronic tinnitus as a direct result. The changes are subject to a range of possibilities, such as the amplification or improvement of already existing tinnitus phenomena, or the reappearance and even the complete cessation of chronic tinnitus[10,11] . The incongruent changes observed after the nerve dissection led to the conclusion that tinnitus might have several causes and therefore changes unpredictably[1].

The first distinction was made between central or peripheral tinnitus. Peripheral tinnitus results from abnormal activity of the cochlear nerve, while central tinnitus originates in the central auditory pathways at the cortical level[12,13].

Peripheral models describe irregular or absent cochlear activity and changes in the neuronal input as the basic mechanism of tinnitus. This mechanism would explain why tinnitus can occur or increase when the auditory nerve is severed. It does not explain how tinnitus can improve or vanish altogether. Again, the peripheral model may only be one facet of the tinnitus phenomenon[14].

It has been proven that tinnitus is associated with hearing loss in the vast majority of cases[15]. Gradually, techniques have been developed to measure and visualize brain activity. These possibilities have led to attempts to isolate the central pathomechanisms that promote hearing loss and may underlie tinnitus[16].

Several key mechanisms associated with chronic tinnitus and hearing loss have already been identified. These models are summarized in the following chapters.

1.2.1 Subcortical hyperactivity models

The subcortical hyperactivity models describe tinnitus as a consequence of increased subcortical neural activity and its effects on the central auditory pathways. Examples of these models are central gain[17,18,19], frontostriatal gating[20] and thalamocortical dysrhythmia[21].

The central gain model describes a compensation mechanism that responds to a reduced output of the cochlea with an increase in nerve activity along the central auditory pathways. This mechanism has been associated with both tinnitus and hyperacusis. Central gain serves as the basis for the theory of synaptopathy, which will be described in more detail below[22].

Frontostriatal gating is a theoretical model that describes the ventromedial prefrontal cortex and the nucleus accumbens as the central "gatekeeper" for incoming sensory information. The incoming information is evaluated and the flow of information is controlled via descending neurological pathways. Damage or imbalances in this system have been linked to both chronic tinnitus and chronic pain[20].

Thalamocortical dysarthria (TCD) describes a possible pathomechanism for tinnitus in that the brain slows down alpha to theta EEG frequency bands due to thalamic deafferentation, while gamma activity is increased[7]. Alpha waves are in the frequency range between 8 and 13 Hz. These are associated with the state of relaxed alertness[23]. Theta waves are described in a frequency range between 4 and 8 Hz. They occur more frequently during drowsiness and light sleep phases. Gamma waves are signals in the frequency range above 30 Hz and occur during strong concentration and learning processes. The latest findings combine the occurrence of the gamma band with the so-called top-down regulation and the synchronization of different brain areas to integrate different qualities of a stimulus. This mechanism is a point of attack for the genesis of tinnitus and is described with the TCD model[24].

According to the TCD model, a cross frequency coupling between theta (former alpha) and gamma activity occurs, which in turn increases the synchronicity and the recruitment from adjacent brain areas. Under normal conditions this pathological signal is filtered out by inhibitory feedback signals from the limbic system[25]. If these filter mechanisms fail, the misinformation reaches the consciousness and is misinterpreted as tinnitus[21].

Recent studies found a correlation not in the gamma, but slow wave delta band activity and, while confirming the TCD model, suggest that delta waves might be a better correlate for tinnitus[26].

However, this correlation is not maintained when the tinnitus is subjected to modulations by acoustic stimulation. Residual stimulation is the process by which the perceived loudness of the tinnitus is increased after a certain acoustic stimulus. Residual inhibition, on the other hand, describes a phenomenon in which the tinnitus is temporarily suppressed after being masked by an acoustic stimulus. The delta and gamma bands that appear to correlate with the tinnitus are suppressed when exposed to residual inhibition. However, during residual excitation, where the perceived tinnitus is amplified, the delta waves appear to remain unchanged while the gamma band is reduced. Neither of them can therefore correlate with the tinnitus phenomenon alone[27].

1.2.2 Neural synchrony models

Other examples for central changes associated with hearing loss and tinnitus are shifts in the balance of excitation and inhibition in the auditory cortical regions[28], increased synchronous activity[15,29] and increased neuronal bursts in these areas[30]. Tonotopic map reorganization of the affected regions of the auditory cortex have been observed in animals models[31], as well as in normal-hearing subjects experiencing chronic tinnitus [32].

It has been known since the 1960s that some cells in the brains of mammals are active even when the organism is in a resting phase or when synaptic transmission to the cell is interrupted. This cellular activity emanating from the cell itself has been called "spontaneous firing"[33]. In the course of time it became increasingly clear that these cellular self-activities are no exception, but rather encode synaptic input in a whole range of neuronal plasticity. It has been found that these cells fire specifically at a certain frequency and that changing this rate can have various effects on the neuronal pathway the corresponding cell is a part of. Increased firing rates have been shown in tinnitus patients in brain areas associated with the central auditory pathway[34].

Regarding the spontaneous firing rates (SFR) it is noteworthy that even though people experience tinnitus right after an acoustic trauma, the SFRs take hours to increase in the auditory cortex and even days to increase in the dorsal cochlear nucleus (DCN)[9,35] so they can not solely explain the tinnitus phenomenon. DCN hyperactivity itself might also cause VCN hyperactivity and vice versa[19].

Filling in models try to explain tinnitus by the reduced subcortical input reaching the auditory cortex which is compensated by neural information gathered by adjacent cortex areas or auditory memory engrams[36,37].

1.2.3 Global workspace model

It is still unclear whether each tinnitus results from the same pathomechanism. The *Global Workspace model* describes chronic tinnitus as an interplay of different subnetworks that each encode specific aspects of tinnitus perception, such as lateralization, volume perception, level of distress, etc. The neuronal communication between these subnetworks takes place in certain brain areas, which have their parts in multiple subnetworks simultaneously. In this model, too, a disturbed inhibition mechanism, similar to top-down regulation, is described in order to bring these pathological signals into consciousness [8,38,39].

1.2.4 Central models summary

There are a number of theoretical neural models that describe the origin and pathomechanism of tinnitus at the levels of the sensory organ, the auditory pathway and the higher cognitive brain centers (Figure 1). However, none of these models alone, or in combination with other models, can explain all the data collected to date in relation to Tinnitus research. Furthermore, many of these models are mutually exclusive. For example, the central gain model describes increased ascending activity in the brainstem, while the TSD-model describes the hyperpolarization of the thalamus by reduced activity in the brainstem[1].

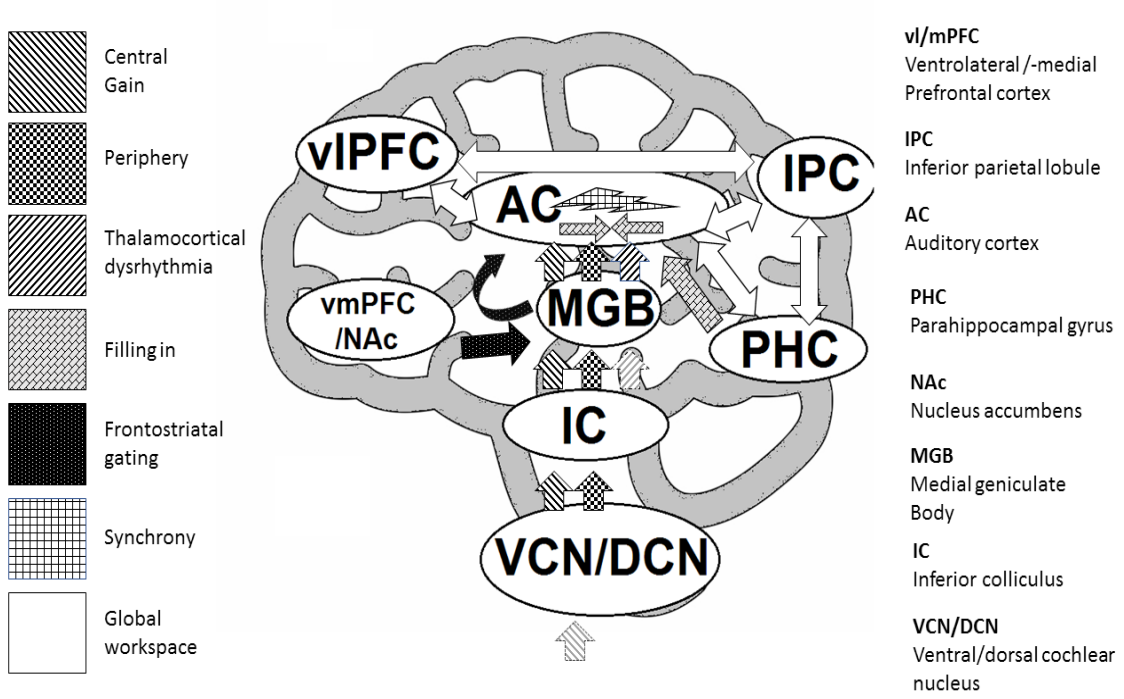

Figure 1: Schematic of currently proposed pathological pathways of tinnitus generation. The arrows show neuronal amplification between the different brain areas, while the transparent arrows symbolize downregulation[1]. Picture is adopted from Sedley et. al. (2016)[1].

1.3 Cochlear synaptopathy

1.3.1 Cochlear synaptopathy in the animal model

Between 2006 and 2009 Kujawa and Liberman raised attention by identifying noise induced permanent neuronal pathologies (dubbed "synaptopathy") with congruent decreases in Wave I amplitudes after recovery of temporary threshold shifts (TTS) in animal models. The induced noise trauma exposure relied on sound levels of 100 dB at 2 hours duration[40,41,42]. This pathology has been traced to the loss of ribbon synapses in inner hair cells[43] as well as afferent fibers without loss of inner hair cells itself[41].Initially observed in mice, these findings were confirmed in guinea pigs[44] and primates even though primates seem to have a higher resilience to noise induced hair cell and neuronal damage[45]. Fernandez et al. (2015) reported that the noise trauma must be severe to be synaptopathic. They showed no changes in wave I amplitudes or in the number of ribbon synapses in mice with exposure sound levels of 91 dB for 2 hours compared to a control group, suggesting that not all noise traumas with TTS trigger synaptopathy. However, the same study showed that the severity of TTS does not necessarily predict the amount of synapse

loss and thus the extent of synaptopathy suggesting that the configuration of the TTS (tilt and/or notching) may also play a role[46].

1.3.2 Cochlear synaptopathy in humans

Degeneration of auditory nerve fibers due to the progress of age as well as a decline in spinal ganglion cells and hair cells[47] have been confirmed in post mortem human tissue samples of the auditory system[48,49]. Noise damage seems to accelerate this age related degeneration[40]. The same age related progression of synaptic loss has been demonstrated in animal models[49] so the assumption can be made that the animal model at least in part can be transferred to human physiology. However, since we cannot gather human tissue samples right after acoustic trauma, we have to rely on indirect measurements in order to confirm noise induced synaptopathy in the human ear. Based on the initial results of Kujawa and Liberman (2006), the measurement of auditory brainstem responses seems to be the non-invasive method of choice for the detection of synaptopathy[13].

The “failure to mobilize ARC ” meaning the failure of the organism to adapt to reduced cochlear input at the auditory pathways via activity-regulated cytoskeleton-associated protein, has been linked to severe ribbon loss as well as reduced auditory brainstem responses and tinnitus and could explain the pathophysiological connection of synaptopathy[50].

1.3.3 Linking synaptopathy to tinnitus via auditory brainstem responses

In 2011, Schaette et al. compared auditory brainstem responses with reduced Wave I amplitudes in a group of female subjects suffering from tinnitus without hearing loss, to a control group without tinnitus[18]. These findings were explained by the tinnitus model of central gain[9] and homeostatic plasticity[51] as a result of cochlear synaptopathy, eventually coining the term “hidden hearing loss”.

There are numerous studies that deal with the genesis of tinnitus when its origin is due to a hearing loss caused by noise trauma. However, chronic tinnitus can also occur without correlated noise trauma and the affected person may have normal-hearing without evidence of hearing loss. Studies that try to explain this phenomenon are still relatively sparse and the best evidence so far is the explanation by synaptopathy.

1.4 Gender difference in auditory brainstem responses

Since the discovery of ABR, gender-specific differences have been detected very soon after. These differences concern the shorter latency time, as well as the higher amplitudes

of wave III and V in women. In the 1990s, this difference was primarily attributed to the smaller head circumference in women. In theory this led to a faster signal conversion (latency) and higher amplitudes because the potentials had to travel less distance to the measuring electrode. Head circumference alone could not explain this difference. Differences in the measurements between pre- and postmenopausal women gave evidence for a hormonal genesis of the different measurement results[52]. Through better measurement methods and the possibility of imaging, new physiological correlates have been discovered over time that could lead to a gender-specific difference in ABR. These include morphological differences in the cochlea, compliance of the basilar membranes, differences in efferent modulation and, most importantly, varying degrees of activity along the central auditory pathway and its associated brain areas during the processing of sounds. Krizman et al. (2012) demonstrated sex differences in the encoding of the fast, but not the slow elements of speech, with females having significantly faster and larger magnitude responses to only the transient aspects of the stimulus compared to males. Regarding gender differences in ABR, the authors concluded that women had an average 32% higher amplitude of wave V detectable[53]. The amplitude of wave I however remained without statistically difference.

1.5 Hypotheses and Study goal

The aim of the present study is to determine whether there is audiologically measurable irregularity in normal-hearing tinnitus patients compared with a normal-hearing control group. For this purpose, parameters describing "normal-hearing" were developed and consecutively it was tested whether extended and more precise measurement methods can detect hearing losses that escape standard clinical diagnostics such as manual pure-tone audiometry. Synaptopathy is one of the mechanisms that is currently most likely to explain the tinnitus phenomenon in people with normal-hearing. The current data from other study groups supporting synaptopathy is still inhomogeneous and inconclusive, so that attempts were made to reproduce the results via auditory brainstem responses (ABR), which may point to synaptopathy as the origin of tinnitus. Furthermore, DPOAEs and Békésy sliding audiometry results were analyzed in detail to identify possible abnormalities that might be associated with the tinnitus phenomenon.

2 Material and Methods

2.1 Recruitment of normal-hearing test subjects

Subject recruitment was carried out via a wide selection of advertisements including hangouts, information flyer, a website and web presences in social networks. Inclusion criteria were an ongoing Tinnitus (> 6 months), age between 18 and 40, the absence of injuries or chronic diseases of the inner or outer ear, as well as no current medication with known ototoxic properties. As outlined in section 1.4, Gender differences in ABR amplitudes (mainly wave III and V) were not considered because differences in wave I amplitudes are not related to gender[53]. With this in mind, men and women were recruited equally for this study.

2.2 Screening of subjects

To create a cohort of normal-hearing subjects, clinical manual pure-tone audiometry was used for screening. Schaette and Mc Alpine (2011) applied a hearing threshold of 20 dB HL to define normal-hearing in their subjects. The choice of the threshold level is based on the common literature that examines normal-hearing and places the hearing thresholds for inclusion criteria between 20- and 30-dB HL. In the present study, the allowed hearing threshold was set at 10 dB HL including a single permitted exception of one frequency threshold of up to 15 dB HL. The inclusion criteria are therefore stricter than those of any other study dealing with the same subject.

All subjects underwent otoscope examinations of the outer ear (Piccolight F. O. KaWe, Asperg, Germany), as well as tympanometry (Tympstar, GSI, William Demant Holding, Smørum, Denmark). A Rinne- and Weber test was conducted with each participant. Air conduction hearing thresholds were assessed by means of manual pure-tone audiometry (Test frequencies: 0.125 kHz, 0.25 kHz, 0.5 kHz, 0.75 kHz, 1 kHz, 1.5 kHz, 2 kHz, 3 kHz, 4 kHz, 6 kHz, 8 kHz, audiometer Audiomaster CA 540/1, Hortmann AG, Bavaria, Germany, HDA200 headphones Sennheiser, Wedemark, Germany, MedAkustik 99 V3.2.11, audiometer program database, custom application). The audiograms were screened and candidates were included when the criteria defined above was met. Overall, only one third of the tested candidates passed the hearing threshold criteria.

2.3 Selected subjects

After screening, 29 normal-hearing adults serving as subjects were recruited, 15 suffering from tinnitus (Tinnitus group TG) and the other 14 serving as a control group (CG),

without a history of tinnitus. The test groups are composed of relatively young adults, the mean age being in the mid-twenties. Older subjects tended to show hearing impairments in the high frequency spectrum of PTA11 and therefore failed to meet the inclusion criteria. There are more female test subjects in the Tinnitus group and vice versa. The overall hearing capacity was determined by adding the average threshold value of each test frequency. Age, gender distribution and overall hearing capacity showed no statistical difference between the two test groups.

Unfortunately, there was a loss of data during the course of the study, so that some of the measurements were irretrievably lost. As a result of this incident, mainly data from the DPOAE measurements and the ABR is missing. (residual number of cases DPOAE: TG, $N = 10$; CG, $N = 12$, residual number of cases ABR: TG, $N = 12$; CG, $N = 13$).

Table 1: Descriptive statistics and statistical comparison (mean and standard deviation) for tinnitus group (TG) and control group (CG). Sum of PTA11 threshold (pure-tone audiometry with eleven fixed test frequencies between 0.125 kHz and 8 kHz). *P*-Value for independent samples after Levene-test for variance homogeneity.

	TG	**CG**	***p***	**Test**
n	15	14		
male/female	4/11	10/4	0.26	Fisher
age	25.2±3.7	27.1±2,7	0.14	t-test
PTA11 [dB HL]	18.0±26	21.4±21.7	0.71	t-test

2.4 Pure-tone manual audiometry

Pure-tone manual audiometry was performed for each subject and each ear individually to ensure that the hearing threshold was within the study's inclusion criteria. The subject was exposed to sounds of different frequencies in one ear through headphones, while the opposite ear was masked by a noise signal. The volume for each frequency was increased in 5 dB HL steps and the subject pressed a signal button when he heard the sound. The test frequencies (see above) were tested several times, but at least twice, to determine an accurate threshold value.

2.5 Fine structure audiometry

To assess the individual fine-structure of the hearing threshold, Békésy audiometry was applied sweeping between 0.02 kHz and 16 kHz consisting of 794 logarithmically scaled frequency steps. A DT48KH headphone (Beyerdynamic, Heilbronn, Germany) connected

to an amplifier (HD53R, CEC, Saitama, Japan) served as a transducer. Customized MATLAB (MathWorks, 7.3.0) software provided by Prof. Bernhard Seeber, Technical University Munich, was applied for conduction of the test. The calibration was controlled prior to each measurement.

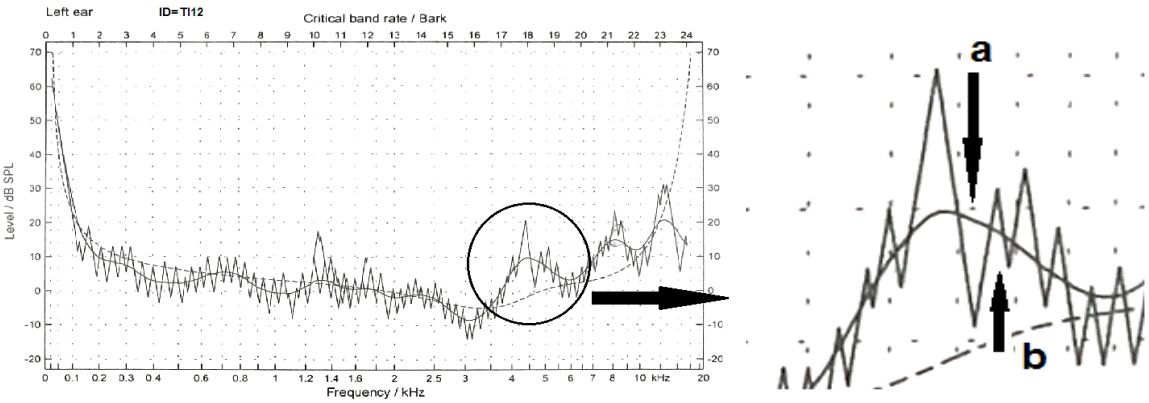

Figure 2 Left: Example of Békésy sliding audiometry, obtained from subject TI 12-L. Dotted line: normal-hearing threshold (ISO 226:2003). Continuous line: smoothed average threshold.

Right: Zoomed region between 4 – 6 kHz. (a) Level decreases as the subject presses the button to indicate perception. (b) Level increases as the subject is not responding by pressing the control button.

2.6 Distortion-product otoacoustic emissions

Outer hair cell integrity was assessed via DPOAE-Diagnostics (Eclipse, OtoAccess 1.2.1, Interacoustics, Middelfart, Denmark. Frequency-ratio: $fdp = 2x\,f1 - f2$, stimulus level; L1=65 dB, L2= 60 dB.) Stimuli were provided in a 1 kHz-8 kHz range with 35 different presentations.

The sound levels of the Distortion products (L_{DP}) as well as the Signal-Noise ratio (L_{SNR}) was determined at 36 single discrete frequencies ranging between 1 kHz - 8 kHz for both study groups.

2.7 Auditory brainstem responses

Auditory brain stem responses (ABR) were recorded using an Eclipse device. (Interacoustic, Middelfart, Denmark with OtoAccess 1.2.1). Level of Stimuli were 75 dB nHL and 85 dB nHL, click-stimulus 50 µs pulse duration, repetition rate 11 clicks/sec, bandpass filter setting 100-1500 Hz, stimuli presented with insertion headphones (E.A.R. Tone 3A, 3M, Neuss, Germany). At least 8000 repetitions with test level 75 dB nHL were averaged and at least 6000 repetitions with a test level of 85 dB nHL were measured to minimize

residual noise. Disposable electrodes were applied on the left and right mastoid and the forehead of the subjects. The impedances were controlled to stay below < 2 kΩ. In order to maintain a preferably clear judgement of brainstem potentials the measured FMP-ratio had to be above the value of 3.1. FMP is a value used for response quality of the ABR recording representing a statistical confidence of a true detection of a response. Basically, The FMP value describes the ratio between the response amplitude and the residual noise. The residual noise is decreased by increasing the number of sweeps. As the number of sweeps increases, the variability decreases and the noise is "averaged away". A FMP value >3.1 correlates with > 99% true responses and acts as a quality meter for the ABR waveform[54]. The resulting curves were printed out and the amplitude value was determined visually with manual measurement.

2.8 Tinnitus assessment

Tinnitus was determined with the method of adjustment[55]. The subject adjusted his tinnitus frequency with pure-tone frequencies (range 0.125 kHz-8 kHz) by responding with "higher" and "lower" while presenting pure-tone frequencies from one side of the spectrum to the other (125 Hz-8 kHz→250 Hz-6 kHz etc.) until the most appropriate frequency was narrowed down. The procedure was repeated up to seven times per subject, if match inconsistencies were present. A visual analog scale (VAS) was used to determine individual subjective loudness and the degree of discomfort related to tinnitus. The VAS appears as a line with the starting point marked with "0 %" and represents the absence of possible perception or worst imaginable stress. The marked position on the VAS is expressed as a percentage (Figure 3)[3].

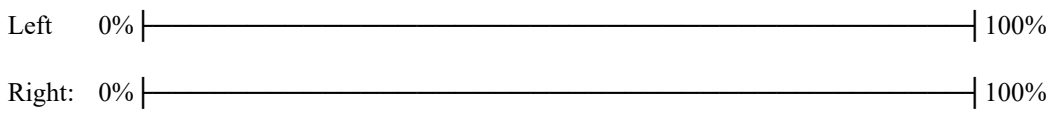

Figure 3: Example of the visual analog scale used to determine the subjective loudness and level of disturbance for each ear individually.

In addition, sound quality of the tinnitus was assessed by using a list of common classifications (Table 2)[56].

Table 2: Questionnaire used to determine the quality of tinnitus sensation for each ear individually.

Quality of tinnitus:	Left	Right
Humming		
Squeaking (chalk on blackboard)		
Whirling (noise of a fan)		
Sea waves		
Whistling		
Clicks		
Running water		
Cricket		
Beating heart		
Steam boiler (escape of steam)		
Waterfall		
bell		
Roaring of a lion		
Air leakage from a car tire		
Sizzling fat		
Sanding (sandpaper on wood)		
Sanding (sandpaper on metal)		
Other		

2.9 Statistical methods

The statistical evaluations were carried out by inserting the data into a spreadsheet program (Excel 2016, Microsoft, Redmond, USA). The tables created there were then inserted into statistical software (SPSS 20, IBM, Armonk, USA). The data analysis was following an algorithm proposed by the Department of IT training of the ETH Zürich [57]. The statistical analysis was carried out depending on whether differences or correlations were to be looked for. For differences, when testing 2 variables, a *t*-test was used if the homogeneity of variances had been determined by a Levene-test. This procedure was chosen if the dependent variable intervals were scaled and normally distributed, tested via the Shapiro-Wilk-test. Failure for normal distribution or homogeneity of variances resulted in the use of the Mann-Whitney-*U*-test (MWU). For ordinally or nominally scaled dependent variables, the central tendency was also tested using the Mann-Whitney-*U*-test.

Depending on the type of scaling of the dependent variable, possible correlations were tested using the Bravais-Pearson method (interval-scaled), Spearman's rank correlation

coefficient or Spearman's ρ (ordinal-scaled) or the Pearson chi² test (nominal-scaled $n > 20$). If the sample size is less than 20, the exact test according to Fischer was used. Again, the interval scaled samples were tested for variance homogeneity by Levene-test and for normal distribution via Shapiro-Wilk-test. The Null hypothesis H_0 was rejected when a p-value of < 0.05 was reached.

3 Results

3.1 Tinnitus assessment

To understand tinnitus as a symptom it is necessary to categorise it different aspects. For this purpose, subjective frequency and loudness of the tinnitus, as well as the quality and side of perception (localization) with the corresponding level of disturbance was evaluated for each subject of the TG. The majority (12 out of 15) of the test subjects experience the tinnitus as a "whistling sound". 7 out of 15 subjects perceive the tinnitus equally loud on both sides, while 8 out of 15 perceive the tinnitus increased on one side. The perceived frequencies range from 1-16 kHz. The level of disturbance ranges from 5%- to 80% of maximal conceivable discomfort (Table 3).

Table 3: Tinnitus group (TG), descriptive statistic details on tinnitus location, quality and level of disturbance. Localization, quality and subjective level of disturbance (Dist-L, Dist-R) were identified via visual analog scale and questionnaires. The matching frequency, loudness and side of the tinnitus were measured via pure-tone audiometry (PTA 11 with method of adjustment). ID = Subject ID.

ID	Localisation	Quality	f [kHz]	L [dB HL]	Dist-L [%]	Dist-R [%]
TG1	L>R	whistle	1	25	24	23
TG2	R>L	whistle	16	10	5	5
TG3	R=L	whirl	6	10	70	70
TG4	R>L	whistle	4	25	31	48
TG5	R=L	whistle	6	20	30	36
TG6	R=L	whistle	8	10	17	17
TG7	R=L	whistle	9	5	42	42
TG8	L	whistle	6	5	27	0
TG9	R>L	whistle	3	5	2	2
TG10	R=L	whistle	8	10	5	5
TG11	L>R	whistle	2	5	82	17
TG12	R=L	waterfall	8	20	27	27
TG13	L>R	whistle	1.5	15	48	10
TG14	R=L	sanding	12.5	15	58	58
TG15	L	whistle	3	10	48	17
Descriptive statistics						
Mean			6.27	12.67	34.37	25.30
SD			4.05	6.80	22.85	20.71
Min/Max			1/16	5/25	2/82	0/70

3.2 Pure-tone manual audiometry

Pure tone audiometry is the standard procedure for determining individual hearing thresholds. In the course of the screening, this procedure was chosen to obtain a group of normal-hearing test subjects. The individual pure-tone manual audiometry results of all subjects are listed in the appendix (XI).

Figure 4 shows the averaged hearing threshold for each test frequency calculated for both study groups. Hearing thresholds are almost identical in both groups. Only in the high

frequency range (8 kHz) there seems to be a larger difference, but this difference remains without statistical significance (8 kHz, left ear TG/CG, $p = 0.637$; 8 kHz right ear TG/CG, $p = 0.118$; t-test after Levene-test) The dotted line at 15 dB HL depicts the threshold boarder above which the subject would not have been included in the study. In accordance with the current inclusion criteria, all subjects had normal-hearing and there was no significant difference in average hearing threshold between the two test groups.

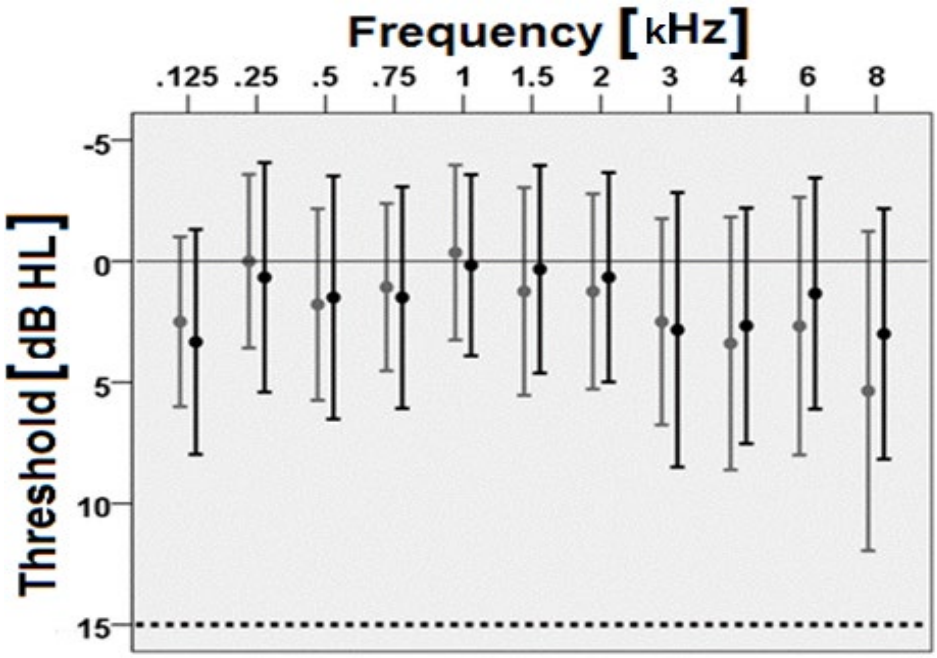

Figure 4: Average pure-tone audiometry results, tinnitus (black) and control group (grey). Whiskers show the standard deviation. TG: $n = 15$ CG: $n = 14$. Dotted line: Threshold boarder for study inclusion. Mean value of sum of threshold values between TG and CG p = 0.711; t-test after Levene-test.

The sensation of tinnitus is experienced in different ways. It differs in perceived frequency, loudness and subjective distress. An attempt was made to correlate these parameters with the PTA11 data. The individual hearing impairment calculated from the sum of all 11 threshold values for each ear individually as well as together, was determined. These results were correlated with tinnitus characteristics such as frequency, loudness and subjective distress. The tests were based on the following questions: 1.: *Does the perceived tinnitus loudness correlate with the overall hearing capacity* (hypothesis: the better/worse the hearing, the louder the Tinnitus)? 2.: *Does the perceived tinnitus frequency correlate with the overall hearing capacity* (hypothesis: the better/worse the hearing, the higher, lower the tinnitus pitch)? 3.: *Does the overall hearing capacity correlate*

with the level of disturbance (hypothesis: the better/worse hearing, the better worse the level of discomfort)?

The mentioned tinnitus parameters were also tested for correlation with the hearing impairment value of difference between right and the left side. The results are shown in Table 4. No significant correlation between PTA11 data and tinnitus parameters was observed.

Table 4: Correlation between manual pure-tone audiometry results and tinnitus parameters: PTA11 for each ear individually (PTA11-L, PTA11-R), averaged threshold (sum of PTA11-L and PTA11-R divided by 2) and threshold value of difference between both sides (ΔL/ R = PTA11-L - PTA11-R), checked for difference between groups (TG vs CG), Levene-test for variance homogeneity. Numbers: level of significance (*p*-value). (TMF = tinnitus matching frequency [kHz]; TML = tinnitus matching loudness [dB HL]; VAS=visual analog scale for subjective disturbance [%]). Statistical test explained in Chapter 2.9)

	TG vs CG	TMF	TML	VAS-L	VAS-R
PTA11-L	.925	.803	.502	.566	.622
PTA11-R	.413	.803	.984	.478	.531
$\frac{\mathbf{PTA11-L+PTA11-R}}{\mathbf{2}}$	.711	.771	.411	.460	.551
Δ L/R	.665	.568	.829	.617	.526
Statistical test for correlation	**ANOVA**	**Pearson's *r***		**Spearman's Rho**	

3.3 Fine-structure audiometry

Fine structure audiometry was used to obtain more accurate hearing thresholds in order to detect differences in the test groups. Furthermore, it was important to find out to what extent hearing impairments could be unmasked that could not be depicted in pure tone audiometry. Figure 5 shows the averaged fine-structure hearing threshold curves of both test groups derived from the averaged values of each of the 794 individual test frequencies. For the purpose of clarity, standard deviation is depicted separately. It can be observed that small hearing threshold deviations occur in 3 different frequency regions in the range 1-2 kHz, 2.5-4 kHz and 5-8 kHz. These sections were examined separately and the data is presented in Table 5. All frequencies in those areas where tested for statistically significant differences. The frequencies at which significant difference begins

($p < 0.05$) reaches greatest difference (smallest p-value) and ends (shift from $p < 0.05$ to $p \geq 0.05$) where determined and represented in Table 5.

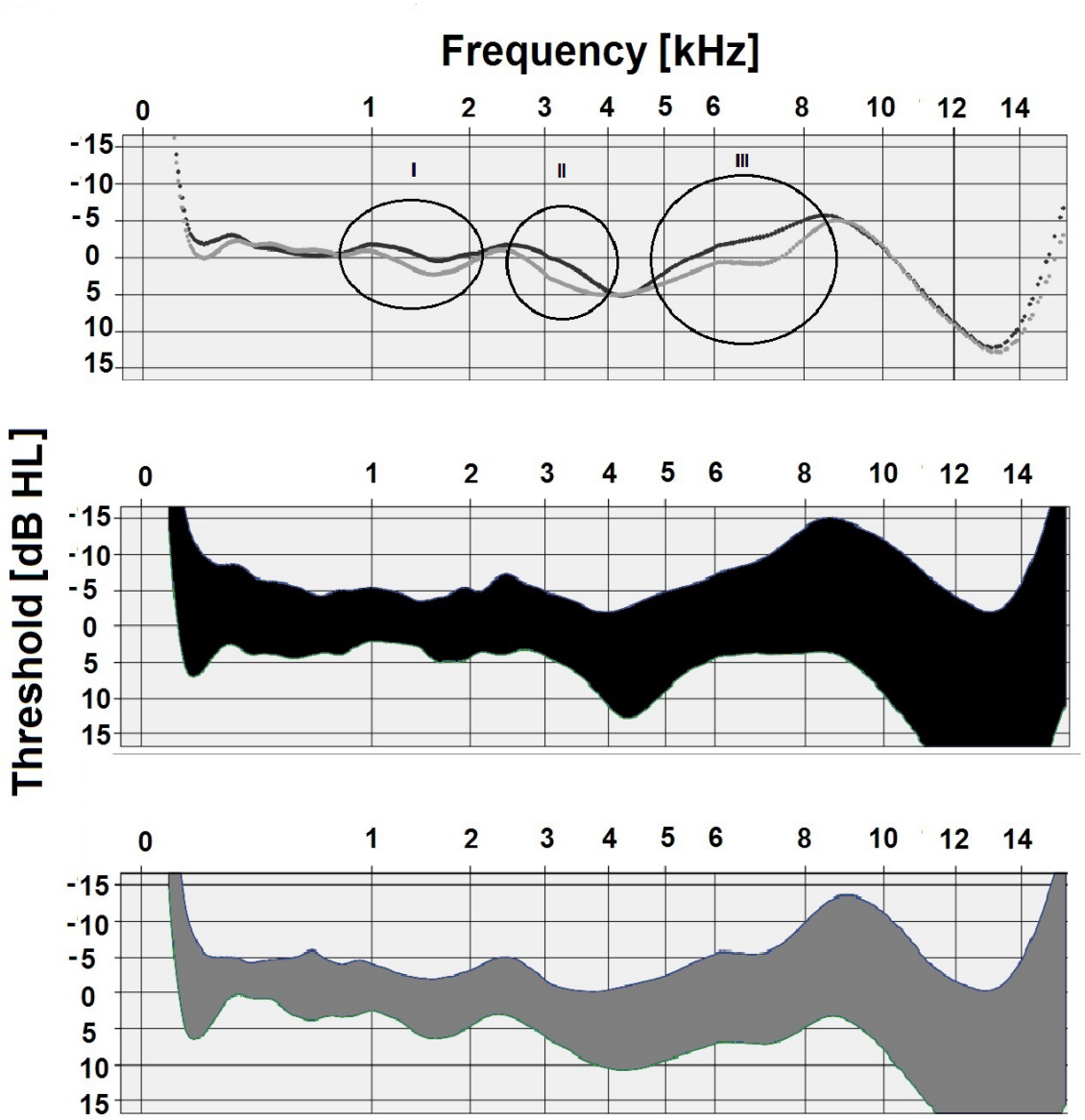

Figure 5: Top: Mean fine-structure hearing threshold for tinnitus group (black) and control group (grey) Sections of deviations are circled and marked with roman numeral's I-III. Mid and Bottom: Standard deviation. Tinnitus group (black), control group (grey).

Table 5: Descriptive statistics (mean and standard deviation) as well as statistical analysis of the frequency ranges I-III from Figure 5. Areas I-III described by the first frequency with CG/TG difference $p < 0.05$, frequency with lowest p-value, and last frequency with $p < 0.05$. The test for variance homogeneity was performed using the Levene-test. Shapiro-Wilk-test for normal distribution.

Frequency [Hz]	Study Group	mean [dB HL]	SD [dB HL]	*T*-value	Levene Test *p*-value	t-test *p*-value
I						
1177	CG	-0.14	3.27	-2.00	0.352	0.049
	TI	1.67	3.64			
1433	CG	-1.85	3.97	-2.69	0.637	0.009
	TI	0.68	3.32			
1569	CG	-2.26	4.19	-2.04	0.415	0.046
	TI	-0.04	4.21			
II						
2941	CG	-1.70	4.01	-2.03	0.403	0.047
	TI	0.54	4.49			
3169	CG	-3.15	4.05	-2.34	0.226	0.023
	TI	-0.49	4.64			
3453	CG	-4.18	4.49	-2.02	0.426	0.048
	TI	-1.72	4.92			
III						
6760	CG	-0.88	6.32	-2.03	0.933	0.047
	TI	2.36	6.06			
7103	CG	-0.88	6.45	-2.23	0.742	0.030
	TI	2.89	6.58			
7554	CG	0.56	6.86	-2.01	0.422	0.049
	TI	4.36	7.69			

df = 58

3.3.1 Links between threshold morphology and tinnitus

The Békésy fine structure analysis with its 794 individual test frequencies creates a very individual threshold curve for each individual test person. Several statistical tests were carried out to investigate whether there are morphological similarities of the tinnitus curves that may show correlations with tinnitus loudness (TML), tinnitus frequency (TMF) or tinnitus level of disturbance (VAS-L, VAS-R). The fine structure audiometry curve shows dips with different morphological expressions. The largest dip was visually identified and its corresponding amplitude of hearing loss (variable = *a @max HL*) and matching frequency (variable = *f @max HL*) was determined. The steepness of the slope of the steepest dip, which was not necessarily the largest dip, was also measured (*max slope*). In addition, the frequency of the beginning of the steepest dip (*f-begin*), the frequency of the end (*f-end*) and the frequency range between the beginning and the end (*f-range =f-begin-f-end*) was determined. The overall goal was to investigate whether hearing loss regions with steep slopes or large dips do correlate with tinnitus qualities. An example is shown in Figure 6.

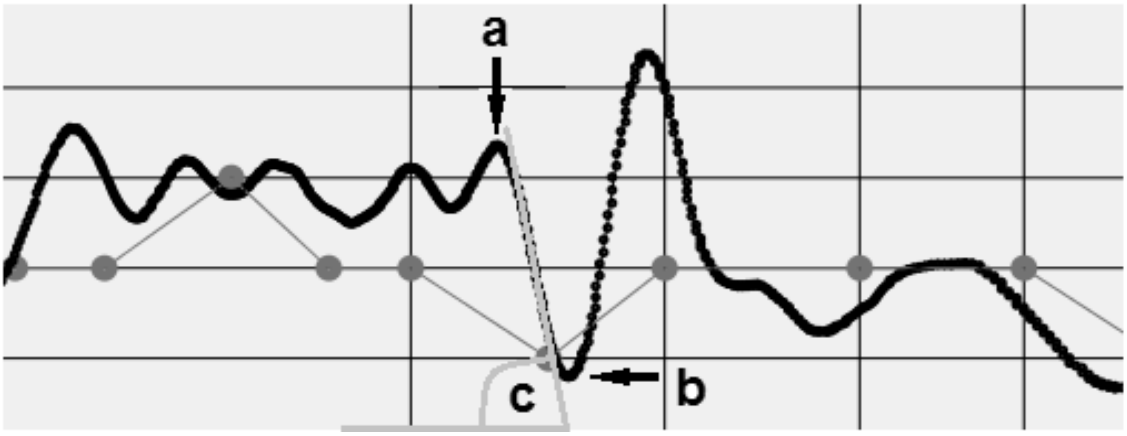

Figure 6: Example of Békésy analysis “steepest hearing loss”. a: Starting frequency (*f-begin)* b: Ending frequency (*f-end*) Range defined as range of frequency between a and b. Slope steepness as angle (c)

In addition, the number of individual dips (variable = *num.dips*) was determined. A dip was defined as any dipping of the threshold curve that exceeds a hearing loss amplitude of 2.5 dB HL. Depending on the number of dips some threshold curves have many dips and appear oscillating, others are rather flat in appearance (see appendix: Békésy audiograms). The question was whether or not a flat or oscillating hearing curve correlates with the perceived loudness, frequency or discomfort of tinnitus. Results are listed in Table 6.

Table 6: Derived parameters from Békésy audiometry of tinnitus subjects: frequency and amplitude of maximal hearing loss (*f@max HL, a@max HL*) and number of dips (see text). Tinnitus characteristics (TMF: tinnitus matching frequency [kHz]; TML: tinnitus matching loudness [dB HL]; VAS: visual analog scale for subjective tinnitus disturbance [%]) were tested for correlation with "steepest" hearing loss measured in Békésy audiometry for each ears slope, angle, start frequency and its ending frequency and a-b range (see Figure 6) Numbers = *p*-value.

	TMF	**TML**	**VAS-L**	**VAS-R**
f@max HL	.032*	.254	.664	.826
a@max HL	.951	.374	.868	.456
num.dips-L	.391	.349	.938	.778
num dips-R	.242	.312	.807	.504
Max-slope Steepness-L (°)	.301	.546	.994	.604
Max-slope Steepness-R (°)	.917	.417	.439	.511
f-begin@max slope-L	.707	.319	.532	.32
f-begin@max slope-R	.617	.602	.229	.542
f-range@max slope-L	.815	.386	.263	.346
f-range@max slope-R	.204	.613	.463	.765
f-end@max slope-L	.728	.318	.472	.403
f-end@max slope-R	.409	.573	.444	.958
Statistical test for correlation	**Pearson's**		**Spearman's**	

Neither slope steepness nor flanking start and end points of dips correlate significantly with any tinnitus characteristic. An exception is the frequency at the peak of the largest dip, which is mildly correlated with the corresponding matching frequency of the tinnitus (TMF) ($r = 0.554$).

3.4 Comparison of clinical manual pure-tone and fine-structure (Békésy) audiometry results

One of the hypotheses of the present study states that a fine structure measurement of a person's hearing can detect hearing damage that would remain hidden from conventional pure-tone audiometry. Due to the extended frequency range of the test, the inclusion criteria may also be violated.

Regarding hearing loss in the higher frequencies, 9 test subjects showed thresholds higher than the inclusion criteria of 15 dB HL above 8 kHz (TG: $N = 4$, CG: $N = 5$). Related to the higher frequency resolution of the fine-structure audiometry, 4 test subjects showed thresholds of more than 15 dB HL in between manual pure-tone audiometry test frequencies (TG: $N = 1$, CG: $N = 3$).

In terms of the pure-tone audiogram inclusion criteria of the present study, 12 out of 29 subjects would have been excluded if Békésy audiometry was used instead of manual audiometry. 9 subjects would have been excluded because hearing losses were above 15 dB HL in the extended frequency range above 8 kHz (TG: $N = 4$, CG: $N = 5$), and 3 (TG: N=1, CG: $N = 2$) would have been excluded because of hearing losses within the range of pure-tone audiometry (0.125kHz-8 kHz). Examples are depicted in Figure 7.

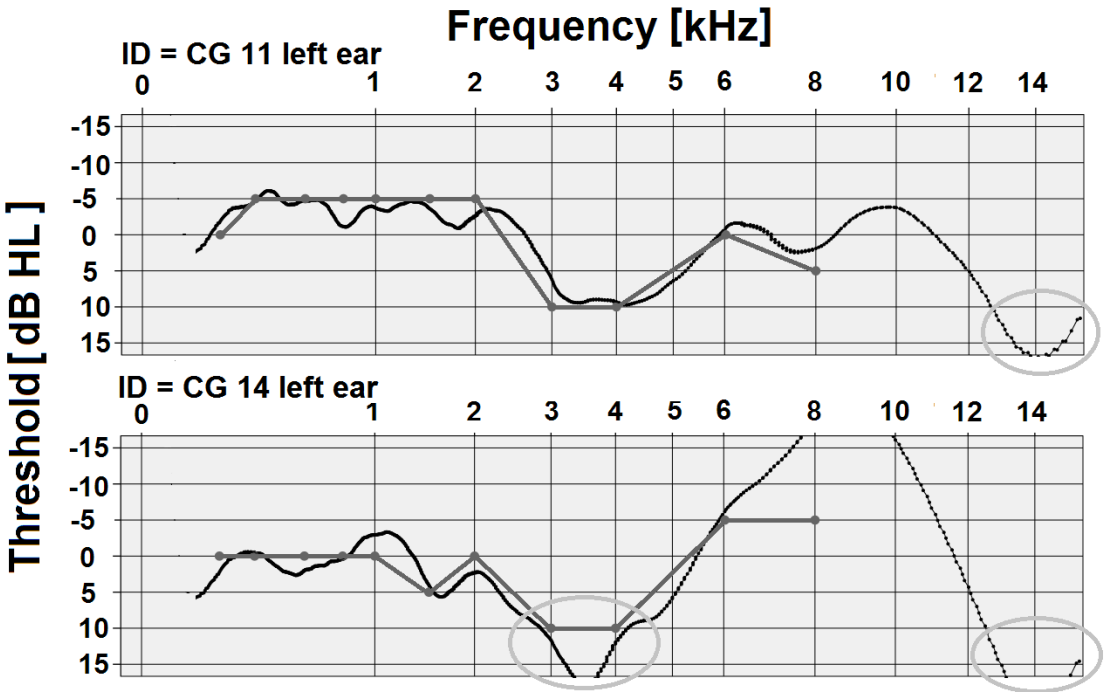

Figure 7: Examples of Békésy audiometry smoothed average converted to dB HL (black) in relation to corresponding manual pure-tone audiometry results (PTA11, grey). Top: Subject CG 11 (left ear) with nearly similar results. Bottom: Subject CG 14 (left ear) demonstrating a narrow hearing loss dip between 3 and 4 kHz. Circled areas: deviation from inclusion criteria.

3.5 Distortion-product otoacoustic emissions

3.5.1 Study group comparison

The sound pressure levels of the distortion-products (L_{DP}) as well as the signal-to-noise ratio (L_{SNR}) was determined at 36 single discrete frequencies ranging between 1 kHz and 8 kHz for both study groups. The aim of the measurement was to examine the subjects for possible hearing impairment that was not registered in the initial screening by manual tone audiometry. Furthermore, potential differences in L_{DP} and L_{SNR} between groups should be tested for correlation with tinnitus subjects.

Figure 8 (top) displays average distortion-product signal and noise level for the respective study group, figure 8 (bottom) shows the signal-to-noise ratio (SNR). Comparing the mean of both ears of each study group there were no statistical differences comparing the level of distortion products and SNR. For statistical analysis the Mann-Whitney-*U*-Test was used since a few test frequencies failed the Levene-test for variance homogeneity. For those frequencies the degree of freedoms ranged from $df = 31$ to $df = 40$. For all other frequencies the freedom of degree was $df = 42$. All p-values were > 0.05, ranging from 0.139 to 0.960.

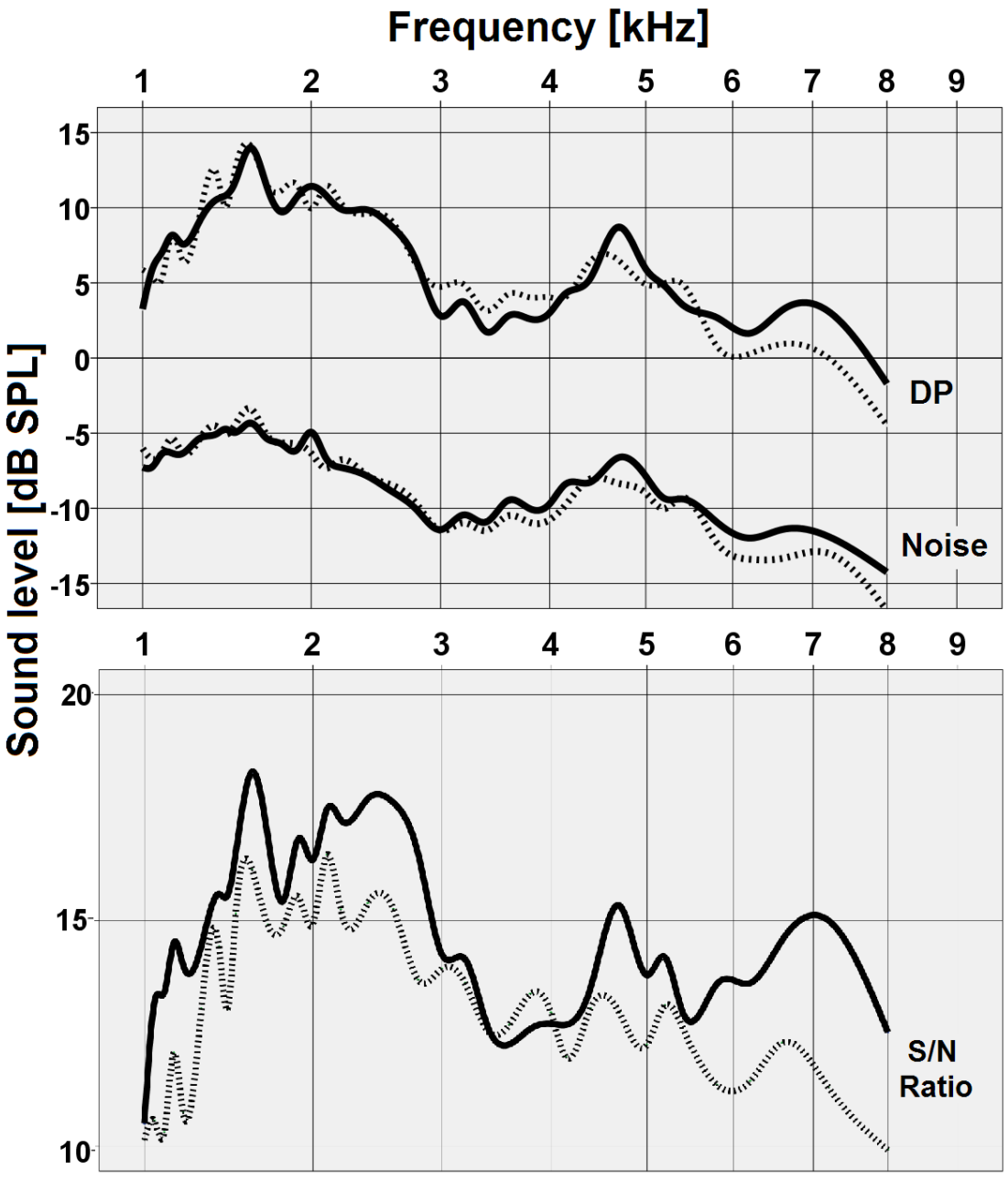

Figure 8: Top: Mean distortion-product sound pressure level (both ears averaged) and noise level, tinnitus group (continuous line), and control group (dashed line).

Bottom: Mean level of signal/noise ratio for tinnitus group (continuous line) and control group (dashed line). (TG, $N = 10$; CG, $N = 12$)

3.5.2 Subjects with side localized tinnitus

In the previous chapter, the measurements of distortion-products have been examined regardless of lateralization of tinnitus. In the following, we focus on data of the subjects who perceive their tinnitus completely or dominantly either in the left or the right ear and

compared them with control group DPOAE results. This analysis was carried out with the purpose of potentially isolating tinnitus related DPOAE result irregularities (Figure 9).

DPOAE results of subjects with tinnitus lateralization were extracted (N = 6 Subjects, TG 1, TG 8, TG 9, TG 11, TG 13, TG 15) and compared against the mean DP sound level values of the control group. The results are similar to those in the previous chapters. Again, the mean values of the test frequencies between the two test groups are almost identical. For statistical analysis the Mann-Whitney-U-Test was used for every single test frequency since a few test frequencies failed the Levene-test for variance homogeneity. For those frequencies the degree of freedoms ranged from df = 32 to df = 41. For all other frequencies the freedom of degree was df = 42 (all p-values >0.05, ranging from 0.459-0.966).

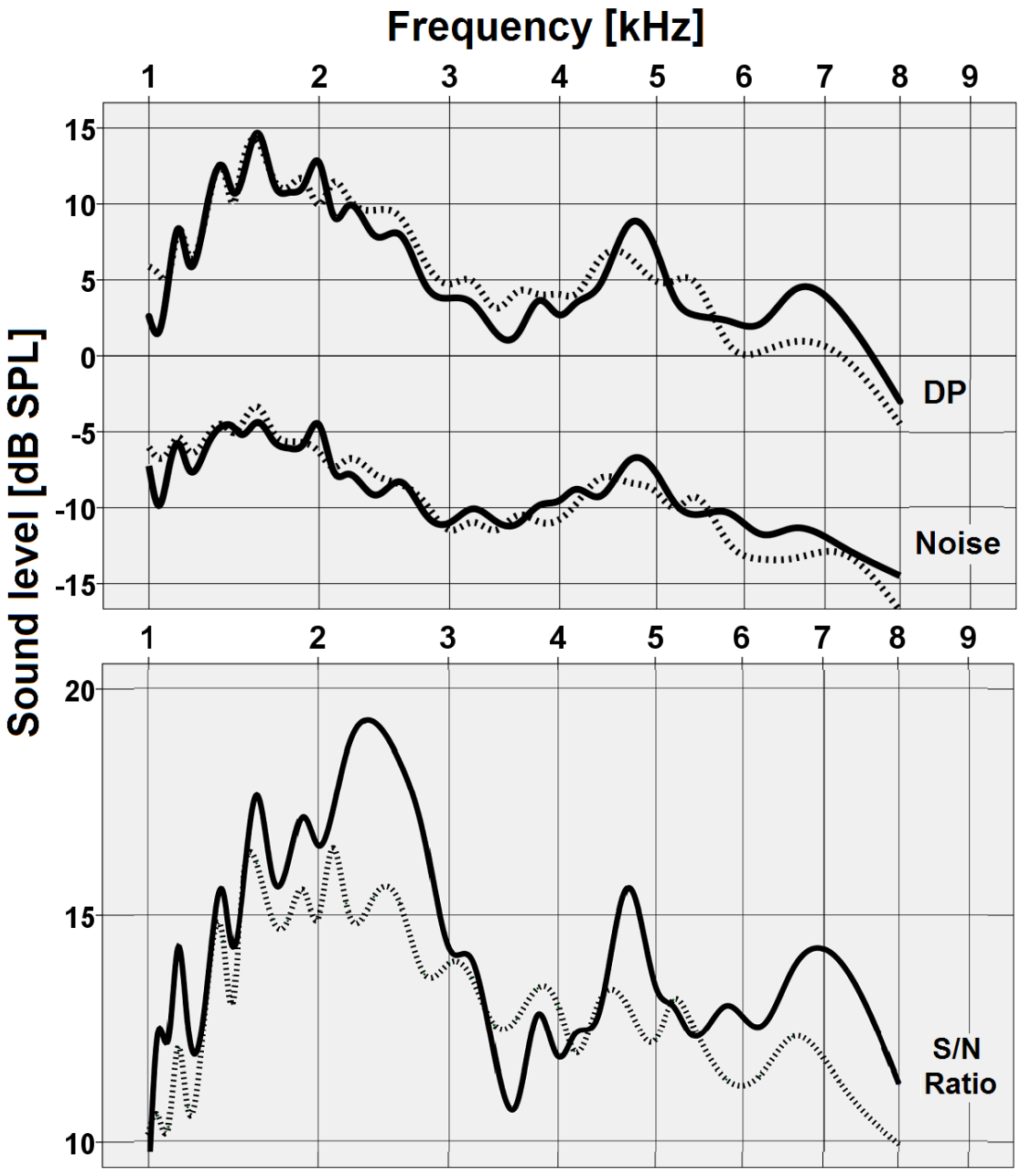

Figure 9: Top: Mean distortion-product sound pressure level (DP) and noise level for subjects with tinnitus-lateralization (continuous line) and control group (dashed line). Bottom: Mean level of signal/noise ratio for subjects with tinnitus lateralization (continuous line) and control group (dashed line). (TG, *N*=6; CG, *N*=12).

3.5.3 DPOAE results compared to Békésy sliding audiometry

With the Békésy audiometry and the DPOAE measurements there are two sets of data available that very accurately represent the hearing capacity and the function of outer hair

cells respectively. A comparison was sought to see whether the two measurement methods show differences between the two test groups in a direct comparison. To this end, the Békésy sliding audiometry data was compared with the data of the DPOAEs and the hearing threshold curve was superimposed with the corresponding DP-gram. (Example Figure 10)

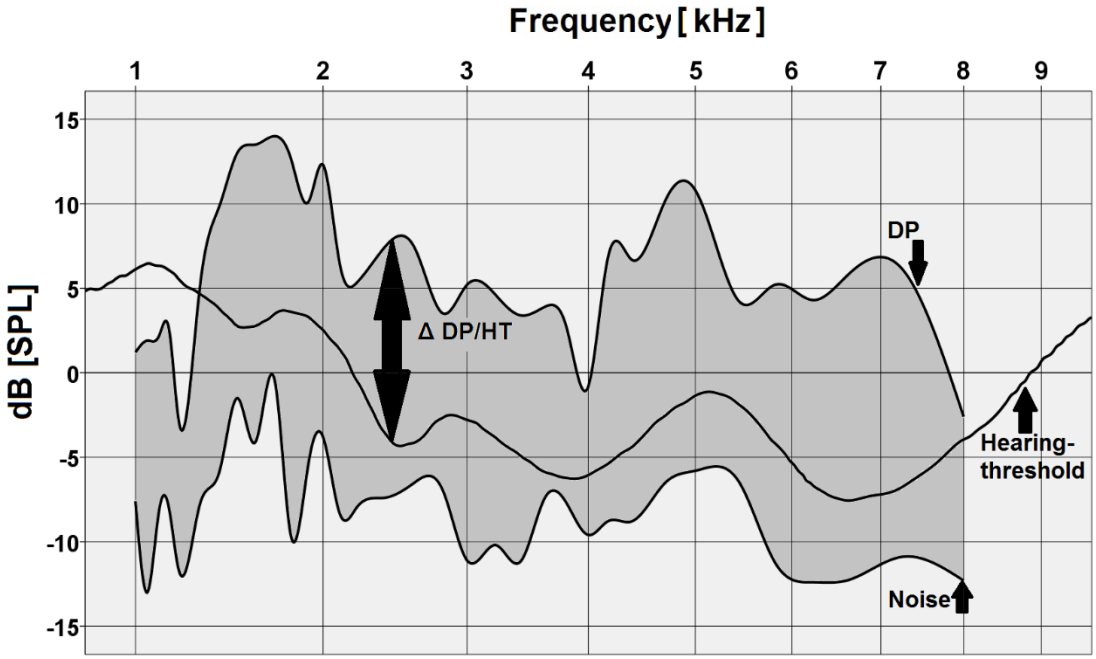

Figure 10: Subject TG 08-L. DP-gram (indicated "DP"), Békésy sliding audiometry ("Hearing-threshold") and noise floor ("Noise"). ΔDP/HT: difference between hearing threshold and DP-level.

The absolute value of the difference (ΔDP/HT) between the level of the distortion-products (DP) and the frequency-corresponding hearing threshold (HT) has been determined for the 36 DP test frequencies ranging between 1 kHz and 8 kHz. Likewise, signal-to-noise ratios (SNR) were compared with individual hearing threshold ΔSNR/HT (Figure 11).

Direct comparison showed a higher ΔDP/HT as well as ΔSNR/HT in the tinnitus group in the frequency range between 2 and 3.2 kHz. These frequencies were further analyzed and are represented in Figure 12.

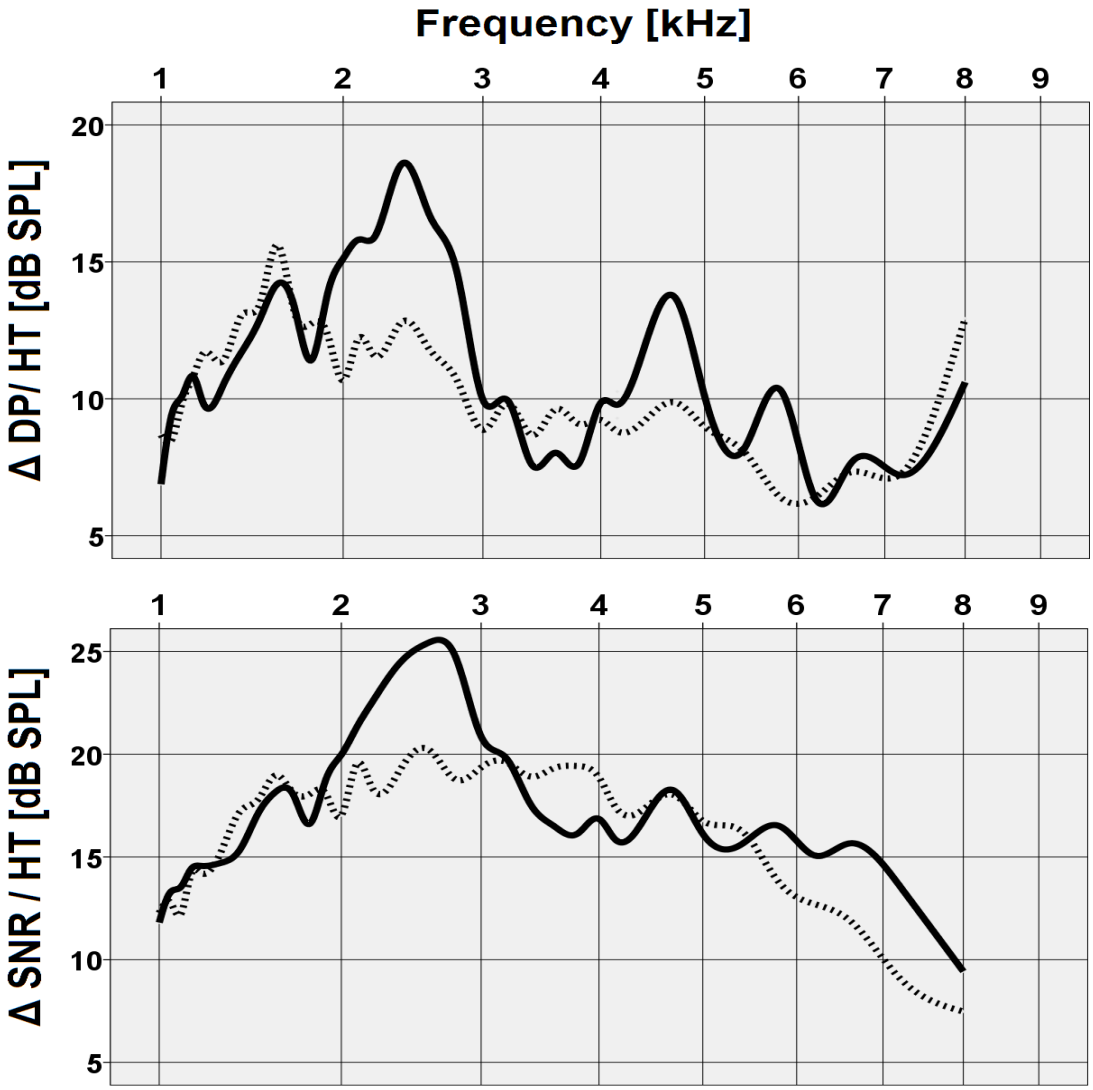

Figure 11, top: ΔDP/HL: Difference between hearing threshold (HT) and distortion product level (DP), tinnitus group (continuous line), and control group (dashed line). Bottom: ΔSNR/HT: difference between the hearing threshold (HT) and signal-noise-ratios (SNR), tinnitus group (continuous line), and control group (dashed line) (TG, *N*=10; CG, *N*=12).

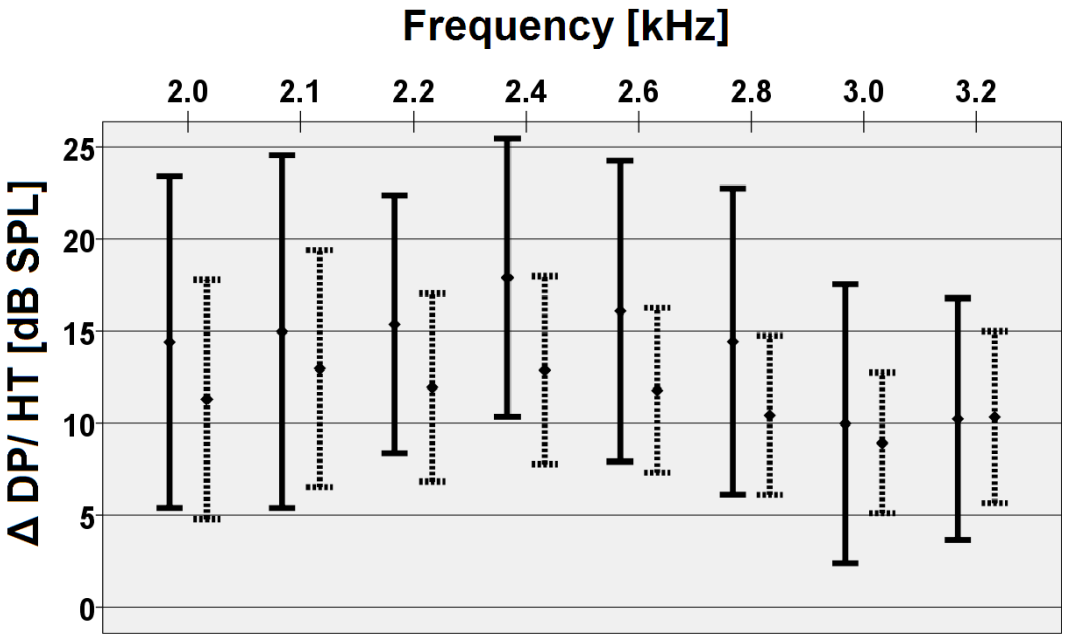

Figure 12: Mean ΔDP/HT (see Figure 11), tinnitus group (continuous lines), and control group (dashed lines) in the range between 2 and 3.2 kHz. Whiskers show the standard deviation (TG, *N*=10; CG, *N*=12).

The individual DP-test frequencies depicted in Figure 12 are listed in numbers in Table 7 for the purpose of descriptive statistics and analysis of potential significant differences. The ΔDP / HT shows a significant difference in the range of 2.2 kHz and even more so at 2.4 kHz. The standard deviations spread wide with a big overlap so that one can only assume a statistically relevant difference to a limited extent, especially given the small number of cases.

Table 7: Descriptive Statistic and statistical analysis of the value of the difference (ΔDP/HT) between hearing threshold and distortion-products as depicted in Figure 12. Statistical analysis with Levene test for variance homogeneity. (*= failure to reject H_0, therefore Mann-Whitney-*U* test (MWU) for statistically significant difference.)

Frequency [Hz]	Study Group	mean [dB HL]	*df*	SD [dB HL]	Levene Test p-value	MWU p-value
2000	CG	10.68	24	6.10	*0.008	0.122
	TI	15.12		9.01		
2100	CG	12.20	24	6.37	*0.017	0.194
	TI	15.81		9.59		
2200	CG	11.60	38	5.08	0.251	0.038
	TI	15.86		7.00		
2400	CG	12.82	38	5.22	0.264	*0.007
	TI	18.60		7.56		
2600	CG	11.77	21	4.52	*0.004	0.057
	TI	16.64		8.17		
2800	CG	10.67	22	4.75	*0.005	0.151
	TI	14.60		8.33		
3000	CG	8.87	38	3.93	0.510	0.912
	TI	9.96		7.58		
3200	CG	9.83	38	5.04	0.315	0.740
	TI	9.93		6.56		

3.6 Auditory brainstem responses

Analogous to the study by Schaette and McAlpine (2011), the experiment was replicated which was utilized to link synaptopathy to tinnitus by measuring wave I of the ABR. For this purpose, the amplitudes of the ABR of wave I and V were evaluated and displayed in a box plot diagram (Figure 13 left). In Figure 13 (right), similar to Schaette and McAlpine (2011), the Wave I amplitudes have been normalized by the respective amplitude of Wave V.

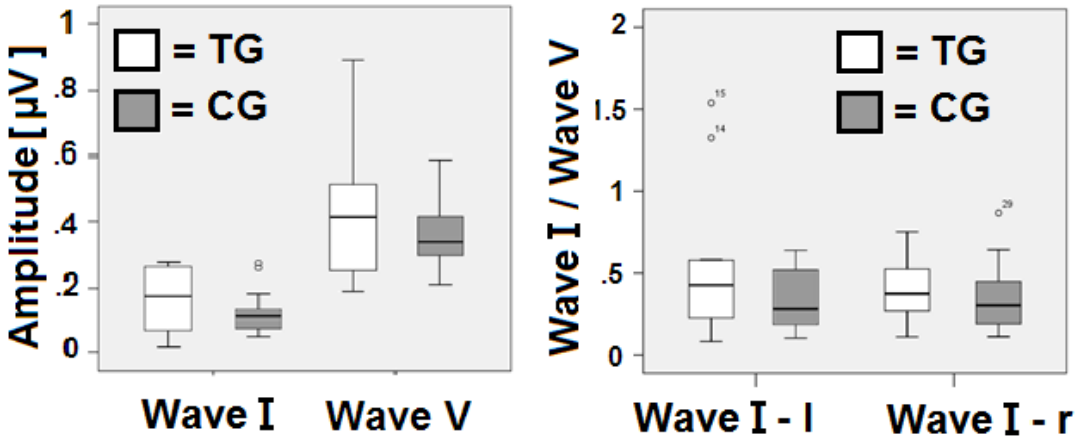

Figure 13 left: Wave I and V mean (thick line), first and third quartile (box) min/max (whiskers) and outliners (dots) for tinnitus (white) and control group(grey) (data from both ears averaged. Level of stimuli 85 dB nHL) (TG *N*= 11; CG *N*= 13).

Right: Wave I normalized by wave V (see text), mean first and third quartile (box) min/max (whiskers) and outliners (dots) for tinnitus (white) and control group (grey).

It can be observed that the mean values of the amplitudes of wave I of the ABR are very close together with the tinnitus group showing a higher amplitude on average. The amplitudes of wave V seem to be subject to a larger variance. It should be mentioned that the spread of the values of wave V can be explained by the gender-specific differences in amplitude. The values of the normalizations of the waves are also very close to each other. The statistical evaluation of the results can be found in Table 8.

Table 8: Descriptive statistic and statistical analysis of ABR amplitudes of wave I [A1], wave V [A5] as well as for normalized data for each ear individually. Homogeneity of variances was tested via Levene-test; normal distribution via Shapiro-Wilk-test. (*= failure to reject H_0 therefore Mann-Whitney-*U* test for statistically significant difference).

ABR amplitude	Study Group	Mean [nV]	*df*	SD [nV]	Levene Test *p*-value	Shapiro-Wilk-test *p*-value	MWU *p*-value
Amplitude Wave I [A1]	CG	114.50	23	71.98	0.13	0.03*	0.06
	TI	199.86		115.15		0.56	
Amplitude Wave V [A5]	CG	364.53	18	95.21	0.04*	0.33	0.46
	TI	446.34		224.81		0.38	
Amplitude I/V L	CG	0.31	23	0.46	0.74	0.06	0.277
	TI	0.55		0.19		0.01*	
Amplitude I/V R	CG	0.35	23	0.22	0.66	0.19	0.569
	TI	0.39		0.18		0.97	

The mean amplitude of wave I of the ABR for the control group was lower than the tinnitus groups wave I of the ABR. The difference however remains without statistical difference. The difference in mean amplitude regarding wave V of the ABR showed similar results, namely a lower value for the control group but without statistically significant difference as well. In accordance to the metrics introduced by Schaette and McAlpine (2011)[18] wave I amplitude was normalized by wave V amplitude (A1 [nV] /A5 [nV]). Similar to the absence of significant differences with wave I and wave V amplitude averages, the normalized value showed no statistical difference between tinnitus group and control group. There are no indications of wave I amplitude discrepancy between subjects with normal-hearing threshold who suffer from chronic tinnitus and those with normal-hearing without chronic tinnitus.

3.6.1 Gender differences in ABR amplitudes

As already mentioned in the introduction and in the M&M section, gender-specific differences in the amplitudes of the ABR are a potential source of error in the measure-

ments. Since this study focuses on wave I, which should not show any significant differences according to the current study situation, the ABR were examined gender-specifically and compared with the current data situation. As shown in Figure 14 the averaged amplitude values of waves I and V have been plotted by gender in a box plot diagram. In the current study female test subjects had an average higher wave V amplitude by 31% (mean value male: 320 nV± 87 nV [SD]; mean value female 517 nV± 187 nV [SD]) with a significant difference (p = .001, t-test after Levene-test for variance homogeneity, df = 23). The measurements of wave I remained without a significant gender-based difference (mean value male: 130 nV± 89 nV [SD]; mean value female: 150 nV±84 nV [SD] p = 0.941, t-test after Levene-test for variance homogeneity, df = 23). The wave V amplitudes of the study's male test subjects were enlarged by the gender difference in wave V amplitude of 32% concluded by Kizman et al. (2011) to see if the resulting amplitudes would negate the gender-based difference in wave V amplitudes. The resulting averaged amplitudes of Wave V are very similar to the female results and showed no statistical difference.

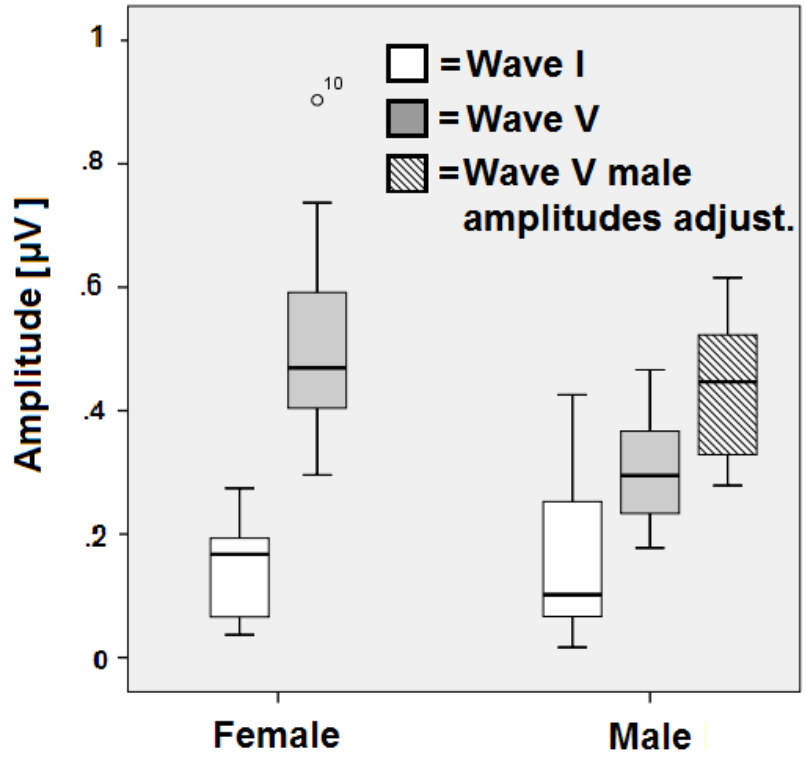

Figure 14: Mean first and third quartile (box) min/max (whiskers) and outliners (dots) for wave I (white) and wave V (grey) for male and female test subjects. Also Wave V Amplitudes for all males have been multiplied with mean difference in amplitude (+32%) as described by Kritzman et al. (2012) (shaded) N = 25 (10 male and 15 female).

3.7 Tinnitus level of disturbance

Individual tinnitus related levels of disturbance were determined via visual analogue scale (Figure 3) The value of the tinnitus disturbance is displayed as a function of the amplitude of the wave I as scatter plot in Figure 15. It can be observed that the higher the amplitude of the corresponding wave I, the larger the degree of distress the patients have indicated in regards to their tinnitus. This correlation seems to be subject to a strong trend even if it does not reach the level of statistical significance.

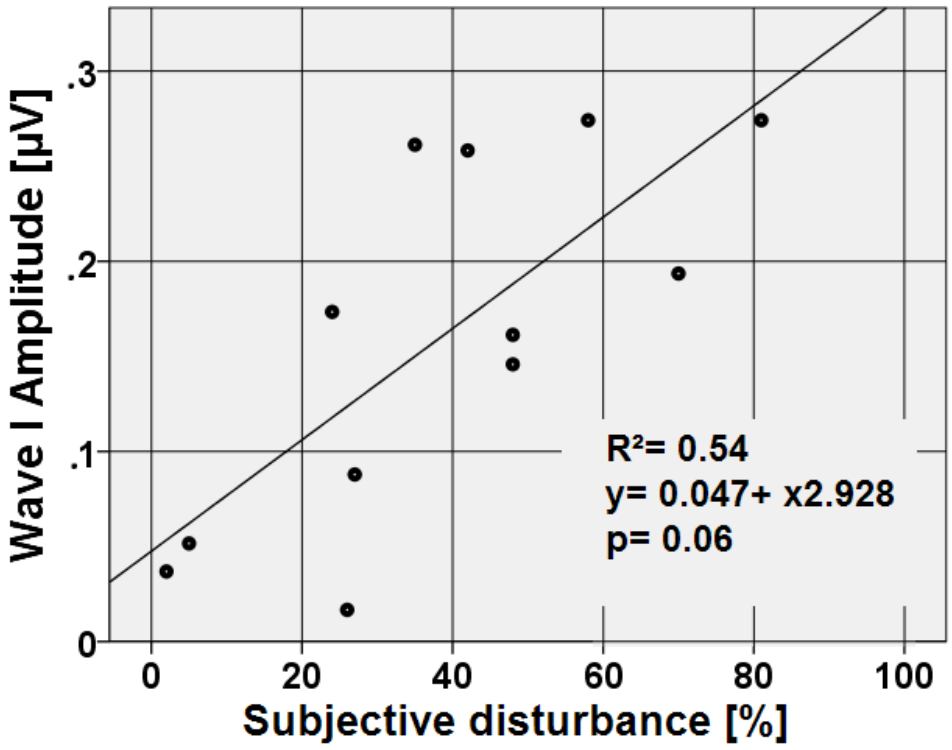

Figure 15: Correlation between Wave I amplitude and subjective disturbance by tinnitus (Visual analog scale). $N = 12$, p-value via analysis of variance (ANOVA), linear regression line.

4 Discussion

Since the tinnitus phenomenon is still not fully understood and it is still not known whether there is only one or more triggering pathophysiologies, we are very much dependent on indirect measurement methods for research. Clinical pure-tone audiometry has been the standard method to determine whether or not hearing damage is present in tinnitus patients. The search for a pathomechanism that cannot be explained by hearing loss led via the animal model and the theory of synaptopathy to the theory of hidden hearing loss to be proven via the recording of ABR. The present study aimed to identify whether fine-structure analysis of tinnitus patients without hearing loss generates more precise data which helps in identifying tinnitus specific abnormalities in hearing thresholds. Furthermore, it had been tested if there are tinnitus specific abnormalities in the hearing threshold morphology. Synaptopathy as a basis for the "hidden hearing loss" is a suggested mechanism for tinnitus. The diminished wave I amplitudes of tinnitus subjects, as was presented by Schaette and McAlpine (2011) could not been reproduced. We also tested whether there were abnormalities in the DPOAEs that we could correlate with the occurrence of chronic tinnitus. Finally, the Békésy data was compared with the DPOAE data in order to identifying abnormalities that correlate with tinnitus. In addition, a mild trend between the amplitude of wave I of the ABR and the subjective level of disturbance of the tinnitus has been found.

4.1 Summary of hypotheses and results

The results of this study showed that fine-structure audiometry is superior to conventional pure-tone audiometry in the detection of subtle hearing disorders. Analysis of hearing thresholds with fine-structure audiometry showed an overall better hearing in the tinnitus patients as well as a mild correlation (p= 0.32) between the frequency of the largest measured dip of the hearing threshold and the matching frequency of the tinnitus. The DPOAE measurements showed no correlation with tinnitus describing parameters. A trend between the amplitude of ABR wave I and the subjective disturbance related to tinnitus was observed. Evidence for synaptopathy as the underlying mechanism of tinnitus in normal-hearing patients could not be provided.

One of the aims of the present study was to replicate the findings of Schaette and McAlpine (2011), who demonstrated reduced wave I amplitude in ABR recordings in a tinnitus

group designated as having normal hearing. Furthermore, it was investigated whether manual pure-tone audiometry up to 8 kHz is sufficient to detect relevant hearing impairments. To answer this question, in the present study the diagnostic procedure was extended to include Békésy sliding audiometry and testing of DPOAEs to detect hearing impairment more precisely. Additional data such as tinnitus quality and subjective distress was collected by questionnaire.

There was no indication of a significant difference in the amplitudes of ABR wave I between the tinnitus group and the control group, so the data of the current study does not suggest a "hidden hearing loss" that could link inner ear synaptopathy to chronic tinnitus. Our extended hearing threshold analysis uncovered hearing losses that had previously gone undetected by manual pure-tone audiometry. Firstly, these newly detected hearing losses would have disqualified the inclusion of nearly half of the subjects, calling into question the definition of "normal-hearing". Secondly, a weak correlation was found between the largest Békésy threshold dips and the matching frequency of the tinnitus, which may indicate that acoustic trauma may be a primary cause of tinnitus in normal-hearing subjects as well.

Other morphologic irregularities, such as the slope steepness of small hearing loss dips and the respective number of dips could not be related to the tinnitus phenomenon.

The DP-Gram curves were also examined for tinnitus-specific irregularities, but no correlation could be found. However, a tinnitus-specific abnormality was found in the direct comparison between the Békésy hearing threshold and the DP measurements in the 2 kHz to 3 kHz range. In the direct comparison between Békésy fine-structure audiometry and DPOAEs, our results showed a significantly higher value of the difference between the hearing threshold and distortion products in tinnitus patients between 2 kHz and 3 kHz.

Typical known changes in ABR amplitudes as a function of subject gender were observed and remained within the results of the currently published data.

4.2 Review of methodology

The data collection of the present study had primarily the same weakness as most other studies dealing with this topic, namely the small number of subjects. The strictness of the inclusion criteria made the recruitment of suitable subjects very difficult, since more than half of the subjects had hearing impairments demonstrated by the PTA11 measurement,

which led to exclusion. In this context, the validity of the test results should be treated with caution. It would be advisable to reproduce the measurement results with a larger number of subjects.

It should also be mentioned that a gender-independent recruitment was performed. Since, according to our results and analogous to the current study situation, gender related differences in the measurements only concern ABR waves III and V, but not wave I, this source of error could be excluded. It should be noted that the results of this study, gender related differences in wave V amplitude, are consistent with the current data with a variation of 1% (32% vs 31%)[53].

It should also be noted that the survey of tinnitus parameters is purely subjective. It was the experience of the author of the present study that many subjects had difficulties classifying their tinnitus phenomenon in terms of frequency and perceived loudness. One reason for this was the fact that the tinnitus could only be compared to pure sinusoidal tones, so that subjects who perceive their tinnitus as a combination of several tone qualities could not make any concrete statements about perceived loudness or frequency range. As a special exception, a professional musician should be mentioned here who was able to assign a pitch to his tinnitus over days with his own instruments, which was found in the tinnitus evaluation test exactly in the frequency that was initially indicated by the subject. This experience raises the question whether professional musicians are generally a better clientele for tinnitus research. Furthermore, it should be considered whether a pure comparison with sinusoidal tones is a sufficient method to evaluate the tinnitus of test persons.

Commonly, in studies which address the difference in ABR wave I amplitudes, hearing thresholds were recorded by means of clinical manual pure-tone audiograms with typically less than a dozen test frequencies[18,57,57]. Frequencies above 8 kHz were mostly not included[58,57]. As an exception, Gilles et al. (2019) recorded hearing thresholds in 15 test frequencies up to 16 kHz[59].

The results of the fine structure measurement showed hearing losses that were not recorded in conventional manual pure tone audiometry. These hearing losses were found both between the test frequencies of pure tone audiometry and also in the higher test frequency ranges. If Békésy audiometry would have been used for screening instead of

PTA 11, 12 out of 29 test subjects would have been excluded from participation in accordance with the exclusion criteria of the present study. This further hints toward the necessity of permanent threshold shifts (PTS) even at a very small scale for the genesis of chronic tinnitus. Regarding these micro threshold shifts (MSS), they can originate from a threshold above average, meaning that the hearing loss, represented in the threshold dip, can be severe, but if originated for example at a threshold value of -10 dB HL, the subject still remains with a pretty good hearing ability at that certain point. That raises the question whether or not acoustic traumas, represented in the hearing curve should be measured from the point of origin, meaning the subjects own threshold, rather than the standardized minimum audibility curve which represents the hearing threshold of the average human.

4.2.1 Fine-structure audiometry for tinnitus research

The superiority of Békésy audiometry in contrast to pure-tone audiometry for detecting hearing losses has been well established[60]. For auditory research it has been tried to link certain configuration of the hearing threshold curves to pathologies like hearing loss or tinnitus[61] or certain subgroups within these cohorts[62]. The most well-known pathological configuration of the PTA11 is the "high frequency threshold notch" between 3 and 6 kHz measured in subjects with NIHL[61,63]. Norena et al. (2002), as well as Roberts et al. (2008) reported a correlation between the threshold shift at the beginning of the notch and their measured peak in tinnitus spectrum. The tinnitus spectrum was determined by having the subjects to judge their subjective tinnitus with several pure tones on a 1 to 10 scale, describing how much the presented comparison sinusoid tone contributed (qualification of similarity) to their tinnitus[29,63]. However, Pan et al (2009) tried to match tinnitus pitches with the frequency of the edge of the high frequency hearing loss but failed to find a correlation[64]. Scheckelmann et al (2012) found a mild correlation between the frequency of tinnitus pitch and the frequency of maximum hearing loss which concurs with the data of the present study (Table 6)[65].

Besides studies which explore correlations between tinnitus and the notch of the hearing threshold, there also have been several studies exploring the role of the steepness of the slope of the threshold shift with clear indication that the steepness of high frequency slopes directly correlate with tinnitus and better differential limen for frequency (DFL), indicating cortical reorganization after noise trauma[66,67]. DFL describes a different ap-

proach for frequency matching by using methods of measuring differential sensitivity instead of just using a simple matching procedure. The ability to distinguish between two nearly equal stimuli is characterized by a difference limen.

The threshold level itself does not seem to give a clear indication on if and when people develop chronic tinnitus[66]. It must be mentioned, that the amount of studies addressing the overall configuration of an audiometric curve for tinnitus research is rare and most of the times cohorts without difference in hearing thresholds, underlying pathologies, gender or age were addressed. One of the largest review studies carried out by Gollnast et al. (2017) analyzed the data from 37,661 patients with sensorineural or conductive hearing loss from all age groups with or without tinnitus and reported distinguished differences in audiometry curve configuration[68]. The assumption can be made, that as long as tinnitus is affiliated with a certain sensory hearing loss, the configuration of the curve of the hearing threshold correlated with certain parameters of the tinnitus perception. However, it seems that the tinnitus without hearing loss does not correlate with the morphology of the audiometry curve, even when measured as thorough as with Békésy audiometry.

4.3 Cochlear Synaptopathy

One of the purposes of the present study was the investigation of the proposed link between tinnitus and synaptopathy. However, a reproduction of the results reported by Schaette and McAlpine (2011) failed, as a significant difference in ABR recordings of Wave I amplitudes between tinnitus group and control group was absent.

During the last 30 years a considerably amount of tinnitus research was carried out using auditory brainstem responses in order to find abnormalities in tinnitus subjects[13]. Milloy et al. (2017) published a meta-analysis which identified 12 studies comparable to Schaette et al. (2011) with only 4 of them reporting significant decreased in wave I amplitudes in tinnitus subject without hearing loss. The authors concluded that there is no sufficient data so far that would generally link normal-hearing tinnitus patients to reduced wave I amplitudes[13]. Likewise, Shim et al. (2011) as well as Guest at al. (2011) compared ABR in tinnitus ears and non-tinnitus ears in unilateral tinnitus patients with a normal audiogram and reported no significant difference in ABR wave I amplitude or latency[69,70]. These heterogeneous results argue against synaptopathy as a sole pathomechanism for chronic tinnitus. Possible reasons for this finding are discussed below.

4.3.1 Links between synaptopathy and tinnitus

The overall premise of the tinnitus model of central gain in tinnitus patients with normal-hearing is a "hidden hearing loss", defined as residual physical damage e.g. the cochlear nerve, represented in a reduced ABR wave I[71],without shifts in hearing threshold[69]. The question is what constitutes normal hearing and what method is suitable for screening. Presbycusis excludes older subjects[72,73] and finding young subjects who were not exposed to recreational or technology-generated noise, which could be deemed harmful, represents a challenge[59], especially since noise overexposure does not necessarily need to be painful or discomforting[41]. The first animal experiments regarding synaptopathy were carried out in animal models under controlled conditions and with specific noise sources. However, it is very unlikely to find human subjects who also suffered only one hearing trauma during their lifetime, which then led to synaptopathy and the generation of tinnitus. For this reason, the results of the animal model experiments seem not to be transferable to humans[40,41,44,45].

Prendergast et al. (2017) tried to prove synaptopathy in young adults. 126 test subjects with normal audiometric hearing underwent a thorough interview to estimate the amount of noise exposure they experienced up to this point. This data was compared to ABR recorded wave I amplitudes but no significant correlation could be observed[74]. Threshold equalizing noise (TEN) tests have been used to determinate dead regions in inner hair cell topography in populations with normal clinical audiogram[75].This method has been used to demask inner hair cell damage in tinnitus patients with normal audiogram. It has been concluded that hair cell damage, even to the smallest degree, might be a requirement for the genesis of tinnitus[76,77]. Since it has been established, that hearing loss, followed by progressing age, is the leading risk factor for developing tinnitus[1] possible hearing damage in the normal-hearing tinnitus patients may just be undiagnosed.

Another reason for the current problem of linking synaptopathy with human tinnitus might be the fact, that ABR amplitudes differ not only due to the numbers of active nerve fibers[78] but also due to the level of inter cell synchronization[13]. Paradoxically, both increased[15] and decreased[79] synchrony have been suggested as a possible mechanism of tinnitus origin and even as an compensation to avoid tinnitus[80].

4.4 Are distortion-product otoacoustic emissions linked to tinnitus?

Since the discovery of OAEs[81] and their diagnostic value to the assessment of inner ear function is has been theorized that spontaneous otoacoustic emission could be a source of

tinnitus or at least share similar underlying pathologies[82]. Additionally, the direct measurement of the function of the outer hair cells might detect hearing damage which would not be seen in a standard audiogram[41]. There are many studies that have tried to correlate the sound levels of distortion products with tinnitus characteristics. The results are very inhomogeneous and describe almost every possible scenario like no difference at all[83,84], lower DP amplitudes in tinnitus patients[85,86,84,87], hinting towards OHC dysfunction as a possible cause for tinnitus[88,89] or higher DP amplitudes in tinnitus patients theorized to be because of higher motility of the OHC´s [90,91]. In alignment with most studies describing "normal-hearing" the distinction was made using clinical audiometry without including frequencies above 8 kHz thus suffering the same inaccuracies as described in chapter 4.2., and thereby explaining the inhomogeneous results. To our knowledge the present study had the strictest inclusion criteria concerning "normal-hearing "so far and we could not find a significant difference in OHC function between normal-hearing tinnitus patients and a control group. The relation between distortion product sound level and the fine structure threshold levels is slightly significant and could indicate small hearing loss. This would further support the theory that hearing loss, even at a very small scale, is a prerequisite for chronic tinnitus.

4.5 Linking ABR´s and Tinnitus related distress

The severity of tinnitus is not necessarily linked to the perceived loudness of the phantom sound but rather to the level of distress and the strain it puts on the quality of life[8,40], which at the worst can lead to suicide[92]. In the present study the level of distress shows a trend towards correlation with the amplitude of ABR wave I and therefore with the amount and/or synchronization rate of auditory nerve fibers[13]. Tinnitus itself was not only been linked to central auditory processes but to a variety of non-auditory areas as well. Primarily the limbic systems which shows several bidirectional neural connections with the auditory pathways[93,94] is researched in order to find irregularities concerning the emotional strain and anxiety related to chronic tinnitus[95]. These connections have been linked to brain functions like fear conditioning[96] or plasticity within the auditory pathways in response to sounds[97], and show that the amygdala might even support the processing of nonlinguistic emotional stimuli in the auditory domain[98]. Neuroimaging in animal models showed tinnitus related hyperactivity of the amygdala when changes were salicylate induced[99] as well as when the animals were exposed to intense sound. The Fos-like immunoreactivity induced by these sounds could show neuronal connections with tinnitus

within the limbic system[100]. Given the current data and possibilities for neural imaging a considerable amount of studies suggests the involvement of numerous neural networks including a variety of brain structures like the dorsolateral prefrontal cortex, the primary and secondary auditory cortex, the limbic system, thalamus precuneus, hippocampus, parahippocampus[101,102].

The data indicated that the different aspects of the tinnitus phenomenon, such as distress, memory, perceived loudness and emotional linkage is represented by different neuronal networks[38].

In conclusion, there is currently no data-supported explanation why subjective tinnitus distress should be linearly related to the amplitude of wave I of the ABR. Further studies on this topic are needed.

4.6 Conclusion and outlook

In this study, no difference in ABR wave amplitudes was measured between normal-hearing tinnitus patients and a comparable control group. Thus, evidence of synaptopathy as a possible cause of the tinnitus phenomenon could not be demonstrated. This result reflects the problematic nature of the basic question, namely how exactly to define normal hearing. Despite intensive efforts to generate a group of patients with as normal hearing as possible, precise measurement methods revealed hearing impairment in almost one third of the candidates, who should not have participated in the study according to the inclusion criteria. In addition, we used the standard method (PTA11) of measuring hearing loss based on the threshold for normal hearing to determine whether or not the potential hearing loss was within the inclusion criteria. There are several definitions of the minimum audibility curve specified in different international standards, and they differ significantly, resulting in differences in audiograms depending on the audiometer used[103]. The minimum audibility curve indicates the average normal hearing of a human being. However, if a subject has above-average hearing, a hearing loss that would normally violate the exclusion criteria may not be sufficient to exclude that subject. Likewise, comparatively smaller hearing losses in a subject with below-average hearing would lead to exclusion. In summary, the question arises whether the minimum audibility curve should not be replaced in favor of the individual base-line threshold as the starting point for measuring hearing impairment. The author of the present study believes that there can be

no such thing as normal hearing by definition, since everyone will have hearing impairments if measured only accurately enough.

From this point of view, if one wants to generate a patient clientele with minimal hearing loss, one should define the severity of hearing loss by the baseline value of the hearing threshold and not by the deviation from the internationally standardized zero line of the audiograms. Since it is not possible to determine the hearing threshold that was present before the event that led to hearing loss, the authors of this study propose a prospective study in which hearing thresholds are measured, especially in young people, using a fine-structure measurement method. Over the years, follow-up examinations could then determine the absolute micro hearing loss based on the initial hearing measurement and, if necessary, correlate it with patients who developed chronic tinnitus during the course of the study. Because the development of tinnitus is unpredictable, the number of subjects would have to be appropriately large to ensure that a sufficient number of individuals with tinnitus would be identified during the course of the study.

Determining actual hearing performance and isolating individual hearing impairment is not the only difficult task. The most common method of quantifying a person's tinnitus is to compare it to a pure tone to determine loudness and frequency. However, it is common for tinnitus to be heard in multiple frequencies and to be "elusive" because it is not perceived as a pure tone. The fact that tinnitus rarely resembles a pure sinusoidal tone leads to measurement distortions, which in turn complicate the correlation of tinnitus features with measurable values of various diagnostic tools. Instead of using pure sinus tones, a database in which combinations of typical tinnitus comparison sounds are available would be helpful to make tinnitus analysis more precise.

It remains that although many studies have been concerned with central tinnitus, it is still one of the least understood of the "common diseases". Further studies and more precise investigation methods are in need to understand the central mechanism sufficiently to develop effective therapies in the future.

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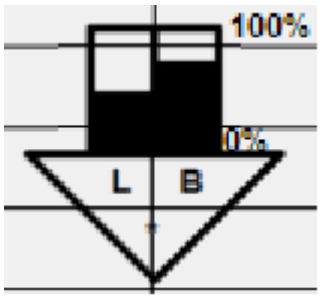
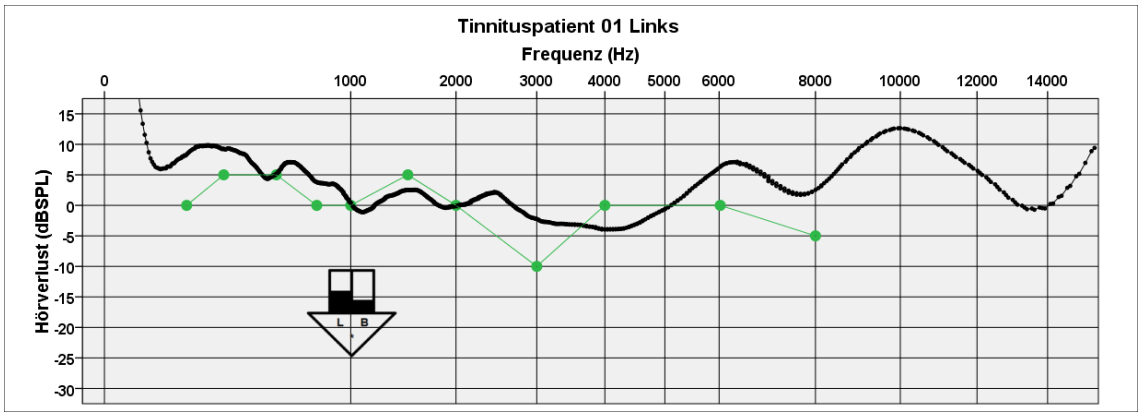
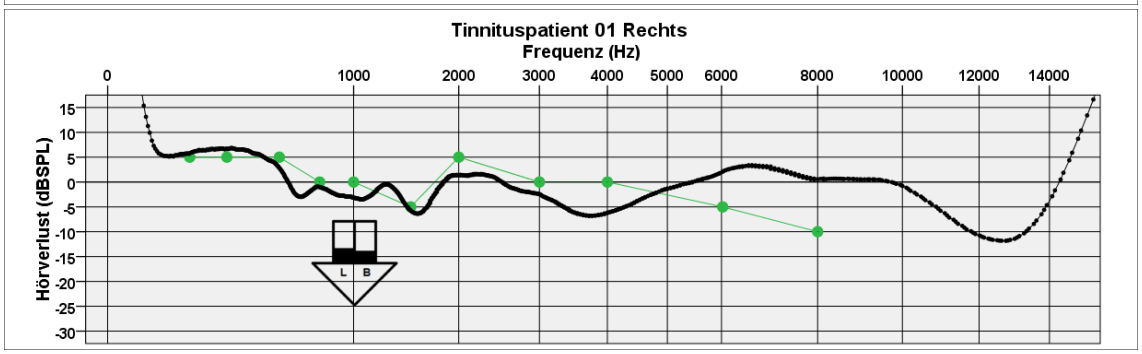
Appendix

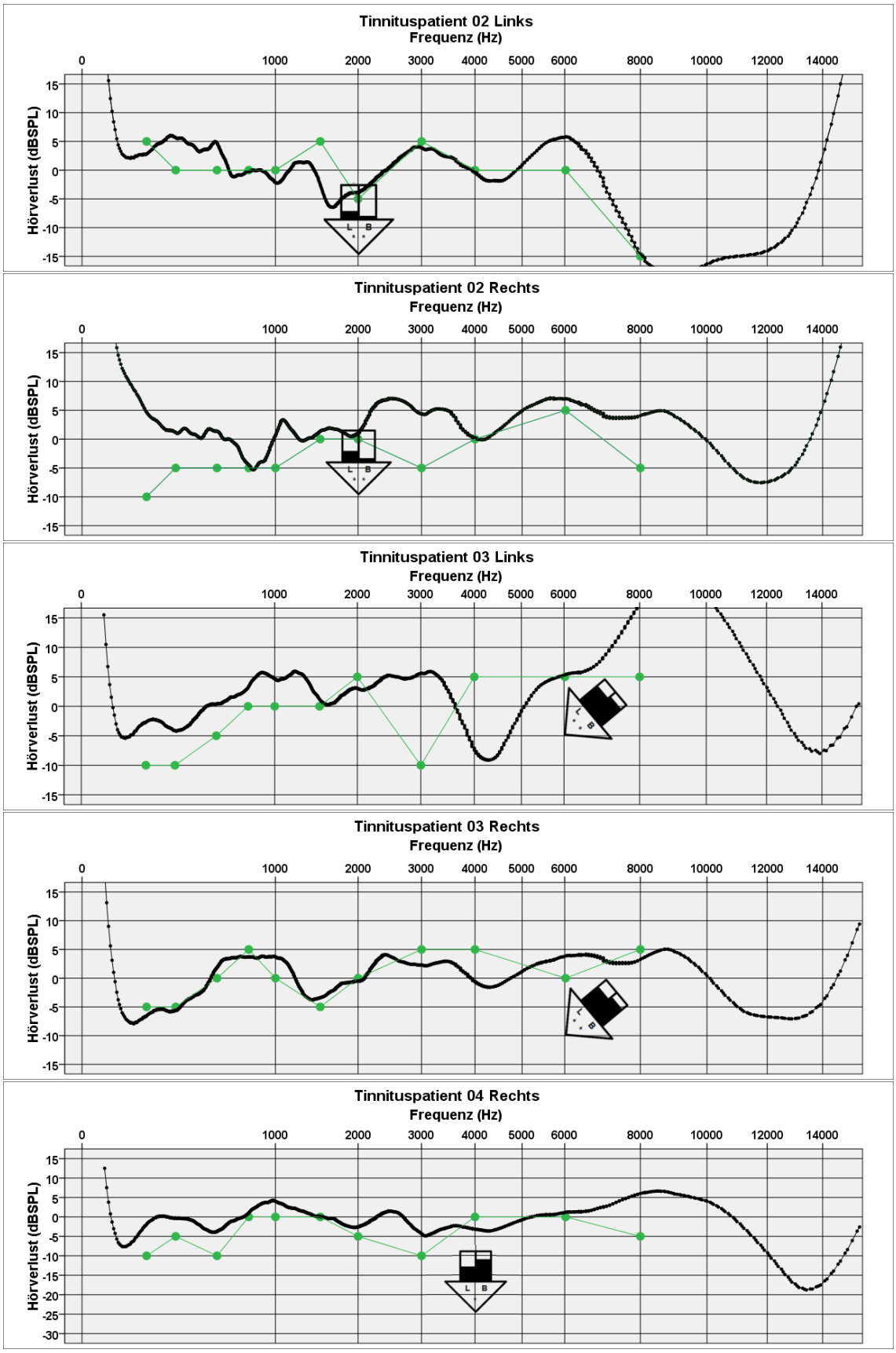
PT11 and Békésy audiograms of all tinnitus test subjects

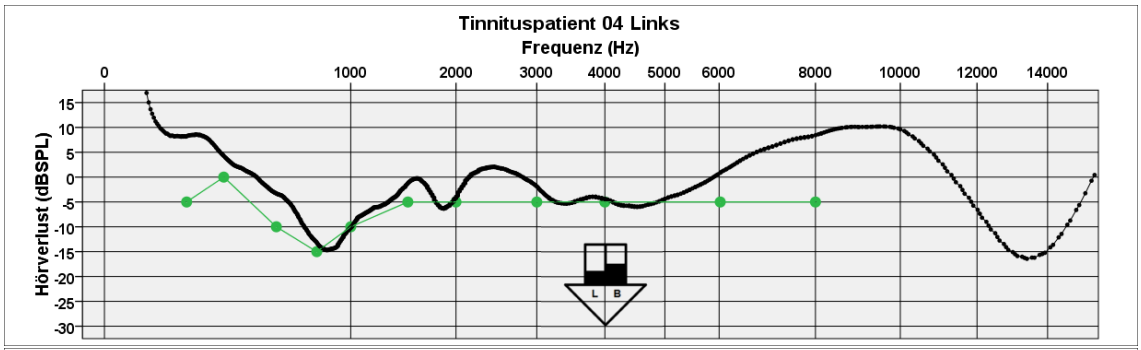
The arrow marks the frequency and subjective loudness of the perceived tinnitus. The black bar marked L shows the subjective loudness of the tinnitus as stated in the survey. The black bar marked B shows the subjective distress as stated in the survey. * marks the ear with dominant tinnitus sensation. ** is used when the tinnitus is perceived equally loud in both ears. Links=left. Rechts =right. Hörverlust = Hearing threshold

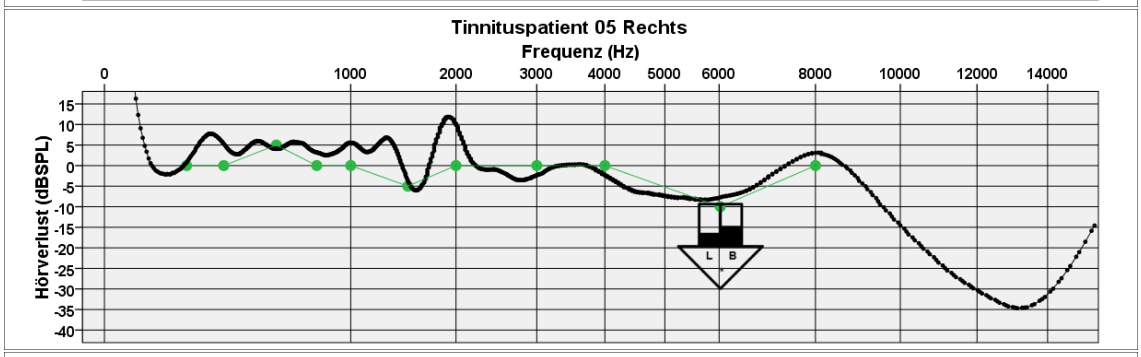


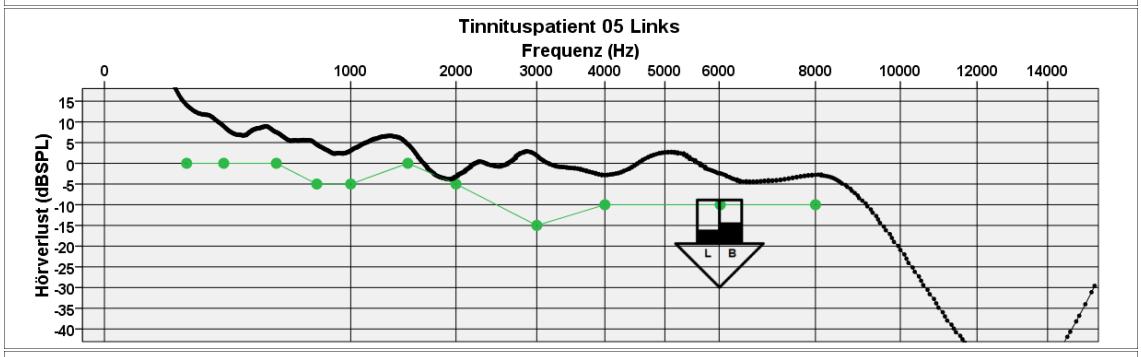


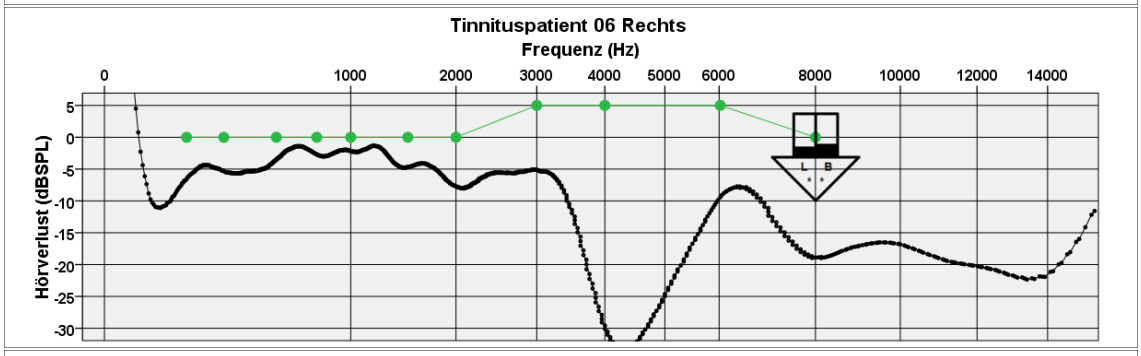


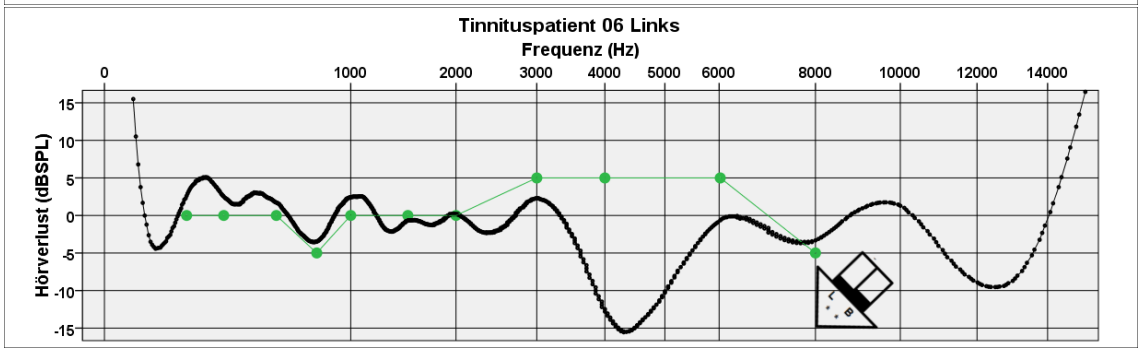

Tinnituspatient 02 Links
Frequenz (Hz)
Hörverlust (dBSPL)
Tinnituspatient 02 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)
Tinnituspatient 03 Links
Frequenz (Hz)
Hörverlust (dBSPL)
Tinnituspatient 03 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)
Tinnituspatient 04 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)

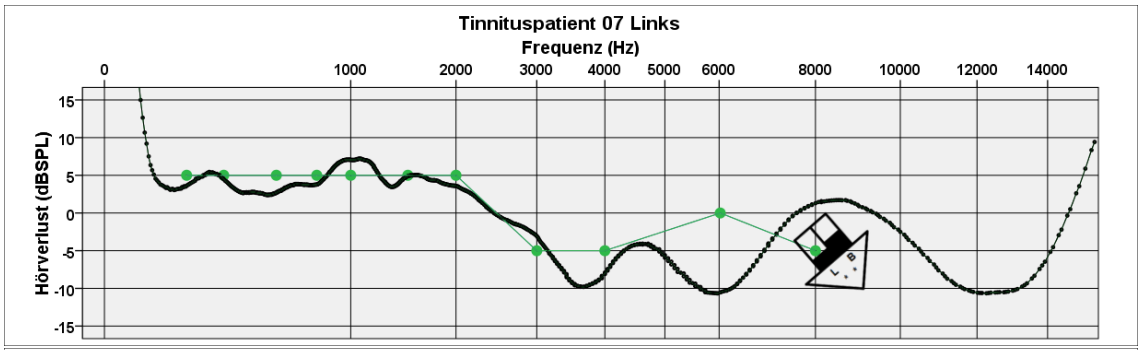

Tinnituspatient 04 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
-20
-25
-30
L
B

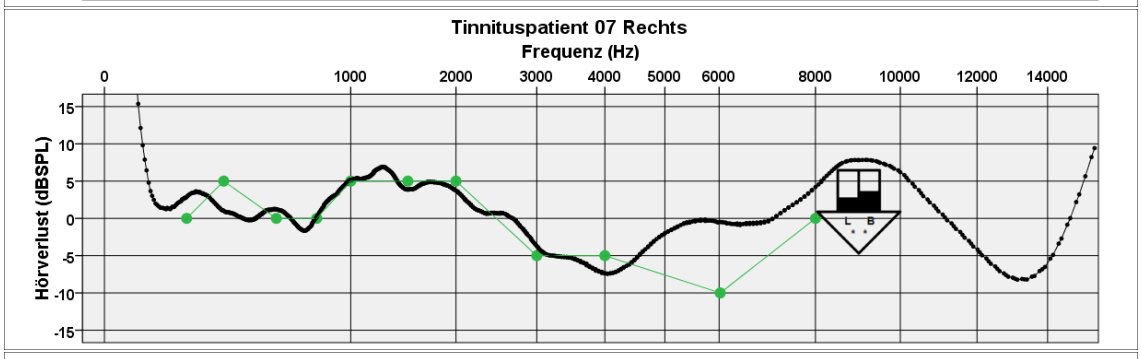

Tinnituspatient 05 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
L
B

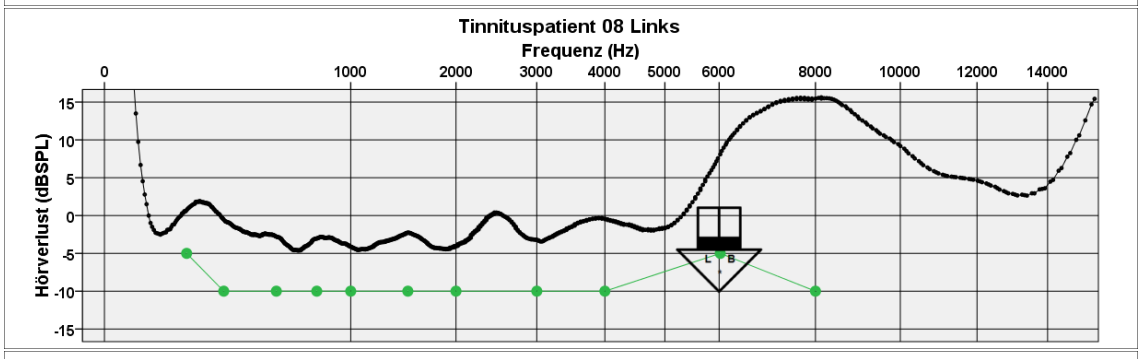

Tinnituspatient 05 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
-20
-25
-30
-35
-40
L
B

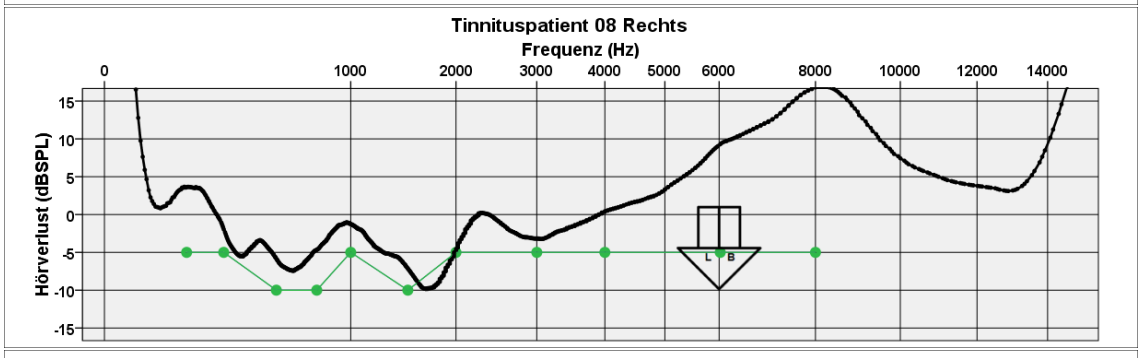

Tinnituspatient 06 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
5
0
-5
-10
-15
-20
-25
-30
L
B

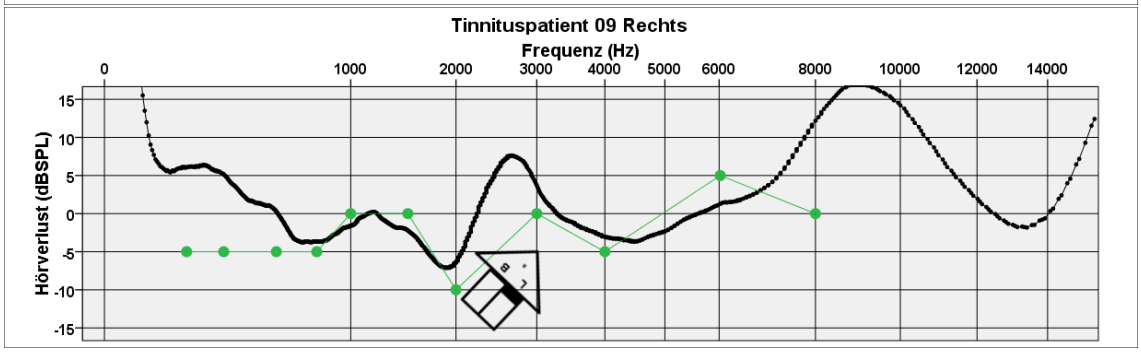

Tinnituspatient 06 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
L
B

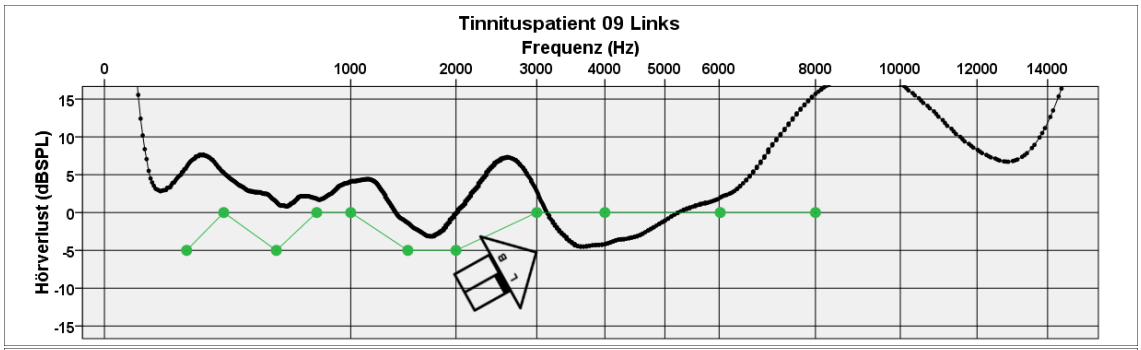

Tinnituspatient 07 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15

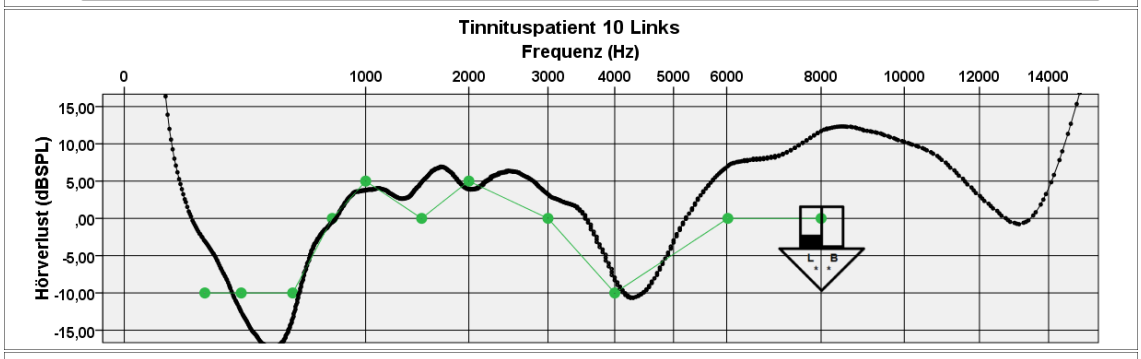

Tinnituspatient 07 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15

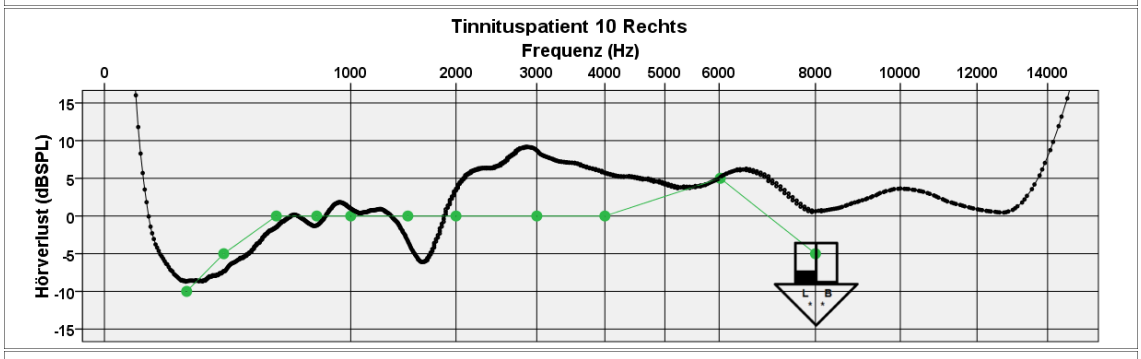

Tinnituspatient 08 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15

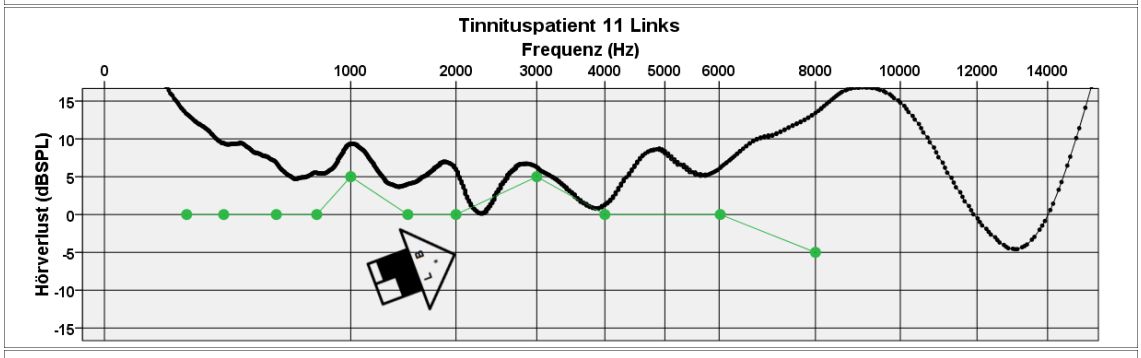

Tinnituspatient 08 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15

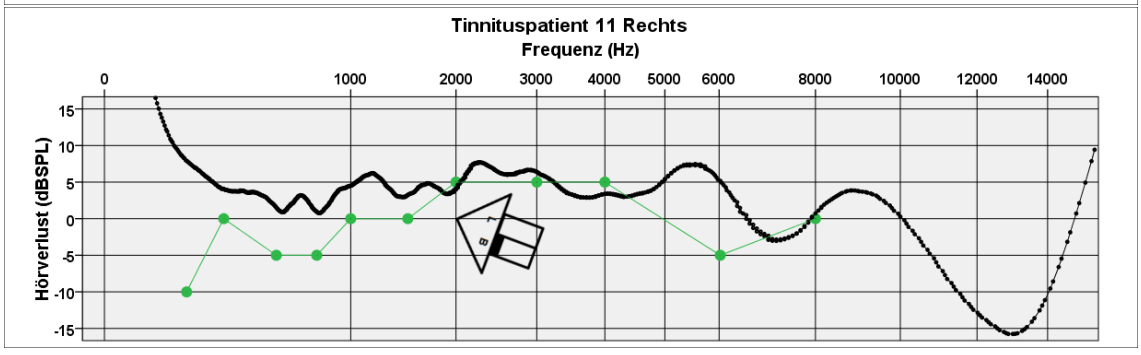

Tinnituspatient 09 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15

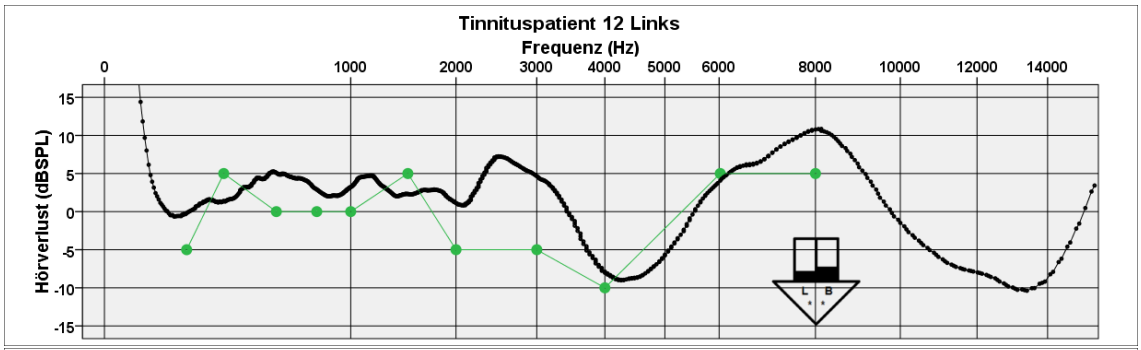

Tinnituspatient 09 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15

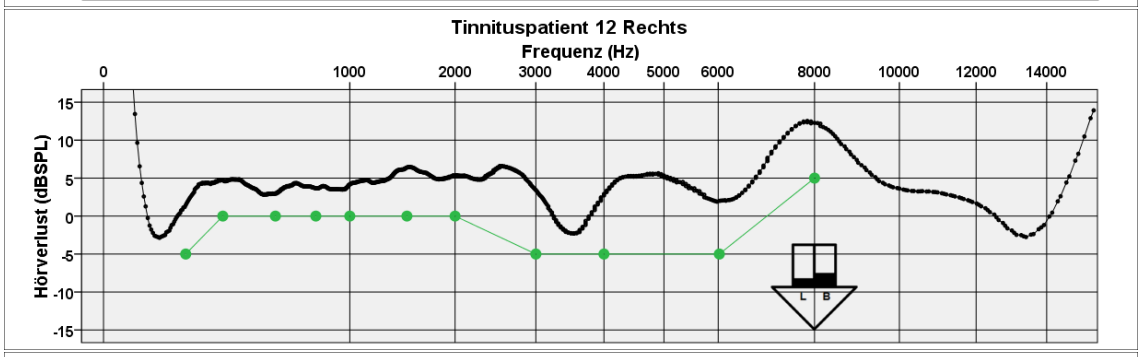

Tinnituspatient 10 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15,00
10,00
5,00
,00
-5,00
-10,00
-15,00

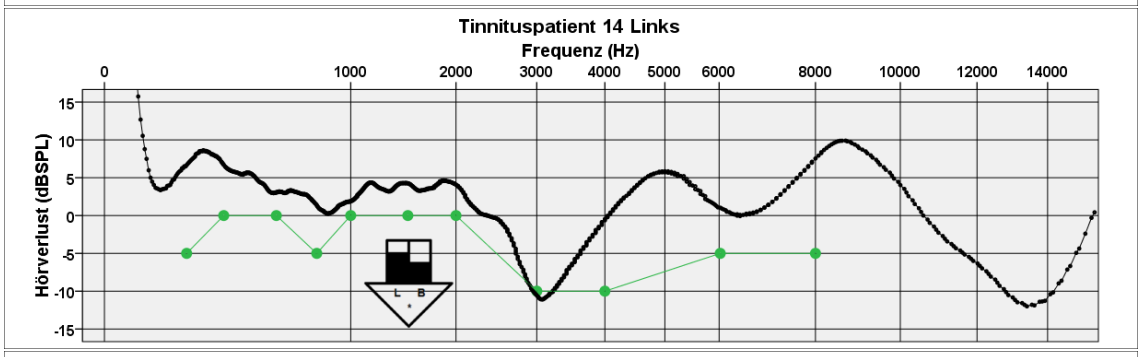

Tinnituspatient 10 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15

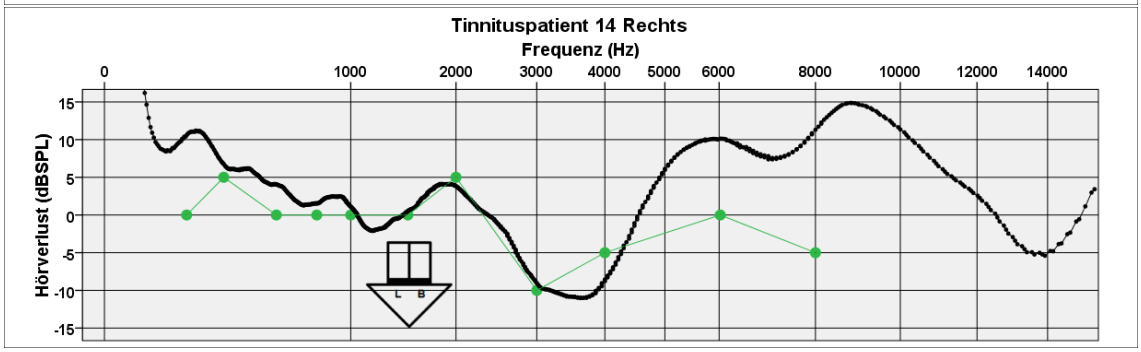

Tinnituspatient 11 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15

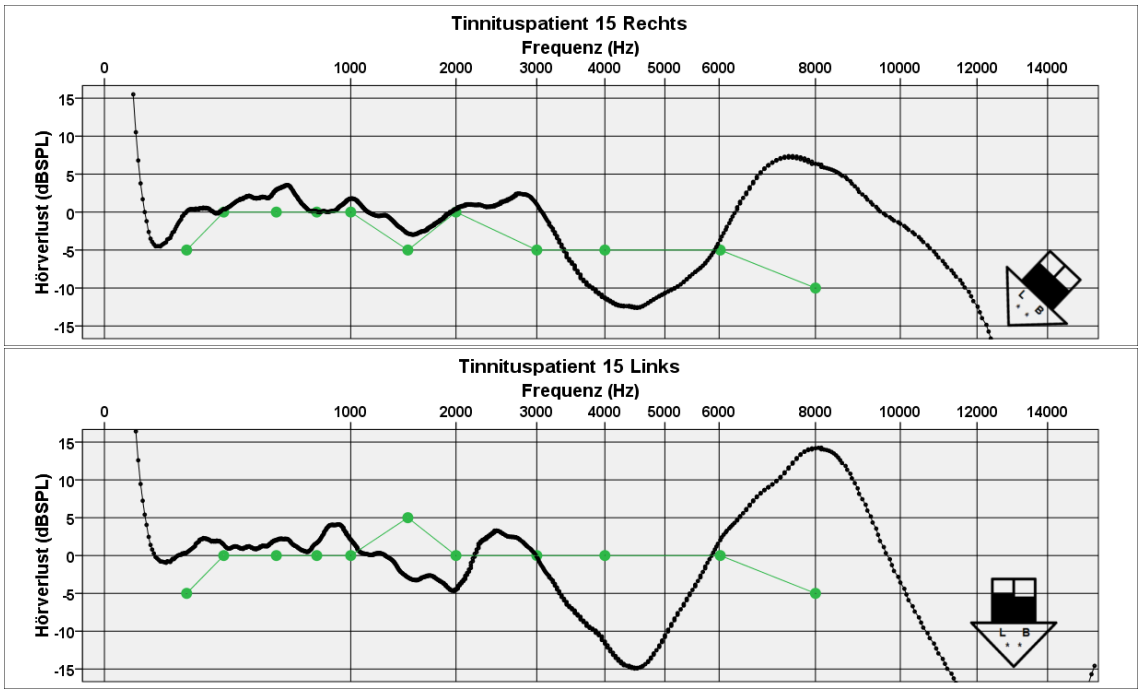

Tinnituspatient 11 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15


Tinnituspatient 12 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
L
B

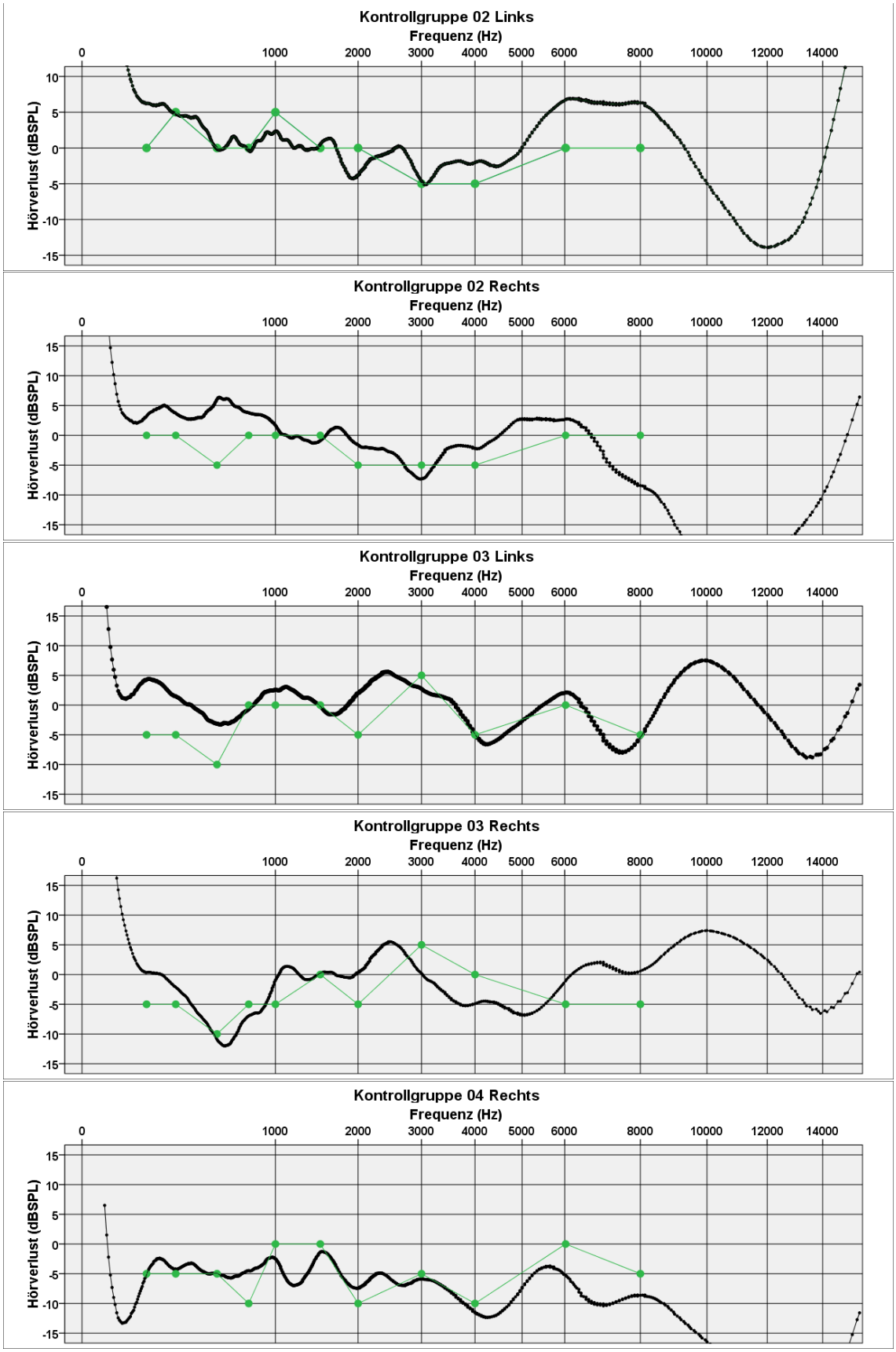

Tinnituspatient 12 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
L
B

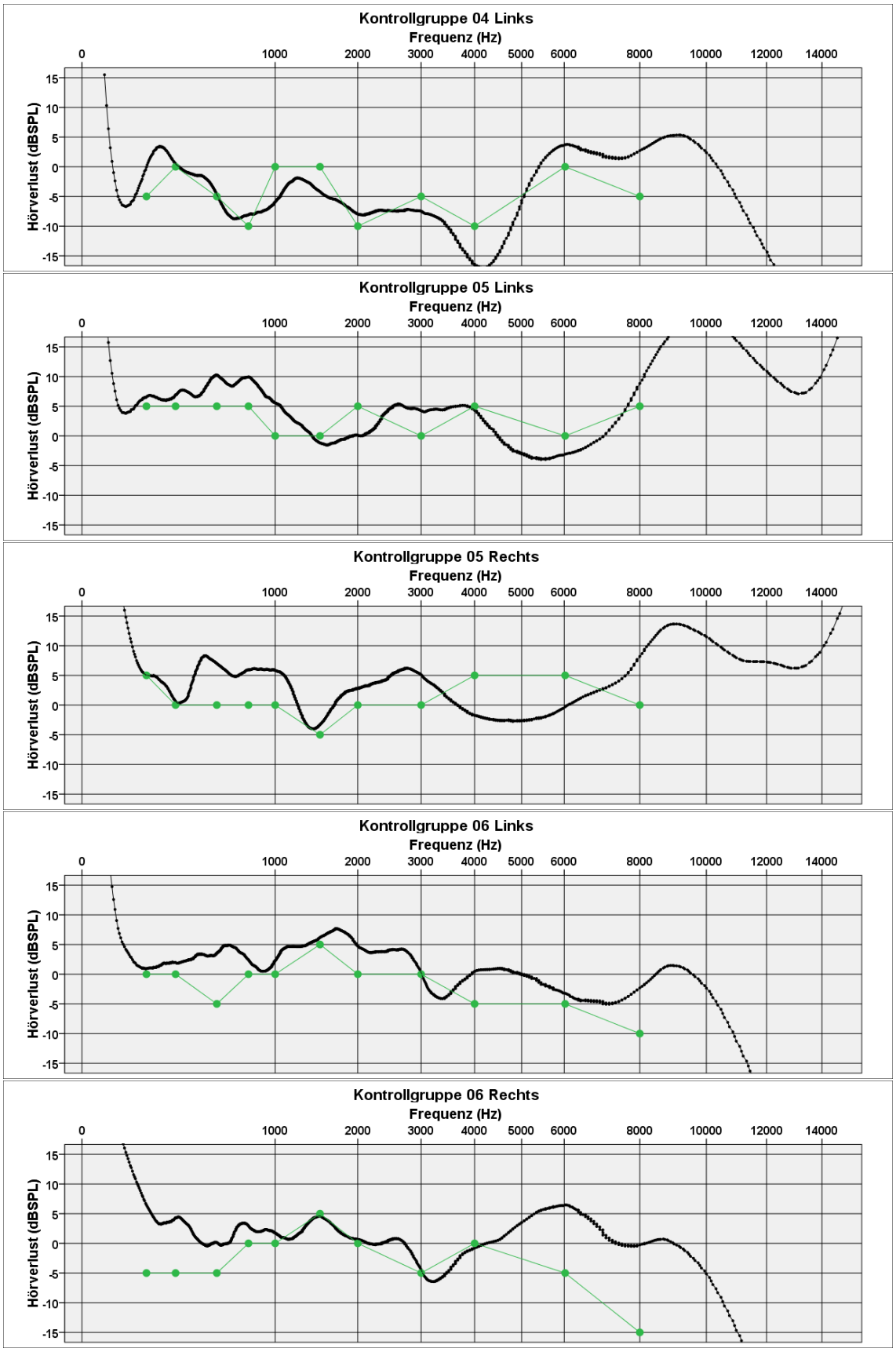

Tinnituspatient 14 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
L
B

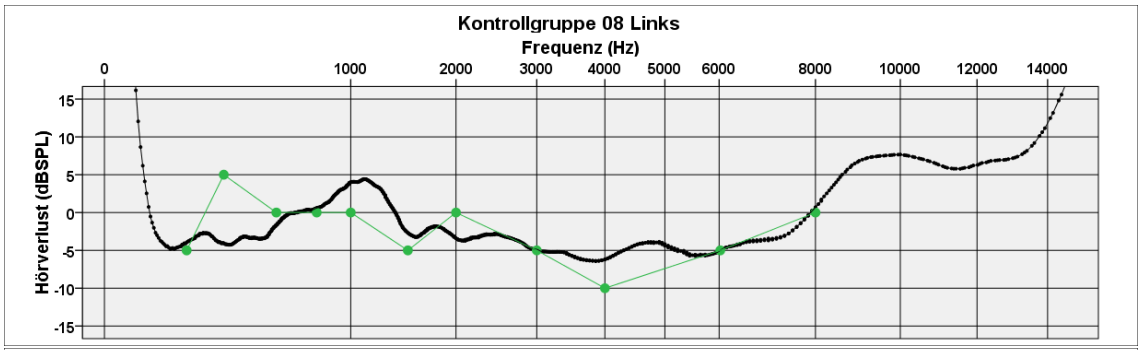

Tinnituspatient 14 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
L
B

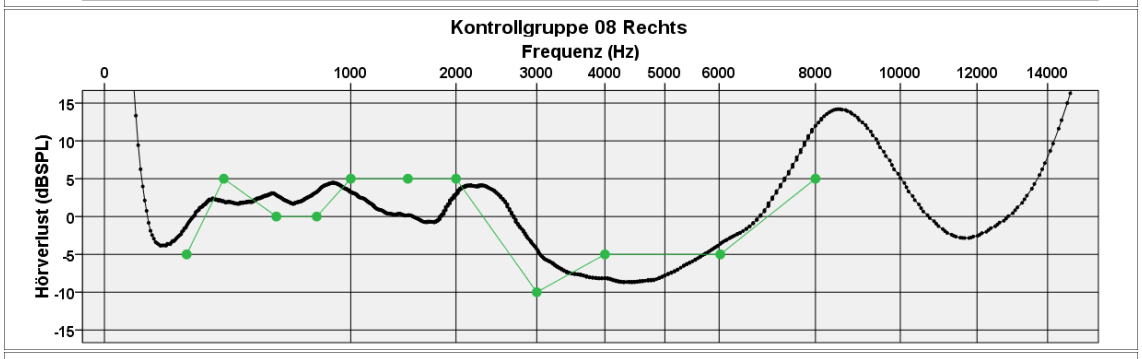

Tinnituspatient 15 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)
L
B
Tinnituspatient 15 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)
L
B

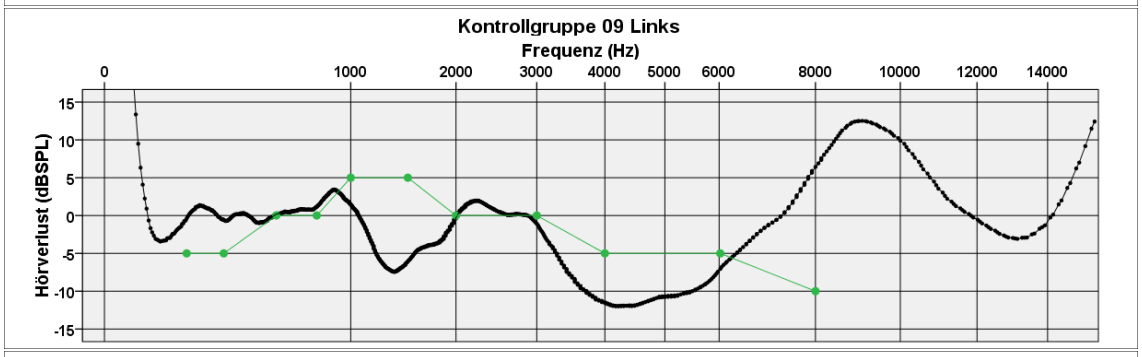
PT11 and Békésy audiograms of all controlgroup (Kontrollgruppe) subjects




Kontrollgruppe 04 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)
Kontrollgruppe 05 Links
Frequenz (Hz)
Hörverlust (dBSPL)
Kontrollgruppe 05 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)
Kontrollgruppe 06 Links
Frequenz (Hz)
Hörverlust (dBSPL)
Kontrollgruppe 06 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)


Kontrollgruppe 08 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)


Kontrollgruppe 08 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)


Kontrollgruppe 09 Links
Frequenz (Hz)
0
1000
2000
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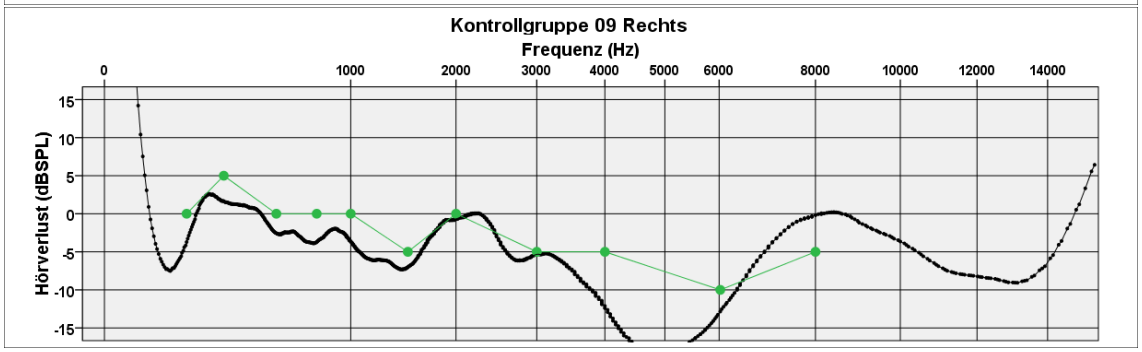
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)


Kontrollgruppe 09 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
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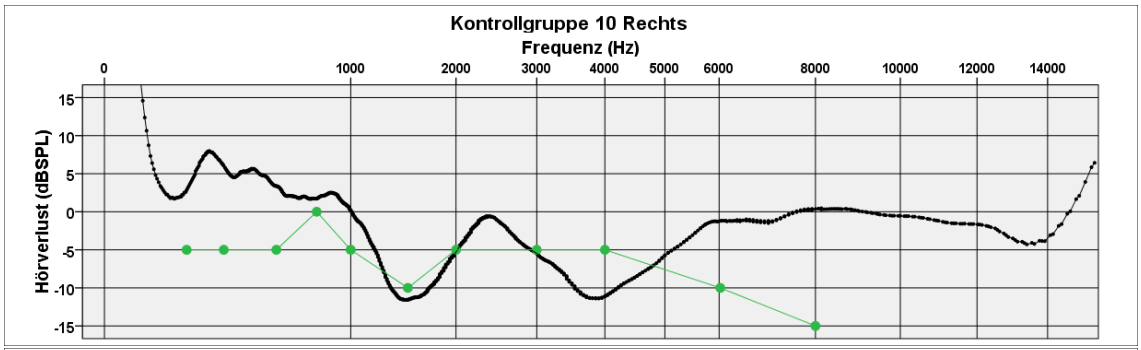
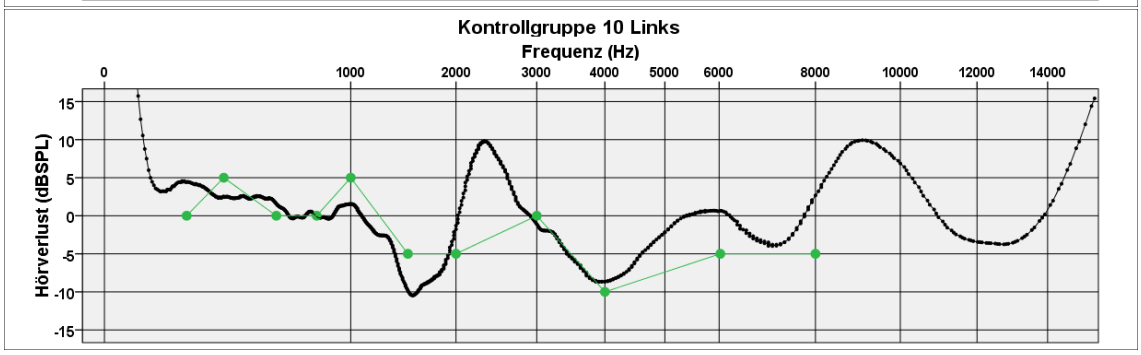
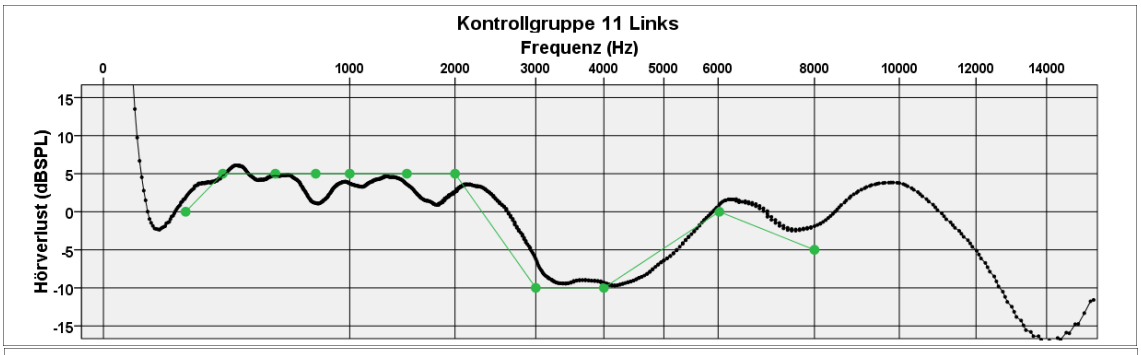
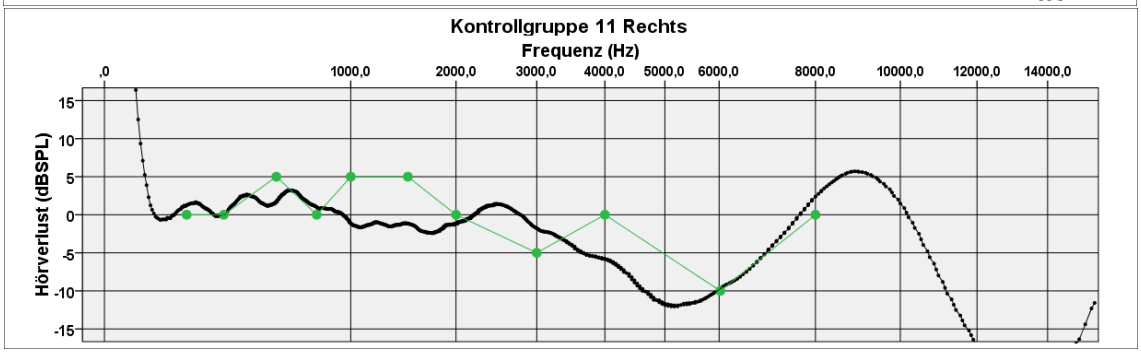
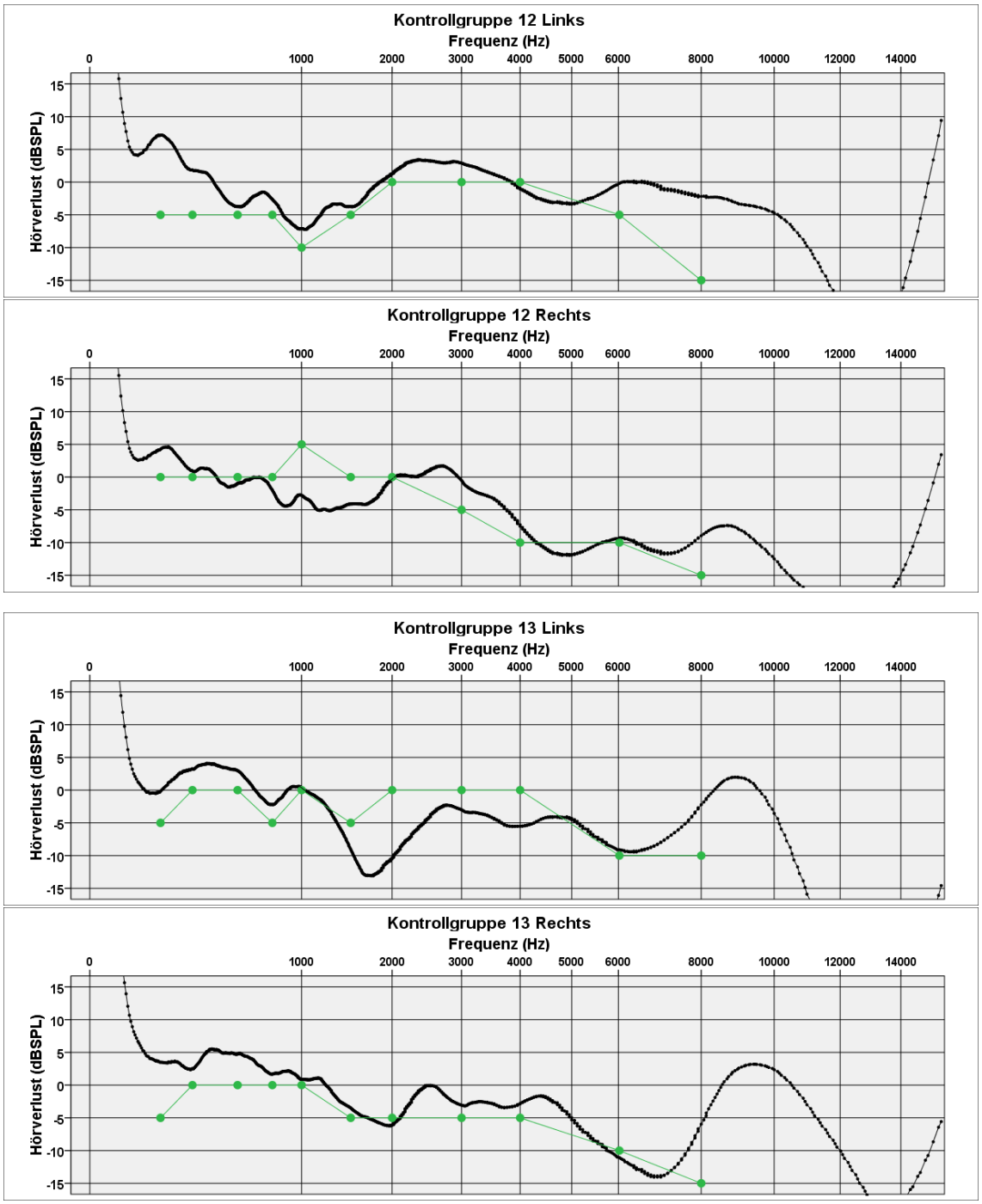
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)

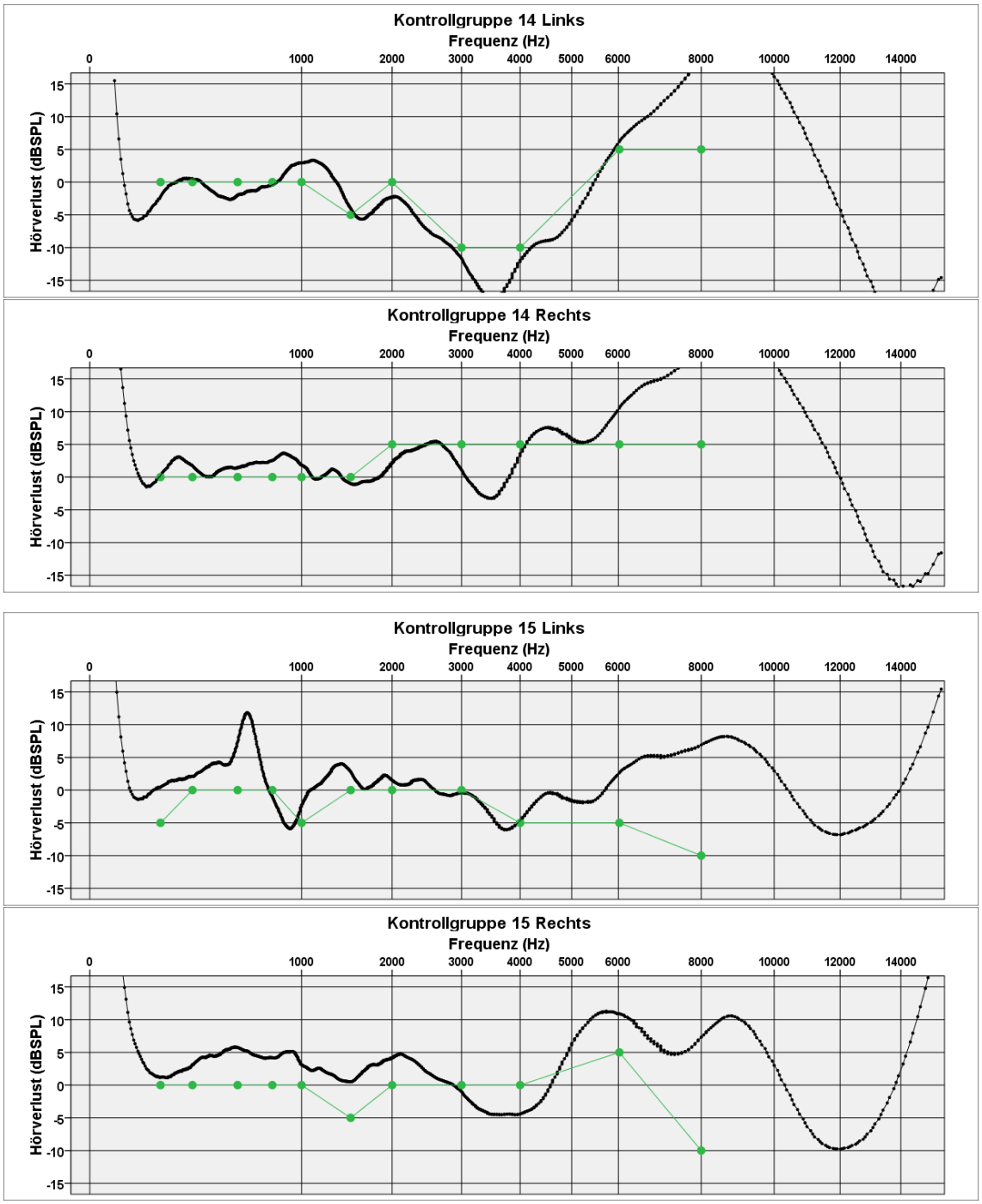

Kontrollgruppe 10 Rechts
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)


Kontrollgruppe 10 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)

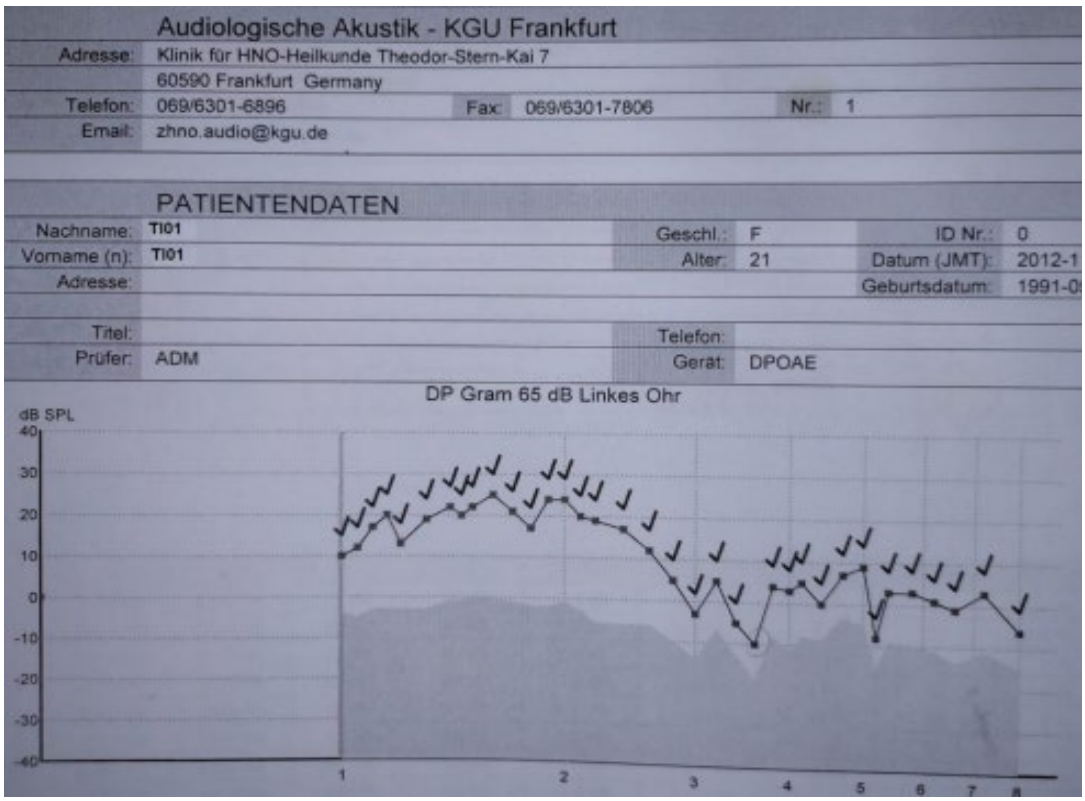

Kontrollgruppe 11 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)

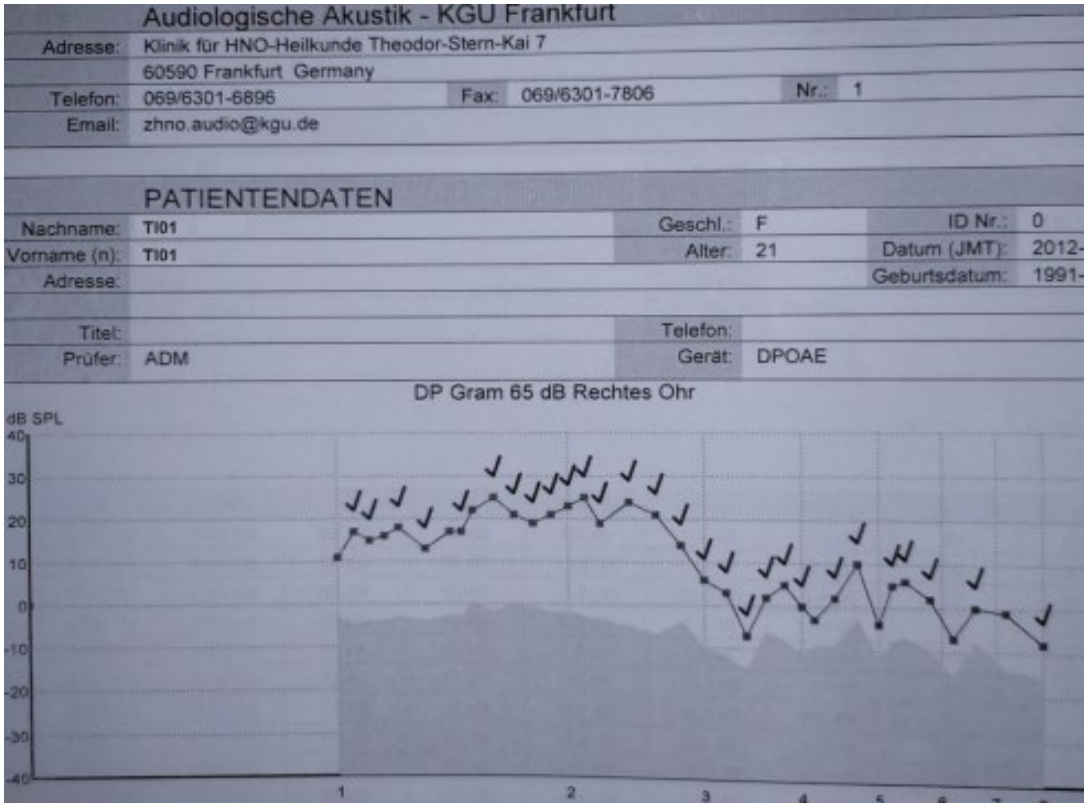

Kontrollgruppe 11 Rechts
Frequenz (Hz)
,0
1000,0
2000,0
3000,0
4000,0
5000,0
6000,0
8000,0
10000,0
12000,0
14000,0
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)


Kontrollgruppe 12 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
Hörverlust (dBSPL)
15
10
5
0
-5
-10
-15
Kontrollgruppe 12 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)
Kontrollgruppe 13 Links
Frequenz (Hz)
Hörverlust (dBSPL)
Kontrollgruppe 13 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)


Kontrollgruppe 14 Links
Frequenz (Hz)
0
1000
2000
3000
4000
5000
6000
8000
10000
12000
14000
15
10
5
0
-5
-10
-15
Hörverlust (dBSPL)
Kontrollgruppe 14 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)
Kontrollgruppe 15 Links
Frequenz (Hz)
Hörverlust (dBSPL)
Kontrollgruppe 15 Rechts
Frequenz (Hz)
Hörverlust (dBSPL)

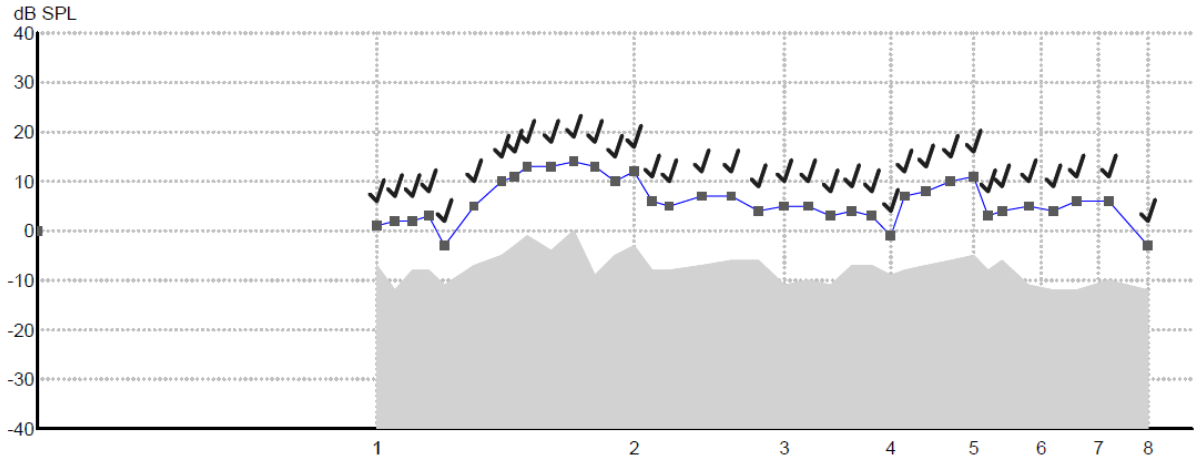
DP-Grams of tinnitus subjects





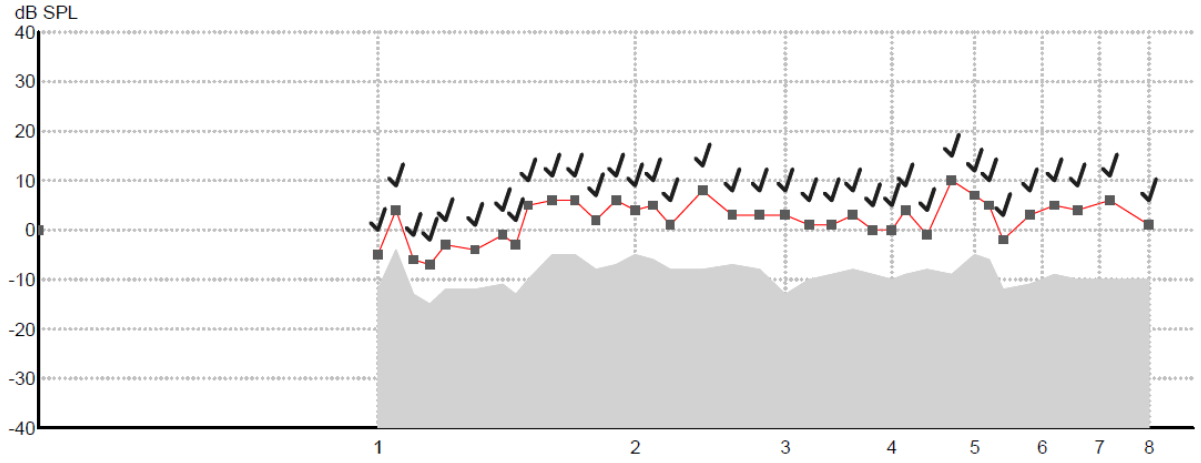
PATIENTENDATEN					
Nachname:	TI08	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI08	Alter:	26	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



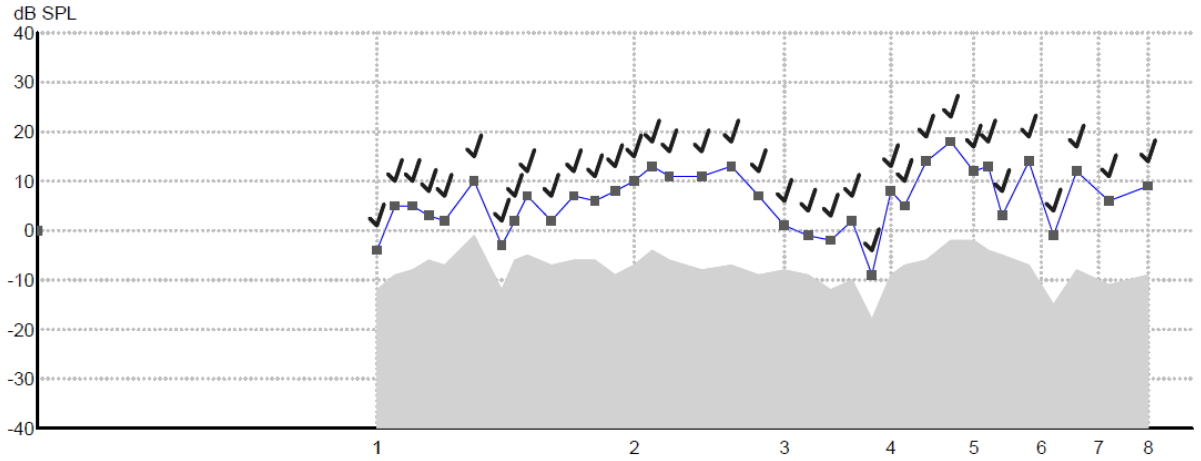
PATIENTENDATEN					
Nachname:	TI08	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI08	Alter:	26	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



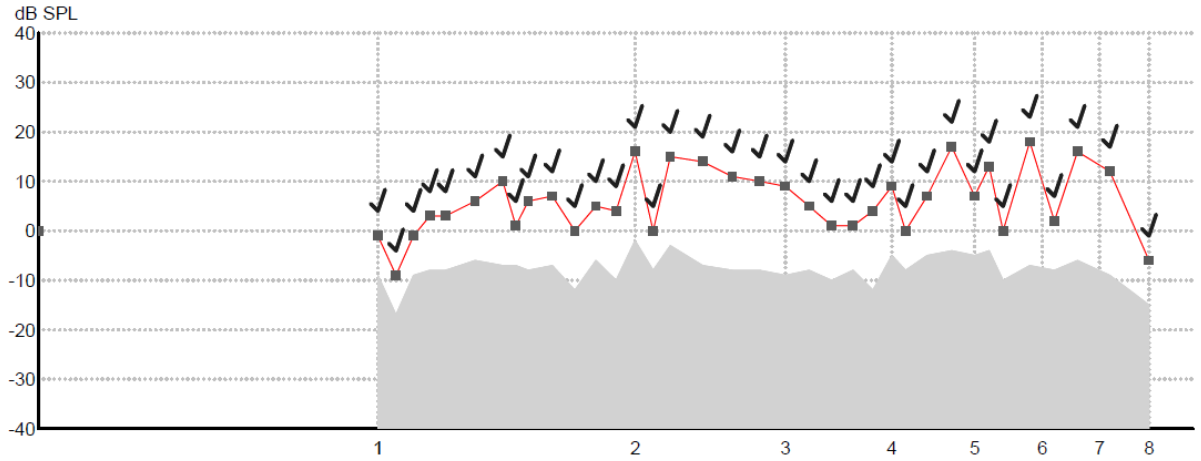
PATIENTENDATEN					
Nachname:	TI09	Geschl.:	F	ID Nr.:	0
Vorname (n):	TI09	Alter:	25	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



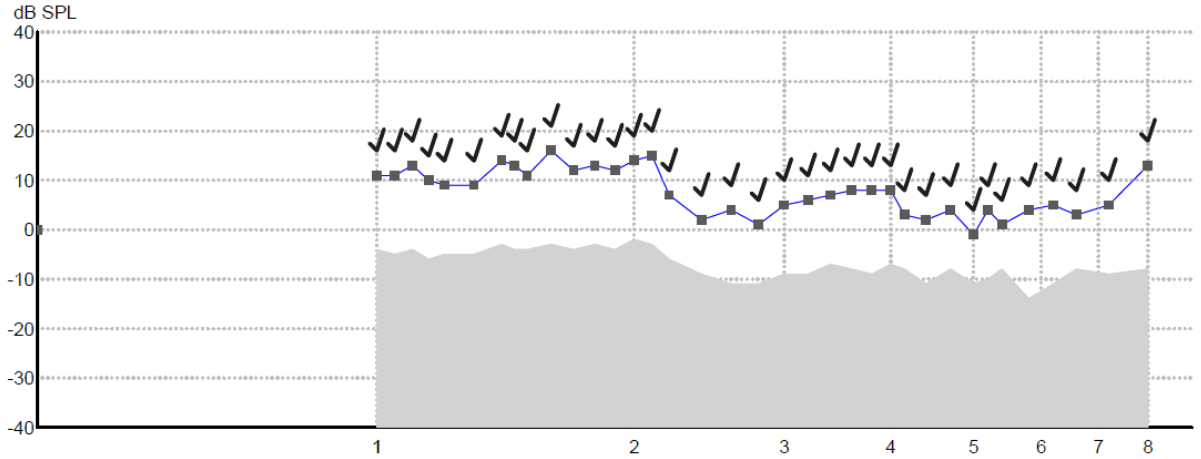
PATIENTENDATEN					
Nachname:	TI09	Geschl.:	F	ID Nr.:	0
Vorname (n):	TI09	Alter:	25	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



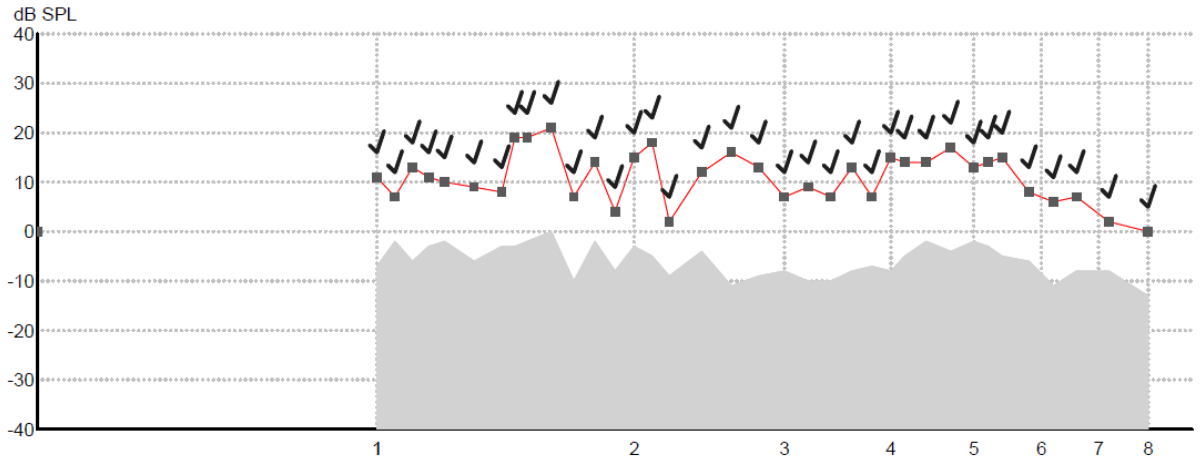
PATIENTENDATEN					
Nachname:	TI10	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI10	Alter:	26	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1988-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



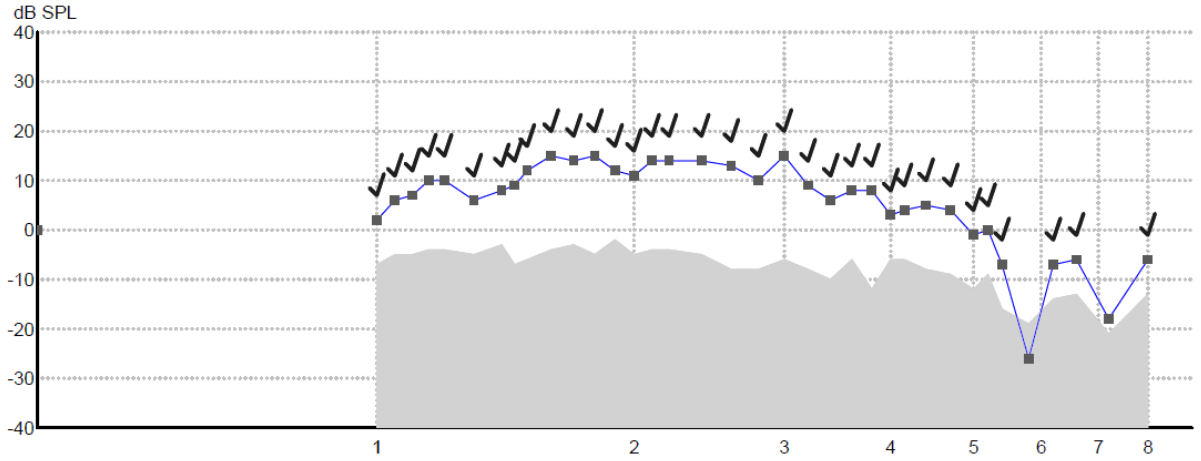
PATIENTENDATEN					
Nachname:	TI10	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI10	Alter:	26	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1988-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



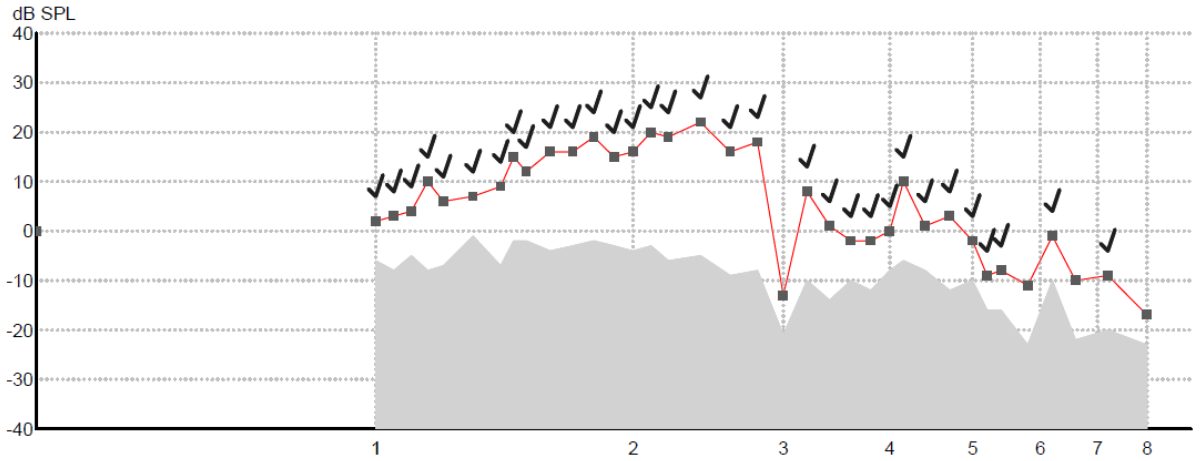
PATIENTENDATEN					
Nachname:	TI11	Geschl.:	F	ID Nr.:	0
Vorname (n):	TI11	Alter:	23	Datum (JMT):	2013-(
Adresse:				Geburtsdatum:	1991-(
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



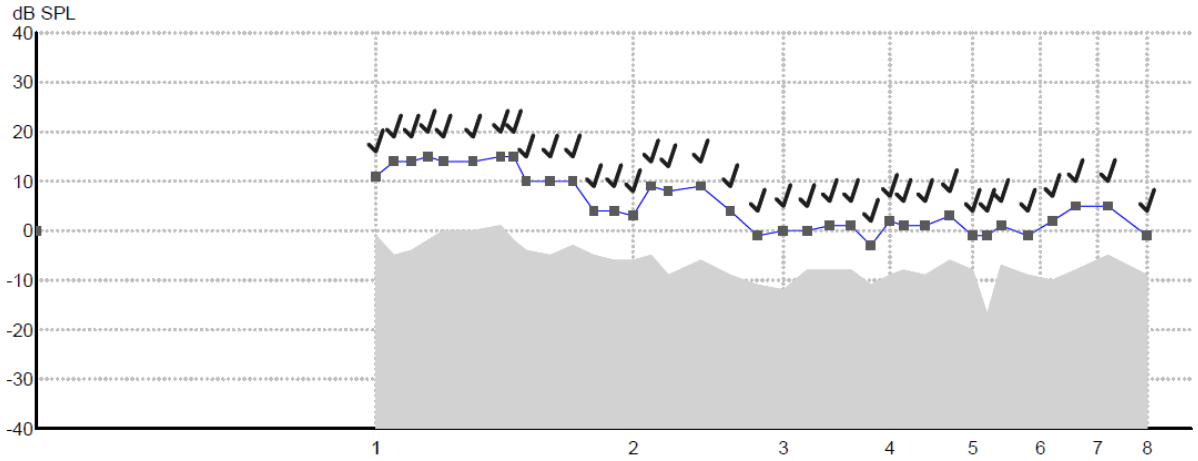
PATIENTENDATEN					
Nachname:	TI11	Geschl.:	F	ID Nr.:	0
Vorname (n):	TI11	Alter:	23	Datum (JMT):	2013-(
Adresse:				Geburtsdatum:	1991-(
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



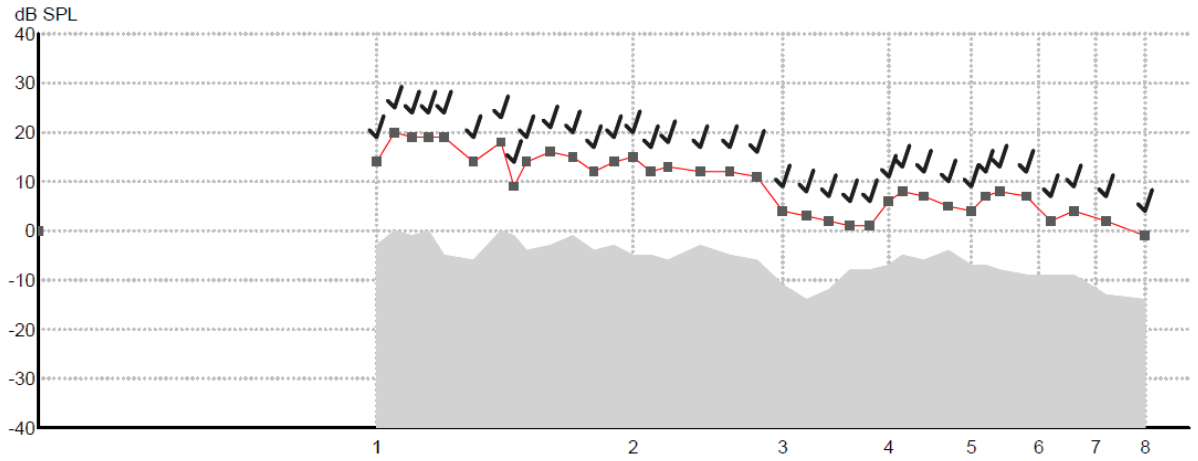
PATIENTENDATEN					
Nachname:	ti12	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI12	Alter:	23	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1992-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



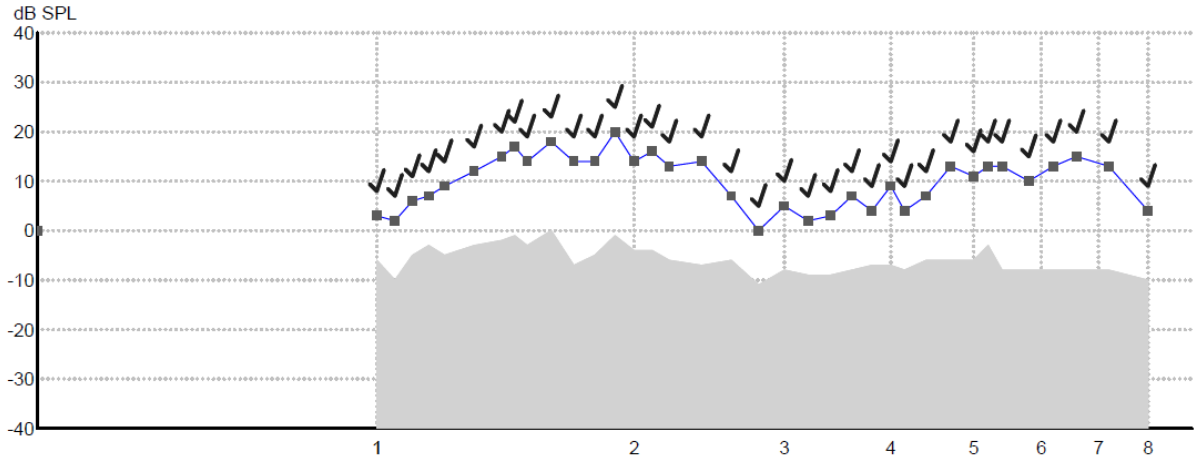
PATIENTENDATEN					
Nachname:	ti12	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI12	Alter:	23	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1992-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



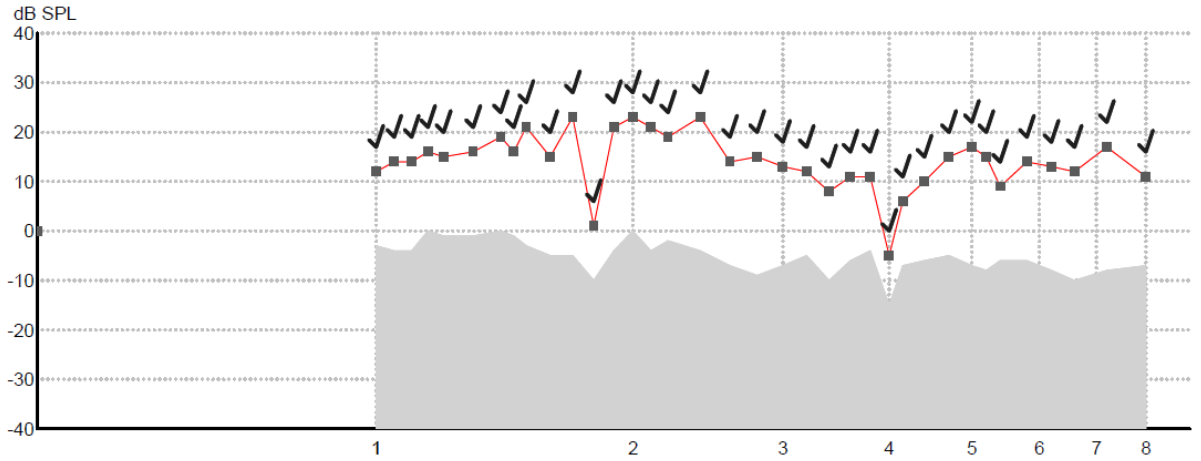
PATIENTENDATEN					
Nachname:	TI 13	Geschl.:	F	ID Nr.:	0
Vorname (n):	TI 13	Alter:	31	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1984-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



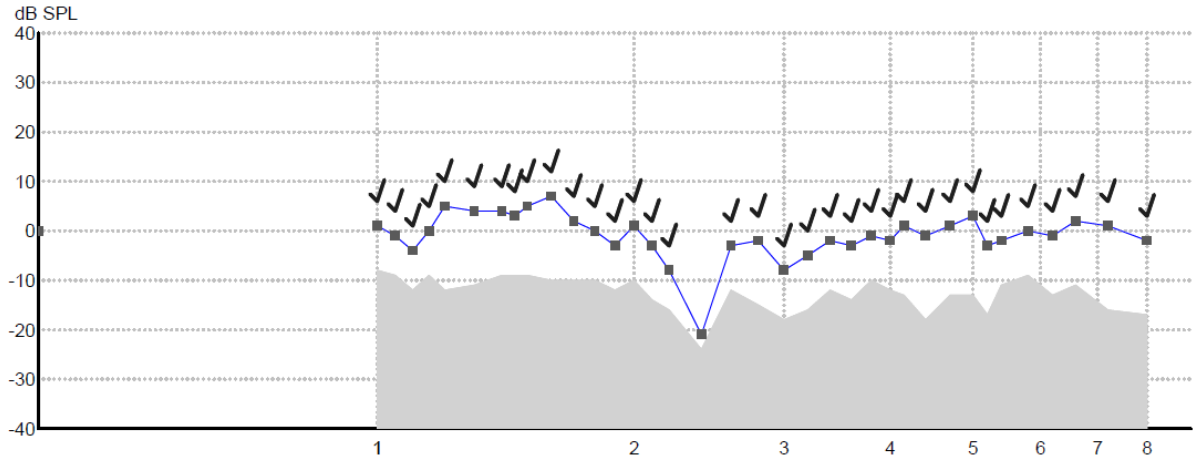
PATIENTENDATEN					
Nachname:	TI13	Geschl.:	F	ID Nr.:	0
Vorname (n):	TI13	Alter:	31	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1984-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



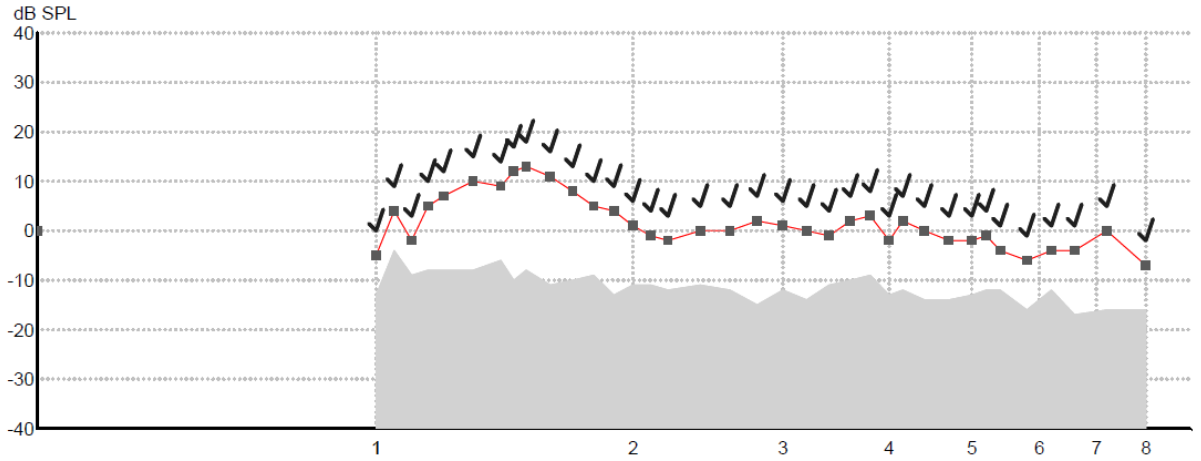
PATIENTENDATEN					
Nachname:	TI14	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI14	Alter:	31	Datum (JMT):	2013-(
Adresse:				Geburtsdatum:	1983-(
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



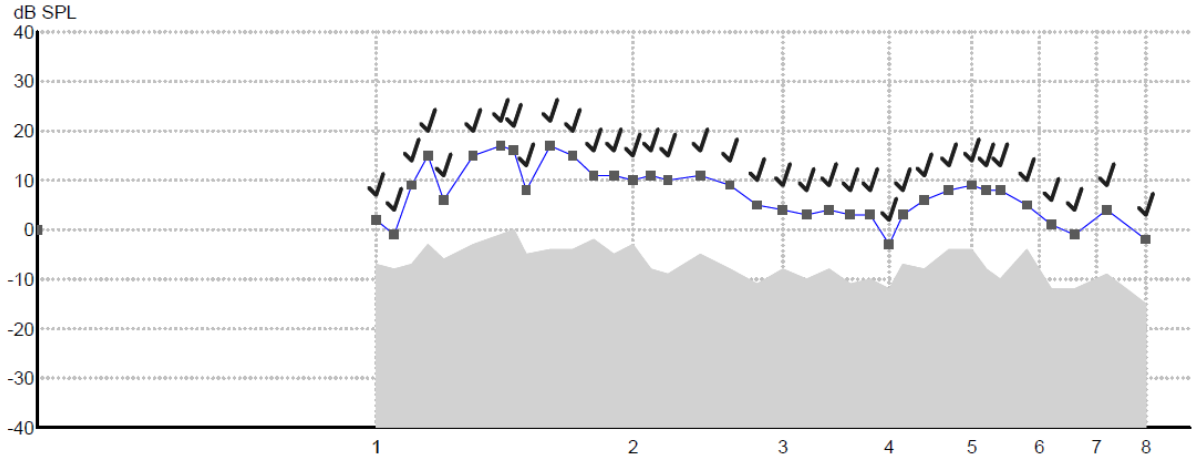
PATIENTENDATEN					
Nachname:	TI14	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI14	Alter:	31	Datum (JMT):	2013-(
Adresse:				Geburtsdatum:	1983-(
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



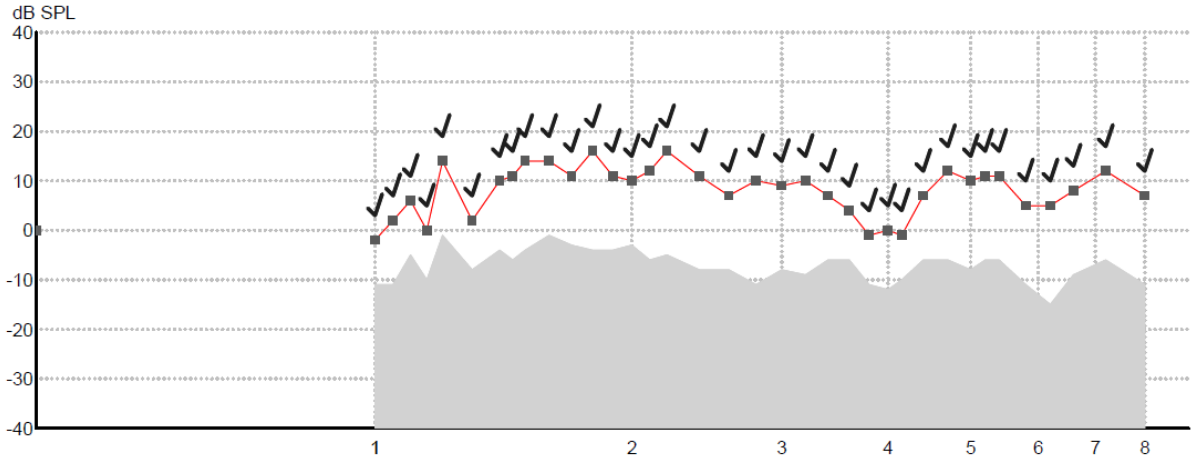
PATIENTENDATEN					
Nachname:	TI15	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI15	Alter:	24	Datum (JMT):	2013-(
Adresse:				Geburtsdatum:	1990-(
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



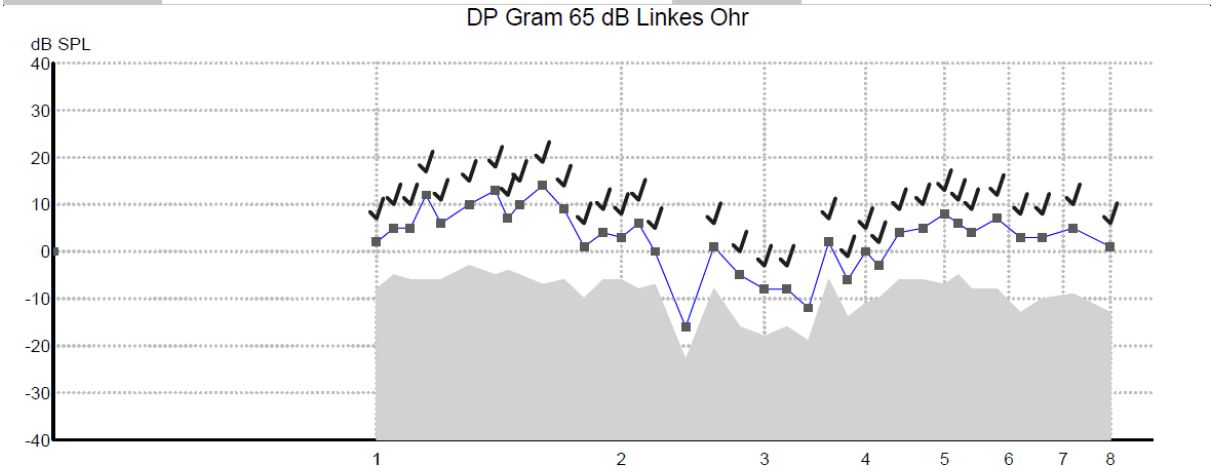
PATIENTENDATEN					
Nachname:	TI15	Geschl.:	M	ID Nr.:	0
Vorname (n):	TI15	Alter:	24	Datum (JMT):	2013-(
Adresse:				Geburtsdatum:	1990-(
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr

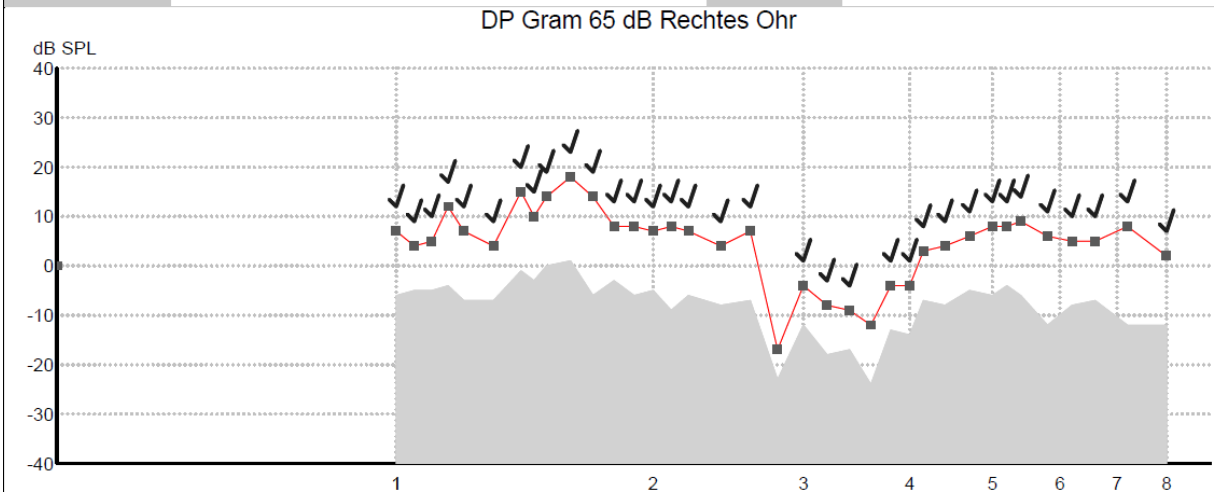


DP-Grams of controlgroup subjects

PATIENTENDATEN					
Nachname:	KG02	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG02	Alter:	25	Datum (JMT):	2013-08-30
Adresse:				Geburtsdatum:	1990-01-05
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

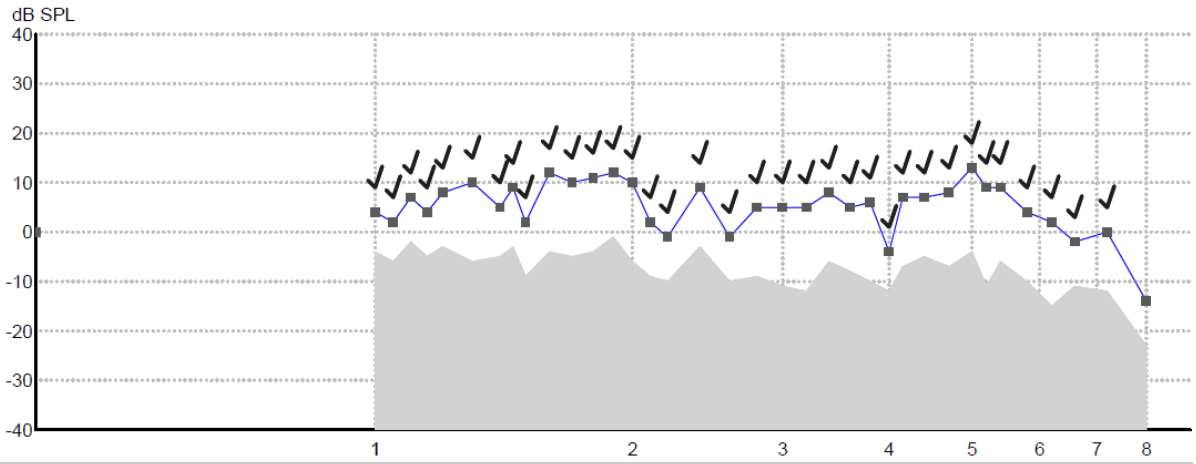


PATIENTENDATEN					
Nachname:	KG02	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG02	Alter:	25	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1990-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		



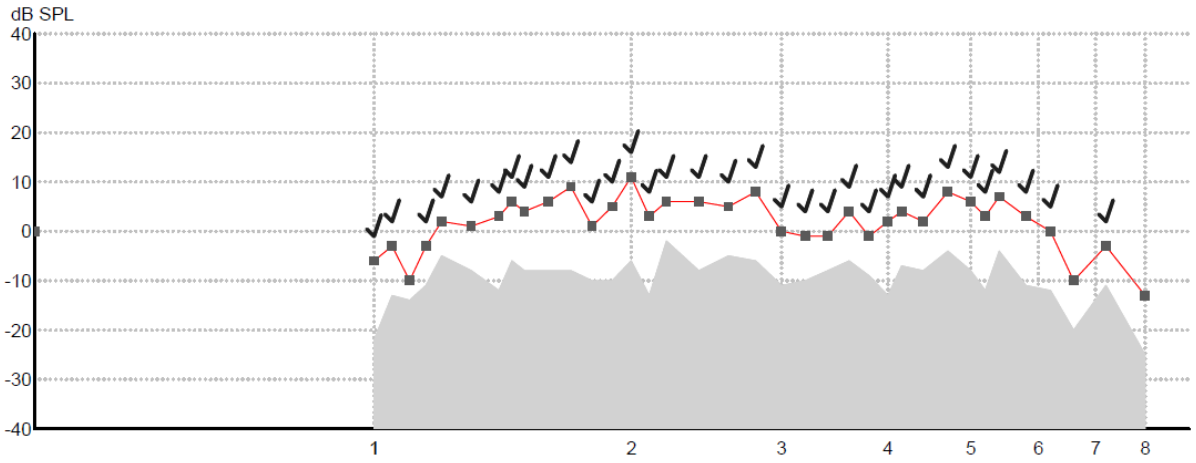
PATIENTENDATEN					
Nachname:	KG03	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG03	Alter:	29	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1986-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



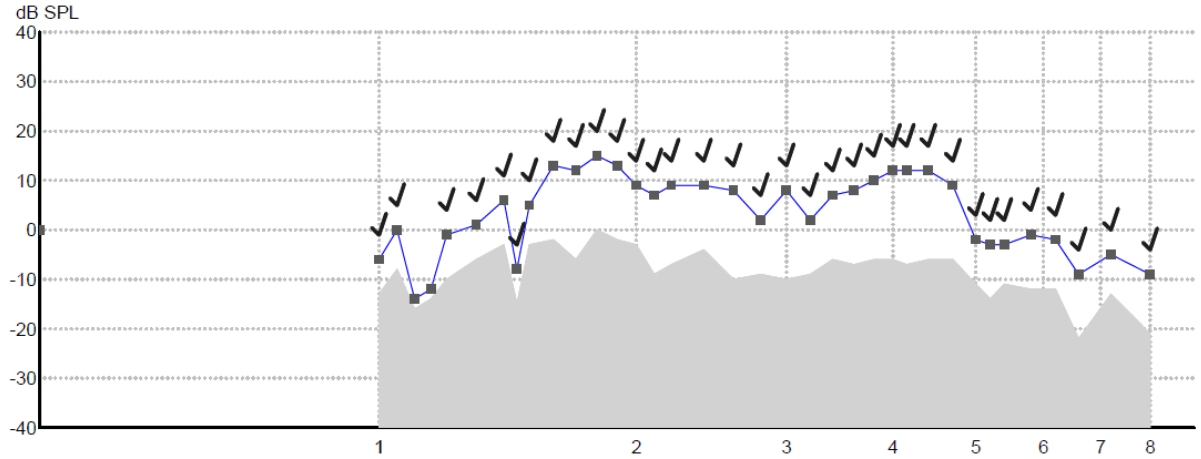
PATIENTENDATEN					
Nachname:	KG03	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG03	Alter:	29	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1986-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



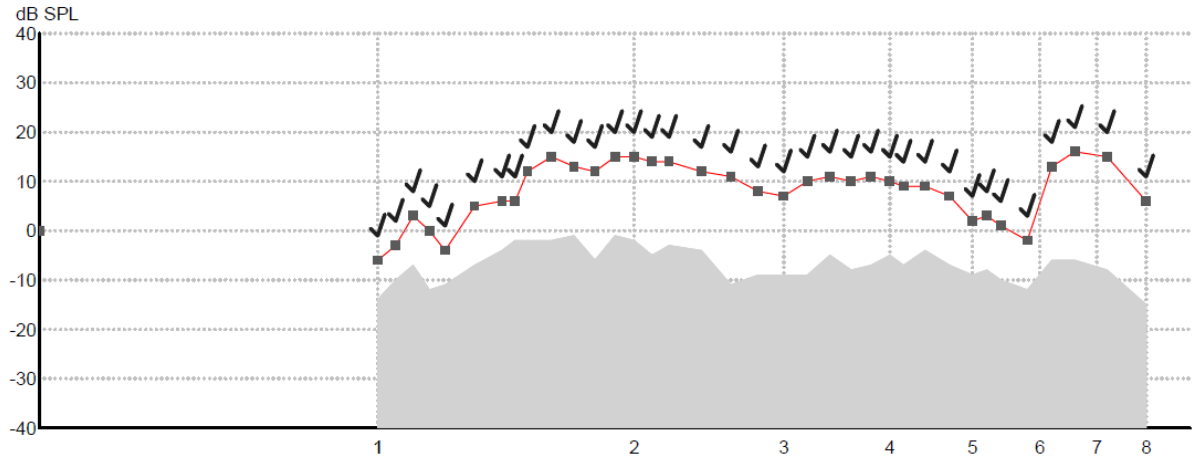
PATIENTENDATEN					
Nachname:	KG04	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG04	Alter:	29	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1985-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



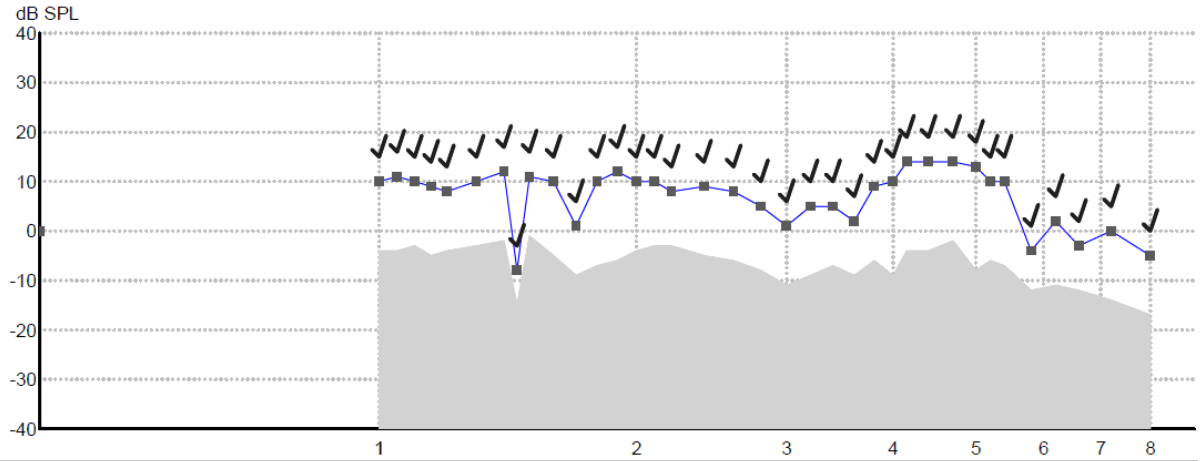
PATIENTENDATEN					
Nachname:	KG04	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG04	Alter:	29	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1985-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



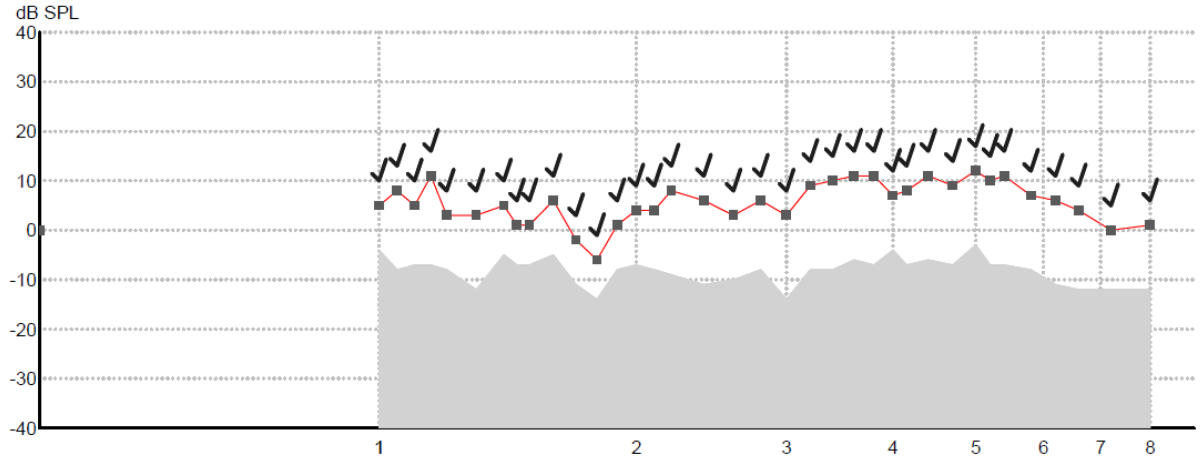
PATIENTENDATEN					
Nachname:	KG05	Geschl.:	F	ID Nr.:	0
Vorname (n):	KG05	Alter:	26	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



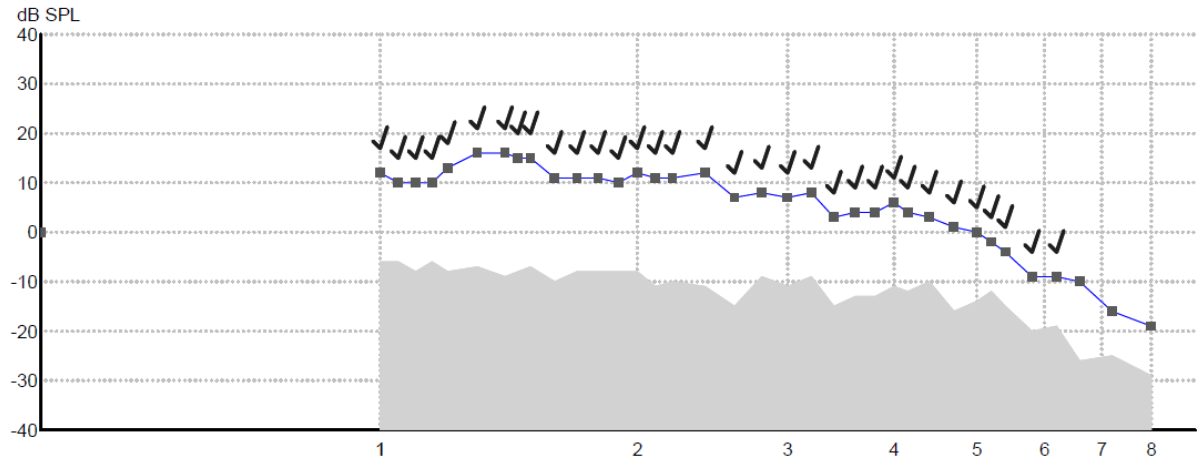
PATIENTENDATEN					
Nachname:	KG05	Geschl.:	F	ID Nr.:	0
Vorname (n):	KG05	Alter:	26	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



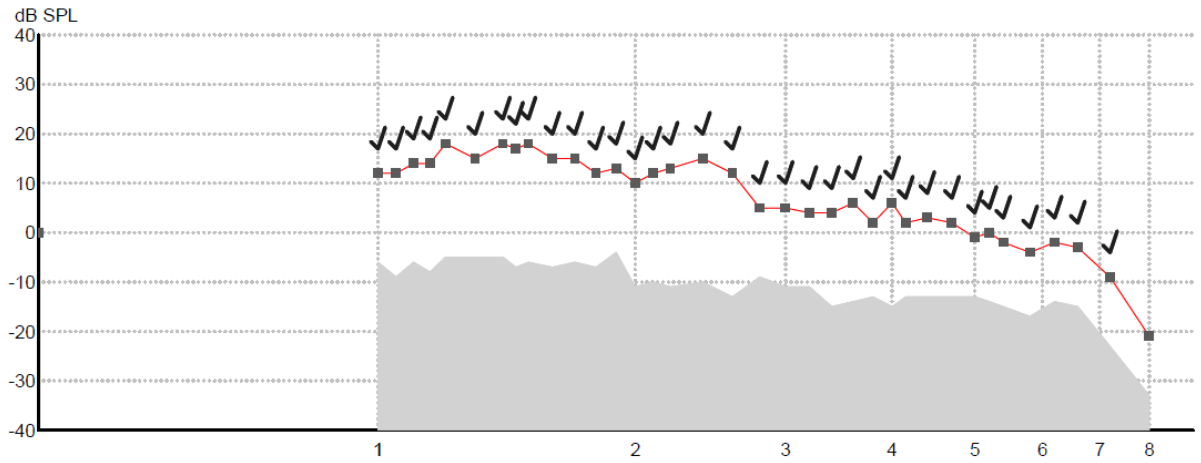
PATIENTENDATEN					
Nachname:	KG06	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG06	Alter:	25	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



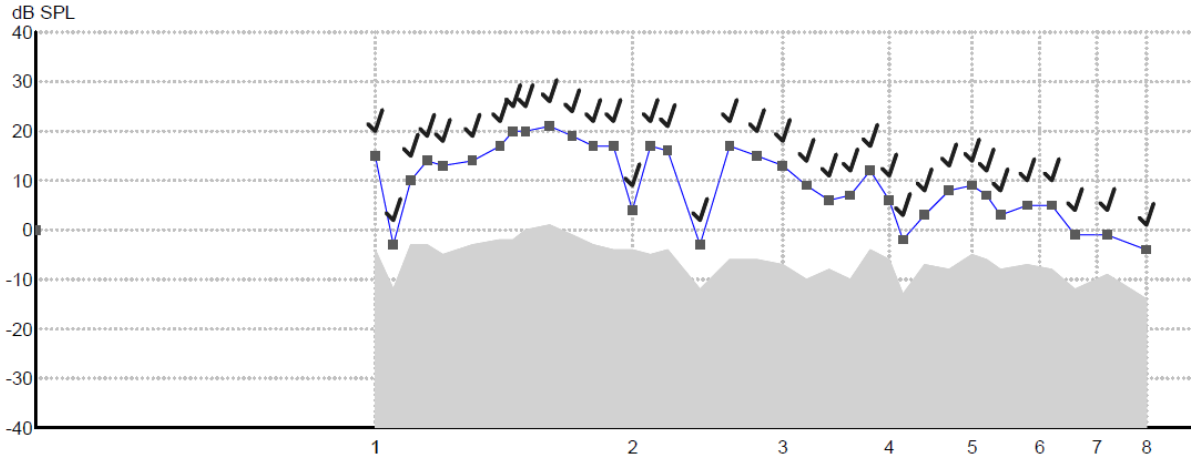
PATIENTENDATEN					
Nachname:	KG06	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG06	Alter:	25	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



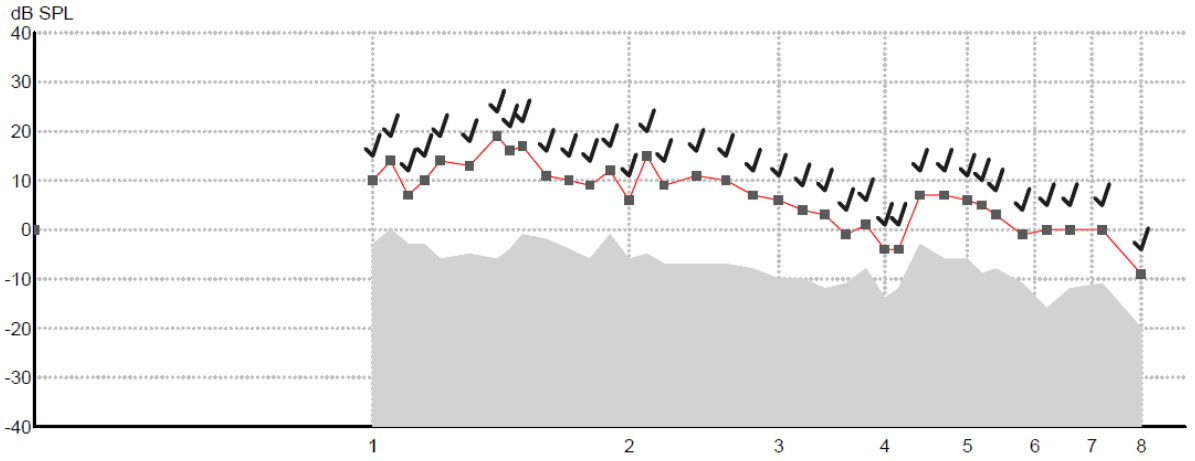
PATIENTENDATEN					
Nachname:	KG08	Geschl.:	F	ID Nr.:	0
Vorname (n):	KG08	Alter:	26	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



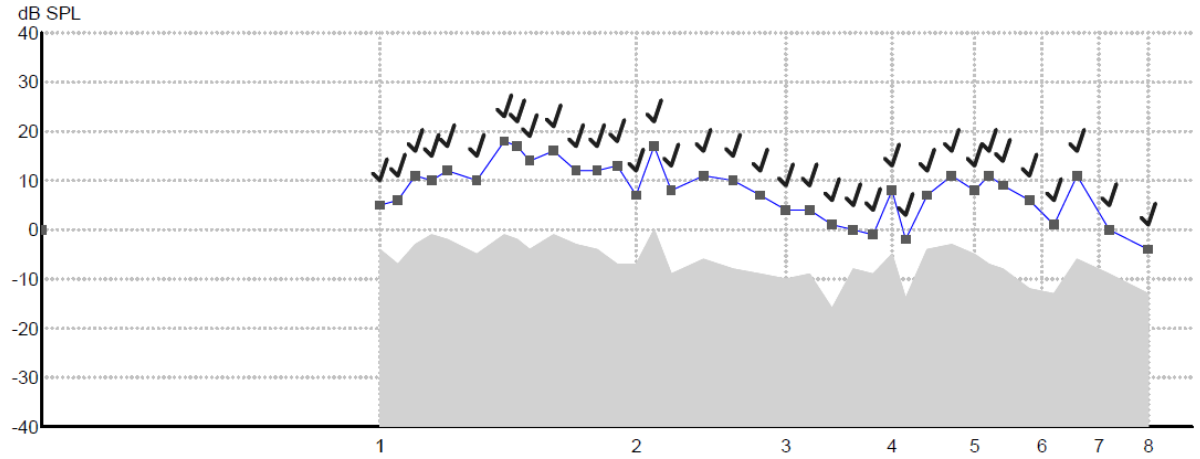
PATIENTENDATEN					
Nachname:	KG08	Geschl.:	F	ID Nr.:	0
Vorname (n):	KG08	Alter:	26	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1989-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



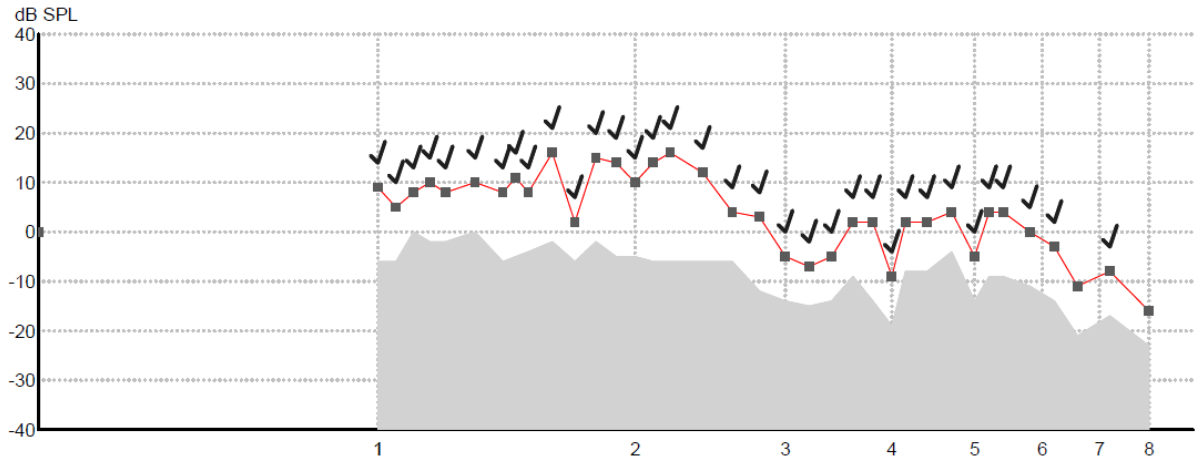
PATIENTENDATEN					
Nachname:	KG09	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG09	Alter:	32	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1982-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



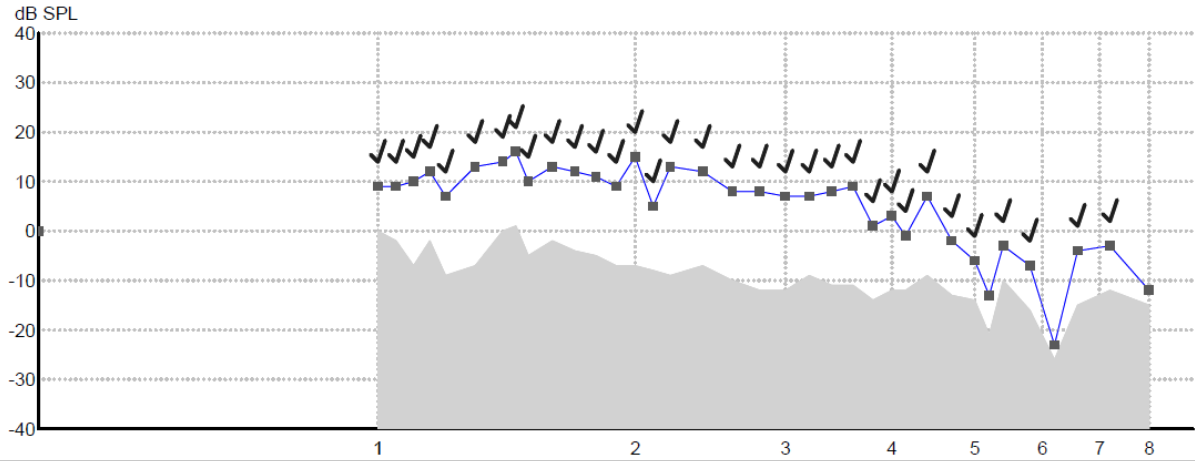
PATIENTENDATEN					
Nachname:	KG09	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG09	Alter:	32	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1982-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



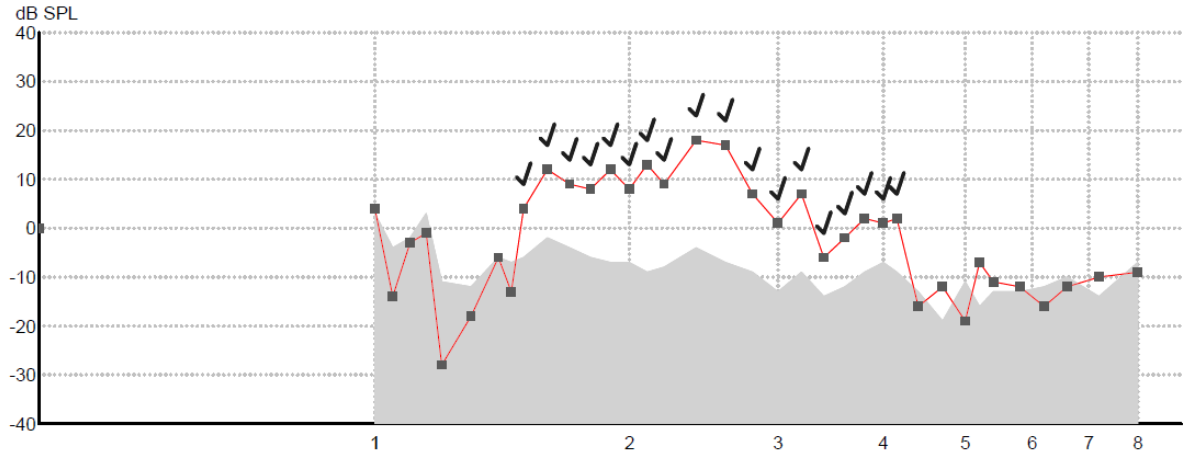
PATIENTENDATEN					
Nachname:	KG11	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG11	Alter:	32	Datum (JMT):	2015-
Adresse:				Geburtsdatum:	1982-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



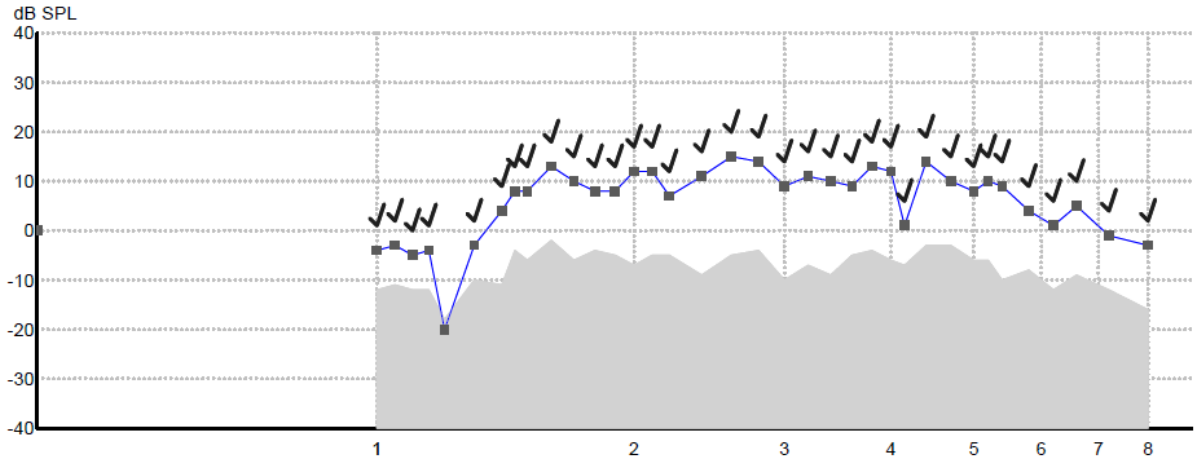
PATIENTENDATEN					
Nachname:	KG11	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG11	Alter:	32	Datum (JMT):	2015-0
Adresse:				Geburtsdatum:	1982-0
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



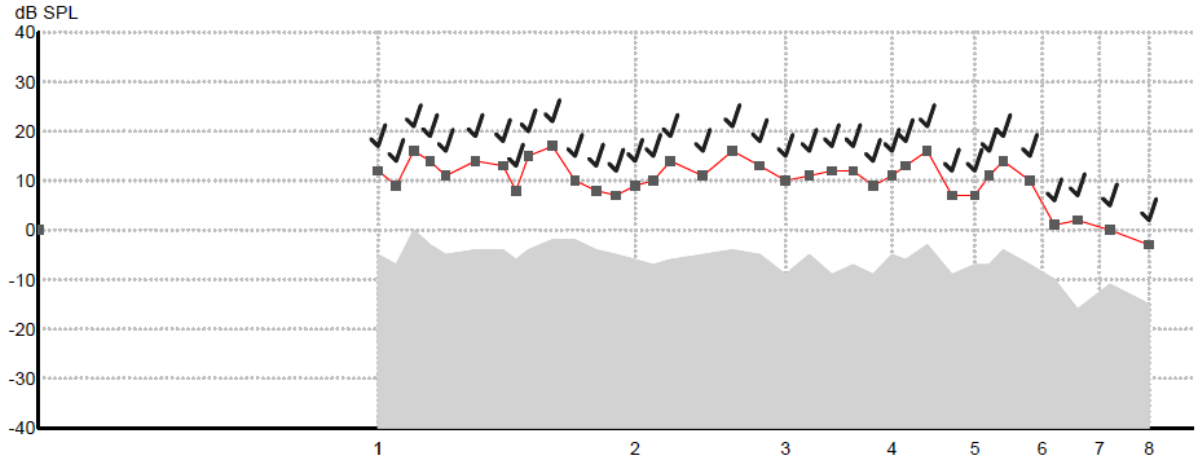
PATIENTENDATEN					
Nachname:	KG12	Geschl.:	F	ID Nr.:	0
Vorname (n):	KG12	Alter:	31	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1983-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



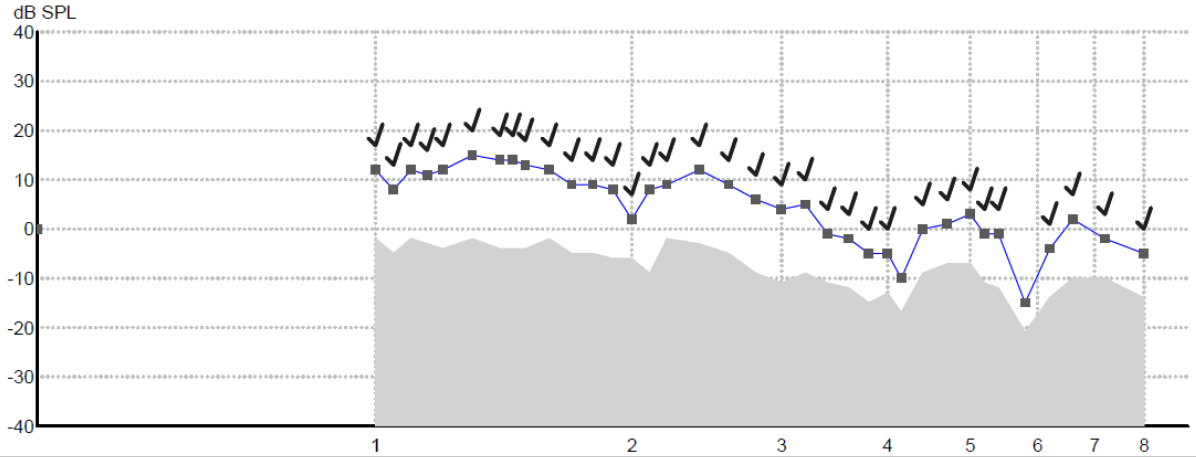
PATIENTENDATEN					
Nachname:	KG12	Geschl.:	F	ID Nr.:	0
Vorname (n):	KG12	Alter:	31	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1983-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



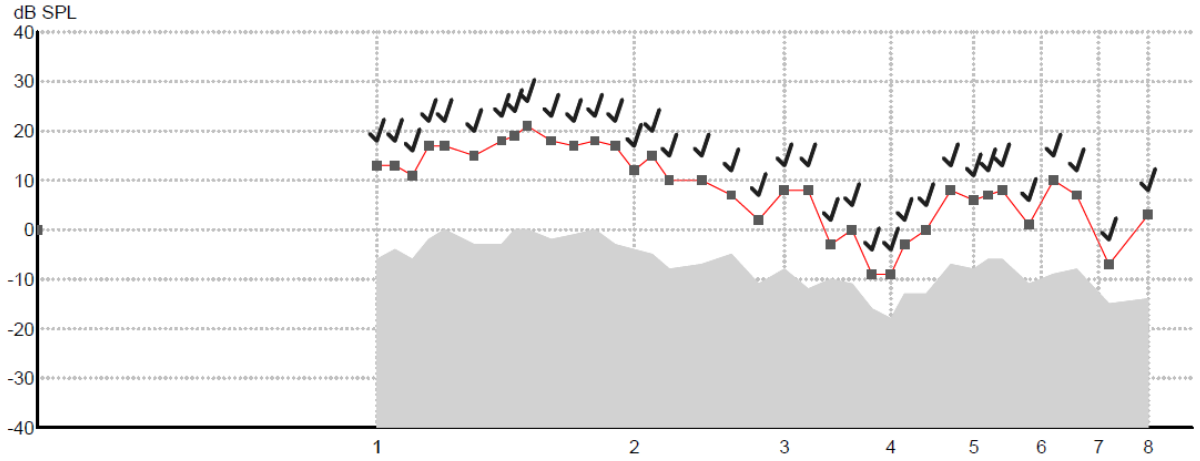
PATIENTENDATEN					
Nachname:	KG13	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG13	Alter:	31	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1983-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



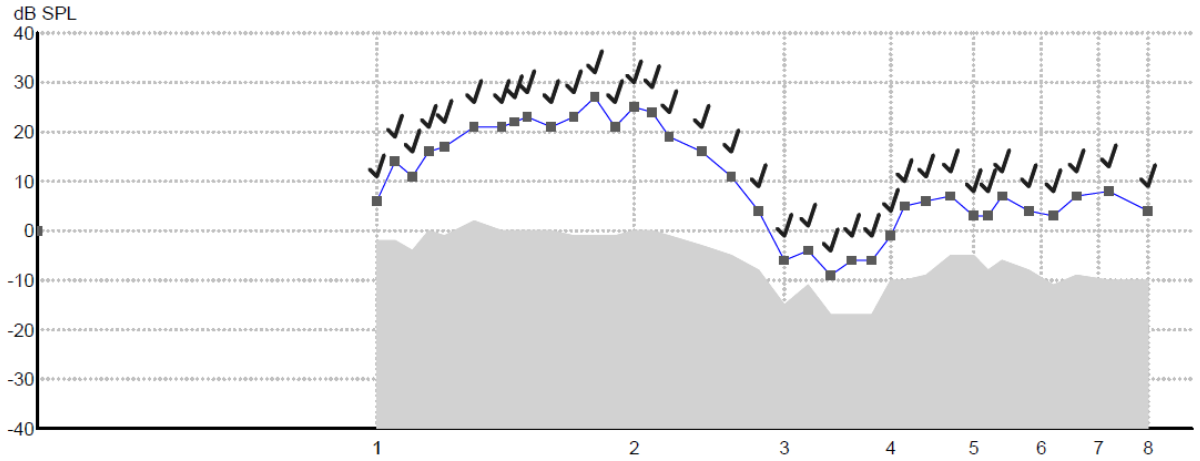
PATIENTENDATEN					
Nachname:	KG13	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG13	Alter:	31	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1983-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



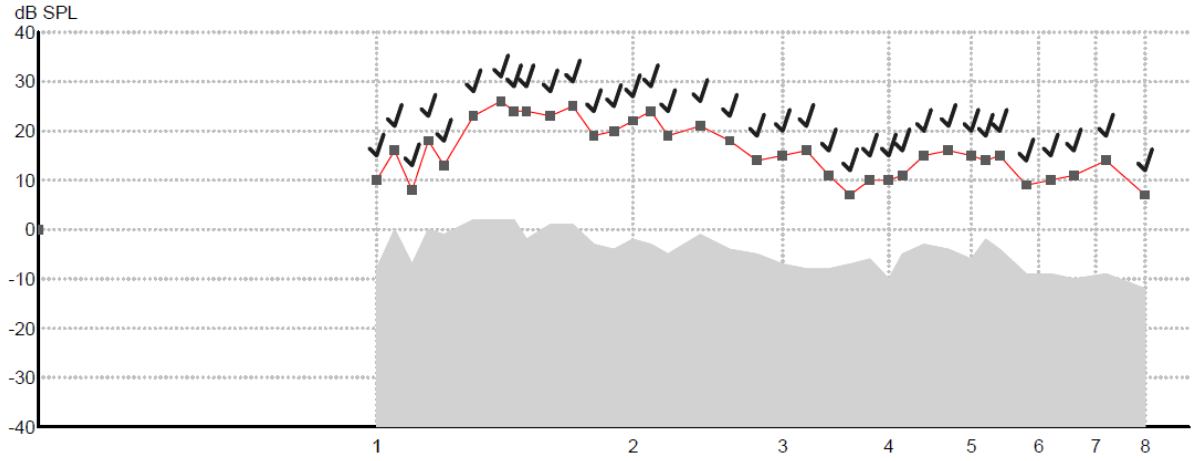
PATIENTENDATEN					
Nachname:	KG14	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG14	Alter:	28	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1986-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



PATIENTENDATEN					
Nachname:	KG14	Geschl.:	M	ID Nr.:	0
Vorname (n):	KG14	Alter:	28	Datum (JMT):	2013-
Adresse:				Geburtsdatum:	1986-
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



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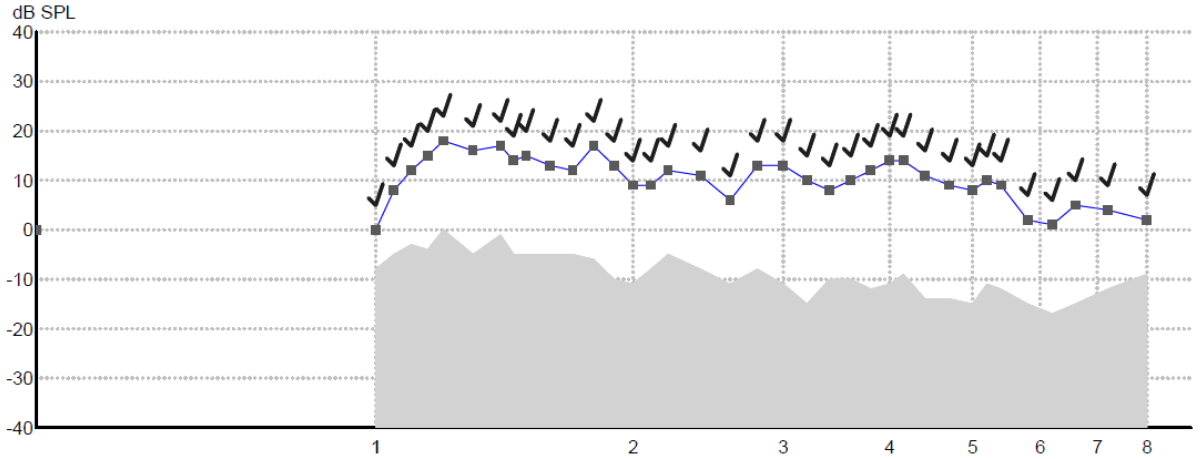
Vorname (n):	KG15	Alter:	31	Datum (JMT):	2015-(
Adresse:				Geburtsdatum:	1984-(
Titel:		Telefon:			
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Linkes Ohr



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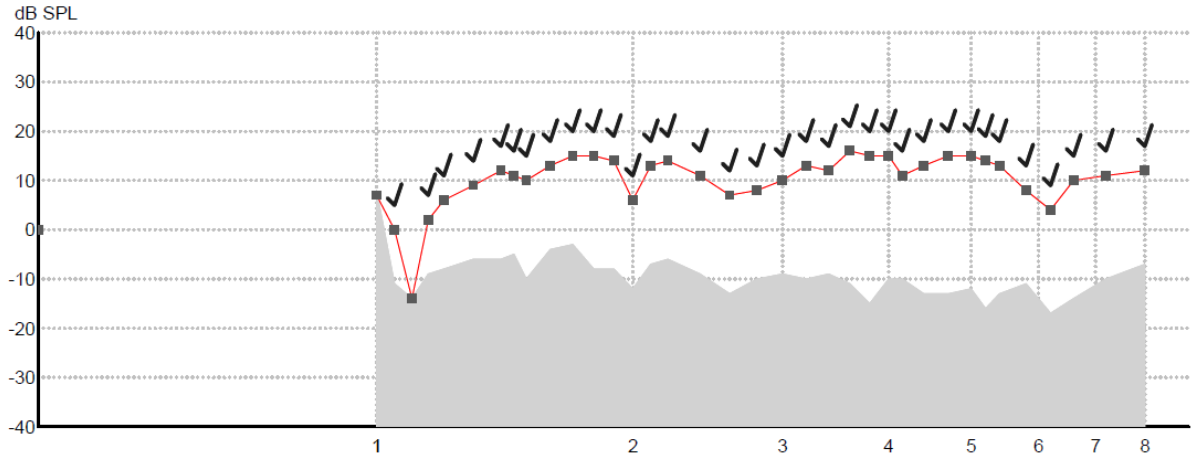
Prüfer:	ADM	Gerät:	DPOAE		

DP Gram 65 dB Rechtes Ohr



ABR amplitude data for Wave I and Wave V

ID	Amplitude Wavel I-L [nV]	Amplitude Wave I-R [nV]	Amplitude Wave V-L li [nV]	Amplitude WaveV-R [nV]
TI01	185	161	435	452
TI03	194	194	458	532
TI05	265	258	619	855
TI07	267	250	465	468
TI09	33	41	394	414
TI10	49	54	246	253
TI11	323	226	555	548
TI12	55	121	218	218
TI13	129	194	710	1097
TI14	355	194	268	261
TI15	35	145	210	294
KG02	73	70	364	315
KG03	171	323	284	645
KG04	60	92	332	258
KG05	153	194	242	432
KG06	32	48	308	376
KG08	62	70	633	550
KG09	120	95	365	312
KG10	117	120	423	409
KG11	137	110	254	171
KG12	42	41	378	214
KG13	72	132	257	328
KG14	74	49	402	443
KG15	229	294	445	339